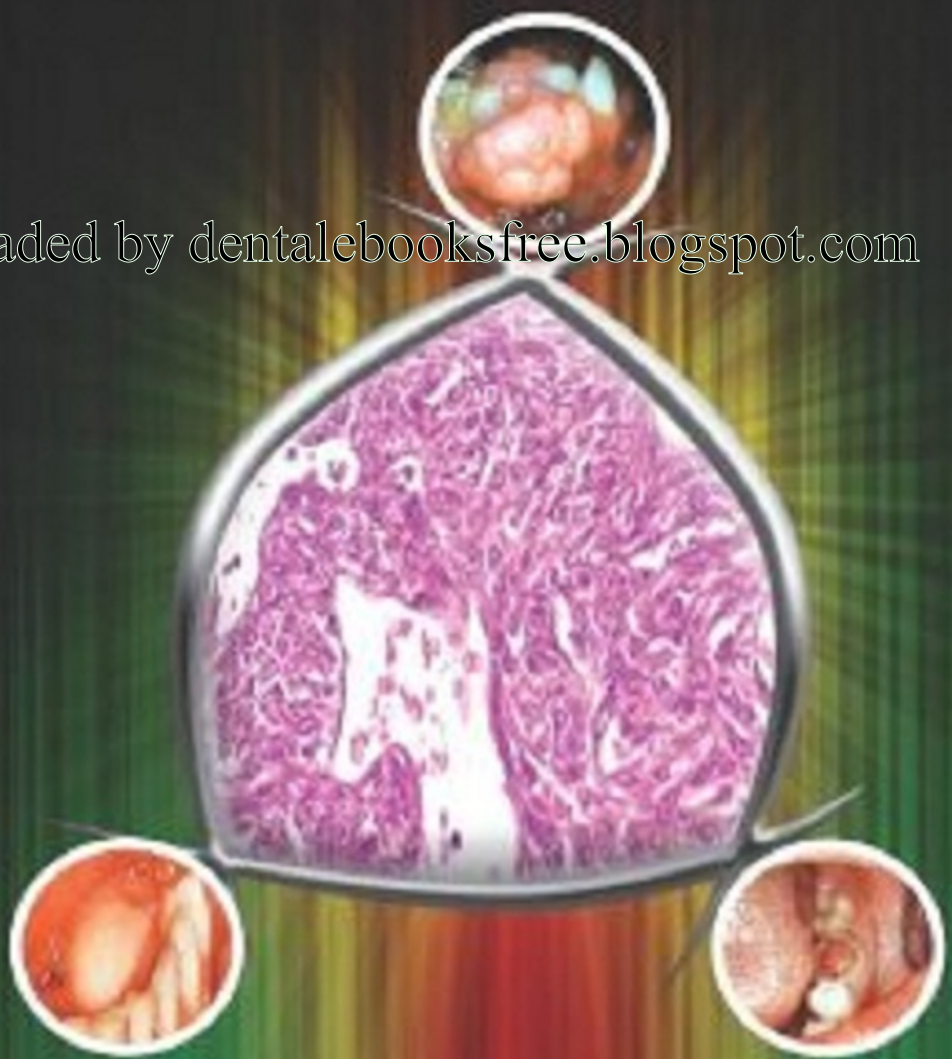
Textbook of

PEDIATRIC ORAL PATHOLOGY



KMK Masthan

Foreword Usha Mohan Das

JAYPEE

Textbook of
Pediatric Oral Pathology

Textbook of Pediatric Oral Pathology

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This book is for my wife Shameem

Foreword

I am indeed humbled by this experience. The attempt by Dr Masthan is commendable.

This text is indeed a comprehensive review with well-compiled chapters which are formatted in an easy-to-understand sequence. This text would soon gain both national as well as international repute because the matter is presented very lucidly and systematically.

Oral pathology is a vast subject, and I am really glad that a dedicated professional has finally contributed in a valid way. This book lends true insight into various aspects of oral pathology in a very comprehendible manner. The illustrations ably back up the author's attempt to simplify the understanding of the subject. Every area in pediatric oral pathology requires serious attention and the author has accomplished it. It is indeed an exemplary effort to include both the academic and application aspects of pediatric oral pathology.

I am extremely elated and grateful to Dr Masthan who has painstakingly made one more contribution to "Pediatric Dentistry" in a latent manner. The author's meticulous approach towards desired knowledge is tremendously beneficial to undergraduates and postgraduates who would be able to understand conclusive evidence and experience-based diagnosis in children with pathological problems.

I am sure Dr Masthan's arduous, painstaking efforts would be beneficial to each and every one of us. I have worked with suffering little children all my life. I consider this book and the author a lifesaver since some of the points he has discussed in this book, would help not just understand, but alleviate the suffering of children. On behalf of the pediatric dentistry fraternity, I take this opportunity to commend you on a valuable adjunct which I am sure many would consider a treasure of knowledge.

This is indeed a much-needed book, a valuable inclusion in the ocean of possibilities.

It is with great pride I extend my heartfelt congratulations to the author and his team for a brilliant attempt to contribute to one of the most challenging branches of dentistry.

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Preface

Oral pathoses in children are often missed since obtaining detailed history and performing thorough clinical examination are more difficult in comparison with an adult. The belief of the clinician that children rarely suffer from oral pathoses further adds to lesser number of early diagnoses. Hence, I have made an attempt at compiling the oral diseases which the children frequently suffer from and which the clinician must consider in his mind while examining a child.

The book is useful for undergraduate dental students and the practising general dentists/medical practitioners. Probably, the simplicity of the book may attract pedodontists, pediatricians and oral/general pathologists for easy reference.

Since the focus of this book is the pediatric population, the oral pathoses affecting mainly adults are not included. This is not an oversight and an intentional one. I do not claim any originality since most of the text is from standard textbooks on pedodontics, pediatrics and oral pathology.

The entire faculty of department of oral pathology was involved in the spade work for bringing out this book and hence the credit goes to everyone of them. Dr Shankar Gowda Patil and Dr Shyam Sundar Behura, PG students, in particular, deserve to be commended for their hard work.

I am greatly indebted to Dr Usha Mohan Das, MDS, President, Indian Society of Pedodontics and Preventive Dentistry, Principal and Head of Department of Pedodontics, VS Dental College and Hospital, Bengaluru, Karnataka for giving Foreword for this book.

My wholehearted thanks to M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi who have published my earlier books (*Guide To Oral Pathology*, *Jaypee Mini Atlas Series on Oral Pathology*, *Textbook of Forensic Odontology* and *Textbook of Human Oral Embryology*, *Anatomy*, *Physiology*, *Histology and Tooth Morphology*) and for publishing this book.

Since this book is a pioneer in this discipline, I may have left out some lessons/topics. Your suggestions regarding lapses and lacunae are welcome at masthankmk@yahoo.com

KMK Masthan

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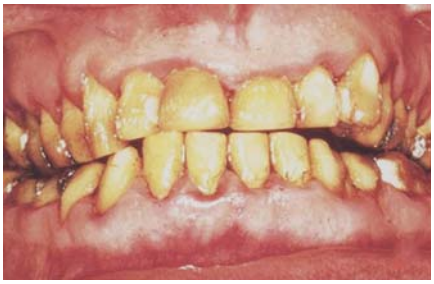

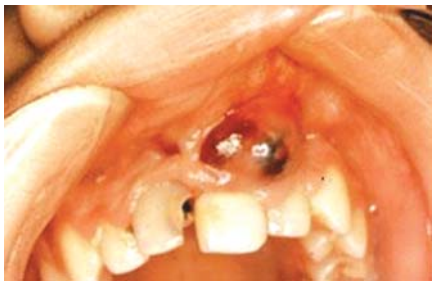

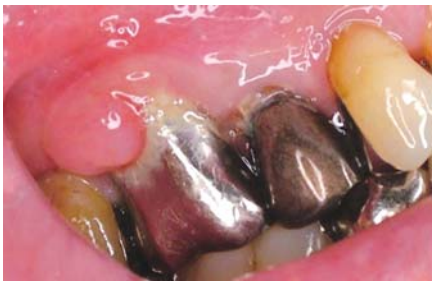

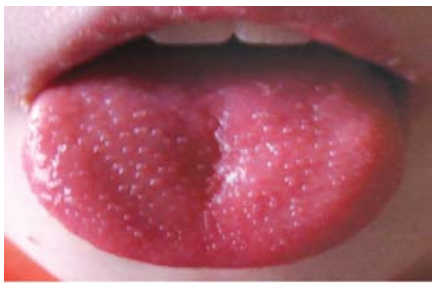

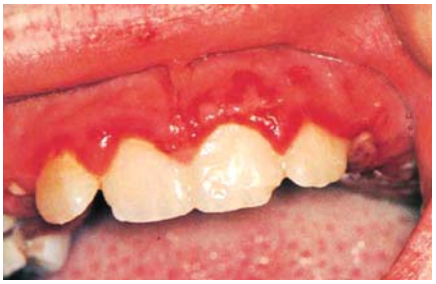

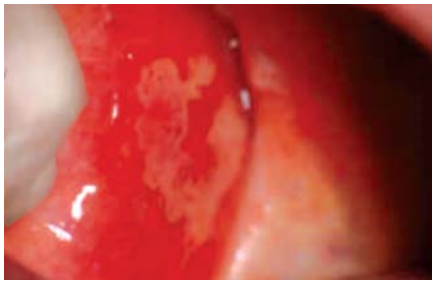

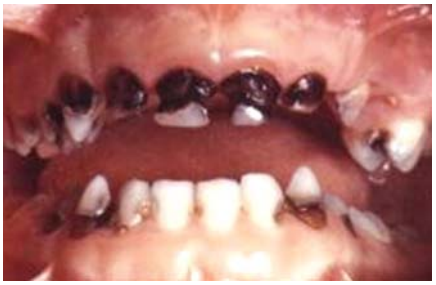

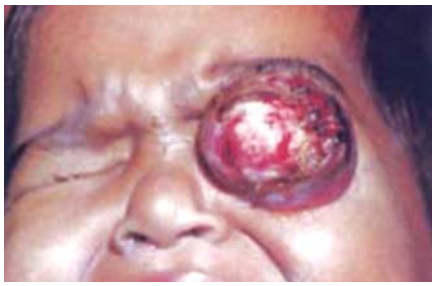

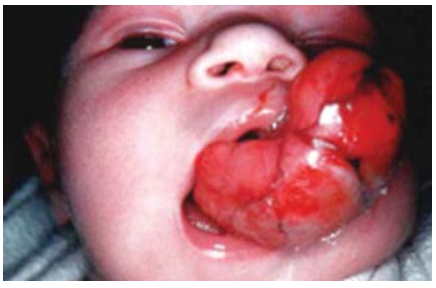

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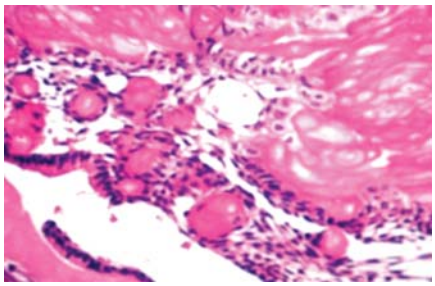

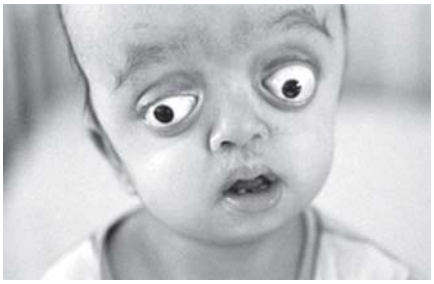

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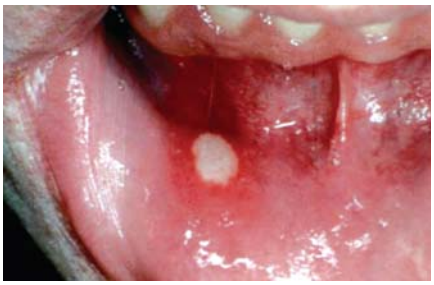

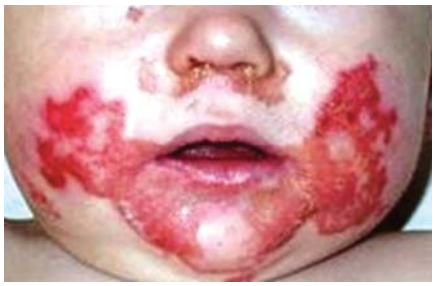

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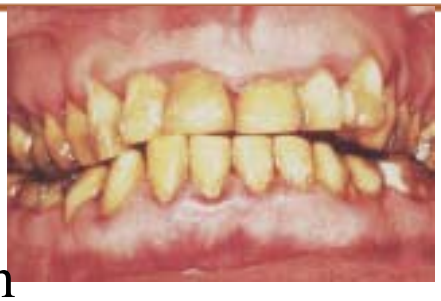
Developmental Disturbances of Oral and Paraoral Structures



CRANIOFACIAL ANOMALIES

Craniofacial anomalies are a diverse group of deformities in the growth of the head and facial bones. Anomaly is a medical term meaning 'irregular' or 'different from normal'.

These abnormalities are congenital (present at birth) and have numerous variations: Some are mild, other are severe and require surgery.

A child may receive a particular combination of gene(s) from one or both parents, or there may be a change in the genes at the time of conception, which results in a craniofacial anomaly.

There is no data that shows a direct correlation between any specific drug or chemical exposure causing a craniofacial anomaly. However, any parental exposure should be evaluated.

Folic acid is a vitamin B found in orange juice, fortified breakfast cereals, enriched grain products, and green leafy vegetables. Studies have shown that women who not take sufficient folic acid during pregnancy, or have a diet lacking in folic acid, may have a higher risk of having a baby with certain congenital anomalies, including cleft lip and/or cleft palate.

Common Types

Cleft Lip and/or Cleft Palate

A separation that occurs in the lip or the palate or both. Cleft lip and cleft palate are the most common congenital craniofacial anomalies seen at birth.

Cleft lip An abnormality in which the lip does not completely form. The degree of the cleft lip can vary greatly, from mild (notching of the lip) to severe (large opening from the lip up through the nose).

Cleft palate Occurs when the roof of the mouth does not completely close, leaving an opening that can extent into the nasal cavity. The cleft may involve either side of the palate. It can extent form the front of the mouth (hard palate) to the throat (soft palate). The cleft may also include the lip.

Craniosynostosis

A condition in which the sutures in the skull of an infant close too early, causing problems with normal brain and skull growth. Premature closure of the sutures may also cause the pressure inside of the head to increase and the skull or facial bones to change from a normal, symmetrical appearance.

Hemifacial Microstomia

A condition in which the tissues on one side of the face are underdeveloped, affecting primarily the ear (aural), mouth (oral), and jaw (mandibular) areas, Sometimes, both side of the face can be affected and may involve the skull as well as the face. Hemifacial microsomia is also known as Goldenhar's syndrome, brachial arch syndrome, facioauriculovertebral syndrome (FAV), oculoauriculovertebral spectrum (OAV), or lateral facial dysplasia.

Vascular Malformation

A birthmark or a growth, present at birth, which is composed of blood vessels that can cause functional or aesthetic problems. Vascular malformations may involve multiple body systems. There are several different types of malformations, named after the type of blood vessel that is predominantly affected. Vascular malformations are also known as lymphangiomas, arteriovenous malformations, and vascular gigantism.

Hemangioma

A type of birthmark, the most common benign (noncancerous) tumor of the skin. Hemangiomas may be present at birth (faint red mark) or appear in the first months after birth. A hemangioma is also known as a port-wine stain, strawberry hemangioma, and salmon patch.

Deformational Plagiocephaly

A mis-shapen (asymmetrical) shape of the head (cranium) from repeated pressure to the same area of the head. Plagiocephaly literally means oblique head (from the Greek "plagio" for oblique and cephale for head).

The frequency of occurrence of cleft lip, with or without cleft palate, has been computed on a global sale and estimated to be 1 in every 800 newborn babies.

Congenital Deformation of the Head and Neck

These are common, and most resolve spontaneously within the first few days of postnatal life.

Approximately, 2 percent of infants are born with extrinsically caused deformations that usually arise during last fetal life from intrauterine causes. Approximately 30 percent of deformed infants have two or more deformations. Deformed infants tend to shown catch up growth towards their genetic potential during the first few postnatal months after release from the intrauterine environment.

Teratogenic Agents

Teratogens are agents that may cause birth defects when present in the fetal environment. Included under such a definition are a wide array of drugs, chemicals, and infectious, physical, and metabolic agents that may adversely affect the intrauterine environment of the developing fetus. Such factors may operate by exceedingly heterogeneous pathogenetic mechanisms to produce alterations of form and function as well as embryonic and/or fetal death.

DEVELOPMENTAL DISTURBANCES OF THE JAW

Agnathia

Agnathia is a lethal anomaly characterized by hypoplasia or absence of the mandible with abnormally positioned ears having an autosomal recessive mode of inheritance. More commonly, only a portion of one jaw is missing. In the case of the maxilla, this may be one maxillary process or even the premaxilla. Partial absence of the mandible on one side may be missing, or more frequently, only the condyle or the entire ramus, although bilateral agenesis of the condyles and of the rami also has been reported.

Micrognathia

Micrognathia literally means a small jaw, and either the maxilla or the mandible may be affected.

True micrognathia may be classified as either congenital, or acquired. The etiology of the congenital type is unknown, although in many instances it is associated with other congenital heart disease and the Pierre-Robin syndrome (qv).

Micrognathia of the maxilla frequently occurs due to a deficiency in the premaxillary area, and patients with this deformity appear to have the middle third of the face retracted.

True mandibular micrognathia of the congenital type is often difficult to explain. Some patients appear clinically to have a severe retrusion of the chin but, by actual measurements, the mandible may be found to be within the normal limits of variation. Agenesis of the condyles also results in a true mandibular micrognathia.

The clinical appearance of mandibular micrognathia is characterized by severe retrusion of the chin, as steep mandibular angle, and a deficient chin button.

Micrognathia may be caused by or may be a feature of several conditions.

Congenital Conditions

- Catel-Manzke syndrome
- Cerebrocostomandibular syndrome
- Cornelia de Lange syndrome
- Femoral hypoplasia unusual facies syndrome
- Fetal aminopterin like syndrome
- Miller-Dieker syndrome
- Nager acrofacial dysostosis
- Pierre-Robin syndrome
- Schwartz-Jampel-Aberfeld syndrome
- Van Bogaert-Hozay syndrome.

Facial Hemihypertrophy

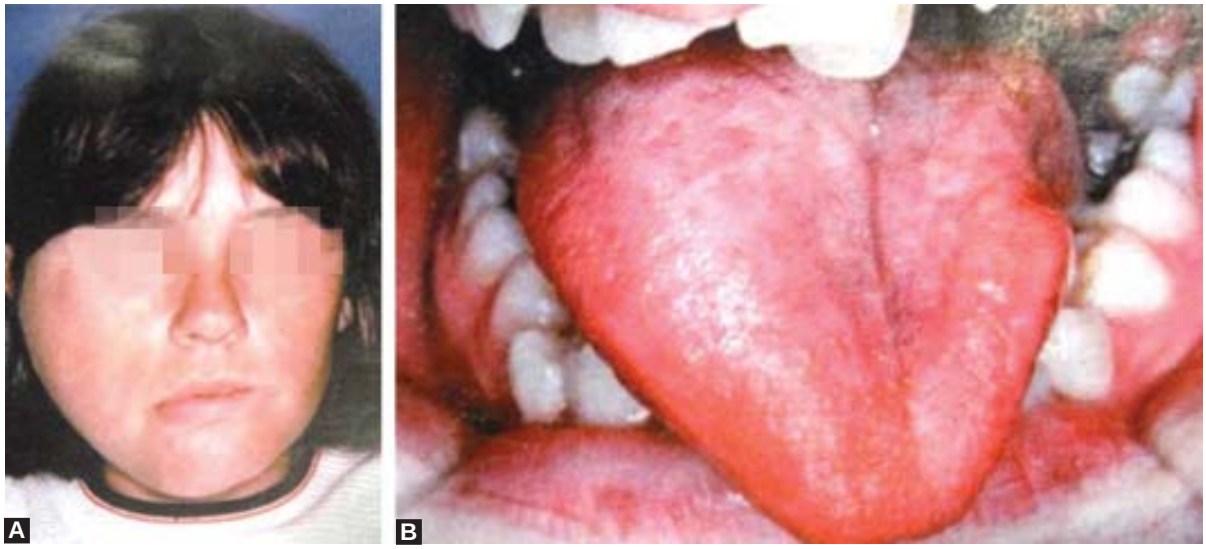
Hemihyperplasia is a rare developmental anomaly characterized by asymmetric overgrowth of one or more body parts.

There is little information about the effects on the deciduous dentition, but the permanent teeth on the affected side are often enlarged, although not exceeding a 50 percent increase in size.

Coincident to this phenomenon is premature shedding of the deciduous teeth.

There are certain diseases of the jaws, such as neurofibromatosis and fibrous dysplasia of the jaws, that may give the clinical appearance of facial hemihypertrophy, but these can usually be differentiated readily by the lack of effect on tooth size and rate of eruption (Figs 1.1A and B).

It progresses over a period of 2 and 10 years, and atrophy appears to follow the distribution of one or more divisions of the trigeminal nerve. The resulting facial flattening may be mistaken for Bell's palsy.



Figs 1.1A and B: (A) A generalized increase in the size of every facial unit is apparent on the left side of this individual with hemifacial hyperplasia. Note the abrupt demarcation at the midline, (B) All structures on the involved side, including the teeth, will have a marked increase in size. In this case, the enlarged teeth also caused a unilateral crowding of the dentition

CONGENITAL LIP AND COMMISSURAL PITS AND FISTULAS

Congenital lip pits and fistulas are malformations of the lips, often following a hereditary pattern, that may occur alone or in association with other developmental anomalies such as various oral clefts.

In 75-80 percent of all cases of congenital labial fistulas, there is an associated cleft lip or cleft palate or both.

Commissural pits are an entity probably very closely related to lip pits, but occur at the lip commissures, lateral to the typical lip pits is also frequently hereditary, possibly a dominant characteristic.

Van der Woude syndrome is an autosomal dominant syndrome typically consisting of a cleft lip or cleft palate and distinctive pits of the lower lips. These variable manifestations include lip pits alone, absent teeth, or isolated cleft lip and palate of varying degrees of severity.

The most prominent and consistent feature of van der Woude syndrome is orofacial anomalies.

In general, van der Woude syndrome affects about 1 in 100,000-200,000 people.

The hallmark of the van der Woude syndrome is the association of cleft lip and/or palate with distinctive lower lip pits.

The cleft lip and palate may be isolated.

Hypernasal voice and cleft or bifid uvula are clues to this diagnosis. It is possible as well that a bifid uvula is an isolated finding in certain individuals with the van der Woude syndrome.

They tend to be centered on small elevations in infancy, but are simple depressions in adults.

Affected individuals may have maxillary hypodontia; missing maxillary incisors or missing premolars.

Accessory nipples, congenital heart defects, and Hirschsprung's disease have also been reported.

Cleft Lip and Cleft Palate (Figs 1.2 to 1.5)

The term cleft lip and palate is commonly used to represent two types of malformation, i.e. cleft lip with or without cleft palate (CL/P) and cleft palate (CP). Cleft lip and palate are common congenital malformations. The reported incidence of clefts of the lip and palate varies from 1 in 500 to 1 in 2500 livebirths depending on geographic origin, racial and ethnic backgrounds and socioeconomic status.

During the 9th and 10th weeks, the mandibular arch enlarges and the tongue drops. The palatal shelves transpose horizontally and fuse with each other and with the anterior part of the palate.

Palatal fusion occurs anteroposteriorly and the process is completed by the 11-12th weeks.

Failure in the fusion of the nasal and maxillary processes leads to the cleft of the primary palate, which can be unilateral or bilateral. The degree of cleft can vary from a slight notch on the lip to complete cleft of the primary palate.

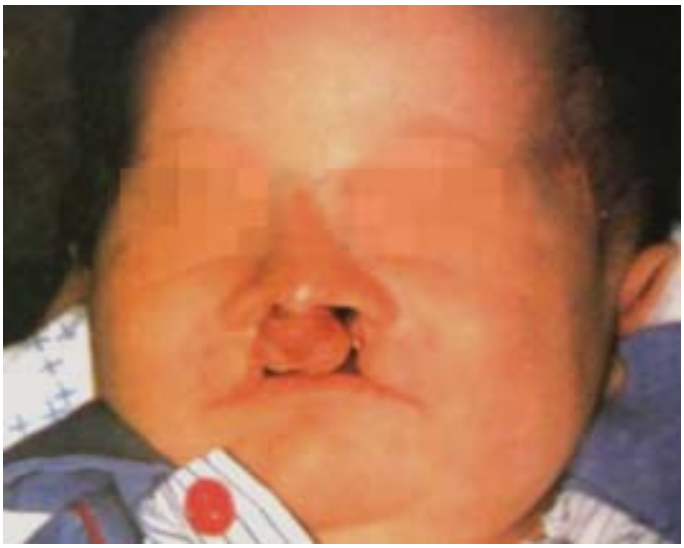


Fig. 1.2: Bilateral cleft of the upper lip

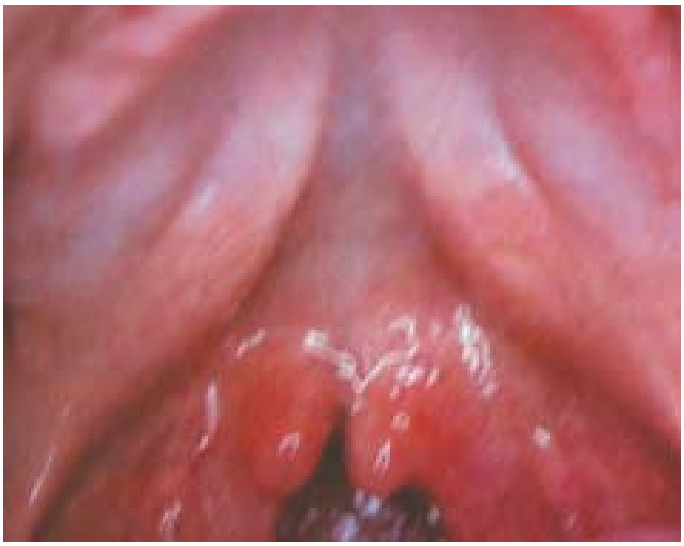


Fig. 1.4: Bifid uvula

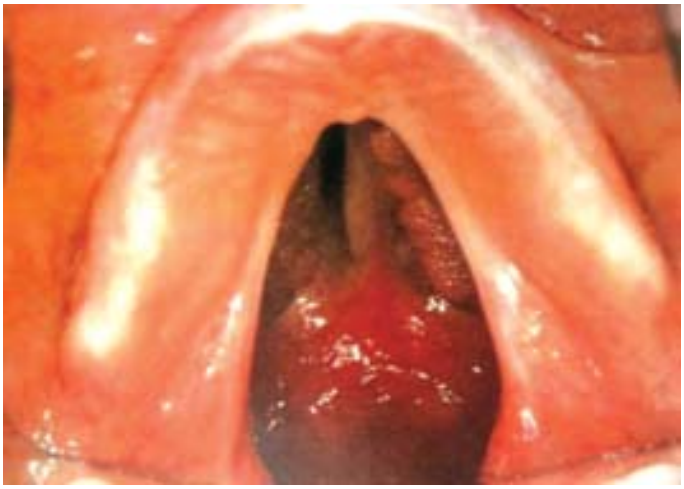


Fig. 1.3: Cleft palatal defect resulting in communication with the nasal cavity

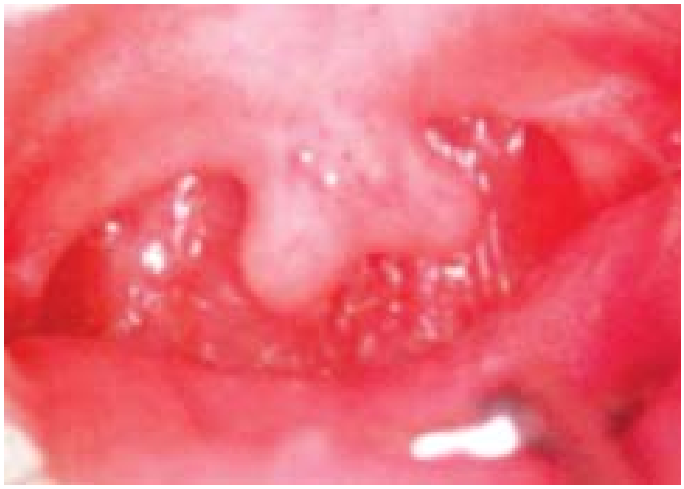


Fig. 1.5: Bifid uvula with constriction of maxillary arch

Heredity is undoubtedly one of the most important factors to be considered in the etiology of these malformations.

Most investigations indicate that the inheritance pattern in cleft lip with or without cleft palate is different from that in isolated cleft palate.

Neither maternal emotional stress nor the lack of a prenatal nutritional supplement was causally related to the occurrence of cleft lip or cleft palate.

Cleft can be divided into nonsyndromic and syndromic forms. Syndromic forms of clefts include those cases that have additional birth defects like lip pits or other malformations, whereas nonsyndromic clefts are those cases wherein the affected individual has no other physical or developmental anomalies and no recognized maternal environmental exposures.

The clefting anterior to the incisive foramen (i.e. lip and alveolus) is also defined as a cleft of primary palate.

The clefting posterior to the incisive foramen is defined as a cleft of secondary plate.

Isolated cleft palate is etiologically and embryologically different from cleft lip with or without cleft palate.

Eating and drinking are difficult because of regurgitation of food and liquid through the nose.

Treatment: Pediatricians used to strictly follow a rule of three 10s as a necessary requirement for identifying the child's status as suitable for surgery (i.e. 10 lb, 10 mg/L of hemoglobin, and age 10 weeks). Although pediatricians

are presently much more flexible and some surgeons many well justify a neonatal lip closure, the rule of three 10s is still very useful.

Anatomical difference predisposes children with CL/P and with isolated CP to care infections. Therefore, ventilation tubes are placed to ventilate the middle car and prevent hearing loss secondary to otitis media with effusion (OME).

Fordyce's Granules

A developmental anomaly characterized by heterotopic collections of sebaceous glands at various sites in the oral cavity. It has been postulated that the occurrence of sebaceous glands in the mouth may result from inclusion in the oral cavity of ectoderm having some of the potentialities of skin in the course of development of the maxillary and mandibular processes during embryonic life.

Clinical Features

Fordyce's granules appear as small yellow spots, either discretely separated or forming relatively large plaques, often projecting slightly above the surface of the tissue.

They are found most frequently in a bilaterally symmetrical pattern on the mucosa of the cheeks opposite the molar teeth but also occur on the inner surfaces of the lips, in the retromolar region lateral to the anterior faucial pillar, and occasionally on the tongue, gingiva, frenum, and palate.

Fewer children than adults exhibit Fordyce's granules, probably because the sebaceous glands and hair system do not reach maximal development until puberty.

Heck's disease primarily occurs in children, but lesions may occur in young and middle aged adults.

Fibromatosis Gingivae

Fibromatosis gingivae is a diffuse fibrous overgrowth of the gingival tissues, described for many years under a variety of terms.

It has been reported, however, in even very young children and, it a few instances, at birth. The tissue is usually not inflamed, but is of normal or even pale color, and it is often so firm and dense that it may prevent the normal eruption of teeth.

When tooth eruption is impeded, surgical removal of the excessive tissue and exposure of the teeth are indicated (Fig. 1.6).

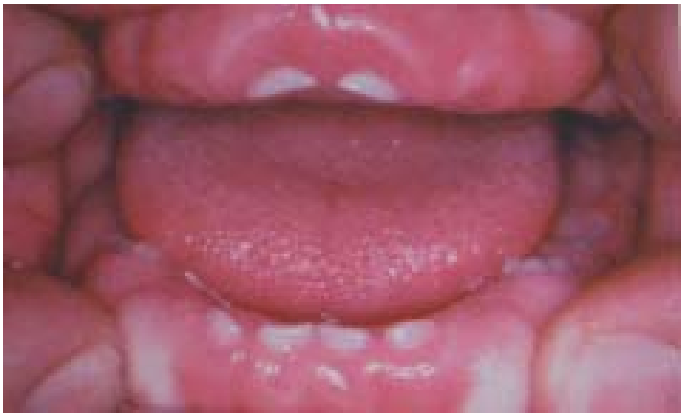


Fig. 1.6: Gingival fibromatosis. A young child with cheeks retracted by the parent. Note erythematous gingival hyperplasia arising in association with erupting deciduous dentition

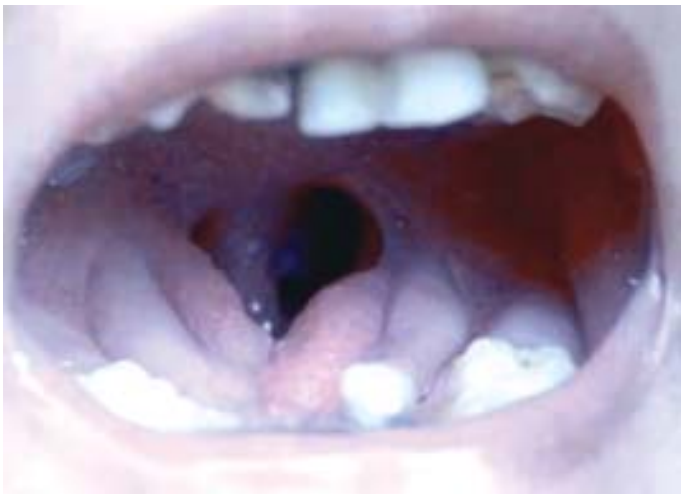


Fig. 1.7: Microglossia. Associated constriction of the maxillary arch in the same patient

AGLOSSIA AND MICROGLOSSIA SYNDROME

Aglossia

This malformation is very rare, since the first publication which was attributed by Gaillard and Nogue to Antoine De Jussieu (1781) to present time there have been less than 35 cases reported (Grinspan, 1976).

This anomaly is always associated to malformations in the extremities, especially the hands and feet, cleft palate and dental agenesia.

Aglossia syndrome is, in reality, a microglossia with extreme glossoptosis.

Its etiology must be searched for in some sort of fetal cell traumatism in the first few weeks of gestation. Neither language nor swallowing are sensibly affected by this condition (Fig. 1.7).

Macroglossia

Macroglossia, meaning large tongue, has been a documented anatomical anomaly for several centuries.

Although the exact incidence of macroglossia is unknown (because the etiologies are too numerous to

quantify), some congenital syndromes often express macroglossia in their phenotypers, most commonly Down's syndrome (1 per 700 livebirths) and Beckwith-Wiedemann syndrome.

The two broadest categories under the heading of macroglossia are true macroglossia and pseudomacroglossia.

In addition to the oral cavity and airway, assess other features in the patient that may indicate congenital or systemic syndromes (Figs 1.8 and 1.9).

Ankyloglossia or Tongue-tie

Tongue tie can cause feeding problems in infants; if this is the case, feeding difficulties are usually noticed early in an infant's life. Feeding difficulties may be a reason to consider early surgery to cut the lingual frenulum and loosen the tongue.

In some children, tongue-tie may also cause speech defects, especially articulation of the sounds: 1, r, t, d, n, th, sh and z.

Preventing speech defects or improving a child's articulation may be another reason to consider surgical intervention. The tongue is remarkably able to compensate, however, and many children have to compensate, however, and many children have no speech impediments due to ankyloglossia. Tongue-tie may contribute to dental problems as well as causing a persistent gap between the mandibular incisors (Fig. 1.10).

Cleft Tongue

A completely cleft or bifid tongue is a rare condition that is apparently due to lack of merging of the lateral lingual swellings of this organ.

Although fissured tongue may be diagnosed initially during childhood, it is diagnosed more frequently in adulthood.

Embryologically, the tongue is formed by two lateral processes (lingual tubercles) meeting in the midline and fusing above a central structure form from the first and second branchial arches, the tuberculum impair.

The lesion is found in one of every 300-2000 adults, depending on the rigor of the clinical examinations. It is seldom biopsied unless the red discoloration is confused with precancerous erythroplakia or its surface shows pronounced nodularity.

Median Rhomboid Glossitis

Median rhomboid glossitis presents in the posterior midline of the dorsum of the tongue, just anterior to the V- shaped grouping of the circumvallate papillae.

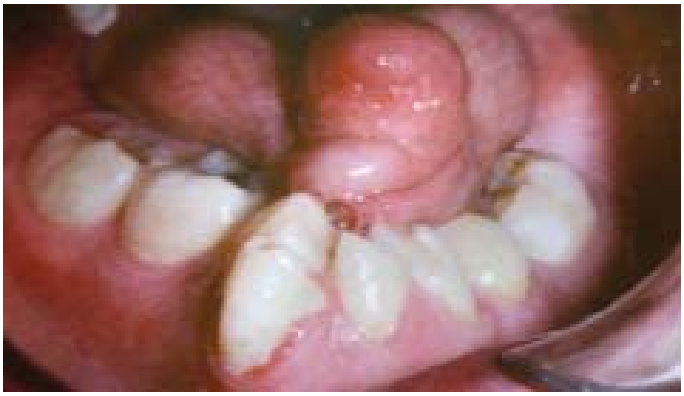


Fig. 1.8: Microglossia. Abnormally small tongue associated with constricted mandibular arch

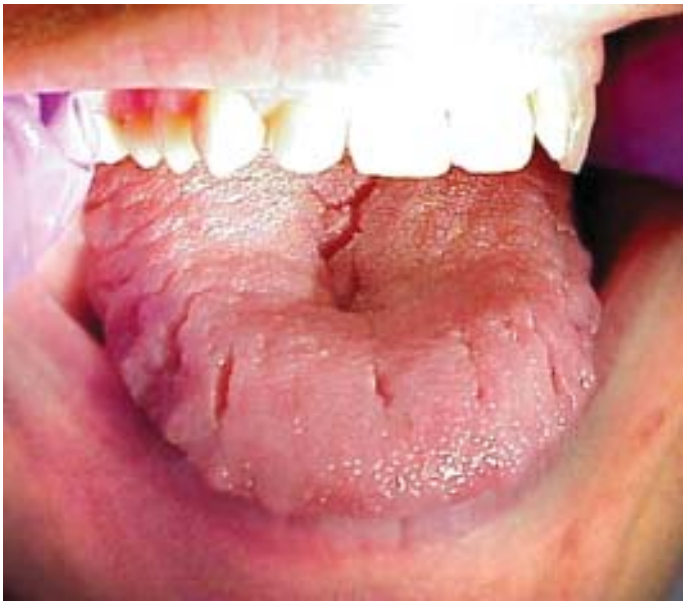


Fig. 1.9: Macroglossia. Large tongue in a patient with Down's syndrome

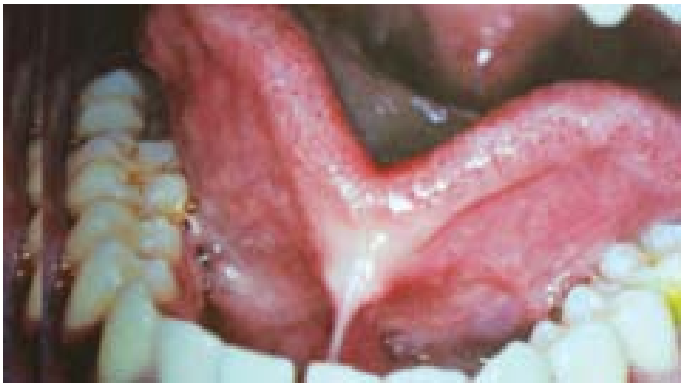


Fig. 1.10: Ankyloglossia. Abnormal attachment of the lingual frenum, limiting tongue mobility

Most cases are not diagnosed until the middle age of the affected patient, but the entity is, of course, present in childhood. There appears to be a 3 : 1 male predilection.

The majority of patients had their onset of symptoms relatively early in life, chiefly during puberty, adolescence and early maturity though cases have been recorded as early as birth and as late as the seventh decade (Fig. 1.11).

ATRESIA

Congenital occlusion or absence of one or more of the major salivary gland ducts is an exceedingly rare condition. When it does occur, it may result in the formation of a retention cyst or produce a relatively severe xerostomia.

Stafne Bone Cyst

A Stafne bone cyst is an unusual form of slightly aberrant salivary gland tissue wherein a developmental inclusion of glandular tissue is found with in or, more commonly, adjacent to the lingual surface of the body of the mandible within a deep and well-circumscribed depression.

The general consensus is that this is a congenital defect, although it rarely has been observed in children. These lesions generally may be regard as developmental rather than pathologic defects (Figs 1.12 and 1.13).

DISORDERS OF TOOTH ERUPTION

Microdontia

This term is used to describe teeth which are smaller than normal, i.e. outside the usual limits of variation.

Microdontia involving only a single tooth is a rather common condition. It affects most often the maxillary lateral incisor and the third molar (Fig. 1.14).

These two teeth are among those most often congenitally missing. It is of interest to note, however, that other teeth often congenitally absent, the maxillary and mandibular second premolars, seldom exhibit microdontia. Supernumerary teeth, however, are frequently small in size.

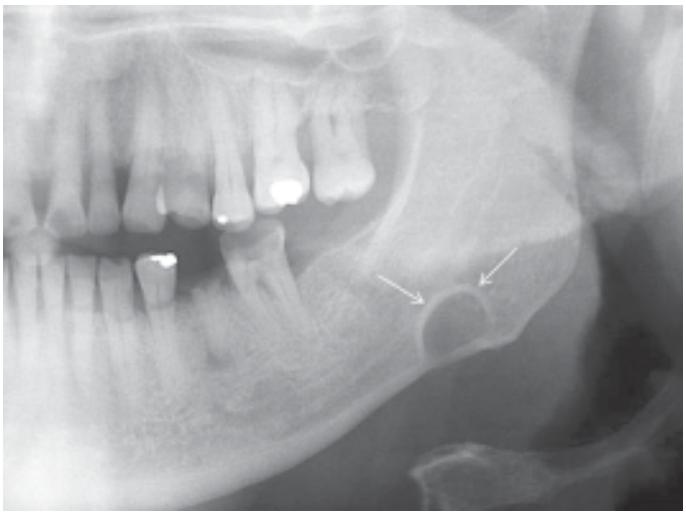


Fig. 1.12: Stafne bone cyst

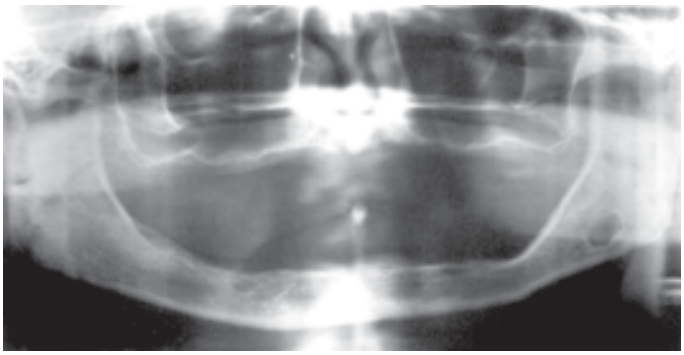


Fig. 1.13: Stafne bone cyst-A well-defined radiolucency in the angle of the left mandible located below the inferior alveolar canal

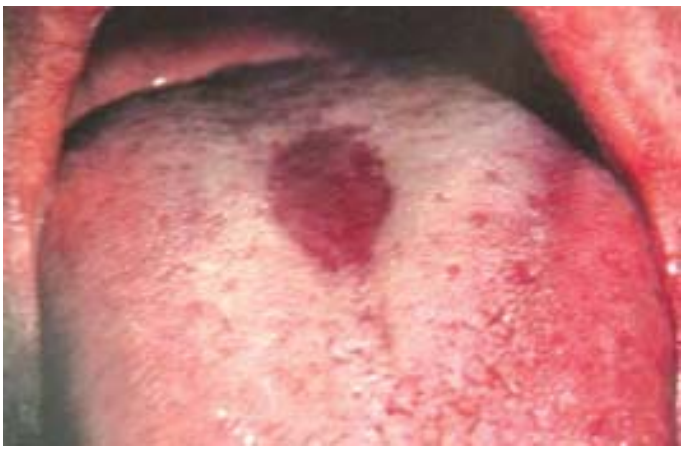


Fig. 1.11: Median rhomboid glossitis

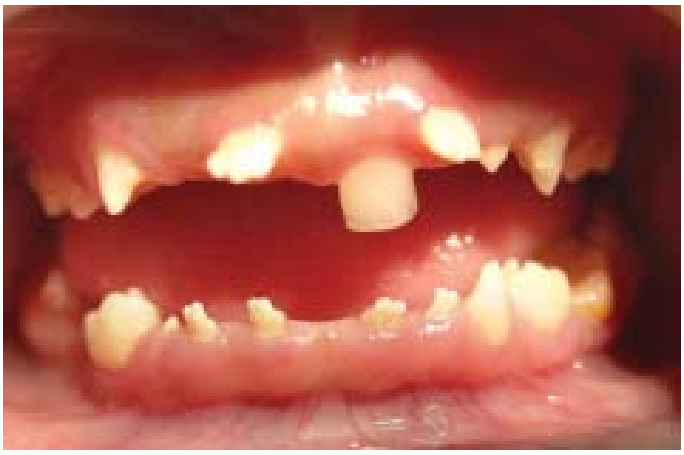


Fig. 1.14: Microdontia

Macrodontia

Macrodontia is the opposite of microdontia and refers to teeth that are larger than normal.

Gemination

Geminated teeth are anomalies which arise from an attempt at division of a single tooth germ by an invagination, with resultant incomplete formation of two teeth.

It is seen in deciduous as well as permanent dentition, and in some reported cases, appears to exhibit a hereditary tendency (Fig. 1.15).

Fusion

Fused teeth arise through union of two normally separated tooth germs. Depending upon the stage of development of the teeth at the time of union, fusion may be complete or incomplete.

Granath have reported that fusion of teeth is more common in the deciduous than in the permanent dentition.

In addition to affecting two normal teeth, fusion may also occur between a normal tooth and a supernumerary tooth such as the mesiodens or the distomolar. In some cases, the condition has been reported to show a hereditary tendency.

Taurodontism

Taurodontism means "bull like teeth". It may affect either the deciduous or permanent dentition, although permanent tooth involvement is more common (Fig. 1.16).

Anodontia

True anodontia, or congenital absence of teeth, may be of two types: Total and partial. Total anodontia, in which all teeth are missing, may involve both deciduous and permanent dentition.

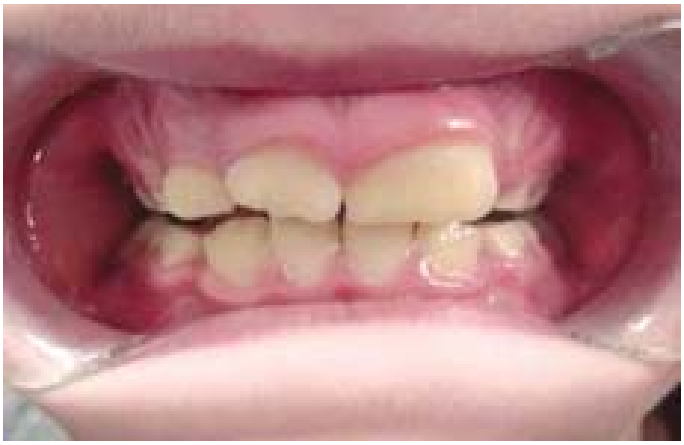


Fig. 1.15: Gemination

Fig. 1.16: Taurodontism

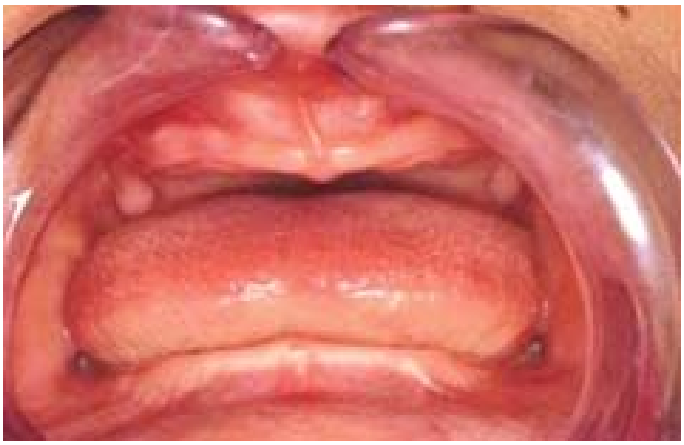


Fig. 1.17: Anodontia

Although any tooth may be congenitally missing, there is a tendency for certain teeth to be missing more frequently than other. Frequency of missing third molars have shown this tooth to be congenitally absent in as many as 35 percent of all subjects examined, with a frequent absence of all four third molars in the same person.

Congenitally missing deciduous teeth are uncommon but, when occurring, usually involve the maxillary lateral incisor.

Correlation between congenitally missing deciduous teeth and their permanent successors, suggesting at least in some instance, a genetic factor.

Congenital absence of teeth, reported the accumulating evidence that it is actually the result of one or more point mutations in a closely linked polygenic system, most often transmitted in an autosomal dominant pattern (Fig. 1.17).

Predeciduous Dentition

Infants occasionally are born with structures which appear to be erupted teeth usually in the mandibular incisor area.

The predeciduous teeth have been described as hornified epithelial structures without roots, occurring on the gingiva over the crest of the ridge, which may be easily removed.

Prematurely erupted true deciduous teeth, of course, are not to be extracted.

These predeciduous teeth have been thought to arise either from an accessory bud of the dental lamina ahead of the deciduous bud or from the bud of an accessory dental lamina.

They are probably correct in believing that considering predeciduous teeth as an entity is a misinterpretation and that such structures, present at birth, undoubtedly represent only the dental lamina cyst of the newborn (qv) (Fig. 1.18).

Enamel Hypoplasia

Enamel hypoplasia may be defined as an incomplete or defective formation of the organic enamel matrix of teeth. Two basic types of enamel hypoplasia are:

- A hereditary type
- A type caused by environmental factors.

In the hereditary type, both the deciduous and permanent dentitions usually are involved and generally only the enamel is affected.

When enamel hypoplasia is caused by environmental factors, either dentition may involve and sometimes only a single tooth is affected.

Clinical studies indicate that most cases of **enamel hypoplasia** involve those teeth that form within the first year after birth, although teeth that form somewhat later may be affected (Fig. 1.19).

Premolars and second and third molars are seldom affected, since their formation does not begin until about the age of three years or later.

Enamel Hypoplasia due to Congenital Syphilis

The hypoplasia due to congenital syphilis is most frequently not of the pitting variety previously described but instead presents a characteristic, almost pathognomonic, appearance. This hypoplasia involves the maxillary and mandibular permanent; incisors and the first molars. The anterior teeth affected are sometimes called **Hutchinson's teeth,** while the molars have been referred to as **Mulberry molars** (Moon's molars, Fournier's molars) (Figs 1.20 and 1.21).

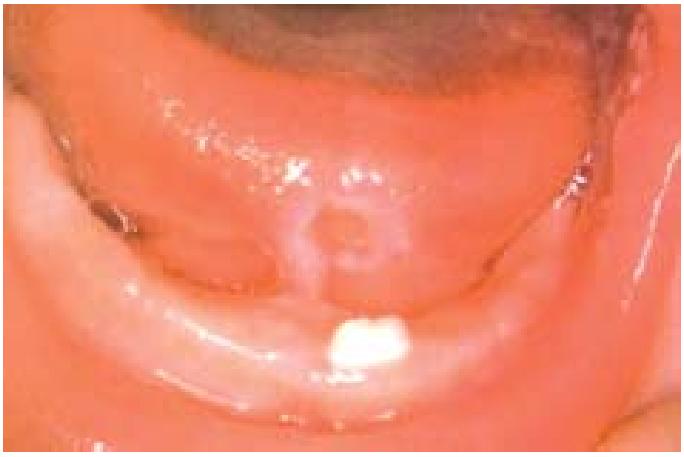


Fig. 1.18: Predeciduous dentition

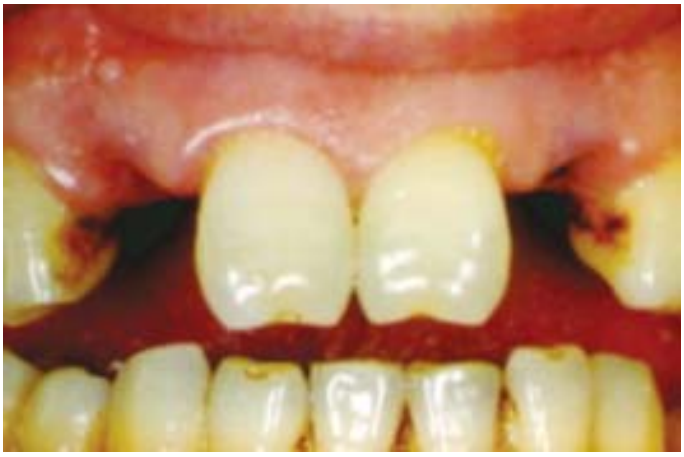


Fig. 1.20: Hutchinson's incisors of congenital syphilis

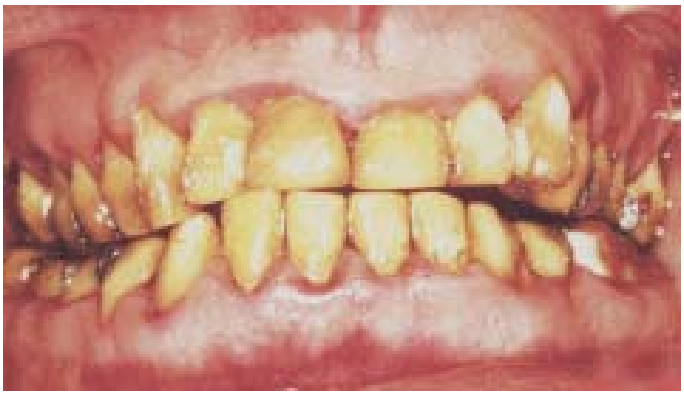


Fig. 1.19: Enamel hypoplasia

Fig. 1.21: Mulberry molar of congenital syphilis

Characteristically, the upper central incisor is 'screw-driver' shaped, the mesial and distal surfaces of the crown tapering and converging toward the incisal edge of the tooth rather than toward the cervical margin.

The crowns of the first molars in congenital syphilis are irregular and the enamel of the occlusal surface and occlusal third of the tooth appears to be arranged in an agglomerate mass of globules rather than in well-formed cusps.

Not all patients with congenital syphilis will exhibit these dental findings.

Hypoplasia due to Birth Injuries

The neonatal line or ring present in deciduous teeth and first permanent molars, may be thought of as a type of hypoplasia because they are produced in the enamel, and in the dentin as well, as a disturbance indicative of the trauma or change of environment at the time of birth.

In traumatic births, the formation of enamel may even cease at this time.

Common in prematurely born children than in normal term infants.

Recognized staining of teeth in children who had suffered from Rh hemolytic disease at birth (qv) but also reported enamel hypoplasia in these cases.

Although the literature indicates that most cases of enamel hypoplasia of deciduous teeth involve enamel formed after birth, it is seen also in prenatal enamel.

Hypoplasia due to Local Infection or Trauma

Due to some infection or trauma, any degree of hypoplasia, ranging from a mild brownish discoloration of enamel to a severe pitting and irregularity of the tooth crown may be seen.

If a deciduous tooth becomes carious during the period when the crown of the succeeding permanent tooth is being formed, a bacterial infection involving the periapical tissue of this deciduous tooth may disturb the ameloblastic crown.

This type of hypoplasia is due to a disturbance of the ameloblasts during the formative stage of tooth development.

Enamel Hypoplasia due to Fluorosis

This type of hypoplasia is due to a disturbance of the ameloblasts during the formative stage of the tooth development.

Epidemiologic studies have reported that not all children born and reared in an area of endemic fluorosis exhibit the same degree of mottling even though they all have used the same water supply.

DENTINOGENESIS IMPERFECTA

This is an autosomal dominant condition affecting both deciduous and permanent teeth. Affected teeth are gray to yellowish-brown and have broad crowns with constriction of the cervical area resulting in a 'tulip' shape.

The crown of the deciduous and permanent teeth wear rapidly after eruption and multiple pulp exposures may occur.

Both dentitions are affected, although the teeth appear clinically normal in morphologic appearance and color.

Both dentitions are also affected in this form of dentin dysplasias, although the involvement of each dentition is different clinically, radiographically, and histologically.

In both dentitions, the roots are short, blunt, conical, or similarly malformed. In the deciduous teeth, the pulp chambers and root canals are usually completely obliterated, while in the permanent dentition a crescent shaped pulpal remnant may still be seen in the pulp chamber.

The deciduous teeth exhibit amorphous and atubular dentin in the radicular portion, while coronal dentin is relatively normal.

Premature Eruption

Deciduous teeth that have erupted into the oral cavity are occasionally seen in infants at birth. These are called natal teeth in contrast with neonatal teeth, which have been defined as those teeth erupting prematurely in the first 30 days of life usually only one or two teeth erupt early, most often the deciduous and mandibular central incisors.

The premature eruption of permanent teeth is usually a sequela of the premature loss of deciduous teeth. Cases occur involving the entire dentition and here again the possibility of an endocrine dysfunction (e.g. hyperthyroidism) must be considered.

Eruption Sequestrum

The eruption sequestrum is an anomaly associated with the eruption of teeth in children.

The **eruption sequestrum** is a tiny irregular spicule of bone overlying the crown of an erupting permanent molar, found just prior to or immediately following the emergence of the tips of the cusps through the oral mucosa.

If the bony spicule is large or eruption is fast, complete resorption can not occur and the eruption sequestrum is observed.

Occasionally, a child may complain of a slight soreness in the area, probably produced by compression of the soft tissue over the spicule during eating and just prior to its

breaking through the mucosa, or by the movement of the spicule in the soft tissue crypt during mastication and following eruption through the mucosa.

Delayed Eruption

Retarded or delayed eruption of the deciduous teeth is difficult to establish unless the eruption is grossly overdue.

Delayed eruption of the permanent dentition as a whole may be associated with the some local or systemic conditions causing the retardation of deciduous tooth eruption.

The person affected may retain this deciduous teeth, or more commonly the deciduous teeth may have been shed but the permanent teeth have failed to erupt.

Ankylosed Deciduous Teeth

Submerged teeth are deciduous teeth, most commonly mandibular second molars, that have undergone a variable degree of root resporption and then have become ankylosed to the bone.

After the adjacent permanent teeth have erupted, the ankylosed tooth appears to have submerged below the level of occlusion. Continued growth of the alveolar process and also the crown height of the deciduous tooth is less than that of the adjacent permanent teeth, so that the relative level of occlusion has been changed, not he position of the deciduous tooth (Figs 1.22A and B).

PALATAL AND ALVEOLAR CYSTS OF NEWBORN

A special from of odontogenic cyst is found in as many as 80 percent of newborn infants.

A similar palatal cyst of the newborn is commonly found in the posterior midline of the hard palate, where it arises from epithelial remnants remaining in the stroma after fusion of the palatal processes which meet medially to form the plate.

Today these two terms are used interchangeably for both palatal and gingival cysts of newborns.

Palatal cysts of the newborn typically present as multiple (usually less than six) 1-4 mm yellow-white, sessile mucosal papules of the posterior hard palate, and occasionally of the anterior soft palate. Occasional cysts are located same distance from the midline (Fig. 1.23).

Dermoid Cyst

A hamartomatous tumor containing multiple sebaceous glands and almost all skin adnexa, this may contain substance such as nails the dental, cartilage like, and bone like structures.

Only a few cases describe oral dermoid cysts in newborns or children. Dermoid cysts that are congenital and localized on the neck, head, or truck are usually visible at birth.

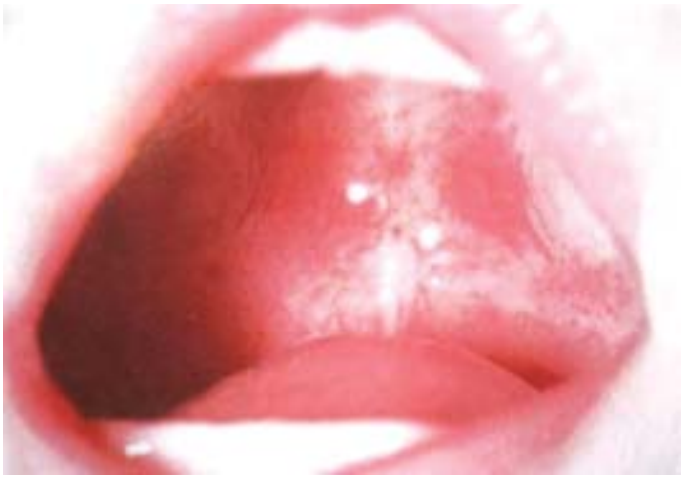
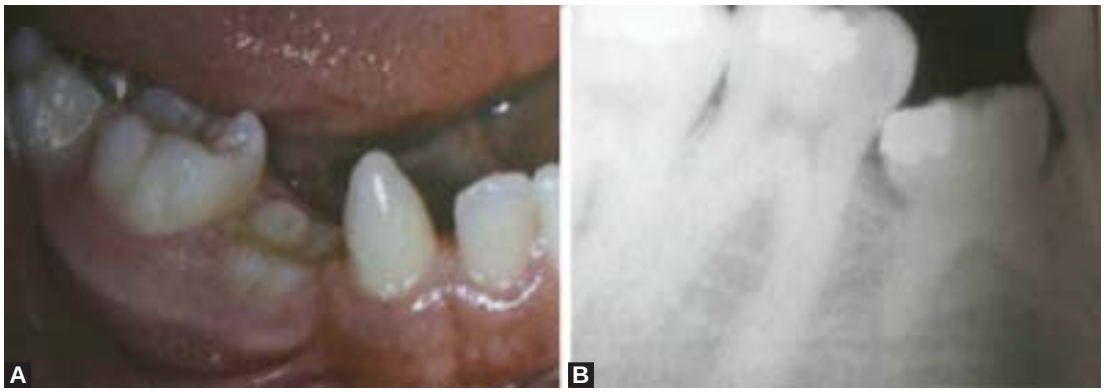


Fig. 1.23: Epstein's pearls. Small keratin-filled cysts at the junction of the hard and soft palates



Figs 1.22A and B: (A) Ankylosis—Deciduous molar well below the cuspal points of the adjacent teeth (B) Ankylosis—Radiograph of an ankylosis of first molar. Note the lack of periodontal ligament space

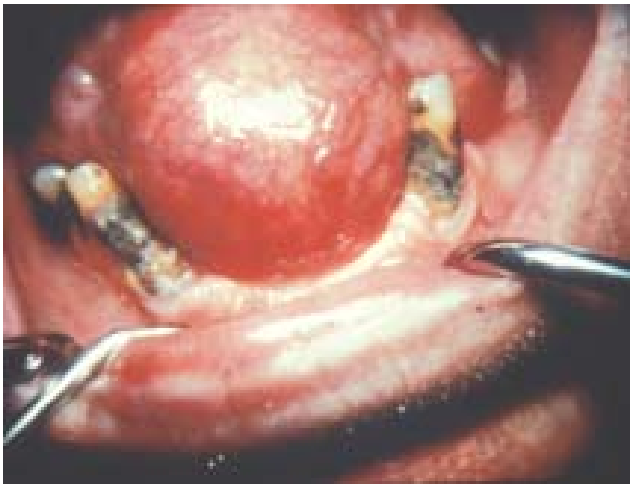


Fig. 1.24: Dermoid cyst. Fluctuant midline swelling in the floor of the mouth

There subclasses or congenital mouth cysts are described in the literature: **epidermoid (simple) cysts, dermoid (complex) cysts, and teratoid (complex) cysts** (Fig. 1.24).

Heterotropic Oral Gastrointestinal Cyst

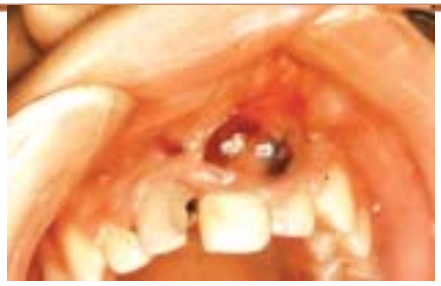
The cyst present as a small nodule entirely within the body of the tongue either anterior or posterior, in the floor of mouth, the neck or adjacent submaxillary gland. It may be asymptomatic or may cause difficulty in eating or speaking.

Heteroptopic island of gastric mucosa have been found in the esophagus, small intestine, thoracic cysts, omphalomesenteric cysts, pancreas, gallbladder, and Mickel's diverticulum.

This choristomatic cyst can be found in patients at any age, although the majority have been infants or young children.

2

Diseases of the Pulp and Periapical Tissues



DISEASES OF THE DENTAL PULP

The dental pulp is a delicate connective tissue liberally interspersed with tiny blood vessels, lymphatics, myelinated and unmyelinated nerves and undifferentiated connective tissue cells. Like other connective tissues throughout the body, it reacts to bacterial infection or to other stimuli by an inflammatory response known as pulpitis, which is the most common cause of odontalgia or toothache. The enclosure of the pulp tissue within the rigid calcified walls of the dentin precludes the excessive swelling of tissue that occurs in the hyperemic and edematous phases of inflammation in other tissues. The fact that the blood vessels supplying the pulp tissue must enter the tooth through the tiny apical foramina precludes the development of an extensive collateral blood supply to the inflamed part.

The diseases of the dental pulp to be considered in this section are those occurring chiefly as sequelae of dental caries.

Etiologic Factors in Pulp Disease

Most cases of pulpitis are primarily a result of dental caries in which bacteria or their products invade dentin and pulp tissue. Changes in the pulp may occur even with very early dental caries represented by demineralization limited to the enamel alone, appearing as white spots without actual cavitations. Occasionally, there is bacterial invasion in the absence of caries, as in cases of tooth fracture due to trauma or cracked tooth syndrome that expose the dental pulp to the oral fluids and microorganisms. In cracked tooth syndrome, a tooth particularly a restored premolar may split, usually under masticatory stress. These cracks are often minute and invisible clinically; and they allow the bacteria into the pulp. Bacterial invasion may also occur as a result of a bacteremia and septicemia. Pulpitis may rarely follow chronic periodontal disease wherein the microorganisms enter through the accessory canals of the exposed root surface especially through lateral canals in furcation areas of molars. Robinson and Boling reported that bacteria circulating in the bloodstream tend to settle out or accumulate at sites of pulpal inflammation such as that which might follow some chemical or mechanical injury to the pulp. They termed this particular phenomenon as 'anachoretic pulpitis'. Anachoresis is a phenomenon by which blood borne bacteria dyes, pigments, metallic substances, foreign proteins and other materials are attracted to the site of inflammation. One probable cause of this phenomenon is increased capillary permeability in the particular area.

Pulpitis may also arise as a result of chemical irritation of the pulp caused by erosion or use of acidic restorative materials. This may occur not only in an exposed pulp to which some irritating medicament is applied but also in intact pulps beneath deep or moderately deep cavities into which some irritating filling material is inserted. This is undoubtedly a result of penetration of the irritating substances into the pulp tissue via the dentinal tubules, in many instances, however, the pulp may respond to the irritation either by dentinal sclerosis or by forming reparative dentin rather than progressing to pulpitis.

Severe thermal change in a tooth may also produce pulpitis. Polishing procedures, tooth restored with exothermic restorative materials, or large metallic restorations, particularly, in which there is inadequate insulation between the restoration and the pulp are more prone to pulpal inflammation. Heat produced by over-rapid tooth preparation or without sufficient coolant may also cause pulpal irritation. Heat, and more particularly, cold are transmitted to the pulp, often producing pain, and if the stimulus is prolonged and severe, leading to actual pulpitis. Mild thermal changes are most apt to stimulate only the formation of reparative dentin, and this is a relatively common phenomenon.

When two dissimilar metallic restorations are present, the saliva acts as an electrolyte and there will be formation of a galvanic current. This may be transmitted to the pulp through metallic restoration and may thus initiate pulpitis.

A condition clinically simulating pulpitis by the occurrence of toothache was reported during World

War II in flying personnel and has been called aerodontalgia. This has also been described in aircrew flying at high altitudes, astronauts, submarine crews and in deep sea divers. This pain has been attributed to the formation of nitrogen bubbles in the pulp tissue or vessels. It is relatively uncommon and is associated particularly with recently filled teeth. Aerodontalgia is really a marker of inadequate pulp protection from the atmosphere and this usually means caries. It is not a direct cause of caries, rather an exacerbating factor.

Classification of Pulpitis

Pulpitis has been classified in a variety of ways, the simplest being a division into acute and chronic pulpitis. Furthermore, some investigators classify both acute and chronic pulpitis in several different ways. There may be a partial pulpitis or a subtotal pulpitis, depending upon the extent of involvement of the pulp. If the inflammatory process is confined to a portion of the pulp, usually a portion of the coronal pulp such as a pulp horn, the condition has been called partial or focal pulpitis. If most of the pulp is diseased, the term total or generalized pulpitis has been used. But this is of marginal clinical significance (Fig. 2.1).

Another classification of both acute and chronic pulpitis is based upon the presence or absence of a direct communication between the dental pulp and the oral environment, usually through a large carious lesion. The term open pulpitis (pulpitis aperta) has been used to describe those cases of pulpitis in which the pulp obviously communicates with the oral cavity, whereas the cases in which no such communication exists are described as closed pulpitis (pulpitis clausa).

Focal Reversible Pulpitis

One of the earliest forms of pulpitis is the condition known as focal reversible pulpitis. At one time, this was often referred to as pulp hyperemia. However, it is known that vascular dilatation can occur artifactually from the 'pumping' action during tooth extraction as well as pathologically as a result of dentinal and pulpal irritation. Therefore, this early mild transient pulpitis, localized chiefly to the pulpal ends of irritated dentinal tubules, is now known as focal reversible pulpitis.

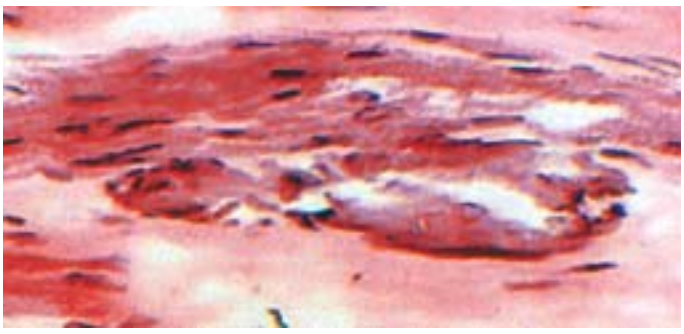


Fig. 2.1: Irreversible pulpitis

Clinical Features

A tooth with focal pulpitis is sensitive to thermal changes, particularly to cold. The application of ice or cold fluids to the tooth results in pain, but this disappears upon removal of the thermal irritant or restoration of the normal temperature. It will be found also that such a tooth responds to stimulation by the electric pulp tester at a lower level of current, indicating a lower pain threshold (or a greater sensitivity) than that of adjacent normal teeth.

Teeth in which this condition exists usually show deep carious lesions large metallic restorations (particularly without adequate insulation), or restorations with defective margins.

Histologic Features

Focal pulpitis is characterized microscopically by dilatation of the pulp vessels. Edema fluid may collect because of damage to the capillary walls, allowing actual extravasation of red blood cells or some diapedesis of white blood cells. Slowing of the blood flow and hemoconcentration due to transudation of fluid from the vessels conceivably could cause thrombosis. The belief has prevailed also that self-strangulation of the pulp may occur as a result of increased arterial pressure occluding the vein at the apical foramen.

Treatment and Prognosis

Focal pulpitis is generally regarded as a reversible condition, provided the irritant is removed before the pulp is severely damaged. Thus, a carious lesion should be excised and restored or a defective filling replaced as soon as it is discovered. The tooth should be kept under observation to ensure that irreversible damage has not occurred. If the primary cause is not corrected, extensive pulpitis eventually results, with subsequent death of the pulp.

Acute Pulpitis

Extensive acute inflammation of the dental pulp is a frequent immediate sequela of focal reversible pulpitis, although it may also occur as an acute exacerbation of a chronic inflammatory process.

Clinical Features

Acute pulpitis usually occurs in a tooth with a large carious lesion or restoration, commonly a defective one around which there has been 'recurrent caries'. Even in its early

stages when the inflammatory reaction involves only a portion of the pulp, usually in the area just beneath the carious lesion, relatively severe pain is elicited by thermal changes, particularly those caused by ice or cold drinks. Characteristically, this pain persists even after the thermal stimulus has disappeared or been removed.

The pulpal pain is poorly localized and may be felt in any of the teeth of the upper or lower jaw of the affected side, since the pulp of the individual teeth are not represented precisely on the sensory cortex.

As a greater proportion of the pulp becomes evolved with intrapulpal abscess formation, the pain may become even more severe and is often described as lancinating or throbbing type. The pain generally lasts for 10-15 minutes but may be more or less continuous, and its intensity may be increased when the patient lies down. The application of heat may cause an acute exacerbation of pain. The tooth reacts to the electric pulp vitality tester at a lower level of current than adjacent normal teeth, indicating increased sensitivity of the pulp. When necrosis of the pulp tissue occurs, this sensitivity is lost.

Severe pain is more likely to be present when the entrance to the diseased pulp is not wide open. The pulpal pain is not only caused by the pressure built up due to lack of escape of inflammatory exudate but also by the pain producing substances released by the inflammatory reaction. Soon there is rapid spread of inflammation throughout the pulp with pain and necrosis. Until this inflammation or necrosis extends beyond the pulp tissue within the root apex, the tooth is not particularly sensitive to percussion. When a large open cavity is present, there is no opportunity for a build-up of pressure. Thus the inflammatory process does not tend to spread rapidly throughout the pulp. In such a case the pain experienced by the patient is a dull, throbbing ache, but the tooth is still sensitive to thermal changes. Mobility and sensitivity to percussion are usually absent. Figure 2.2 shows photograph of a case of acute pulpitis which has been treated.

The patient with a severe acute pulpitis is extremely uncomfortable and at least mildly ill. He/she is usually apprehensive and desirous of immediate attention from the dentist.

Histologic Features

Early acute pulpitis is characterized by the continued vascular dilatation seen in focal reversible pulpitis, accompanied by the accumulation of edema fluid in the connective tissue surrounding the tiny blood vessels. The pavementing of polymorphonuclear leukocytes becomes apparent along the walls of these vascular channels, and these leukocytes rapidly migrate through the endothelium-lined structures in increasing numbers. Soon great collections of white blood cells may be found, especially beneath an area of carious penetration. By this stage, the odontoblasts in this area have usually been destroyed (Fig. 2.3).

Early in the course of the disease, the polymorphonuclear leukocytes are confined to a localized area, and the remainder of the pulp tissue appears relatively normal. The rise in pressure in the pulp associated with an inflammatory exudate causes local collapse of the venous part of the circulation. This leads to local tissue hypoxia and anoxia, which in turn may lead to localized destruction of pulp tissue and the formation of a small abscess known as a pulp abscess, which contains pus arising from breakdown of leukocytes and bacteria as well as from digestion of tissue. This necrotic zone contains polymorphonuclear leukocytes

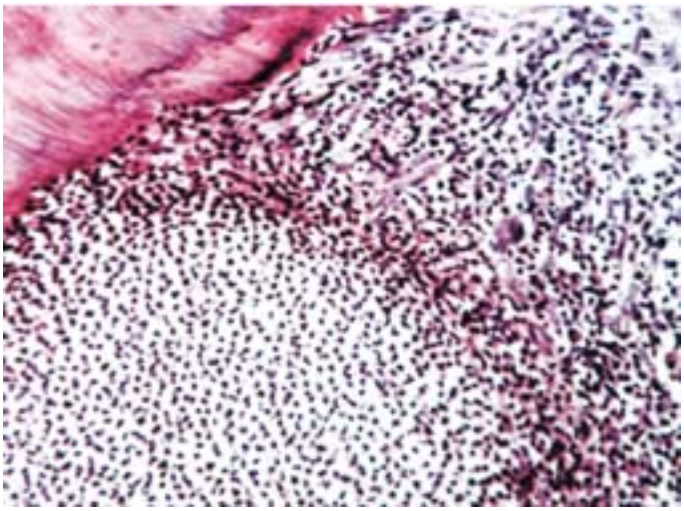


Fig. 2.2: Histopathology section shows chronic inflammatory cells mainly polymorphonuclear leukocytes. Hemorrhagic area are also appreciated

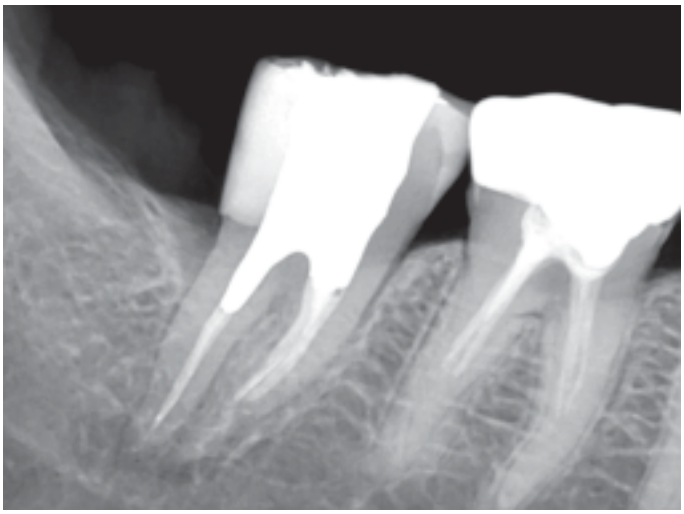


Fig. 2.3: Acute pulpitis treated

and histiocytes. Abscess formation is most likely to occur when the entrance to the pulp is a tiny one and there is lack of drainage. The chemical mediators released from the necrotic tissue lead to further inflammation and edema.

Eventually, in some cases in only a few days, the acute inflammatory process spreads to involve most of the pulp so that neutrophilic leukocytes fill the pulp. The entire odontoblastic layer degenerates. If the pulp is closed to the outside, there is considerable pressure formed, and the entire pulp tissue undergoes rather rapid disintegration. Numerous small abscesses may form, and eventually the entire pulp undergoes liquefaction and necrosis. This is referred to as ***acute suppurative pulpitis***.

The pulp, especially in the later stages of pulpitis following carious invasion, contains large numbers of bacteria. These microorganisms are usually a mixed population and consist essentially of those found normally in the oral cavity.

Treatment and Prognosis

There is no successful treatment of an acute pulpitis involving most of the pulp that is capable of preserving the pulp. Once this degree of pulpitis occurs, the damage is irreparable. Occasionally, acute pulpitis—especially with an open cavity may become quiescent and enter a chronic state. This is unusual, however, and appears to occur most frequently in persons who have a high tissue resistance or in cases of infection with microorganisms of low virulence.

In very early cases of acute pulpitis involving only a limited area of tissue, there is some evidence to indicate that pulpotomy (removal of the coronal pulp) and placing a bland material that favors calcification, such as calcium hydroxide, over the entrance to the root canals may result in survival of the tooth. This technique is also used in cases of mechanical pulp exposures without obvious infection.

Teeth involved with acute pulpitis may be treated by filling the root canals with an inert material, provided the pulp chamber and root canals can be sterilized. When the pulp is initially opened to evacuate any pus, a drop of yellowish fluid frequently escapes, and if the operation is performed without anesthesia, the patient is afforded immediate relief from pain.

Chronic Pulpitis

Chronic pulpitis may arise on occasion through quiescence of a previous acute pulpitis, but more frequently it occurs as the chronic type of disease from the onset. As in most chronic inflammatory conditions, the signs and symptoms are considerably milder than those in the acute form of the disease.

This form of pulpitis has also been classified into both an open and a closed form, but, as in acute pulpitis, the classification is artificial. A special form of chronic pulpitis known as chronic hyperplastic pulpitis has characteristic features and will be described separately.

Clinical Features

Pain is not a prominent feature of chronic pulpitis, although sometimes the patient complains of a mild, dull ache, which is more often intermittent than continuous. The reaction to thermal change is dramatically reduced in comparison to that in acute pulpitis. Because of the degeneration of nerve tissue in the affected pulp, the threshold for stimulation by the electric pulp vitality tester is often increased, in contrast to cases of acute pulpitis, in which it is usually decreased.

The general features of chronic pulpitis are not distinctive and serious involvement of the pulp may be present in the absence of significant symptoms. Even in cases of chronic pulpitis with wide open carious lesions and with exposure of the pulp to the oral environment, there is relatively little pain. The exposed pulp tissue may be manipulated by a small instrument, but though bleeding may occur, pain is often absent.

Histologic Features

Chronic pulpitis is characterized by infiltration of the pulp tissue by varying numbers of mononuclear cells, chiefly lymphocytes and plasma cells and more vigorous connective tissue reaction. Bacterial products may act as antigens and the dendritic cells of the pulp capture the antigens, migrate to lymph nodes and present them to lymphocytes. These activated T cells then leave the lymph nodes and reach the pulp. Capillaries are usually prominent; fibroblastic activity is evident; and collagen fibers are seen, often gathered in bundles (Fig. 2.4).

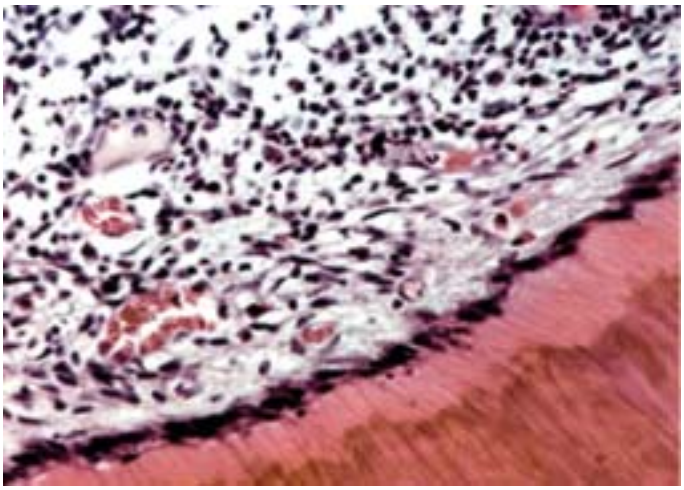


Fig. 2.4: Histopathology shows infiltration of pulp tissue by inflammatory cells chiefly lymphocytes and plasma cells. Few dentin component is also appreciated

There is sometimes an attempt by the pulp to ward off the infection through deposition of collagen around the inflamed area. The tissue reaction may resemble the formation of granulation tissue. When this occurs on the surface of the pulp tissue in a wide-open exposure, the term ulcerative pulpitis is applied. A pulp abscess may become quiescent and be surrounded by a fibrous connective tissue wall is known as the pyogenic membrane.

Treatment and Prognosis

The treatment of chronic pulpitis does not differ dramatically from that of acute pulpitis. The integrity of the pulp tissue is lost sooner or later, necessitating either root canal therapy or extraction of the tooth.

Chronic Hyperplastic Pulpitis (Pulp Polyp)

This is a unique form of pulpitis wherein the inflamed pulp, instead of perishing by continual suppuration, reacts by excessive and exuberant proliferation. It occurs either as a chronic lesion from the onset or as a chronic stage of a previously acute pulpitis (Fig. 2.5).

Clinical Features

Chronic hyperplastic pulpitis occurs almost exclusively in children and young adults who possess a high degree of tissue resistance and reactivity, and readily respond to proliferative lesions. It involves teeth with large, open carious lesions. A pulp so affected appears as a pinkished globule of tissue protruding from the chamber and not only fills the caries defect also extends beyond. Because hyperplastic tissue contains few nerves, it is relatively insensitive to manipulation. The lesion may or may not bleed readily, depending upon the degree of vascularity of the tissue and epithelization.

The teeth most commonly involved by this phenomenon are the deciduous molars and first permanent molars. These have an abundant blood supply because of the large root opening, and this, coupled with the high tissue resistance and reactivity in young persons, accounts for the unusual proliferative property of the pulp tissue. On occasion the gingival tissue adjacent to a brokendown, carious tooth may proliferate into the carious lesion and superficially resemble an example of hyperplastic pulpitis. In such cases the distinction can be made by careful examination of the tissue mass to determine whether the connection is with pulp or gingiva.

Histologic Features

The hyperplastic tissue is basically granulation tissue made up of delicate connective tissue fibers interspersed with variable numbers of small capillaries. Inflammatory cell infiltration, chiefly lymphocytes and plasma cells, sometimes admixed with polymorphonuclear leukocytes, is common. In some instances, fibroblast and endothelial cell proliferation is prominent (Fig. 2.6).

This granulation tissue commonly becomes epithelialized as a result of implantation of epithelial cells on its surface. The epithelium is stratified squamous in type and closely resembles the oral mucosa, even to the extent of developing well-formed rete pegs. The grafted epithelial cells are thought to be normally desquamated cells carried to the surface of the pulp by the saliva. The origin of these epithelial cells is unknown. Most desquamated epithelial cells in the saliva are degenerated superficial squames, which have lost their dividing capacity. For the polyp to become epithelialized, the cells should have the capacity to divide and differentiate into stratified squamous epithelium. So, such cells must come from the region of

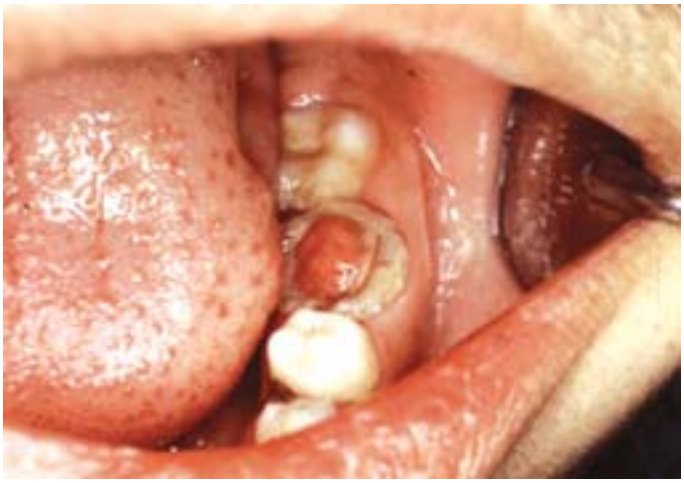


Fig. 2.5: Pulp polyp

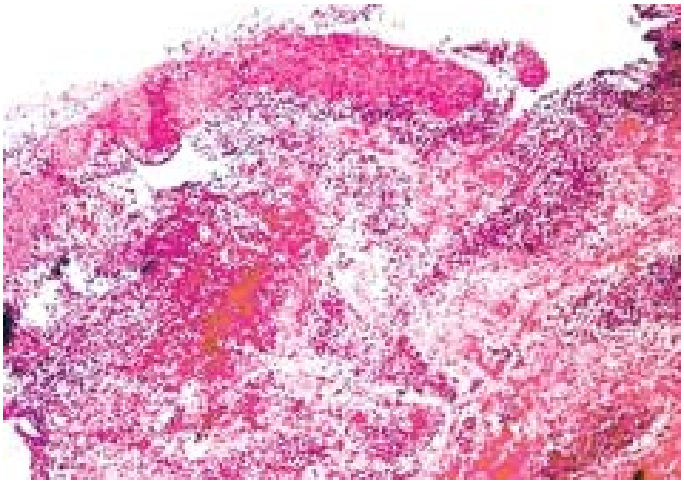


Fig. 2.6: Chronic hyperplastic pulpitis

the basal cell layer and might be released from trauma or from the gingival sulcus.

It should be appreciated that the tissue reaction here is an inflammatory hyperplasia and does not differ from inflammatory hyperplasia occurring elsewhere in the oral cavity as well as in other fibrosis.

Treatment and Prognosis

Chronic hyperplastic pulpitis may persist as such for many months or several days. The condition is not reversible and may be treated by extraction of the tooth or by pulp extirpation.

Gangrenous Necrosis of Pulp

Untreated pulpitis, either acute or chronic, will ultimately result in complete necrosis of the pulp tissue. Since this is generally associated with bacterial infection, the term pulp gangrene has sometimes been applied to this condition, gangrene being defined as necrosis of tissue due to ischemia with superimposed bacterial infection. This gangrenous necrosis of the pulp is associated with a foul odor when such infected pulps are opened for endodontic treatment.

Pulp gangrene should not be considered a specific form of pulp disease but simply the most complete end result of pulpitis in which there is total necrosis of tissue. Necrosis of pulp has been reported in sickle cell anemia where there is blockage of pulp microcirculation by sickle erythrocytes.

A type of gangrene known as dry gangrene sometimes occurs when the pulp dies for some unexplained reason. The nonvital pulp maintains its general histologic characteristics, being nonpurulent. This condition may be due to some traumatic injury or infarction.

DISEASES OF THE PERIAPICAL TISSUES

Once infection has become established in the dental pulp, spread of the process can be in only one direction through the root canals and into the periapical region. Here a number of different tissue reactions may occur, depending upon a variety of circumstances.

It is important to realize that these periapical lesions do not represent individual and distinct entities, but rather that there is a subtle transformation from one type of lesion into another type in most cases (Fig. 2.7).

Apical Periodontitis

This is the inflammation of the periodontal ligament around the apical portion of the root. Though the inflammatory process here is similar to that occurring elsewhere, there may be resorption of the periapical bone and sometimes the root apex. This process may be acute or chronic depending on the virulence of the microorganisms involved, the type and severity of the physical or chemical irritants, and host resistance.

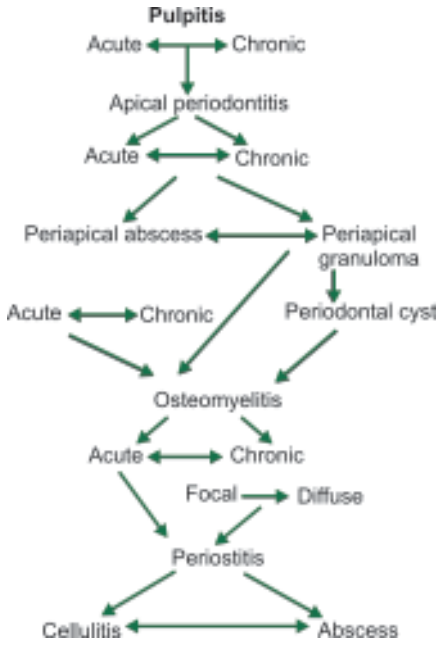


Fig. 2.7: Inter-relationship of periapical infection

The common causes of apical periodontitis include spread of infection following pulp necrosis, occlusal trauma from a high restoration or biting suddenly on a hard object, inadvertent endodontic procedures such as over instrumentation, pushing the infected material into the apical portion or chemical irritation from root canal medicaments.

Acute Apical Periodontitis

Patients suffering from acute apical periodontitis usually give a history of previous pulpitis. Thermal change does not induce pain as in pulpitis. Due to the collection of inflammation edema in the periodontal ligament, the tooth is slightly elevated in its socket and causes tenderness while biting or even to mere touch. The external pressure on the tooth forces the edema fluid against already sensitized nerve endings and results in severe pain. Radiographic appearance is essentially normal at this stage except for a slight widening of periodontal ligament space.

Histologic Features

The periodontal ligament shows signs of inflammation characterized by vascular dilatation and infiltration with polymorphonuclear leukocytes. Initially, these changes are localized around the root apex, as this area is richly vascular. The inflammation is transient if it is caused by acute trauma. If the irritant is not removed, it progresses with resorption of the surrounding bone. Abscess formation may occur if it is associated with bacterial

infection and is known as acute periapical abscess or alveolar abscess.

Treatment and Prognosis

If the inflammation is caused by occlusal trauma, it should be relieved by selective grinding. If the periapical periodontitis occurs due to the spread of pulpal infection, the tooth should be extracted or endodontic treatment be initiated to drain the exudate.

Chronic Apical Periodontitis (Periapical Granuloma)

Chronic apical periodontitis, also known as periapical granuloma, is a low grade infection and one of the most common of all sequelae of pulpitis or acute periapical periodontitis. It the acute process is left untreated, it is incompletely resolved and becomes chronic. The acute inflammatory process is an exudative response whereas the chronic one is proliferative. Periapical granuloma is essentially a localized mass of chronic granulation tissue formed in response to the infection. But the use of this term is not totally accurate since it does not shows true granulomatous inflammation microscopically (Fig. 2.8).

Clinical Features

The involved tooth is usually nonvital and may be slightly tender to percussion, and percussion may produce a dull sound instead of a normal metallic sound because of the presence of granulation tissue around the root apex. Patients may complain about mild pain on biting or chewing on solid food. In some cases, the tooth feels slightly elongated in its socket and may actually be so. The sensitivity is due to hyperemia, edema, and inflammation of the apical periodontal ligament.

The early or even the fully developed chronic periapical granuloma seldom presents any more severe clinical features than those just described. Actually, many cases are entirely asymptomatic. There is usually no perforation of overlying bone and oral mucosa with the formation of a fistulous tract unless the lesion undergoes an acute exacerbation.

Roentgenographic Features

The earliest periapical change in the periodontal ligament appears as a thickening of the ligament at the root apex. As proliferation of granulation tissue and concomitant resorption of bone continue, the periapical granuloma appears as a radiolucent area of variable size seemingly attached to the root apex. In some cases, this radiolucency is a well-circumscribed lesion, definitely demarcated from the surrounding bone. In these instances thin radiopaque line or zone of sclerotic bone may sometimes be seen outlining the lesion. This indicates that the periapical lesion is a slowly progressive one of long standing that has probably not undergone an acute exacerbation (Fig. 2.9).

The periphery of granulomas in other instances appears on the roentgenogram as a diffuse blending of the radiolucent area with the surrounding bone. This difference

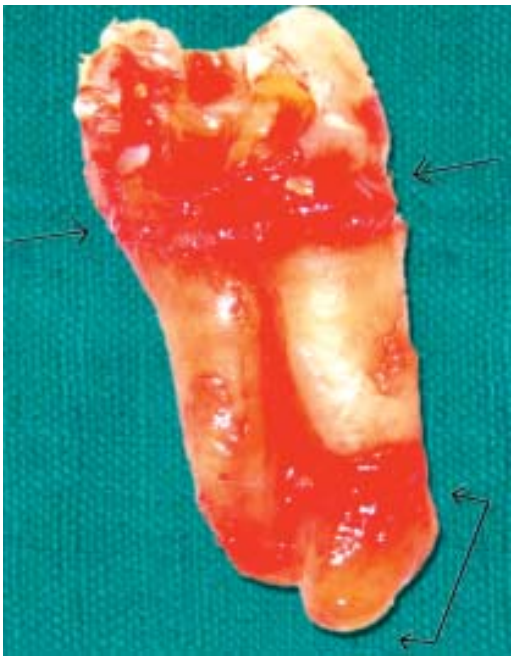


Fig. 2.8: Periapical granuloma—Mass of granulation tissue at the apex of tooth

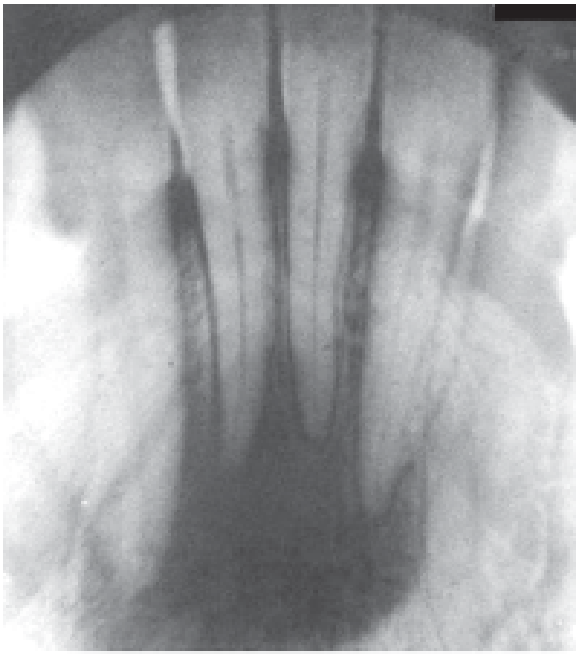


Fig. 2.9: Mandibular Occlusal. X-ray showing well-defined periapical radiolucency in relation to the mandibular anterior teeth which is suggestive of periapical granuloma

in roentgenographic appearance is due to the difference in cellular activity around the margins of the lesion and cannot be used to differentiate between the different forms of periapical disease.

Histologic Features

The periapical granuloma that arises as a chronic process from the onset and does not pass through an acute phase begins as a hyperemia and edema of the periodontal ligament with infiltration of chronic inflammatory cells. The inflammation and locally increased vascularity of the tissue are associated with resorption of the supporting bone adjacent to this area. As the bone is resorbed, there is proliferation of both fibroblasts and endothelial cells and the formation of more tiny vascular channels as well as numerous delicate connective tissue fibrils. The new capillaries are usually lined by swollen endothelial cells. It is a relatively homogeneous lesion composed predominantly of macrophages, lymphocytes, and plasma cells, and less frequently with mast cells and eosinophils, thus qualifying as an immunotype granuloma (Fig. 2.10).

Macrophages and other mononuclear phagocytes are the hallmarks of granulomatous inflammation, a specific form of chronic inflammation.

In some granulomas, large numbers of phagocytes will ingest lipid material and become collected in groups, forming sheets of so called foam cells. Abundant mast cells may be found also. Deposits of cholesterol as well as hemosiderin are often present and both are probably derived from the breakdown of extravasated red blood cells. Cholesterol crystals are almost invariably associated with multinucleated giant cells of the foreign body type.

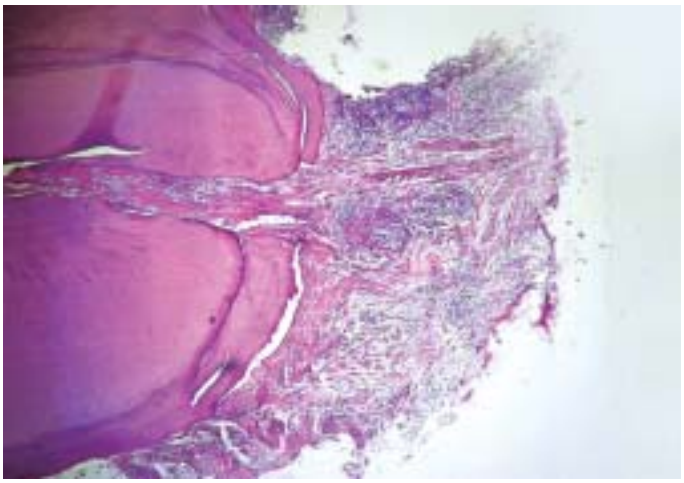


Fig. 2.10: Periapical granuloma—Granulation tissue showing proliferation of both fibroblasts and endothelial cells. Small vascular channels are also seen

Connective tissue activity is usually most prominent on the periphery of the granuloma, and the bundles of collagen become condensed there, apparently as a result of the slow expansion of the soft tissue mass, to form a continuous capsule separating the granulation tissue from the bone.

Other important feature noted in the maxillary periapical granuloma is the presence of epithelium. This epithelium originates in nearly all cases from the epithelial rests of Malassez, although in some instances it arises from:

- Respiratory epithelium of the maxillary sinus in cases in which the periapical lesion perforated the sinus wall.
- Oral epithelium growing in through a fistulous tract.
- Oral epithelium proliferating apically from a periodontal pocket, or bifurcation or trifurcation involvement by periodontal disease also with apical proliferation.

In early periapical granulomas, the epithelium is confined to the immediate vicinity of the periodontal ligament. In course of time, the epithelium undergoes proliferation by the inflammatory stimuli, in an attempt to wall off the irritant coming out through the apical foramen, which becomes extensive, and presents as sheets of stratified squamous epithelial cells as well as anastomosing cords.

Treatment and Prognosis

The treatment of periapical granuloma consists in extraction of the involved teeth, or under certain conditions, root canal therapy with or without subsequent apicectomy. It left untreated, the periapical granuloma may ultimately undergo transformation into an apical periodontal cyst through proliferation of the epithelial rests in the area.

Apical Periodontal Cyst (Radicular Cyst, Periapical Cyst, Root End Cyst)

The apical periodontal cyst is the most common odontogenic cyst encountered in a dental clinic. It is the usual but not inevitable sequela of the periapical granuloma originating as a result of bacterial infection and necrosis of the dental pulp, nearly always following carious involvement of the tooth. It is a true cyst, since the lesion consists of a pathologic cavity that is lined by epithelium and is often fluid-filled. The epithelial lining is derived from the epithelial rests of Malassez, which proliferate as a result of the inflammatory stimulus in a pre-existing granuloma. The epithelium may be derived in some cases from:

- Respiratory epithelium of the maxillary sinus when the periapical lesion communicates with the sinus wall.
- Oral epithelium from a fistulous tract.
- Oral epithelium proliferating apically from a periodontal pocket.

Pathogenesis

This type of periodontal cyst exhibits a lumen that is almost invariably lined by stratified squamous epithelium, while the wall made up of condensed connective tissue. Although the stimulus for the proliferation of epithelium in the periodontal cyst is recognized to be inflammation in the periapical granuloma, the reason why all such granulomas do not eventually develop into cysts is not known. It might be that if all periapical granulomas persisted for a sufficiently long time, they would eventuate in cysts (Fig. 2.11).

The actual mode of development of the apical periodontal cyst is an interesting phenomenon. The initial reaction leading to cyst formation is a proliferation of the epithelial rests in the periapical area involved by the granuloma. This epithelial proliferation is induced by the keratinocyte growth factor elaborated by the periodontal stroma cells, or inflammatory stimulus. This epithelial proliferation follows an irregular pattern of growth and occasionally presents a frightening picture because of the pseudoinvasiveness and inflammatory altered appearance of the cells. As this proliferation continues with the epithelial mass increasing in size by division of the cells on the periphery, corresponding to .the basal layer of the surface epithelium the cells in the central portion of the mass become separated further and further from their source of nutrition, the capillaries and tissue fluid of the connective tissue. As these central cells fail to obtain sufficient nutrients, they eventually degenerate, become necrotic and liquefy. This creates an epithelium-lined cavity filled with fluid, the apical periodontal cyst.

Once begun, the cyst increases its size by various mechanisms, namely osmosis, local fibrinolysis and continued epithelial proliferation.

Clinical Features

The majority of cases of apical periodontal cysts are asymptomatic and present no clinical evidence of their presence. They are commonly seen between the ages of 20 and 60 years, but the involvement of deciduous dentition is not uncommon. The most commonly involved teeth are maxillary anteriors. The associated tooth is nonvital or shows deep carious lesion or a restoration which is seldom painful or even sensitive to percussion (Fig. 2.12).

The apical periodontal cyst is a lesion that represents a chronic inflammatory process and develops only over a prolonged period of time. In some cases, such a cyst of long standing may undergo an acute exacerbation of the inflammatory process and develop rapidly into an abscess that may then proceed to a cellulitis or form a draining fistula. The cause of such a sudden flare up is not known, but it may be a result of loss of local or generalized tissue resistance.

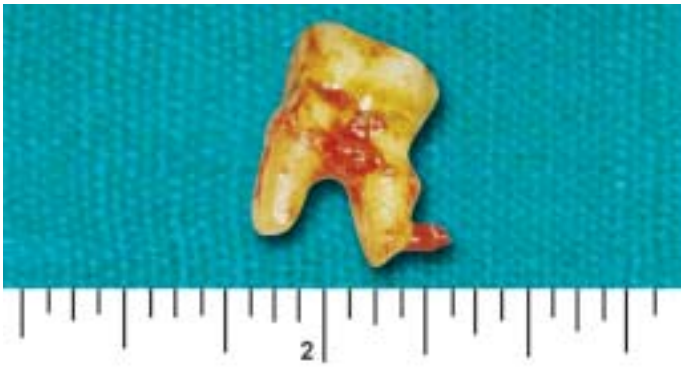


Fig. 2.11: Periapical cyst—A mass appreciated at the apical region of the tooth

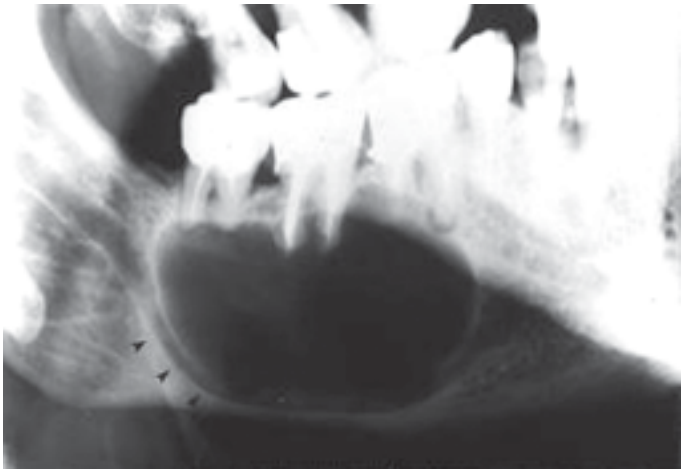


Fig. 2.12: Large radicular cyst in the mandible displacing the mandibular canal inferiorly (arrows)

Roentgenographic Features

The roentgenographic appearance of the apical periodontal cyst is identical in most cases with that of the periapical granuloma. Since the lesion is a chronic progressive one developing in a pre-existing granuloma, the cyst may be of greater size than the granuloma by virtue of its longer duration, but this is not invariably the case.

Occasionally, the apical periodontal cyst exhibits a thin, radiopaque line around the periphery of the radiolucent area, and this indicates a reaction of the bone to the slowly expanding mass. The actual diagnoses were established by histologic examination of the tissue after its removal.

Histologic Features

The apical periodontal cyst is histologically identical with the periapical granuloma, from which it is actually derived, except for the presence of the epithelium-lined lumen. The epithelium lining the apical periodontal cyst is usually stratified squamous in type.

The usual squamous epithelium seldom exhibits keratin formation. This lining epithelium varies remarkably in thickness. In newly formed cysts the epithelial thickness is uneven and often shows hyperplasia while in established cysts it is of regular appearance and of fairly even thickness. It may be only a few cells thick, or exceedingly thick with a great deal of proliferation into the adjacent connective tissue. Actual rete peg formation sometimes occurs. The epithelial lining many times is discontinuous, frequently missing over areas of intense inflammation. Despite the presence of long standing inflammation, alterations in individual epithelial cells, such as dyskeratosis, are uncommon. Shear has reported that there is no apparent relationship between the degree of inflammation present, either in the connective tissue wall or within the epithelium itself and the thickness of the epithelial lining of the cyst (Fig. 2.13).

An interesting and peculiar structure, the hyaline body or Rushton body, often found in great numbers in the epithelium of apical periodontal or residual cysts. These hyaline bodies are tiny linear or arc shaped bodies, generally associated with the lining epithelium, that appear amorphous in structure, eosinophilic in reaction, and brittle in nature, since they evidence fracture in some cases. They appear to have no clinical or diagnostic significance and their origin is unknown but they may represent some type of epithelial product.

The connective tissue that makes up the wall of the apical periodontal cyst is composed of parallel bundles of collagen fibers that often appear compressed. Variable numbers of fibroblasts and small blood vessels are also present. A characteristic feature is the almost universal occurrence of an inflammatory infiltrate in the connective tissue immediately adjacent to the epithelium. This infiltrate varies in its composition but is generally made up of lymphocytes and plasma cells, with some admixed polymorphonuclear leukocytes, depending partially upon the intensity of the infection. In some lesions, dystrophic calcifications and collections of cholesterol slits with associated multinucleated giant cells are found in the wall of the lesion. This mass of cholesterol frequently erodes through the lining epithelium and is extruded into the cyst lumen. The source of this cholesterol is not known. It appears that local tissue damage is a pre-requisite for the cholesterol accumulation. In other instances, collections of lipid-filled macrophages or even macrophages containing hemosiderin are present.

The contents of the cyst lumen vary from watery, straw-colored, blood tinged fluid to semisolid materials, with a low concentration of protein that stains palely eosinophilic. Occasionally, the lumen may contain a great deal of cholesterol which imparts a shimmering effect; in rare instances, limited amounts of keratin are present. Blood is a rare finding except when associated with the surgical procedure involved in removing the cyst.

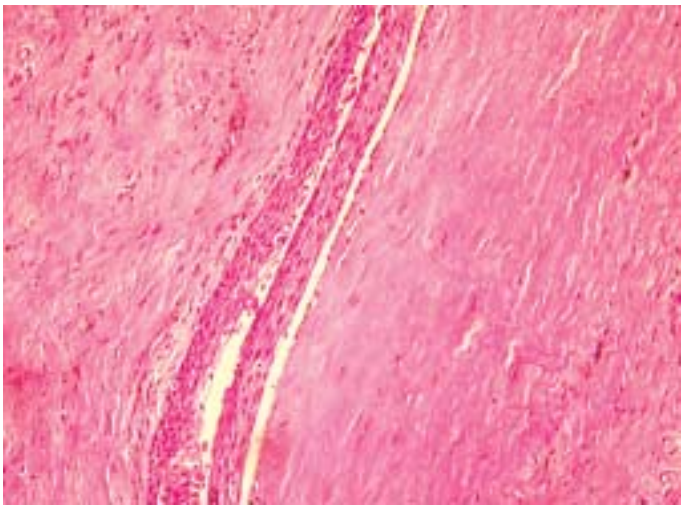


Fig. 2.13: Periapical cyst—Histopathology shows keratinized epithelium and dense connective tissue with chronic inflammatory cells and proliferating blood vessels

Treatment and Prognosis

The treatment of this type of cyst is similar to that of the periapical granuloma. The involved tooth may be removed and the periapical tissue carefully curetted. Under some conditions root canal therapy may be carried out with apicoectomy of the cystic lesion.

The cyst does not recur if surgical removal is thorough.

If untreated, the periodontal cyst slowly increases in size at the expanse of the surrounding bone. The bone undergoes resorption, but seldom is there a remarkable compensating expansion of the cortical plates, as is frequently seen in the case of the dentigerous cyst.

RESIDUAL CYST

This is another type of inflammatory odontogenic cyst development in the edentulous alveolar ridge. It may occur due to extraction of the tooth, leaving the periapical pathology untreated or incomplete removal of periapical granuloma or periapical cyst. Radiographically, it appears as round to ovoid radiolucency in the alveolar ridge. Occasionally, lumen shows radiopacity indicative of dystrophic calcification. A thorough history and clinical examination is a must, to rule out other primary odontogenic and nonodontogenic cysts, tumors, and metastatic lesions. In time, the cyst may get infected and discharge purulent material through a sinus opening (Fig. 2.14).

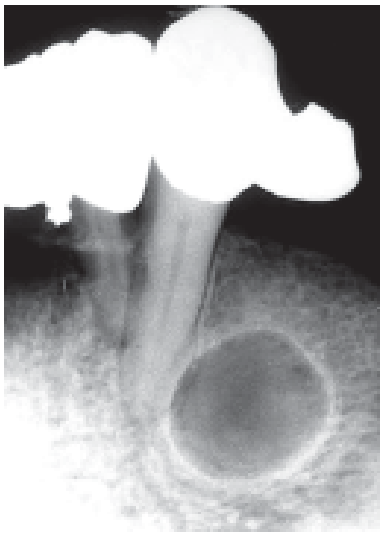


Fig. 2.14: Residual cyst in the mandibular premolar region

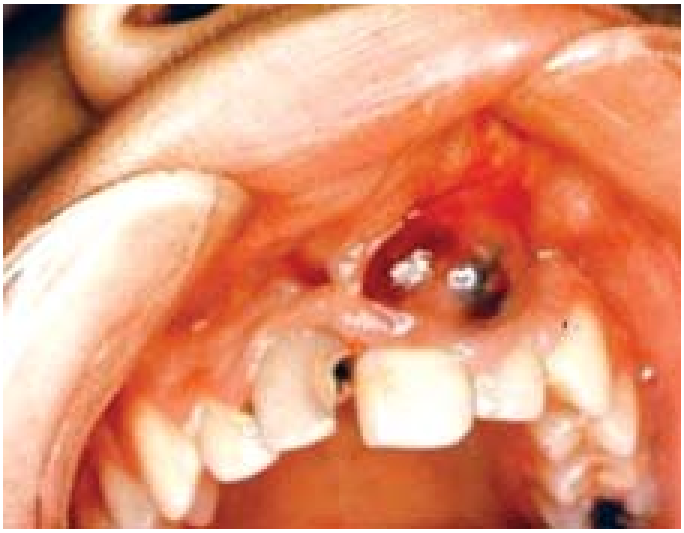


Fig. 2.15: Periapical abscess—Soft tissue swelling on anterior part of gingiva

Treatment and Prognosis

The cyst should be curetted thoroughly and the lining should be subjected to histopathalogical examination.

Usually this cyst does not recur if the inflammatory foci near the cyst are eliminated.

Periapical Abscess (Dentoalveolar Abscess, Alveolar Abscess)

The periapical abscess in an acute or chronic suppurative process of the dental periapical region. It may develop either from acute periapical periodontitis or more commonly from a periapical granuloma. Acute exacerbation of a chronic periapical lesion is also called a Phoenix abscess. It usually arises as a result of infection following carious involvement of the tooth and pulp infection, but it also does occur after traumatic injury to the teeth, resulting in necrosis of the pulp, and in cases of irritation of the periapical tissues either by mechanical manipulation or by the application of chemicals in endodontic procedures (Fig. 2.15).

Clinical Features

The acute periapical abscess presents the features of an acute inflammation of the apical periodontium. The initial stages produce tenderness of the tooth, which is often relieved by application of pressure. In time, the tooth is extremely painful and is slightly extruded from its socket. As long as this abscess is confined to the immediate periapical region, there are seldom severe systemic manifestations, although regional lymphadenitis and fever may be present. However, rapid extension to adjacent bone marrow spaces frequently occurs, producing an actual osteomyelitis, but this is sometimes still considered clinically to be a dentoalveolar abscess. In such cases the clinical features may be severe and serious with swelling of the tissues.

The chronic periapical abscess generally presents no clinical features, since it is essentially a mild, well-circumscribed area of suppuration that shows little tendency to spread from the local area.

Roentgenographic Features

The acute periapical abscess is such a rapidly progressive lesion that except for slight thickening of the periodontal ligament space, there is usually no roentgenograpic evidence of its presence. The chronic abscess developing in a periapical granuloma, presents radiolucent area at the apex of the tooth described previously or the radiolucency may be ill-defined (Fig. 2.16).

Histologic Features

The area of suppuration is composed chiefly of a central area of disintegrating polymorphonuclear leukocytes surrounded by viable leukocytes, occasional lymphocytes, cellular debris, necrotic materials and bacterial colonies. There is dilatation of the blood vessels in the periodontal ligament and adjacent marrow spaces of the bone. These marrow spaces also show an inflammatory cell infiltrate. The tissue around the area of suppuration contains a serous exudate.

Treatment and Prognosis

The principle of treatment of the periapical abscess is the same as for any abscess: Drainage must be established.

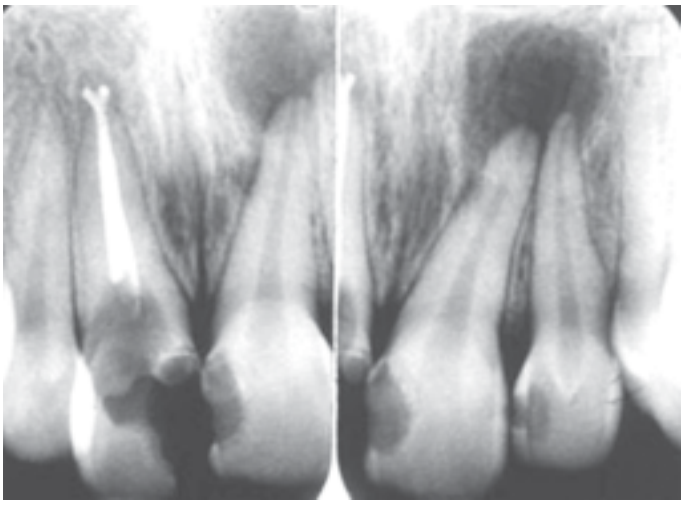


Fig. 2.16: Periapical abscess—Well-defined radiolucency of anterior teeth

This can be accomplished by either opening the pulp chamber or extracting the tooth. Under some circumstances, the tooth may be retained and root canal therapy carried out if the lesion can be sterilized.

If the periapical abscess is not treated, it may lead to serious complications through the spread of the infection. These include osteomyelitis, cellulitis, and bacteremia and the ultimate formation of the fistulous tract opening on the skin or oral mucosa. Cavernous sinus thrombosis has also been reported.

Osteomyelitis

Osteomyelitis is usually defined as inflammation of bone and its marrow contents. Changes in the calcified tissue are secondary to inflammation of the soft tissue component of the bone. Though the pathologic changes of periapical abscess can even be considered as osteomyelitis as there is involvement of bone, the term 'osteomyelitis' is reserved for infections which spread through the bone to a larger extent. The dividing line between osteomyelitis and a localized abscess involving the bone is, however, still unclear. Though osteomyelitis commonly occurs as a complication of dental sepsis, it is also seen in various other situations.

Predisposing factors include fractures due to trauma and road traffic accidents; gunshot wounds, radiation damage, Paget's disease, and osteopetrosis. Systemic conditions like malnutrition, acute leukemia, uncontrolled diabetes mellitus, sickle cell anemia, and chronic alcoholism may also predispose to osteomyelitis. The disease may be acute, subacute or chronic and presents a different clinical course, depending upon its nature.

Acute Suppurative Osteomyelitis

Acute suppurative osteomyelitis of the jaw is a serious sequela of periapical infection that often results in a diffuse spread of infection throughout the medullary spaces, with subsequent necrosis of a variable amount of bone. The clinical features of this form of osteomyelitis, which arises from a dental infection, are the same as those present after infection due to a fracture or the jaw, a gunshot wound, or even hematogenous spread.

Dental infection is the most frequent cause of acute osteomyelitis jaws. It may be a rather well localized infection involving a great volume of bone. A periapical infection (usually an abscess), if it is a particularly virulent one and not walled off may spread spontaneously throughout the bone. In other instances, a chronic periapical infection such as a granuloma, or even a cyst that is walled off, may undergo an acute exacerbation, especially if the area is traumatized or surgically disturbed without establishing and maintaining drainage (Fig. 2.17).

It is usually a polymicrobial infection. Different types of organisms may be cultured from these lesions; the most common are *Staphylococcus aureus* and *Staph albus*, and various streptococci. Anaerobes such as bacteroides, porphyromonas or prevotella species also predominate. Cases of specific infectious osteomyelitis in tuberculosis, syphilis, actinomycosis, and so forth, are considered in the discussions of these diseases.

Clinical Features

Acute or subacute suppurative osteomyelitis may involve either the maxilla or the mandible. In the maxilla, the disease usually remains fairly well localized to the area of initial infection. In the mandible, bone involvement tends to be more diffuse and widespread.

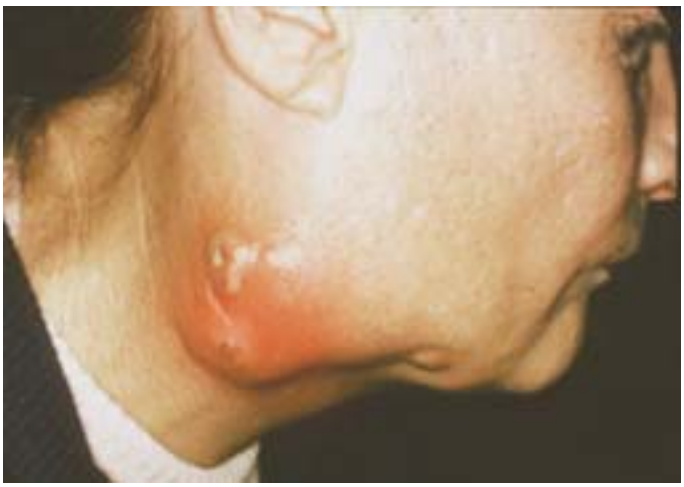


Fig. 2.17: Acute suppurative osteomyelities—Soft tissue swelling showing ulcer and sinus formation

The disease may occur at any age. A particular form of acute osteomyelitis, referred to as neonatal maxillitis in infants and young children, is a well-recognized entity that is fortunately becoming extremely uncommon nowadays because of antibiotic drugs. In some instances, this osteomyelitis of infants is of hematogenous origin, but at other times, it seems to be a result of local oral infection following some minor injury or abrasion. Infants so affected are seriously ill and may not survive the disease. In some cases, the source of the infecting organisms cannot be discovered.

The adult afflicted with acute suppurative osteomyelitis usually has severe pain, trismus and paraesthesia of the lips in case of mandibular involvement and manifests an elevation of temperature with regional lymphadenopathy. The white blood cell count is frequently elevated. The teeth in the area of involvement are loose and sore so that eating is difficult, if not impossible. Pus may exude from the gingival margin. Until periostitis develops, there is no swelling or reddening of the skin or mucosa.

Roentgenographic Features

Acute osteomyelitis progresses rapidly and demonstrates little roentgenographic evidence of its presence until the disease has developed for at least one to two weeks. At this time diffuse-lytic changes in the bone begin to appear. Individual trabeculae become fuzzy and indistinct, and radiolucent areas begin to appear. These areas have ill-defined margins and have a moth-eaten appearance (Fig. 2.18).

Pathology

The infection causes acute inflammation of the marrow tissue and the resultant inflammatory exudate spreads through the marrow spaces. This causes compression of blood vessels in the bone, leads to thrombosis and obstruction of blood flow, resulting in necrosis of bone. Liquefaction of the necrotic tissue, dead and dying inflammatory cells, and bacteria form the pus and this may fill the marrow spaces. This suppurative reaction extends through the cortical bone to involve the periosteum causing lifting of the periosteum, which further leads to compromise in the blood supply to the underlying bone resulting in further necrosis. By osteoclastic activity, the necrozied bone, known as sequestrum, is separated from the surrounding vital bone and exfoliates through the sinus.

Histologic Features

The medullary spaces are filled with inflammatory exudate. The inflammatory cells are chiefly neutrophilic polymorphonuclear leukocytes but may show occasional lymphocytes and plasma cells. The osteoblasts bordering the bony trabeculae are generally destroyed and depending upon the duration of the process, the trabeculae may lose their viability and begin to undergo slow resorption (Fig. 2.19)

Treatment and Prognosis

General principles of management include debridement, drainage, and antimicrobial therapy. When the intensity of the disease becomes attenuated, either spontaneously or under treatment, the sequestrum begins to separate from the living bone. If the sequestrum is small, it gradually exfoliates through the mucosa. If large, surgical removal may be necessary, since its removal by normal processes of bone resorption would be extremely slow. Sometimes an involucrum forms when the sequestrum becomes surrounded by new living bone.

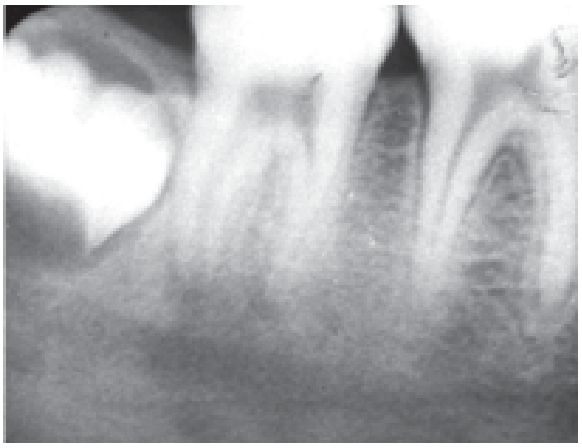


Fig. 2.18: Acute suppurative osteomyelitis—Note the ill-defined radiolucency in the mandible

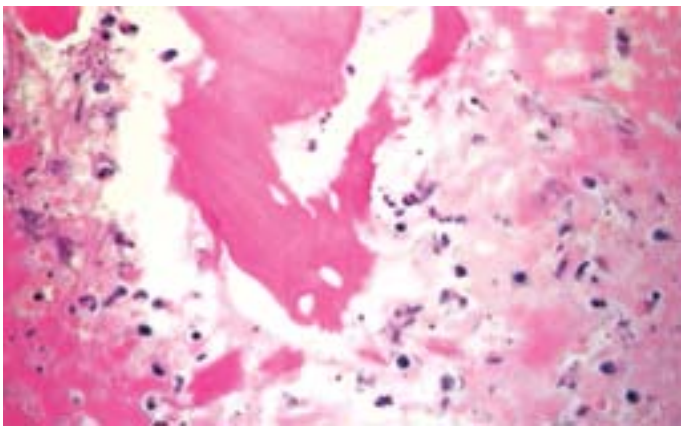


Fig. 2.19: Acute suppurative osteomyelitis– Histopathology shows necrotic bone with loss of osteocytes from the lacunae. Inflammatory cells are also appreciated

Unless proper treatment is instituted, acute suppurative osteomyelitis may proceed to the development of periostitis, soft tissue abscess or cellulitis. Pathologic fracture occasionally occurs because of weakening of the jaw by the destructive process.

Chronic Suppurative Osteomyelitis

Chronic suppurative osteomyelitis may develop in inadequately treated acute osteomyelitis or may arise from a dental infection without a preceding acute stage. Rarely may it occur as a complication of irradiation. The clinical features are similar to those of acute osteomyelitis except that all signs and symptoms are milder. The pain is less severe; the temperature is still elevated, but only mildly; and the leukocytosis is only slightly greater than normal. The teeth may not be loose or sore, so that mastication is at least possible even though the jaw may not be perfectly comfortable.

Acute exacerbations of the chronic stage may occur periodically, and these present all features of acute suppurative osteomyelitis. The suppuration may perforate the bone and overlying skin or mucosa to form a fistulous tract and empty on the surface. This form of the disease should be treated on the same principles as its acute counterpart.

Chronic Focal Sclerosing Osteomyelitis (Condensing Osteitis)

Chronic focal sclerosing osteomyelitis is an unusual reaction of the bone to infection: A reaction to mild bacterial infection entering the bone through a carious tooth in persons who have a high degree of tissue resistance and tissue reactivity. In such instances, the tissues react to the infection by proliferation rather than destruction, since the infection acts as a stimulus rather than an irritant (Fig. 2.20).

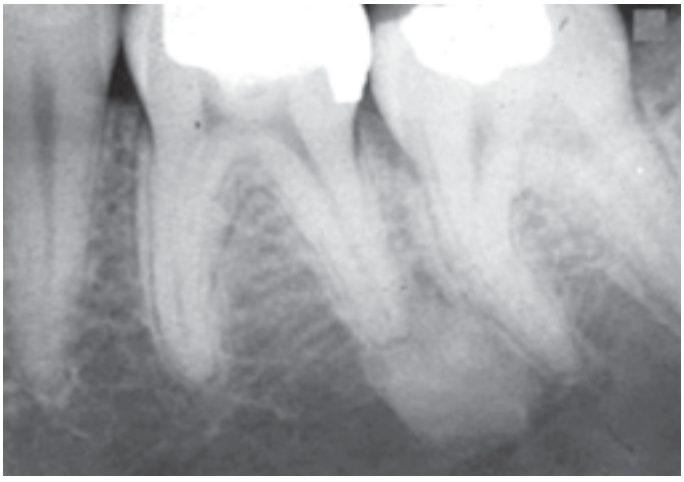


Fig. 2.20: Chronic focal sclerosing osteomyelitis—Increased areas of radiodensity surrounding mandibular first molar

Clinical Features

This form of osteomyelitis arises most commonly in children and young adults and rarely in older individuals. The tooth most commonly involved is the mandibular first molar, which presents a large carious lesion. There may be no signs or symptoms of the disease other than mild pain associated with an infected pulp.

Roentgenographic Features

The periapical roentgenogram demonstrates the pathognomonic, well circumscribed radiopaque mass of sclerotic bone surrounding and extending below the apex of one or both roots. The entire root outline is nearly always visible, with an intact lamina dura. Periodontal ligament space is widened and this is an important feature in distinguishing it form the benign cementoblastoma (qv) that it roentgenographically may closely resemble. The border of this lesion, abutting the normal bone, may be smooth and distinct or appear to blend into the surrounding bone in contrast to focal cemento-osseous dysplasia, which has radiolucent border. In either case, the radiopacity stands at indistinct contrast to the trabeculation of the normal bone.

Histologic Features

The histologic examination reveals only a dense mass of bony trabeculae with little interstitial marrow tissue. The osteocytic lacunae appear empty. The bony trabeculae exhibit many reversal and resting lines giving pagetoid appearance. If interstitial soft tissue is present, it is generally fibrotic and infiltrated only by small numbers of lymphocytes. Osteoblastic activity may have completely subsided at the time of microscopic study.

Treatment and Prognosis

The tooth with which this specific lesion is associated may be treated endodontically or extracted, since the pulp is infected and the infection has spread past the immediate periapical area. The sclerotic bone constituting the osteomyelitis is not attached to the tooth and remains after the tooth is removed. This dense area of bone is sometimes not remodeled but in many cases may be recognized on the roentgenogram even years later and is referred to as bone scar.

Since the condition is actually an indication that the body has been able to deal effectively with the infection, surgical removal of the sclerotic lesions is not indicated unless symptomatic.

Chronic Diffuse Sclerosing Osteomyelitis

Chronic diffuse sclerosing osteomyelitis is a condition analogous to the focal form of the disease and also

apparently represents a proliferative reaction of the bone to a low grade infection. In many of these cases, the portal of entry for the infection is not through a carious lesion with subsequent pulp infection, as in chronic focal sclerosing osteomyelitis but rather through diffuse periodontal disease (Fig. 2.21).

Clinical Features

The diffuse type of sclerosing osteomyelitis may occur at any age, but is most common in older persons, especially in edentulous mandibular jaws or edentulous areas and does not exhibit any gender predominance. Often the disease is of such an insidious nature that it presents no clinical indications of its presence. On occasion, there is an acute exacerbation of the dormant chronic infection and this results in vague pain, unpleasant taste, and mild suppuration, many times with the spontaneous formation of a fistula opening onto the mucosal surface to establish drainage.

Roentgenographic Features

The roentgenographic appearance of chronic diffuse sclerosing osteomyelitis is that of a diffuse patchy, sclerosis of bone often described as 'cotton-wool' appearance. This radiopaque lesion may be extensive and is sometimes bilateral. In occasional cases, there is bilateral involvement of both the maxilla and the mandible in the same patient. Because of the diffuse nature of the disease, the border between the sclerosis and the normal bone is often indistinct. The pattern may actually mimic Paget's disease of bone or cemento-osseous dysplasia.

Histologic Features

Microscopic study of tissue taken from the lesion shows dense, irregular trabeculae of bone, some of which are bordered by an active layer of osteoblasts. Focal areas of osteoclastic activity are sometimes seen. The bone in some lesions shows a pronounced 'mosaic' pattern, indicative of repeated periods of resorption followed by repair The soft tissue between the individual trabeculae is fibrous and shows proliferating fibroblasts and occasional small capillaries as well as small focal collections of lymphocytes and plasma cells. Polymorphonuclear leukocytes may be present, particularly if the lesion is undergoing an acute phase. In some lesions, the inflammatory component is completely 'burned out', leaving only sclerotic bone and fibrosis, but this does not contravene a diagnosis of chronic sclerosing osteomyelitis (Fig. 2.22).

Treatment and Prognosis

The treatment of chronic diffuse sclerosing osteomyelitis is a difficult problem. Resolution of adjacent foci of chronic infection often leads to improvement of this lesion. The lesion is usually too extensive to be removed surgically, yet it frequently undergoes acute exacerbations. The most reasonable approach to this disease is a conservative one of treatment of the acute episodes by antibiotic administration, but no other intervention. Although the lesion may be slowly progressive, it is not particularly dangerous, since it is not destructive and seldom produces any complications.

If a tooth is present in one of these sclerotic areas and must be extracted, the probability of infection and

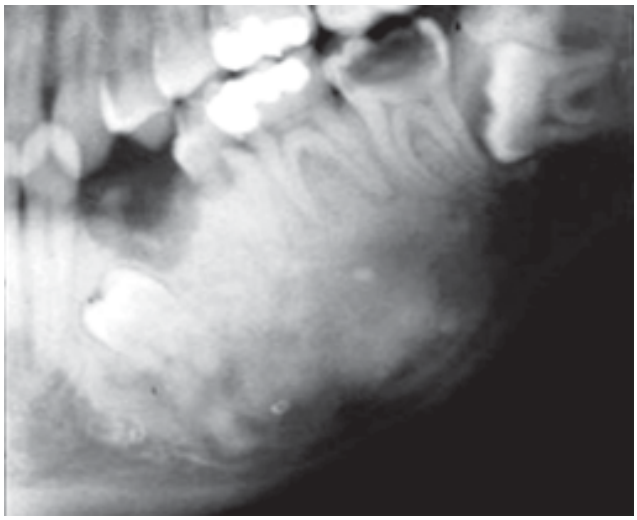


Fig. 2.21: Chronic diffuse sclerosing osteomyelitis—Diffuse areas of increased radiodensity seen in the mandible

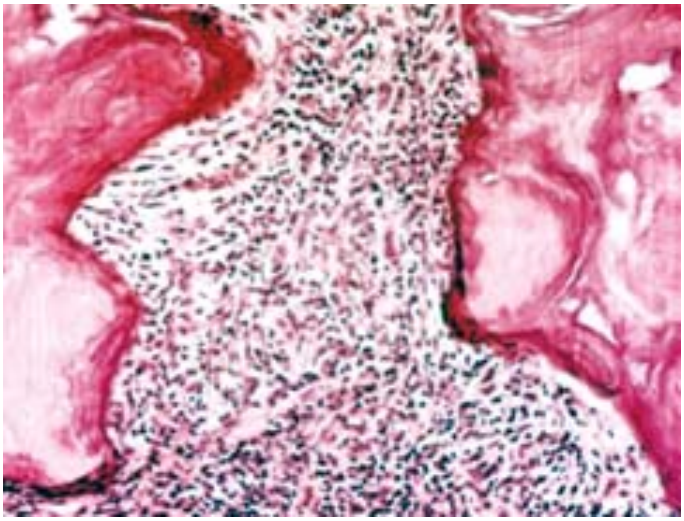


Fig. 2.22: Chronic diffuse sclerosing osteomyelitis—Histopathology shows dense irregular trabeculae of bone bordered by osteoblasts. Few fibrous component is appreciated between the trabeculae

protracted healing must be recognized. Sclerotic bone is hypovascular and responds poorly to any bacterial infection.

Sclerotic Cemental Masses

A series of 38 cases of lesions of the jaws with striking similarities to those lesions described as chronic diffuse sclerosing osteomyelitis has been reported by Waldron and his coworkers under the term 'sclerotic cemental masses of the jaws'.

Clinical Features

Just as in chronic diffuse sclerosing osteomyelitis, the majority of cases reported by Waldron and his associates occurred in older black females, who often presented with multiple. Symmetric lesions that sometimes produced pain, drainage or localized expansion. The roentgenographic appearance was also similar to that of diffuse sclerosis.

Histologic Features

The only significant difference between the two diseases, described in one case as sclerosing osteomyelitis and in the other as sclerotic cemental masses, was in the microscopic appearance of the radiopaque lesional tissue. In sclerosing osteomyelitis, the tissue was essentially sclerotic bone, while in the cemental masses, the tissue usually was interpreted as cementum. In some instances, this cementum was in the form of large solid masses, with smooth, lobulated margins, often with a globular accretion pattern. In other cases, variable amounts of bone were admixed.

The remarkable similarities between the diseases suggest very strongly that these represent two closely related facets of the same basic disease process.

Florid Osseous Dysplasia

This is another disease that appears very closely related to both chronic diffuse sclerosing osteomyelitis and sclerotic cemental masses and was described by Melrose and his associates under the term 'florid osseous dysplasia'.

The clinical and roentgenographic features, as well as the microscopic findings, are virtually identical with those described under the former two diseases. However, Melrose and his coworkers did describe one additional feature that had not been reported previously; the simultaneous occurrence of simple bone 'cysts' in approximately 40 per cent of their series of 34 cases of florid osseous dysplasia. The suggested cause for the occurrence of these cysts is obstruction of the normal interstitial fluid by the fibroosseous proliferation.

It appears that the term florid osseous dysplasia has been used to imply rather broad parameters of an "exuberant variant of osseous dysplasia, defined by Robinson to be an abnormal reaction of bone to irritation or stimulation," according to Melrose and his associates, and includes chronic diffuse sclerosing osteomyelitis and sclerotic cemental masses.

Chronic Osteomyelitis with Proliferative Periostitis (Garre's Chronic Nonsuppurative Sclerosing Osteitis, Periostitis Ossificans)

This is a distinctive type of chronic osteomyelitis in which there is focal gross thickening of the periosteum, with peripheral reactive bone formation resulting from mild irritation or infection. It is essentially a periosteal osteosclerosis analogous to the endosteal sclerosis of chronic focal and diffuse sclerosing osteomyelitis (Fig. 2.23).

Clinical Features

This sclerosing osteomyelitis occurs almost entirely in young persons before the age of 25 years and most frequently involves the anterior surface of the tibia. Since there is probably greater opportunity for infection to enter the bone of the maxilla and the mandible than any other

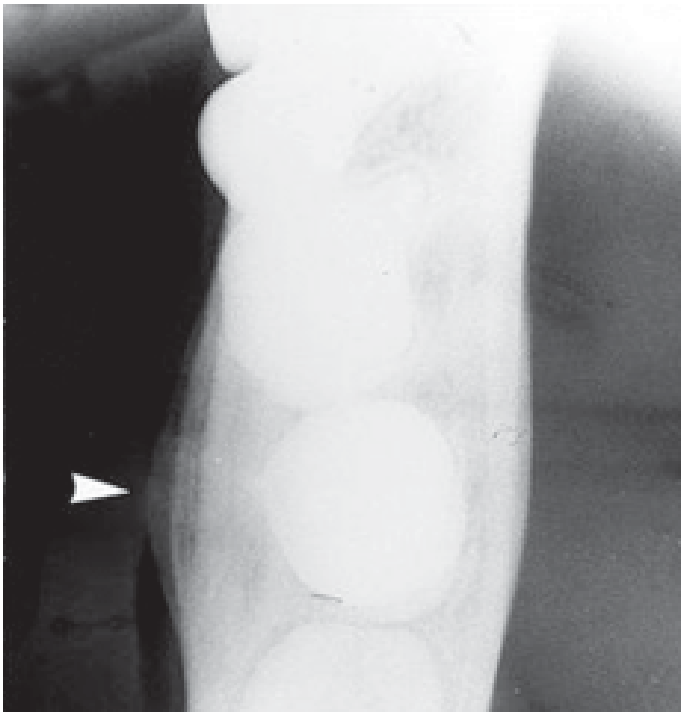


Fig. 2.23: Chronic osteomyelitis with proliferative periostitis—Periosteal bone fomation (arrow) on the buccal side of the mandible

bone of the body, because of the peculiar anatomic arrangement of the teeth situated in and protruding from the bone, it is surprising that the disease has not been described more frequently as a dental complication.

The condition in the jaws occurs almost exclusively in the mandible in children and young adults, and most cases occur in the bicuspid and molar region. The maxilla is seldom affected, and the reason for this is not clear. The patient usually complains of a toothache or pain in the jaw and a bony hard swelling on the outer surface of the jaw. This mass is usually of at least several weeks duration. Occasionally, this reactive periostitis may develop not as a result of a central dental infection of the jaw that perforates outward but as a result of an overlying soft tissue affection or cellulitis that subsequently involves the deeper periosteum.

Roentgenographic Features

Intraoral roentgenograms will often reveal a carious tooth opposite the hard bony mass. An occlusal roentgenogram shows a focal overgrowth of bone on the outer surface of the cortex, which may be described as duplication of the cortical layer of bone. This mass of bone is smooth and rather well calcified and may itself show a thin but definite cortical layer.

Histologic Features

This supracortical but subperiosteal mass is composed of much reactive new bone and osteoid tissue, with osteoblasts bordering many of the trabeculae. These trabeculae often are oriented perpendicular to the cortex, with the trabeculae arranged parallel to each other or in a retiform pattern. The connective tissue between the bony trabeculae is rather fibrous and shows a diffuse or patchy sprinkling of lymphocytes and plasma cells.

The periosteal reaction is a result of the infection from the carious tooth perforating the cortical plate and becoming attenuated, stimulating the periosteum rather than producing the usual suppurative periostitis.

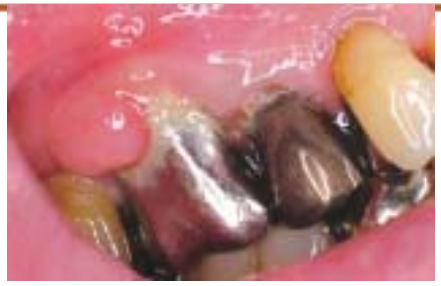
Treatment and Prognosis

Chronic osteomyelitis with a proliferative periostitis is treated endodontically or removal of the carious infected tooth, with no surgical intervention for the periosteal lesion except for biopsy to confirm the diagnosis.

Periosteal new bone formation or neoperiostosis, may occur in a variety of other conditions, and care must be taken to exclude them from the diagnosis. These include infantile cortical hyperostosis (Caffey's disease), hypervitaminosis A, syphilis, leukemia, Ewing's sarcoma, metastatic neuroblastoma and even a fracture callus.

3

Disease of Periodontium



GINGIVAL ABSCESS

It is an acute, localized and painful lesion of sudden onset, caused by sudden forceful penetration of any foreign objects such as a bristle of a toothbrush or an apple core which carries bacteria deep into the gingival tissue (Fig. 3.1).

Clinical Features

It is localized to the marginal gingiva and appears as reddish swelling with a smooth and shiny surface. Within few times it becomes fluctuant and exhibits pointing and through which pus discharges.

Histologic Features

Connective tissue show vascular engorgement, edema and formation of abscess cavity, which is surrounded by a diffused collection of polymorphonuclear leukocytes. The overlying epithelium exhibits secondary changes in the form of intra- and intercellular edema, microabscess formation and sometimes ulceration.

Treatment

Spontaneous healing is common. The invading foreign material, if any will be usually expelled along with the pus.

PERICORONITIS

This is an inflammatory lesion which occurs around an impacted or partially erupted tooth. Incomplete eruption of the tooth provides a large stagnant area for food debris below the gingival flaps. Later it becomes infected easily and results in an inflammatory condition of the pericoronal flap. It exhibits chronic inflammation. If the debris and bacteria are deeply entrapped, an abscess may form, called a pericoronal abscess. It is a mixed infection and various bacteria of the dental plaque (particularly anaerobes) play a significant role in the development of pericoronitis (Fig. 3.2).

Clinical Features

Mandibular third molar is the common site. Pain and swelling of the pericoronal tissue around the affected tooth,

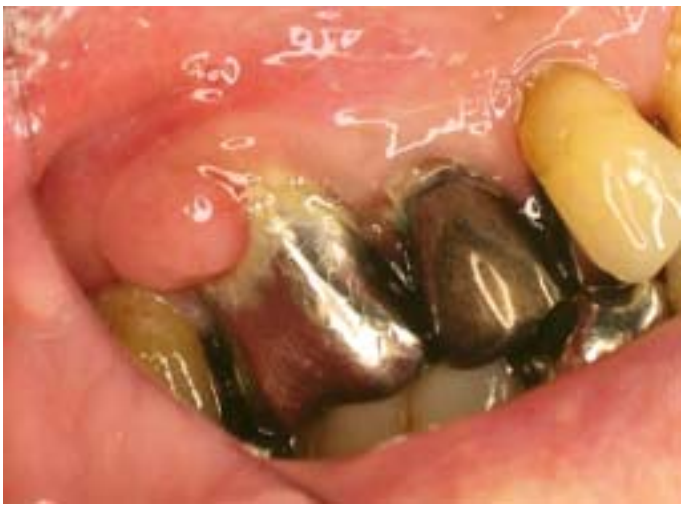


Fig. 3.1: Gingival abscess

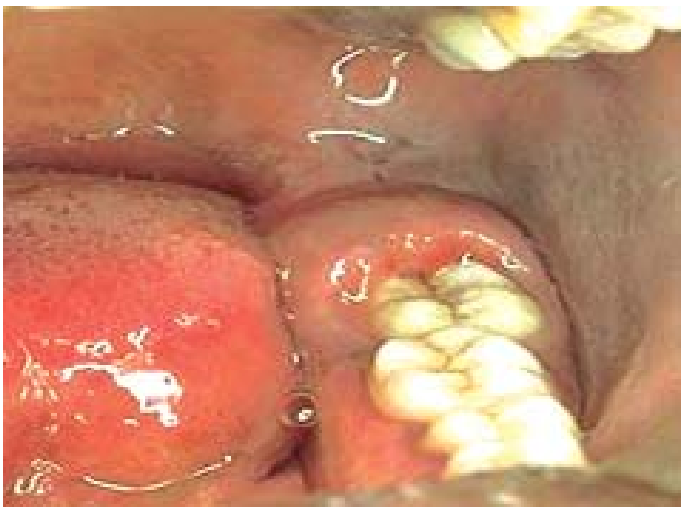


Fig. 3.2: Pericoronitis

difficulty in chewing, and difficulty in opening the mouth are the usual complaints. Mild illness with fever, malaise and regional lymphadenopathy is commonly seen.

Histologic Features

The epithelium of the pericoronal flap shows hyperplasia, intercellular edema, and leukocytic infiltrations. Connective tissue shows increased vascularity, dense diffused infiltration with lymphocytes and plasma cells along with varying number of polymorphonuclear leukocytes.

Management

Entrapped food debris must be removed. In case of upper tooth it should be grounded or extracted, if it is malposed. Radiograph helps in assessing the position of the involved tooth. If a tooth is impacted, the tooth must be removed. Surgical removal of the pericoronal flap is advocated after acute symptoms subside. Antibiotics are administered to relieve the symptoms and prevent further spread.

GINGIVAL ENLARGEMENT

Gingival tissues in the healthy adult completely fill the interproximal spaces between teeth, beginning near the contact area and extending apically and laterally. However there is frequently an increase in the size of the gingiva so that soft tissue overfills the interproximal spaces, balloons out over the teeth and protrudes into the oral cavity. The enlargement of the gingiva may be localized to one papilla or may involve several or all of the gingival papillae throughout the mouth. The enlargement is usually more prominent on the labial and buccal surfaces although it does occasionally develop in the lingual gingiva. It does not involve the vestibular mucosa.

The term 'gingival hyperplasia' was used for a long time for a gross increase in size of gingival tissues, which may result from a number of different conditions. Gingival enlargements are not to be confused with overgrowths of bone, or exostoses, which are noted occasionally on the alveolar bone usually at some distance from the gingiva.

Gingival enlargements can be classified based on etiologic factors and pathologic changes as follows:

- Inflammatory gingival enlargement
- Drug induced gingival enlargement
- Enlargement associated with systemic factors
  - Conditioned enlargement
  - Enlargements due to systemic diseases
- Idiopathic gingival enlargement
- Neoplastic enlargement
- False enlargement.

Inflammatory enlargement of the gingiva usually results from prolonged chronic inflammation of gingival tissue. In most cases, the enlargement results because of local irritations such as poor oral hygiene, accumulation of dental calculus or mouthbreathing and represents a variation in host tissue response to dental plaque accumulation.

Inflammatory Enlargement

In inflammatory enlargement, the gingivae are soft, edematous, hyperemic or erythematous and sensitive to touch. They can bleed easily and present a glossy; nonstippled surface. Usually gingival enlargements are secondary to other types of enlargements. In such cases, dual etiologic factors should be kept in mind during management. Clinical examination often reveals the nature of the local irritation that causes the enlargement, but the histologic picture is usually nonspecific, showing merely inflammation of the gingiva (Fig. 3.3).

The local irritation results in hyperemia, edema and lymphocytic infiltration. Many times the irritation results also in a proliferation of the fibrous elements of the gingival tissues. The proliferation of the occasion is increased by some predisposing systemic factors.

Drug-induced Gingival Enlargement

It is now well established that gingival enlargement sometimes occurs as a result of the use of the anticonvulsants, immunosuppressants, and calcium channel blockers.

Diphenylhydantoin (Dilantin sodium) was the first reported anticonvulsant to produce gingival enlargement. Other hydantoins known to induce gingival enlargement are ethotoin and mephenytoin. Other anticonvulsants such as valproic acid, methsuximide, and succinimides also produce gingival enlargement (Fig. 3.4).

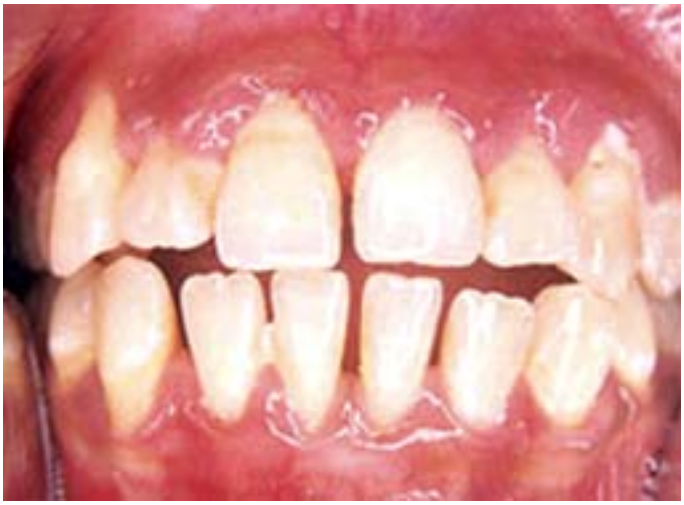


Fig. 3.3: Inflammatory gingival hyperplasia

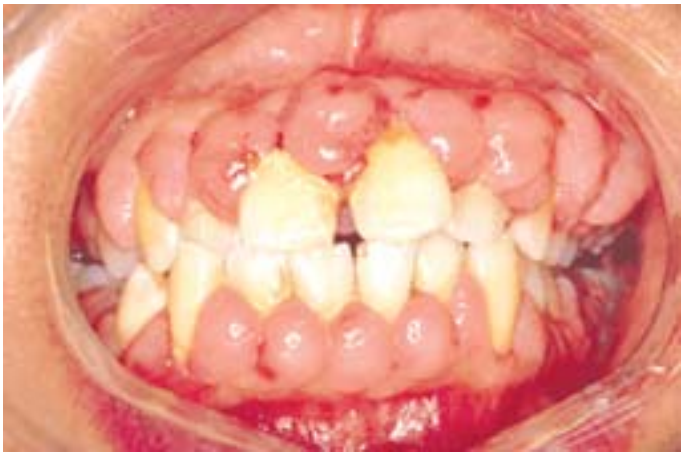


Fig. 3.4: Phenytoin associated gingival growth

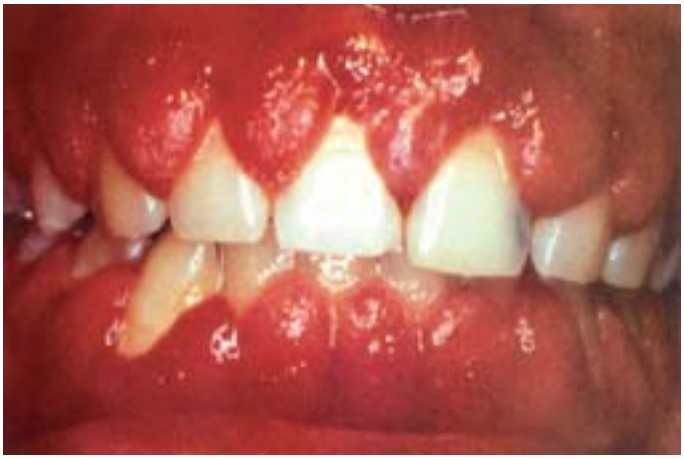


Fig. 3.5: Cyclosporine associated gingival growth

Dilantin sodium induces gingival enlargements in 3-84.5 percent of the patients receiving the drug. Phenytoin stimulates proliferation of fibroblast like cell in tissue culture and also decreases the collagen degradation.

It occurs most commonly in younger individuals, especially shortly after the institution of dilantin sodium therapy.

Cyclosporine, a potent inmunosuppressive agent, has also been reported to produce gingival enlargement in 30% of the patients receiving the drug (Fig. 3.5).

Calcium channel blockers such as nifedipine, nitrendipine and verapamil also induce gingival enlargement. Nifedipine, the commonly used drug in cardiovascular conditions, induces gingival enlargement in 20 percent of the cases.

Drug-induced gingival enlargement begins; painlessly, involving one or two interdental papillae, which present an increased stippling and ultimately a roughened or pebbled surface with lobulations. The gingival tissues are dense, resilient, and insensitive; they show little or no tendency to bleed.

The bulk of the enlargement is due primarily to proliferation of the fibrous connective tissue with numerous fibroblasts. There is a possibility of superimposed chronic inflammation. The enlargement generally presents no difficulties, although it is aesthetically objectionable. It may be as severe as to interfere with everyday functions, and for this reason it may be surgically excised. Unfortunately, its recurrence is common. It has been found that careful oral hygiene will result in slower development of the enlargement, and slower recurrence after surgical excision. Some regression of the enlargement may result if the use of the drug is discontinued. Cyclosporine-induced enlargements are more vascularized and have more amount of plasma cells and extracellular substance.

There is no strict line of demarcation between hyperplasia of connective tissue and benign neoplasia of fibroblasts; indeed, there are several conditions which resemble fibromas but which should not be so designated. Keloid is one such condition, and fibrous enlargement of the gingiva is another, since such growth has never been reported to be precancerous, does not show unlimited growth and may involve one or many gingivae, it seems that they should not be classed as benign neoplasms.

Enlargement Associated with Systemic Factors

Conditioned Enlargement

Conditioned enlargements are caused by the systemic condition of the patient, which exaggerates the usual gingival response to dental plaque. However, bacterial plaque is essential for the initiation of this type of enlargement. There are three types of conditioned enlargements: Hormonal, nutritional, and allergic.

Hormonal

Inflammatory gingival enlargement often occurs at puberty, both in men and women. Some investigators think that this enlargement may result from an endocrine imbalance at this particular stage of the patient's development. Others believe that it may occur, at this age, because oral care is poor. There is local irritation associated with eruption of teeth and/or nutrition may be inadequate. Thus the enlargement may be only indirectly associated with an endocrine disturbance.

One also notices a tendency for gingival enlargement of the inflammatory type during pregnancy. This proliferation may be due to disturbed nutrition, poor oral hygiene, or some systemic predisposition toward proliferation. Increased levels of estrogen and progesterone in pregnancy

causes change in the vascular permeability, which leads to gingivaI edema and altered inflammatory response to dental plaque. The so-called pregnancy gingivitis more properly spoken of as 'gingivitis in pregnancy', is often associated with isolated gingival proliferation, sometimes so severe that it is referred to as a 'pregnancy tumor.' which is basically a pyogenic granuloma. These proliferations resemble those seen in some nonpregnant women who have severe local irritations. Microscopic studies of these gingival lesions reveal increased vascularity multiplication of fibroblasts, edema and infiltration of leukocytes into the gingiva. Diagnosis of the etiologic factors can not be made by microscopic study.

Nutritional

Vitamin C deficiency: The spongy, bleeding gums of scurvy, vitamin C deficiency, have long been recognized as a specific entity. The enlargement of gingiva is generally included in the classic description of scurvy. This enlargement is essentially a conditioned response to bacterial plaque. The combined effect of vitamin C deficiency and inflammation produces this enlargement. Although clinical scurvy is now rare, there are a few occasional cases. Subclinical cases are probably common, since it has been reported that many patients do not include adequate vitamin C in their diets. In such cases, the gingivae become tender, swollen and edematous. They bleed upon the slightest provocation. Gingival sulci are often filled with partially clotted blood and the crests of the interdental papillae are red or purple. There is sometimes ulceration and necrosis of the papillae as infection becomes superimposed upon the susceptible tissues. Hemorrhages following slight trauma to other parts of the body are also noted. Treatment includes improvement of oral hygiene and administration of vitamin C.

Allergic

Plasma cell gingivitis (Atypical gingivitis, plasma cell gingivostomatitis): This distinct from of gingivitis first reported in the United States, usually arises as a hypersensitive reaction to a component of chewing gum, dentrifices, or some of the dietary components. It commonly presents as a mild marginal gingival enlargement, sometimes extending to involve the attached gingiva.

- *Clinical features:* This disease is more prevalent in young women. The initial symptom is soreness in the mouth, which is intensified by hot or spicy food. It starts as mild marginal gingival enlargement and extends to attached gingiva, and in severe cases, extends to buccal and vestibular mucosa. Gingiva appears swollen, erythematous, and friable with loss of stippling. The involvement of other oral tissues like the tongue and lips is common. They appear atrophic, dry, and exhibit cracks or fissures.
- *Histologic features:* The surface epithelium is hyperplastic, shows intracellular edema, and microabscesses. The underlying connective tissue is densely infiltrated with chronic inflammatory cells, predominantly a polyclonal mixture of plasma cells. There is marked vascular dilatation with severe thinning of epithelium over the connective tissue pegs.
- *Treatment and prognosis:* Possible allergens should be identified by careful study of the patient's history and eliminated. Topical and systemic steroids give good results.

Enlargement due to Systemic Diseases

Leukemia

Gingival enlargement is often an early finding in acute monocytic, lymphocytic or myelocytic leukemia. Leukemic enlargement may be diffused or marginal, localized or generalized. Gingiva appears shiny, bluish red, soft, edematous easily compressible, and tender and frequently ulcerated. They show no signs of stippling. The gingivae are usually inflamed, owing to local infection, and occasionally a necrotizing ulcerative gingivitis develops.

Histologic study of this type of gingival enlargement shows that the gingival tissues are packed with immature leukocytes, the specific type depending on the nature of the leukemia. These abnormal white blood cells are unable to perform their defensive function and cannot control the infection at the gingival margin. Capillaries are engorged, and the connective tissue is edematous and unorganized.

Granulomatous Diseases

Some local and systemic glaucomatous diseases may involve the gingiva and present as gingival enlargement. Common diseases in which gingival are involved are Crohn's disease, sarcoidosis. Wegener's granulomatosis and foreign body gingivitis. The latter is caused by the introduction of foreign materials into the sulcular epithelium.

Regional Enteritis (Crohn's Disease)

Regional enteritis is a slowly progressive disease of unknown etiology. Some of the features suggest an unusual reaction to an extrinsic agent, possibly of infective origin. Atypical mycobacteria have been implicated in some cases. It occurs in persons of all ages, involves both genders equally and is characterized by granulomatous, superficial ulcerations of the intestinal tract with frequent fistulae

developing onto body surfaces or viscera, or between intestinal loops. This disease has been reported as having oral manifestations or oral extensions. The most commonly involved areas are the buccal mucosa, where the lesions present a cobblestone appearance; the vestibule, where linear and hyperplastic folds, which may mimic denture-induced hyperplasia of the lips, which appear diffusely swollen and indurated: The gingiva and alveolar mucosa, which exhibit a granular erythematous swelling and the palate, where multiple ulcers occur. Glossitis may be seen secondary to malabsorption of vitamin B_{12}. The oral lesions may either precede or follow the appearance of the intestinal lesions, and like those lesions, commonly show periods of quiescence alternating with exacerbations of the process. The microscopic findings of the oral lesions are those of a chronic granulomatous disease, reminiscent of sarcoid. Microscopically, it consists of fibrosis and a focal dense collection of lymphocytes and plasma cells. Lymph vessels appear dilated. The presence of noncaseating granuloma which is typically small, consisting of macrophages, epitheloid cells and occasional giant cells is seen.

Management: Oral lesions resolve when intestinal Crohn's disease is controlled. The use of oral sulphasalazine or intralesional injection of corticosteroid gives good results.

Idiopathic Gingival Enlargement

There have been a few cases where the patient's gingival tissues are so diffusely enlarged that the teeth are completely covered. If the enlargement is present before tooth eruption, the dense fibrous tissue may even interfere with or prevent eruption. Other names for this condition are 'fibromatosis', 'fibromatosis gingivae' 'elephantiasis gingivae', and 'congenital macrogingiva'. The cause of this developmental enlargement of gingival tissue is not known. It is probably hereditary; being transmitted as an autosomal dominant trait in some instances, since reports have been made of several cases occurring in the same family (Fig. 3.6).

A typical case of idiopathic gingival enlargement presents large masses of firm, dense, resilient, insensitive growth that covers the alveolar ridges and extends over the teeth. It is normal in color, and the patient complains only of the deformity. Often the gingivae are so enlarged that the lips protrude, and the fibrous mat of tissue upon which the patient chews, may be 25 mm wide and as much as 15 mm thick.

This enlargement may be detected at an early age and in a few cases even at birth. Teeth do not erupt normally because of the dense fibrous tissue. Histologic sections of tissue from idiopathic fibrous gingival enlargement show

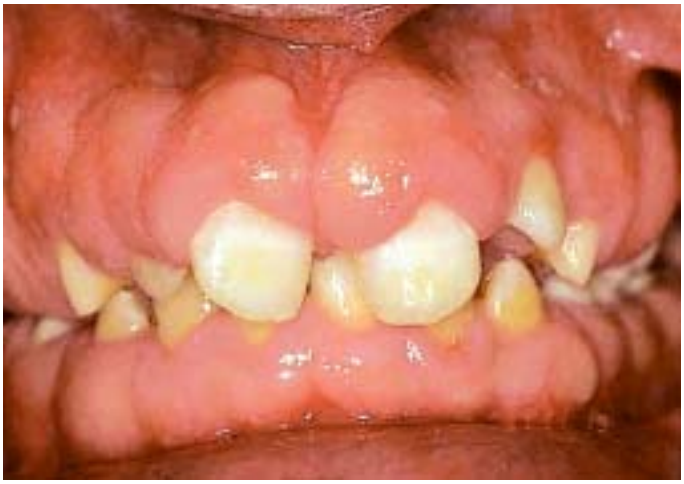


Fig. 3.6: Idiopathic gingival enlargement

hyperplastic epithelium with elongation of rete ridges and mild hyperkeratosis. The underlying stroma is made up almost entirely of dense bundles of mature fibrous tissue with few young fibroblasts present. Occasionally, some chronic inflammation caused by local irritation may also be present.

Surgical removal of the excess fibrous tissue it is the only feasibly treatment. The condition may recur afterwards.

Neoplastic enlargements are due to benign and malignant neoplasms involving the gingiva.

False enlargements occur due to underlying dental or osseous anomalies and are not an abnormality of the gingival as such.

PERIODONTITIS

Periodontitis is defined as "an inflammatory' disease of the supporting tissues of the tooth caused by specific microorganisms or group of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both". It is classified as chronic, aggressive, and as a manifestation of systemic diseases. The so-called acute periodontitis that results from acute trauma is now termed as acute trauma from occlusion.

Chronic Periodontitis (Periodontoclasia, Pyorrhea, Pyorrhea Alveolaris, Schmutz Pyorrhea)

This is the most common form of periodontal disease and is associated with local irritation. This begins as a marginal gingivitis, which usually progresses, if untreated or treated improperly, to chronic periodontitis. This type of periodontitis, sometimes referred to as marginal periodontitis, is most common in the adult, although it is

found occasionally in children, especially when oral hygiene is lacking, or in certain cases of malocclusion. The amount of tissue destruction is consistent with local factors. In the adult, periodontal disease of this type accounts for more than 90 percent of the cases of periodontal disturbances and is responsible for greater tooth mortality than dental caries. In general, the treatment of this form of periodontal disease, as of all others, is dependent upon the removal of etiologic factors, both local and systemic, the maintenance of good oral hygiene and the establishment of a stable, harmonious articulation free from traumatic interferences (Fig. 3.7).

Etiology

Gingivitis may precede and develop into the more severe periodontitis, which involves not only the gingiva but also alveolar bone, cementum and periodontal ligament. Etiologic factors in general are the same as for gingivitis, but are usually more severe or of longer duration. Local factors, microbial plaque, calculus, food impactions and irritating margins of fillings appear to be most important in the development of this common form of periodontal disease. No abnormalities of the immune system seem to appear. Chronic periodontitis is predominantly associated with actinobacillus actinomycetemcomitans, bacteroides forsythus, porphyromonas gingivalis and Prevotella intermedia. The microflora in advanced periodontitis is characterized by the presence of large numbers of asaccharolytic microorganisms, including *Fusobacterium nucleatum, Bacteroides melaninogenicus, Eikenella Corrodens, Bacteroides Corrodens* and *Bacteroides Capillosus*.

Incidence

The incidence of periodontal disease is difficult to determine. This wide variation in the reported prevalence of periodontal disease is doubtless due to lack of uniformity in methods of assessment used, and of course, to inherent differences in the populations examined.

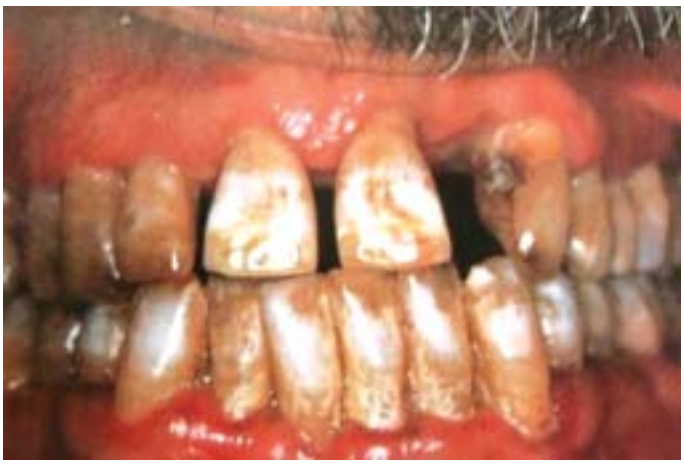


Fig. 3.7: Chronic periodontitis

Clinical Features

Periodontitis usually begins as a simple marginal gingivitis as a reaction to plaque or calculus. An early, and perhaps the first, pathologic finding is a tiny ulceration of the crevicular epithelium. Unless the irritants are removed more plaque and calculus are deposited with the passage of time and the marginal gingivitis becomes more severe. The gingiva becomes more inflamed and swollen and with irritation, the crevicular epithelium suffers ulceration more frequently. It proliferates as a result of the inflammation so that at this stage there is a tendency for the epithelial attachment to extend or 'migrate' apically on the tooth. As it does so it gets easily detached at its coronal portion. Through this process and because of the increased swelling of the marginal gingiva the gingival crevice gradually becomes deeper and is classified as an early periodontal pocket. The presence of periodontal pockets measuring more than 3-4 mm indicates the destruction of periodontal ligament and alveolar bone resorption.

Clinically, the presence of calculus may be detected at this stage. Subgingival calculus may be more readily visualized if the free marginal gingivae are blown back from the tooth by compressed air. Besides the mild visible swelling and hyperemia of the gingivae, there is also a tendency for them to bleed readily: Minute 'spontaneous' hemorrhages will often appear if the gingivae are simply rubbed by the examiner in the region of the interdental papillae. An unpleasant, almost foul type of halitosis is also present.

As periodontitis becomes more severe, the teeth become mobile and give off a rather dull sound and hurt when tapped with a metal instrument. Suppurative material and other debris occasionally may be expressed from the pathologic pocket adjacent to a tooth by slight pressure on the gingiva. Compressed air and instrument exploration will reveal that the tissue detachment may be severe. The embrasures may be open because the interdental papillae are deficient.

The normal festooning is not apparent and the gingivae appear 'boggy' because of hyperemia and edema; no stippling is detected and toe gingival tissues are smoothing shiny and perhaps redder or bluer than normal. The patient may have no subjective symptoms or may complain of a bad taste, bleeding gums and hypersensitivity of the necks of the teeth due to exposure of cementum as the soft tissues recede. In other words, the patient has a severe chronic gingivitis and an involvement of the deeper portions of the periodontium.

Gingival recession is a common phenomenon particularly in later years in life. In such cases the gingival tissues recede toward the apex, exposing the cementum, sometimes to an alarming degree. Since the cementum is softer than enamel, it is often worn away by a toothbrush and an abrasive dentifrice. Gingival recession can occur more rapidly if there has been rapid alveolar bone loss, due to any cause, since gingival tissue in health will maintain uniform relations with alveolar bone crest. Gingival recession often begins as a thin break in the free gingiva adjacent to the center of a tooth. This is called a Stillman's cleft. Abnormal frequency and direction of toothbrushing, occlusal forces or a high muscle attachment will sometimes lead to gingival recession. Gingival recession is preceded by alveolar bone loss, but bone loss is not necessarily accompanied by an equal amount of recession.

Histologic Features

In marginal gingivitis, which is just beginning to undergo transition into early periodontitis, the enlarged free marginal gingiva is densely infiltrated with lymphocytes and plasma cells. The apical border of the inflamed area approaches the crest of the alveolar bone and the crestal fibers of the periodontal ligament. The crevicular epithelium shows various degrees of proliferation and often, tiny ulcerations. One of the early microscopic signs of the encroachment of the inflammatory process on the periodontium is the appearance of the giant cells (osteoclasts) on the surface of the bone crest. They soon appear to be in the little bays of bone resorption known, as howship's lacunae. The underlying tissues of the periodontium show no changes at this stage. The pathologic process involves the alveolar bone prior to involvement of the periodontal ligament.

The next stage of the progress of the disease is a continuation of the factors just described:

- More plaque is deposited in an apical direction on the tooth
- More irritation of the free gingiva occurs
- The epithelial attachment proliferates apically down onto the cementum of the tooth and shows more ulceration
- The alveolar crest of bone is resorbed further apically
- Principal periodontal ligament fibers become disorganized and detached from the tooth. A periodontal pocket exists between the free gingiva and the tooth to depths from 2 mm down, until finally the apex of the tooth is approached.

The deep pocket that then exists between the calculus and plaque-covered tooth surface and the epithelial lining older gingival tissues forms a protective trap for multiplying microorganisms and for leukocytic cellular exudates from the inflamed soft tissue of the pocket wall. The vicious cycle of irritant collection, inflammation and detachment continues, along with periodontal bone resorption in an apical direction.

Immunologic Features

There is considerable evidence indicating that plaque-induced effector mechanisms play a major role in the pathogenesis of inflammatory periodontal disease. Both the cellular and humoral immunologic pathways have been implicated in the destruction of periodontal tissues. Immunoglobulins have minimal influence on the microbial composition of dental plaque. Therefore, if dental plaque is present and the reaction to it is absent or minimal there would be lesser chances of periodontal disease. On the other hand, if the immunologic effector mechanisms are responsible for the signs or symptoms of periodontal disease, there would be inflammation and tissue destruction only in patients able to mount an immunologic response to the presence of dental plaque. It is reported that the earlier mild gingivitis lesion contained predominantly thymus (T)-derived lymphocytes, whereas the more advanced lesions contained large numbers B-lymphocytes and plasma cells. Thus patients with humoral immunodeficiency would be expected to have some gingival inflammation, since many such patients manifest normal T-cell mediated responses.

It seems obvious then that the immune response, while often protective, can also be a highly destructive reaction to injury.

Classification of Periodontal Pockets

In a normal healthy periodontium, the gingiva tissues fit snugly around the teeth, and the gingiva crevice approximates zero. In the presence of inflammation, however, the gingival tissues increase in bulk, causing an increase in the depth of the pocket around the teeth. If the pathologic changes are limited to the gingiva, this is called a gingival or pseudopocket. If, however, the base of the pocket has invaded further into the periodontium, it is called a periodontal pocket. The base of the periodontal pocket is on the root of the tooth, and the epithelial attachment is on cementum. Although, periodontal disease usually progresses apically and advances at the expense of the horizontal loss of the crest of the alveolar bone, sometimes the depth of the pocket extends apically to the crest of the alveolar bone. Such a pocket, which has bone on its lateral wall, is called an infrabony pocket. The infrabony pocket may result from food impaction and is frequently found along the tooth that has shifted

considerably out of its usual position or has been subjected to severe occlusal trauma. Infra-bony pockets are classified according to their shape (narrow and broad) and the number of bony walls. Three wall infrabony pockets are commonly observed in the interdental area; where one finds an intact proximal wall as well in buccal and lingual walls of the alveolar process. Two wall infrabony pockets may be seen in the interdental areas, with the buccal and lingual walls intact, but the proximal wall destroyed. A curtain of soft tissue retrains where the osseous wall has been destroyed. Infrabony pockets with one osseous wall are occasionally seen in the interdental area.

The type of periodontal pocket present can be determined by careful clinical examination and study of good roentgenograms. Consideration of the topography and type of infrabony pocket is important in planning the treatment of periodontal disease. The most favorable type of pocket for reattachment to occur is, of course, the one with three osseous walls. A 'slating fill-in' of bone can occur in a pocket with two bony walls; but when only one wall is present, chances for the formation of additional height of alveolar bone are poor.

Roentgenographic Features

The earliest change in the periodontal bone is a blunting of the alveolar crest due to the beginning of bone resorption. A straight line can be drawn along the edge of alveolar bone at almost any stage of the disease and the bone loss is said to be horizontal. There is a tendency for cupping out of the interdental alveolar bone (Fig. 3.8). The periodontal ligament space retains its usual thickness, and generally no changes are noted except the superficial bone changes that actually may become extensive. It is of interest that roentgenographic evidence of alveolar bone changes has been reported.

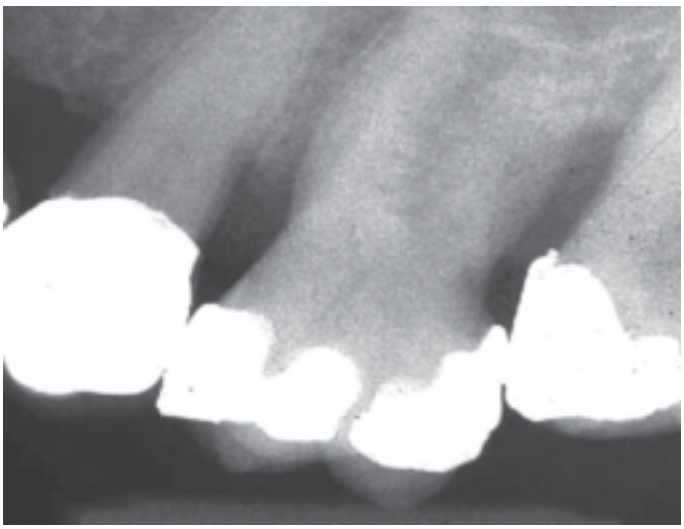


Fig. 3.8: Interdental bone loss in chronic periodontium

Treatment and Prognosis

By careful complete periodontal treatment the teeth involved by periodontal disease can be saved if the bone loss has not been too extreme, if irritants are removed by scaling and curettage and if pockets are eliminated by gingival recession or by surgical removal of the gingival, if osseous deformities are eliminated and the tooth-supporting tissues recontoured to a normal physiologic architecture, if occlusal forces are balanced and systemic factors are corrected.

Clinicians for many years have demonstrated that after the successful treatment of periodontitis, pathologic pockets are shallower, even though no tissue was removed. Obviously this loss of pocket depth can be caused either by gingival recession or by reattachment of periodontal ligament to the tooth surface next to the pocket. Actually, both recession and reattachment may occur in the same case. There is usually a shrinkage or recession of the gingival tissues as inflammation and its associated edema and hyperemia is diminished, for as the gingival tissues return to a state of health the normal relation of gingiva to alveolar bone is gradually re-established just above the bone level. The distance from the crest of the gingiva to the base of the pocket is diminished by the reduction in the size of the gingiva.

The second possible explanation for the shallower pocket after therapy is reattachment. Reattachment may be defined as a re-establishment of fibrous connection of the tooth to the alveolar bone and gingiva by periodontal fibers in an area of cementum which is adjacent to a pathologic pocket. A typical epithelial attachment is described as reforming. The cellular element that would make reattachment possible are all present in the periodontium resorption of the bone and rebuilding of new bone with reattachment of new periodontal ligament fibers go on constantly.

Considering this problem from a purely theoretic point of view, if reattachment is to occur, it is necessary that connective tissues remain in contact with the tooth for an appreciable, but as yet undetermined, period of time. Since the cementum lining the pocket is necrotic, cementoclasts must resorb the cementum to a level at which it is viable. Next, cementoblasts must develop to deposit a new layer of cementum which traps ends of connective tissue fibers. Finally, new alveolar bone must be built opposite the newly attached periodontal fibers in response to the stimulus of the periodontal ligament.

Crevicular epithelium: For reattachment to occur, this epithelium must be destroyed or curetted away. Since cementum can be deposited only by connective tissue, the presence of epithelium interferes with the reattachment. The fresh bleeding connective tissue surface will form a

blood clot in contact with the tooth, which can organize and contribute to reattachment. In certain cases, particularly those with infrabony pockets, the blood clot is easily protected and healing occurs more easily.

Mobility: During the period of reorganization the tooth must be at least relatively immobile, since motion tends to disturb the healing process arid allow any remaining crevicular epithelium to proliferate and reline the pathologic pocket.

Inflammation: Itself apparently interferes with reattachment, perhaps because cementoblasts cannot develop in areas of inflammation.

Necrotic cementum: It is also a barrier to reattachment, since new cementum apparently will not be deposited upon cementum that has been in contact with oral fluids and suppuration for an appreciable time.

Aggressive Periodontitis

This is a rapidly progressing type of periodontitis that occurs in patients who do not have large accumulations of plaque and calculus. This may be either localized or generalized replacing the terms localized and generalized juvenile periodontitis and rapidly progressive periodontitis. It has a familial tendency suggesting a genetic predisposition.

This disease appears to be the result of a defect in the immune response rather than plaque and calculus deposition. Several investigators have shown that patients with aggressive periodontitis display functional defects of polymorphonuclear leukocyte, monocytes or both, but without any systemic manifestations. Because of this, their defensive ability against some of the periodontal pathogens is defective.

Clinical Features

Localized form: This usually occurs around puberty and has a strong familial tendency: It is localized to the first molars and incisors; there is attachment loss in at least two permanent teeth, one of which is the first molar. A striking feature is the absence of clinical inflammation with minimal local factors despite the presence of a deep periodontal pocket. The rate of alveolar bone loss is considerably higher than in chronic periodontitis (Fig. 3.9).

Generalized form: This form usually affects patients under 30 years of age. It involves at least three teeth other than the first molar and incisor and exhibits poor serum antibody response to infecting agents. Many cases represent the localized form which becomes generalized with time. The organism associated with the generalized form is more complex and closely resembles chronic periodontitis.

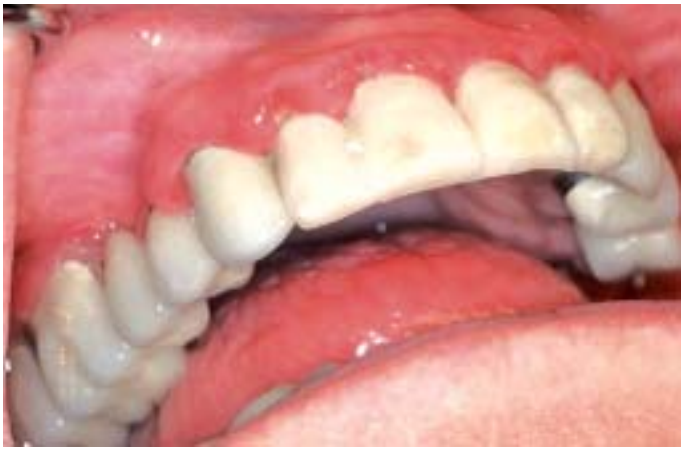


Fig. 3.9: Localized form

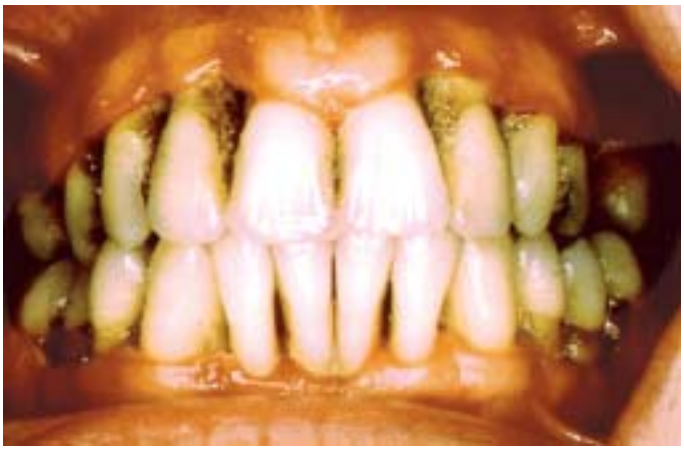


Fig. 3.10: Generalized form

A definitive diagnosis can be made based on finally history, clinical, radiological microbiological and histological examination with leukocyte function tests (Fig. 3.10).

Roentgenographic Features

In the localized form, vertical loss of alveolar bone is seen around the first molar and incisor at around the age of puberty in otherwise healthy patients. An arc shaped alveolar bone loss extends from the distal surface of the second premolar to the mesial surface of the second molar, and there is widening of the periodontal ligament space (Fig. 3.11).

This vertical' pocket formation, with the bone loss often more extensive on one tooth than on an adjacent tooth, differs from the 'horizontal' type of bone loss in periodontitis. In periodontitis, many teeth are involved in about the same degree, so that the bone loss appears to be 'horizontal. In the generalized form, bone loss may range from the involvement of one or more teeth to a maximum number of teeth.

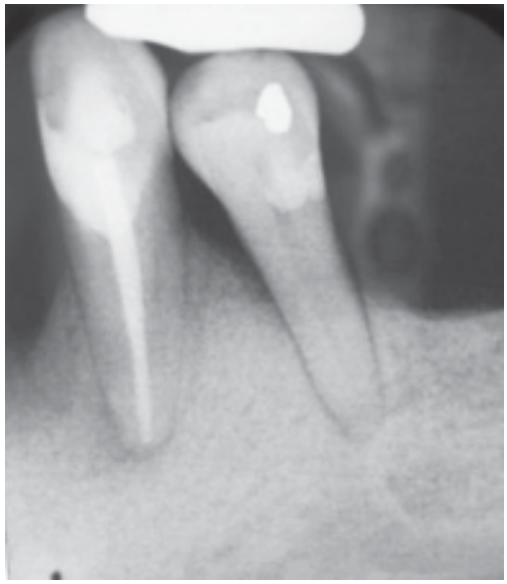


Fig. 3.11: Localized form

Histologic Features

These closely resembles the features of chronic periodontitis.

Management

Antibiotics should be administered in combination with mechanical removal of plaque and inflamed periodontal tissues. Periodontal surgery should be performed with prophylactic antibiotic cover and postoperative usage of chlorhexidine mouth rinse. Periodic follow-up is necessary since there is possibility of reinfection.

Necrotizing Ulcerative Periodontitis

Necrotizing ulcerative periodontitis occurs in younger patients than those with chronic periodontitis. This, along with necrotizing ulcerative gingivitis, is grouped as necrotizing periodontal diseases. These diseases may be accompanied by fever, malaise, and lymphadenopathy. Necrotizing ulcerative periodontitis shows attachment and bone loss and may be associated with immunosuppression or malnutrition. Etiologic and clinical characteristics suggest that necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis represent the same disease with a different degree of clinical manifestations (Fig. 3.12).

Necrotizing ulcerative periodontitis may be observed in HIV-positive patients. The CD4+ cell count is below 200 cell/mm in more than 90% of the HIV-infected patients with necrotizing ulcerative periodontitis. In HIV positive patients, it causes ulceration and necrosis of gingiva with pain and spontaneous bleeding. The exposed underlying bone then undergoes rapid destruction.

Management and Prognosis

If the underlying immunosuppression and malnutrition is corrected it usually responds to oral hygiene and antibiotics.

Lateral Periodontal Abscess (Lateral Abscess)

The lateral periodontal abscess is related directly to a preexisting periodontal pocket. Precipitating factors included subgingival flora, host resistance or both. When such a pocket reaches sufficient depth around 5-8 mm the soft tissues around the neck of the tooth approximate the tooth so tightly that the orifice of the pocket is occluded. Bacteria multiply in the depth of the pocket and cause enough irritation to form an acute abscess with exudation of pus into this area. A foreign body, particularly food debris, may also lead to abscess formation. This may result in enough swelling to destroy the cortical plate of bone. If it still exists, and allow the abscess to balloon the overlying tissues, forming a 'gum boil' or parulis (Fig. 3.13).

Clinical Features

It usually occurs in adults and is rare in children. The most common cause of periodontal abscess is foreign bodies. The acute periodontal abscess will cause the, afflicted tooth to be tender to percussion. Pain, foul taste, mobility of the involved tooth, tenderness over the corresponding gingiva, and lymphadenopathy are the other symptoms.

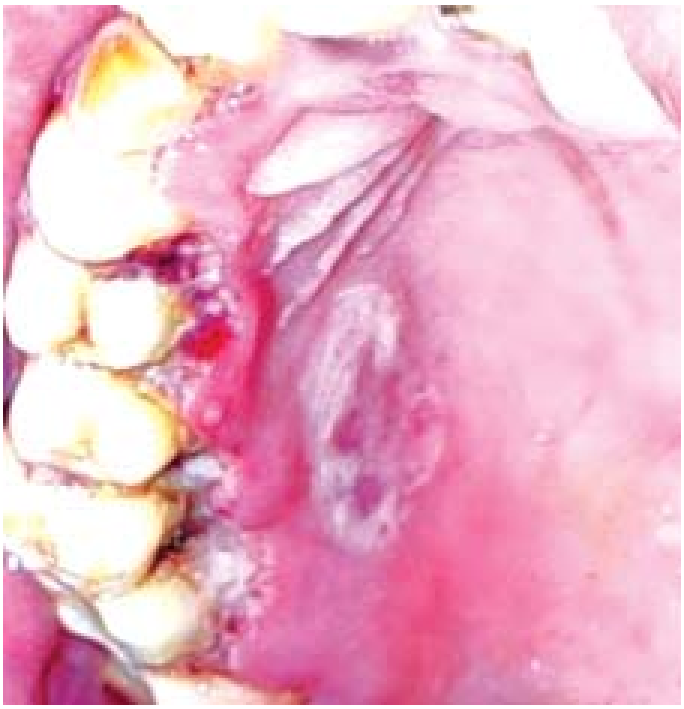


Fig. 3.12: Acute necrotizing ulcerative periodontitis

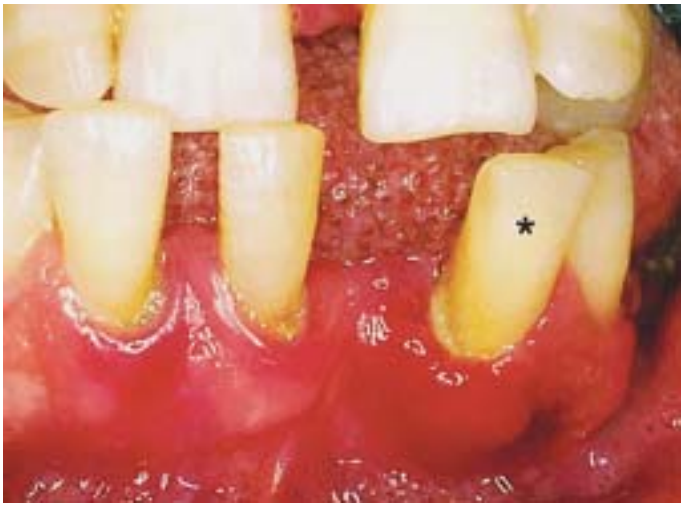


Fig. 3.13: Lateral periodontal abscess

The occurrence of periodontal abscesses of both lateral and periapical types was reported with cortisone for rheumatic fever. The abscesses appeared within two weeks after therapy had been discontinued. The cortisone apparently actuated pre-existing periodontal lesions, but the abscesses were unusual in that pain was very mild or even absent and there was no local swelling or cellulitis. Lymph node involvement was also rare. In some cases, the only clinical manifestation of the abscess was the release of pus from the neck of a loose deciduous tooth upon pressure. It was noted that the erythrocyte sedimentation rate, which is seldom elevated in normal children with a periodontal abscess was usually elevated in cortisone-treated children with rheumatic fever with a periodontal abscess.

Histologic Features

Microscopically, the abscess resembles an abscess elsewhere. It consists of a central cavity filled with pus walled off on one side by the root of the tooth and on the other by connective tissue, because it is likely that in most instances that the epithelial lining of the crevice would have been destroyed by the inflammatory process.

Treatment

Treatment of a periodontal abscess is similar to that of an abscess elsewhere. A direct incision, perpendicular to the long axis of the involved tooth, releases pus. If the abscess does not drain spontaneously through the gingival crevice, and if it is not treated, a fistula may develop to release the pus spontaneously onto the mucosal surface. Careful insertion of a dull probe into the pocket along the tooth will usually induce drainage, and the acute symptoms will subside. The abscess will recur, however, unless the cause is removed and the depth of the pocket is reduced. Cases in which normal tissue contours cannot be developed and maintained, extraction of the tooth is advised after the acute symptoms have subsided.

Papillon-Lefèvre Syndrome

This syndrome was first described by Papillon and Lefèvre in 1924. The disease is thought to be familial, probably transmitted as an autosomal recessive characteristic and is characterized by dermal and oral manifestations. The prevalence of this syndrome is one to four per million in the general population.

The characteristic skin lesions associated with the oral changes consist of keratotic lesions of the palmar and plantar surfaces (hyperkeratosis palmoplantaris). In addition, some patients manifest generalized hyperhidrosis, very fine body hair, and a peculiar dirty-colored skin. These latter features are reminiscent of hereditary ectodermal dysplasia, and in some reported cases all aspects of this disease are present. Calcification of the falx cerebri or dura is also frequently reported.

The Papillon-Lefèvre syndrome is characterized by aggressive periodontitis previously called juvenile periodontitis or periodontosis. Aggressive periodontitis directly related to A actinomycetemcomitans and dysfunction of leukocytes and is characterized by severe destruction of the alveolar bone involving both the deciduous and permanent dentitions. Some reported cases have shown bone loss as early as two years of age with premature exfoliation of teeth. Due to rapid bone loss, mobility and pathological migration occurs, which results in loss of the entire dentition at a much younger age. Inflammatory gingival enlargement, gingival ulceration and formation of deep pockets are usually present, although in other instances there are no inflammatory elements and only the permanent dentition may be affected.

Histopathologic Features

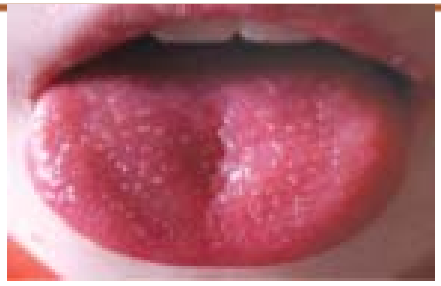
These are not specific but similar to those of chronic periodontitis.

Treatment and Prognosis

Skin lesions are treated by retinoids. Treatment of periodontitis involves removal of all helpless mobile teeth, plaque control, and antibiotics.

4

Bacterial Infections



Certain bacterias, viruses and fungi produce diseases which are manifested in or around the oral cavity. Some of these diseases or lesions are of a specific nature and are produced by a specific microorganism. The microbial specificity or nonspecificity is characteristic of infectious diseases wherever they may occur in the body and is necessarily confined to those of the oral cavity (Fig. 4.1).

SCARLET FEVER

Scarlet fever is a highly contagious systemic infection occurring predominantly in children, caused by beta hemolytic streptococci, streptococci pyogens which produced a exotoxin.

Clinical Presentation and Pathogenesis

Children and young adults with scarlet fever develop a sudden onset of fever and sore throat. There may also be headaches, malaise, irritability and nausea. The pharynx will appear red and swollen, and the cervical lymph nodes will be tender and swollen. At the time of presentation or shortly thereafter, a red macular skin rash will develop, starting on the chest and spreading outward. The rash will be most intense in the axilla and groin areas. The rash blanches on pressure, and some petechiae may form. The rash lasts 4 to 5 days. The face is characteristically red with a circumoral pallor. The tongue develops a white coat within which reddened and swollen fungiform papillae stand out (Strawberry tongue) (Fig. 4.2).

As the disease progresses, the skin erythema fades and the white coating on the tongue is lost, leaving a swollen, irregular, beefy tongue (Raspberry tongue) (Fig. 4.3).

Transmission is via air-water droplet dissemination or infected secretions. The scarlet skin rash is caused by an erythrogenic exotoxin that damages capillary endothelium, which is the cause of the poststreptococcal complications of rheumatic fever and glomerulonephritis.

Stomatitis Scarlatina

It is characterized by congested petechiae scattered on mucosa especially soft palate and throat (Fig. 4.4). It shows a fiery red color. Tonsil and faucial pillars are swollen and covered with grayish exudate. The rash of scarlet fever is due to the elaboration of an erythrogenic toxin by the streptococci, which causes injury to endothelium and dilation of small blood vessels with hyperemia. During recovery, the formation of antibodies neutralizes the toxin.

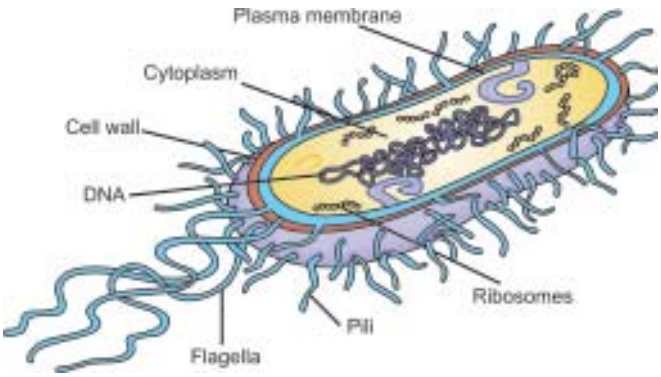


Fig. 4.1: Bacterial cell

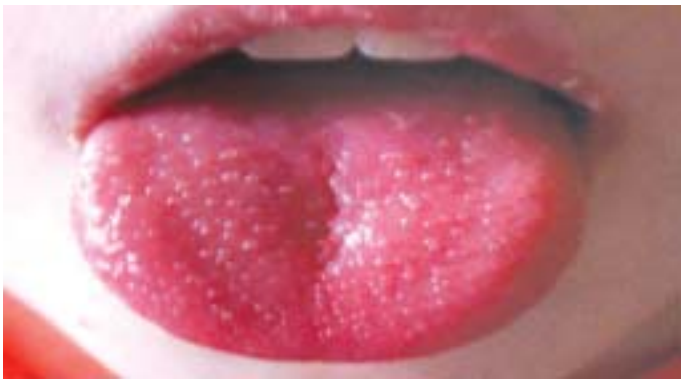


Fig. 4.2: Strawberry tongue

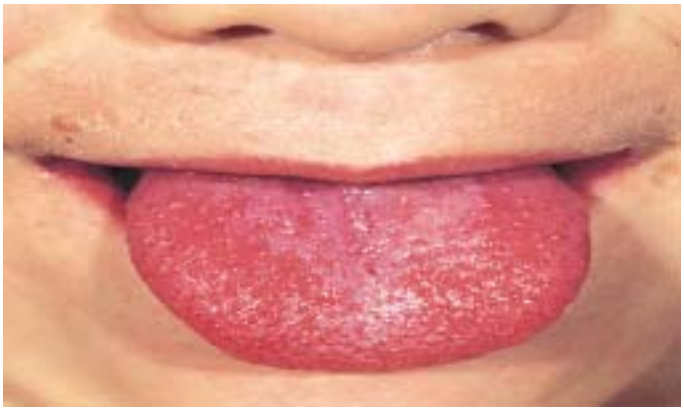


Fig. 4.3: Raspberry tongue

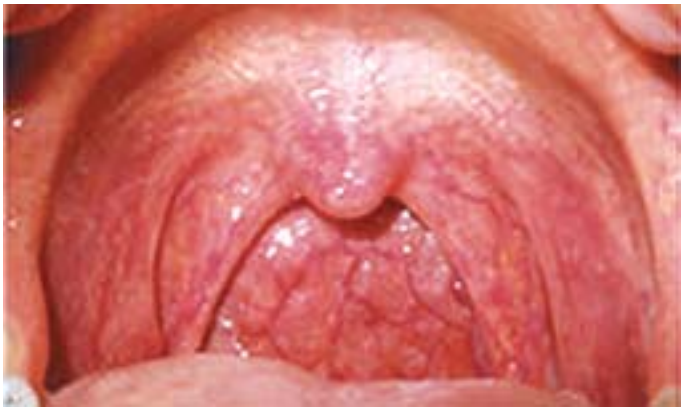


Fig. 4.4: Stomatitis scarlatina

Differential Diagnosis

The initial presentation of a febrile pharyngitis with cervical lymphadenitis is suggestive of infectious mononucleosis and of nonstreptococcal pharyngitis, usually attributable to adenoviruses. Diphtheria will have a similar clinical presentation, as will pseudomembranous candidiasis of the pharynx.

Diagnostic Work-up

The bacterial nature of scarlet fever and streptococcal pharyngitis can be confirmed by a white blood cell count. Streptococcal sore throat will show a leukocytosis with a left shift toward immature forms. Viral pharyngitis, including mononucleosis, will show a leukopenia with an absolute or a relative lymphocytosis. In some cases, atypical lymphocytes are present.

The diagnosis should be confirmed with a throat culture. Throat culture in a single blood agar plate has a sensitivity of 70 to 80 percent. Throat cultures in a two-plate system, one blood agar and the other trimethoprim-sulfamethoxazole (Bactrim, Roche) blood agar to eliminate nonstreptococcal competitors, are almost 100 percent sensitive. Antistreptolysin O antibody titers are elevated in 80% of cases but are more useful for follow-up than for diagnosis. Susceptibility is correlated with results of Dick test.

Treatment

Antibiotics have a minimal effect on symptoms; their role is to shorten the disease course and eradicate the organism to prevent complications. Oral potassium penicillin V, 500 mg four times daily for 10 days, is effective. However, compliance is often a problem because symptoms dissipate in 4 to 5 days and a full 10 days course is needed to prevent complications. Therefore, penicillin G benzathine (Bicillin LA, Wyeth-Ayerst), 1.2 million U intramuscularly as a single dose, is an effective alternative. For penicillin allergic patients, oral erythromycin, 500 mg four times daily or 40 mg/kg per day for 10 days, is recommended. Mupirocin topical ointment can also be used to relative discomfort.

Prognosis

The prognosis is excellent, and complications can be avoided if antibiotics are begun early and the full course is taken. If not, there is a high incidence of otitis media, sinusitis, mastoiditis, and peritonsillar abscesses.

DIPHTHERIA

Diphtheria is an acute, life-threatening, infectious and communicable disease of skin and mucous membrane. It is caused by *Corynebacterium diphtheria* (Fig. 4.5).

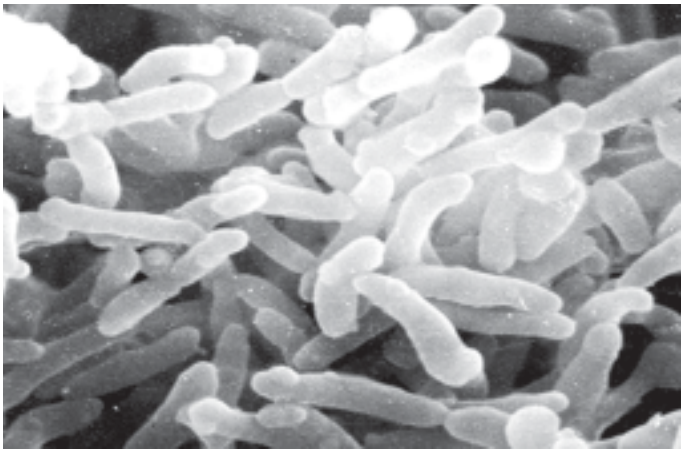


Fig. 4.5: Corynebacterium diphtheriae

Clinical Presentation and Pathogenesis

Diphtheria initially presents with the classic diphtheritic pseudomembrane in the oropharynx which bleeds on removal. At that time, constitutional symptoms of fever, pain, and malaise may not be present or may be just emerging. Within a few days, the patient's condition worsens, with fever, cervical lymphadenopathy, and extensive weakness. Upper airway or bronchial obstruction may occur (Figs 4.6 and 4.7).

It manifests as hoarseness of voice, respiratory stridor and dyspnea causing death in young children. Severely affected patients will give a bull-neck appearance.

Corynebacterium diphtheriae is transmitted by air-water droplets from infected patients or healthy carriers. The incubation period after contact is 2 to 7 days. The organism's virulence is attributable to its exotoxin, the action of which produces the oropharyngeal pseudomembrane as well as the myocarditis and cranial nerve neuropathy complication.

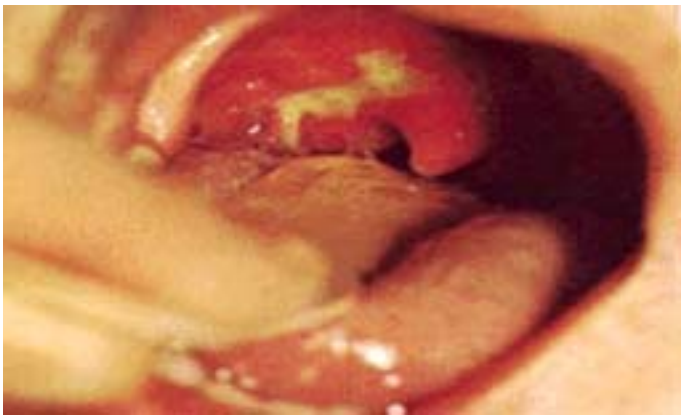


Fig. 4.6: Diphtheritic membrane

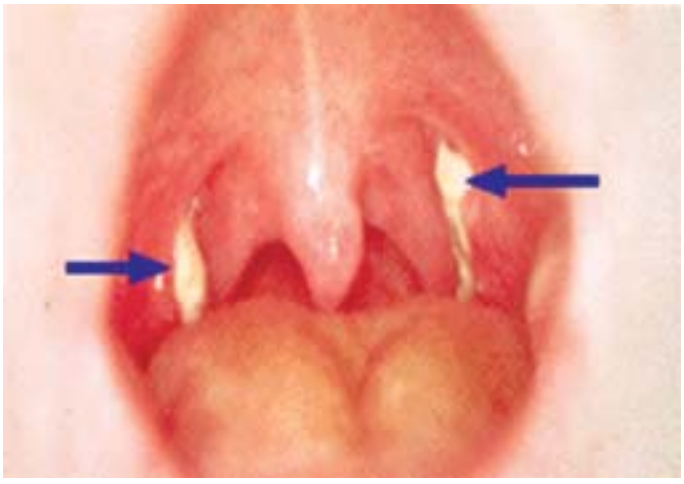


Fig. 4.7: Diphtheria—notice the pseudomembrane in the posterior pharynx. It can become very large and may obstruct the airway

Active immunization is part of childhood immunization programs (diphtheria-pertussis-tetanus [DPT]). Immunity is not directed against the organism but against the toxin, by stimulation of the IgG and IgA classes of antibodies. Neutralizing the toxin with antibodies (antitoxin) protects against primary infection by preventing bacterial adherence to cells. Booster immunization of toxoid is required, particularly in exposed persons. The degree of immunity can be evaluated with the Schick test, in which diphtheria toxin and a control are injected intradermally and the reactions assessed.

Differential Diagnosis

Sore throat, fever, lymphadenopathy, and a pharyngeal exudate should generate considerations of streptococcal pharyngitis, infectious mononucleosis, and adenovirus-related pharyngitis. However, diphtheria is a life threatening disease. Clinically, suspicious cases are best treated without ruling out other lesions on a differential list and without waiting for laboratory confirmation.

Complications

Complications arise in the cardiovascular and nervous systems due to toxemia. Myocarditis and cranial neuropathies are main complications. Myocarditis can cause arrhythmias, heart failure and cardiovascular shock. Cranial nerve complications produce dysphagia, diplopia, slurred speech, etc. Nephritis, pneumonia, acute circulatory failure, bleeding and otitis media are other complications.

Diagnostic Work-up: Treatment begins as throat cultures are taken to identify the causative organism, *C. diphtheriae.*

Histopathology

The organisms attach to the epithelium of the upper respiratory tract but do not penetrate it. There is an acute inflammatory response characterized by hyperemia, edema, focal hemorrhages, and an infiltrate of neutrophils. Considerable amounts of fibrin are formed. A few days after the acute inflammatory response, the epithelium becomes necrotic and, with the debris of inflammation, becomes enmeshed within the fibrin, forming a membrane that is bound to the underlying inflammatory tissue. In areas of stratified squamous epithelium, such as the pharynx, the membrane is tenacious. In areas of thinner respiratory epithelium, such as the nasopharynx, it is more easily separable. The membrane is subsequently coughed up or resorbed.

Treatment

Horse serum antitoxin, 40,000 to 60,000 U, should be given as soon as possible after conjunctival or skin tests for horse

serum hypersensitivity are completed. Simultaneously, aqueous penicillin G, 2 million U intravenously every 6 hours, or oral potassium penicillin V, 500 mg four times daily for 10 days, should be started. In the penicillin allergic patient, erythromycin, 1 g intravenously every 6 hours, or oral erythromycin, 500 mg four times daily for 10 days, is used. In cases that are diagnosed late or in extensive disease, 100,000 U of horse serum antitoxin are given in addition to the antibiotics.

In cases where the pseudomembrane causes obvious upper airway obstruction, removal by direct laryngoscopy or fiberoptic nasopharyngoscopy is useful. If it cannot be removed, intubation is required. If intubation is not possible, a tracheostomy may be necessary.

Prognosis

Early recognition and treatment lead to disease resolution and the prevention of complications.

ORAL TUBERCULOSIS AND SCROFULA

It is a specific infectious granulomatous disease.

Causative microorganism—*Mycobacterium tuberculosis.*

Clinical Presentation and Pathogenesis

Oral lesions of tuberculosis (TB) will present as painful, ragged ulcers, mostly on the posterior aspect of the oral tongue, pharyngeal tongue, or palate. They are almost always secondary to active pulmonary tuberculosis, which seeds the oral site from coughed up sputum. The lesions are painful because, by definition, they are infected ulcers (Fig. 4.8).

Occasionally, further invasion into bone may create a TB related osteomyelitis.

Transmission occurs via aerosolized droplets, which seeds organisms into the lungs that persist within macrophages after ingestion. These organisms and macrophages become contained or "walled off" within a granuloma. Often called the primary infection, this site is asymptomatic. The focus of dormant but viable organisms in the lung has been called the Simon focus; when calcified and apparent on a chest radiograph, it has been called the Ghon focus. Active tuberculosis develops as a reactivation of this primary disease either by reinfection or a change in the individual's immune status. Active lung destruction (usually cavitary lesions) develops, and lymphatic or hematogenous spread can occur.

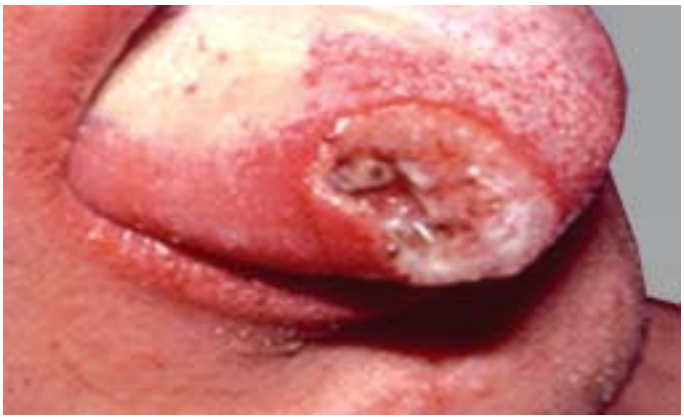


Fig. 4.8: Lesion on the tongue

Differential Diagnosis

Oral TB will closely mimic several other important and well-known diseases, the most important of which is squamous cell carcinoma. In addition, the chancres of primary syphilis and the oral lesions of pulmonary fungal diseases such as histoplasmosis, coccidioidomycosis, and blastomycosis will have a similar appearance.

Histopathology

The histopathologic appearance is due to cell mediated hypersensitivity reaction. Formation of granuloma exhibiting foci of caseous necrosis surrounded by epithelioid cells, lymphocytes and multinucleated giant cells are seen.

Diagnostic Work-up

Suspected oral TB ulcers require biopsy to rule out carcinoma and the fungal lesions that will show suspicious organisms on high power or oil immersion. A tissue specimen should be sent fresh for acid-fast staining (e.g. Ziehl Neelsen stain) and for culture in Löwenstein-Jensen media. Another tissue specimen should be sent for hematoxylin and eosin (H and E) histopathology.

The acid-fast organisms (nearly all mycobacteria species along with some others) will appear as red bacilli, located within the cytoplasm of macrophages (epithelioid cells).

Because oral TB is secondary to pulmonary TB, a chest radiograph should be taken. Active TB will most likely show a cavitary lesion in an apical lobe. More subtle pulmonary foci of TB may show lower lobe cavitation or pleural thickenings. In some cases, overt signs and symptoms such as fatigue, weight loss, fever, and night sweats may further suggest active pulmonary disease. If a chest radiograph is suspicious and/or the oral lesion biopsy specimen shows granulomatous disease, sputum collection for acid-fast staining and culture, preferably by transtracheal irrigation and aspiration, is recommended. Primary pulmonary TB is usually seen in children, which in most cases are asymptomatic.

The purified protein derivative (PPD), also called the TB tine test, and a variant of this test called the Mantoux test, are intradermal skin tests utilizing tubercle bacillus PPD (Fig. 4.9). It is used in a dose of 5 tuberculin units (TU) in a saline solution as the antigen. An erythematous reaction greater than 2 mm with induration after 48 hours indicates that an individual has been exposed to the tubercle bacillus and has cell mediated hypersensitivity to the antigen. CT-scan used to diagnose mediastinal or hilar lymphadenopathy. MRI is the most useful to diagnose extrapulmonary TB. Newer methods of diagnosis of TB includes radioimmunoassays (RIA), fluorescent antibody test and ELISA.

Histopathology

Tuberculosis is a disease that epitomizes the formation of so-called epithelioid granulomas. The granulomas consist of macrophages, epithelioid cells, and multinucleated giant cells usually of the Langhans type, with peripheral lymphocytes, plasma cells, and fibroblasts. The center of the granuloma may show caseous necrosis. This is not usually seen in intraoral lesions but may be an important component in lymph node involvement and in the lung.

Treatment

Children 12 years or older were treated with oral isoniazid (INH), 300 mg daily, and oral rifampin, 600 mg daily, for 9 months. That regimen is oral isoniazid (INH), 5 mg/kg (300 mg maximum) daily; oral rifampin, 10 mg/kg (600 mg maximum) daily; oral pyrazinamide, 15 to 30 mg/kg (2 g maximum) daily; and oral ethambutol, 15 mg/kg daily, or intramuscular streptomycin, 20 to 30 mg/kg per day (1 g maximum).

Prognosis

A responding patient will have a reduction in pain associated with the oral lesion and evidence of healing. The pulmonary lesion will heal with a dense scarring, which causes a "white out" area of the lung in the location of the previous cavitary radiolucency and usually a deviation of the trachea to the involved side.

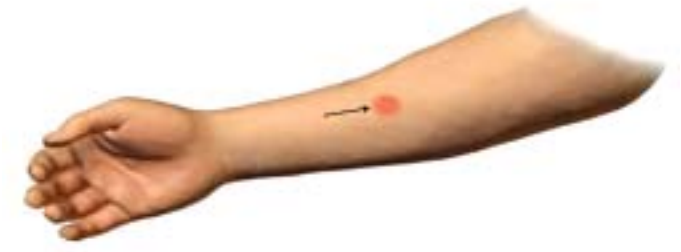


Fig. 4.9: Montoux's test showing positive reaction

TUBERCULOSIS OF THE SKIN

The oral and maxillofacial specialist should recognize that in very rare instances TB may also present as a primary skin infection. In medieval times, it was referred to as lupus vulgaris because of the wolf-like appearance of the face. TB of the skin is almost always independent of pulmonary TB. It will present as a chronic ulcerative involvement of the skin with rolled margins and may resemble the lesions of sarcoidosis, discoid lupus erythematosus, or early leprosy. Caseation is usually mild or absent. Once granulomas are identified by skin biopsy and cultures reveal *M tuberculosis*, treatment with the same drug regimens as are used for pulmonary TB is indicated. Tuberculosis of the skin (lupus vulgaris) is very rare today. It presents as a single set or multiple sets of skin ulcers with rolled margins.

TETANUS (LOCK-JAW)

Tetanus is an acute infection of the central nervous system characterized by intense activity of motor neurons and resulting in severe muscular spasm.

Causative Organism

Clostridium tetani.

Clinical Presentation and Pathogenesis

Tetanus is a life-threatening infection caused by the microorganism *Clostridium tetani*, a ubiquitous inhabitant of soil. Its production of the neurotoxin tetanospasmin produces the hyper-reactive muscle and actual muscle spasms of this disease.

Most cases occur in unvaccinated individuals. Newborns, the elderly, migrant workers, and intravenous (IV) drug users are at greatest risk. Although most cases are the result of a penetrating wound, any wound with nonvital tissues and anaerobic conditions may incubate *C tetani.* Incubation period is usually 6-12 days.

The first symptoms that would be seen by the oral and maxillofacial specialist are limited jaw opening, stiffneck, diplopia, or dysphagia. The site of infection may be normal in appearance or show the typical signs of infection. Pain and spasticity of the nearest muscle to the infection site may be noted as an early sign. As the disease progresses, the increased levels of tetanospasmin will progress, first involving muscles of higher power-to-size ratios (masseter, external ocular, neck muscles) and then involving muscles of lower power-to-size ratios (back muscles, leg muscles,

and diaphragm), that is, the larger muscles. As the disease progresses further, contractions of the facial muscles result in a so called sardonic smile, so named after the island of Sardinia, where the crowfoot plant is known to create the same type of facial muscle spasm. Later in the course, spasms in the back muscles will cause opisthotonos, an arching of the back resembling a wrestler's bridge position. When the diaphragm and intercostal muscles become involved, apnea results and death follows unless the individual is placed on a ventilator and paralyzed with muscle relaxants.

Diagnostic Work-up

The first step in diagnosing a case of tetanus is recognizing that tetanus can occur in modern society. Young individuals of lower socioeconomic status and recent immigrants often do not receive vaccination and are more likely to suffer the classic puncture injury. Since no laboratory tests can aid in the diagnosis of tetanus, an index of suspicion gained from the immunization and social history are of great importance. Intravenous drug abusers will pose the greatest work-up challenge.

Differential Diagnosis

In the early stages of tetanus, the jaw and neck stiffness as well as diplopia may suggest meningitis. Dysphagia, due to spasm of pharyngeal muscle may suggest tonsillitis. Generalized convulsions with muscle contraction, severe clenching of teeth, arched back and extended limbs can suggest epilepsy. Severe contraction of masseter muscle may suggest alveolar abscess or temporomandibular joint involvement. Rigidity of back muscles may suggest orthopedic disorders.

Treatment

Once tetanus is diagnosed, time is of the essence, and therefore several measures need to be taken concurrently. All cases should receive 5,000 U of tetanus immune globulin intramuscularly (passive immunity). The concerning wound requires debridement, irrigation, and cultures. Intravenous aqueous penicillin, 20 million U per day in divided doses, is also required. The strategy of this treatment regimen is for the preformed antibodies (passive immunity) to neutralize the tetanospasmin, for the debridement to remove nonvital tissue and reverse the anaerobic environment, and for the penicillin to reduce the toxin-producing organisms. Inj tetanus toxoid 0.5 ml IM should be given. In mild cases, combination drugs of chlorpromazine (50-100 mg), Phenobarbitone (30-60 mg) and diazepam (10-20 mg) is given in every 2 hrs, so that the patient receives some sedation.

In early cases, the patient needs to be sedated and placed on bed rest in a dark, quiet room with minimal external stimuli. However, respirations and oxygen saturation must be continuously monitored because progression of tetanus will lead to severe respiratory depression and apnea. Later cases or those showing progressive signs of respiratory failure require intubation or tracheostomy with paralysis and mechanical ventilation. Antitetanus serum (ATS) 50,000 units IM/IV can be given or human antitetanus globulin, 3000-4000 units IM can be given.

Prognosis

The chances for survival are directly proportional to the amount of time taken to diagnose and treat tetanus. Cases that are recognized before respiratory failure begins and treated aggressively can be salvaged. It is important to note that contaminated wounds of the head and neck area are more dangerous than wounds elsewhere because of the abundant blood supply absorbing and systemically distributing a greater quantity of the toxin.

SYPHILIS (LEUS)

It is an infectious disease and is caused by *Treponema pallidum* (Figs 4.10 and 4.11).

Clinical Presentation and Pathogenesis

The clinical presentation of syphilis varies with the disease stage. The chancre of primary syphilis is an ulcer with elevated, rolled edges, which emerges at the site of inoculation of *Treponema pallidum*. Chancres occur mostly around the genitals of either sex or on the lips, tongue, and other oral mucous membranes. There is usually regional lymphadenopathy; the nodes are mildly tender, smooth, and freely movable.

Congenital syphilis results from a fetal spirochetemia (caused by the transplacental transmission of viable *T. pallidum* into the circulation of the developing fetus).

Fig. 4.10: Microscopic appearance of *T. pallidum*

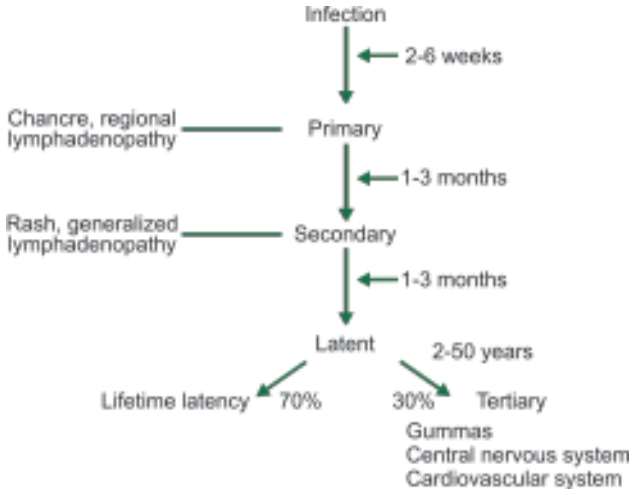


Fig. 4.11: Stages of syphilis

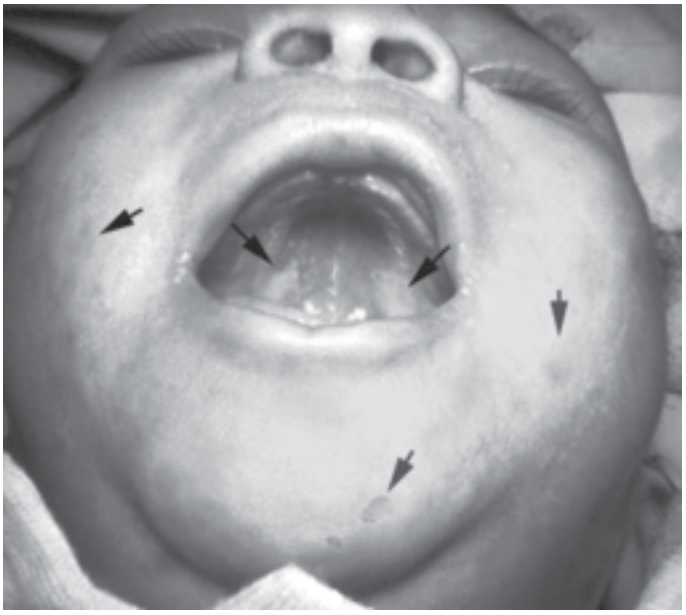


Fig. 4.12: Intraoral mucous patches and facial skin lesions in congenital syphilis

The baby is born with a secondary stage form of the disease (Fig. 4.12). If the infection is fulminant, the child may be stillborn. Among the more common congenital syphilis lesions are so called Saber shins, caused by a tibial bowing resulting from anterior tibial periosteal new bone formation; a saddle nose deformity, caused by destruction of the vomer; perioral creases, called rhagades, caused by skin endarteritis with resultant scarring; interstitial keratitis, caused by active infection of the cornea and conjunctiva; Hutchinson teeth, caused by arrested enamel formation of the permanent molars and incisors; and eighth nerve deafness, caused by endarteritis and ischemia of the eighth nerve. Collectively, these last three entities have been termed Hutchinson's triad.

Diagnostic Work-Up

First flocculation test used widely was Khan's test. This was replaced by simpler and a more rapid VDRL test. Patients suspected of having syphilis should undergo a screening venereal disease research laboratory(VDRL) serologic test. This test is quick, inexpensive, and easy to perform and is, therefore, an ideal test for screening numerous blood samples.

Suspected cases that have a reactive VDRL must be confirmed with a fluorescent treponema antibody-absorption (FTA-ABS) serologic test. The FTA-ABS is, therefore, highly specific, time consuming, and somewhat expensive, but it will confirm the diagnosis of syphilis and rule out false positive VDRL tests. Apart from this, other tests used are rapid plasma regain test (RPR) are also done.

Histopathology

The fundamental changes in syphilis are vascular, exemplified by a proliferative endarteritis in which there is swelling and proliferation of endothelial cells, resulting in constriction of the vascular lumen.

The early stages of syphilis are characterized by dense perivascular infiltrations of plasma cells and lymphocytes, an immunologic reaction to treponemal antigen. In the chancre, the reaction may be so dense at the center of the lesion that clear identification of the cells and the endothelial proliferation may be made only more peripherally. Occlusion of vessels by the endothelium may cause necrosis and ulceration of the chancre, and the epithelial margins may show a reactive acanthosis. The treponemes can be identified within the tissue by means of a silver stain such as Warthin-Starry. They appear as narrow (0.25 um), black, thread-like organisms, often with a corkscrew configuration. Tertiary or late syphilis is characterized by epithelioid granuloma formation. Multinucleated giant cells are usually present. Caseation may or may not be seen, but is extensive ingummatous lesions. Vascular changes with obliterative endarteritis are also present in late syphilis. Organisms are sparse. Granulomas more typical of tertiary syphilis may sometimes be seen in secondary syphilis.

Treatment

1.2 to 2.4 million U of benzathine penicillin intramuscularly in the gluteal region is given. Benzathine penicillin is the drug of choice for all forms of syphilis because it maintains effective tissue levels for weeks, which is required in the treatment of spirochetal disease because of their prolonged turnover time (about 30 hours).

For the penicillin-allergic patient, oral tetracycline, 500 mg four times daily, oral doxycycline, 100 mg twice

daily, or oral erythromycin, 500 mg four times daily for 14 days, are effective.

The Jarisch-Herxheimer reaction is a well-known reaction to initial therapy when penicillin is injected into the patient, particularly secondary syphilis. It results from a massive spirochete kill, which releases large quantities of antigen into the bloodstream. Antigen antibody complexes then lodge into almost all tissues, producing constitutional symptoms of fever, malaise, myalgia, and exacerbation of the syphilitic lesions. It is treated with reassurance, rest, and anti- inflammatory drugs. It usually begins within 24 hours of the treatment and subsides after another 24 hours.

Prognosis

Recurrent syphilis results either from treatment failure (usually due to noncompliance by those using oral medications) or from reinfection. Treponemes have no ability to form resistance to penicillin. Follow-up should be both clinical and serologic. The quantitative VDRL should show a fourfold decrease within 3 months in early syphilis and within 6 months in latent and late syphilis.

NOMA (CANCRUM ORIS, GANGRENOUS STOMATITIS)

It is a rapidly spreading, mutilating gangrenous stomatitis that occurs usually in nutritionally deficient persons. It is chiefly seen in children (Figs 4.13 and 4.14).

Clinical Presentation and Pathogenesis

The classic picture of a noma patient is a child or teenager with a gangrenous, black tissue slough of oral mucosa and skin who has another debilitating infection such as dysentery, pneumonia, severe anemias, severe malnutrition, or

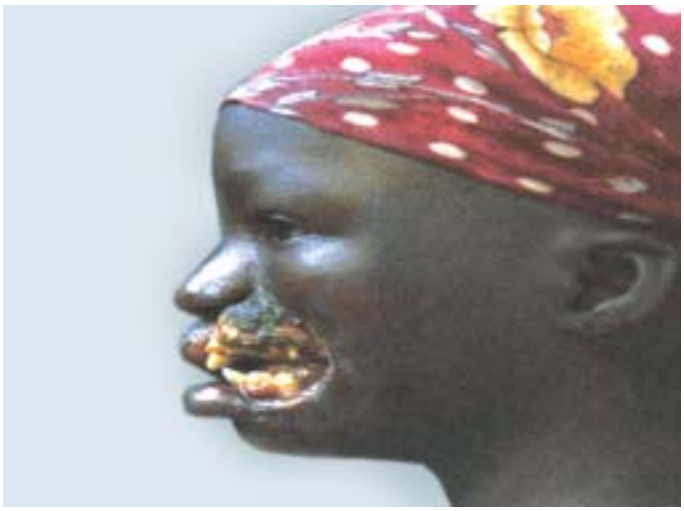


Fig. 4.13: Cancrum oris

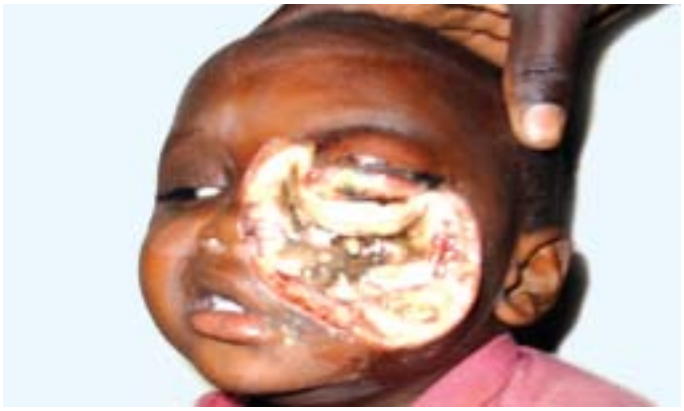


Fig. 4.14: Facial involvement

a leukemia with ongoing chemotherapy. Most are associated with chemotherapy or immunosuppressive drugs.

The lesion often begins as a painful ulcer from trauma or from spontaneous tissue breakdown. The ulcer rapidly extends as inflammation progresses to tissue necrosis, often lysing sufficient mucosa and skin to expose underlying bone, which may also become necrotic. Before the tissue slough, the ulcer will blacken, suggesting ischemic necrosis. A sour odor is often noted during this process. As the disease progresses, a sharp line of demarcation develops, separating necrotic tissue from adjacent healthy, well-perfused tissue.

Noma is not a primary disease but a secondary complication of another disease. The organisms take advantage of host tissue compromise and produce a progressive tissue destruction. Although unproven, it has been suggested that the tissue destruction is caused by bacterial enzymic digestion or via progressive vascular thrombosis, leading to ischemic tissue necrosis. In some areas of Africa, noma is a frequent complication of childhood measles.

Differential Diagnosis

The most important disease from which to distinguish noma is a rapidly progressing malignancy, particularly entities such as immunoblastic lymphoma and leukemias. In addition, necrotizing fasciitis, which is an analogous disease but localized to fascial planes, may in its early stages resemble noma.

Diagnostic Work-up

The diagnosis of noma is based on knowledge of the underlying condition that predisposes tissue to necrosis and the clinical identification of progressive ischemic changes with necrosis. Cultures from the edge of the necrotic tissue in front of and adjacent to seemingly healthy tissue often identify Vincent spirochetes and fusiform

bacilli, making this disease somewhat analogous to acute necrotizing ulcerative periodontitis.

Histopathology

Initially, there is acute inflammation with edema and neutrophils; this is followed by extensive necrosis. Granulation tissue may develop around foci of necrosis, but this tissue becomes infected and also undergoes necrosis. Masses of bacteria are readily identified. The mechanism for the massive necrosis has not been elucidated. Thrombosis of larger vessels is not seen in these lesions.

Treatment

The two most important aspects of treatment are the reversal of the underlying predisposing condition and surgical debridement. In addition, aggressive supportive care in the form of nasogastric high calorie, high protein feedings and intravenous fluids is useful. Antibiotics are of course used but play a secondary role to debridement and improvement of systemic health. Both Vincent spirochetes and fusiform bacilli are sensitive to penicillin. Aqueous penicillin G 1 to 2 million U is given every 4 hours intravenously until the debrided wound shows evidence of healing. Therapy then changes to oral penicillin, 500 mg four times daily, until resolved. For the penicillin allergic patient, erythromycin Ig intravenously every 6 hours then converted to 500 mg by mouth four times daily is useful. Hyperbaric oxygen, if available, may also be used in an attempt to preserve as much unaffected tissue as possible.

Prognosis

Today, noma is resolvable with the treatment described. The tissue loss requires reconstruction when possible to prevent scar retraction from further distorting tissues and limiting function. The soft tissue loss is often so great that a myocutaneous flap or a free microvascular transfer is necessary. Bone loss requires bone graft reconstruction.

CAT-SCRATCH DISEASE (CAT-SCRATCH FEVER, BENIGN LYMPHORETICULOSIS)

Cat-scratch disease is a newly recognized disease, the first actual report being that of Debre and his coworkers, was given in 1950 (Fig. 4.15).

Causative organism

Bartonella henselae

Clinical Presentation

Cat-scratch disease usually presents as a painless, irregular, firm mass of matted lymph nodes. The nodes are initially

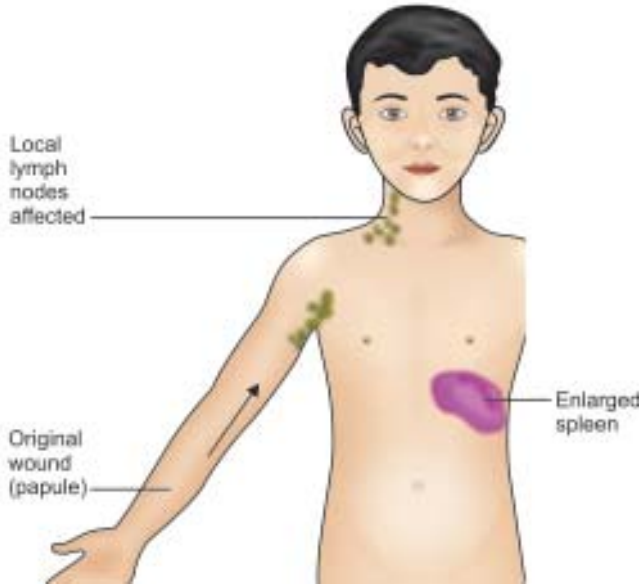


Fig. 4.15: Cat-scratch disease

nontender, although some cases present with painful lymphadenitis. They are fixed to surrounding tissues and often to the mandible if they arise in the submandibular or submental triangle. The nodes present in much the same fashion as one would expect in cervical lymph node metastases from oral squamous cell carcinoma.

The disease is almost always associated with cats and very rarely with dogs or other animals. Peak incidence is between the ages of 5 and 25 years. When lymph nodes become enlarged, they are not necessarily within the lymphatic drainage of the scratch site. The nodes will usually enlarge and achieve a size of 4 to 6 cm within a matter of 1 to 2 weeks. Symptoms of infection such as fever, erythema, and leukocytosis are only rarely seen. Most cases present as asymptomatic, firm lymph node masses.

Differential Diagnosis

The rapid emergence of firm, fixed, and usually painless nodes should give the clinician some concern about squamous cell carcinoma and nodal metastasis despite the young age of these patients. Hodgkin lymphoma, HIV-related lymphadenopathy, and cervical TB adenitis are also distinct considerations. If the nodes are indeed fixed to the mandible or to another bone, desmoplastic fibroma and aggressive fibromatosis become possibilities. In those patients who develop lymph node enlargement in the deep mid cervical chain, a branchial cyst (benign cystic lymph node) also becomes a consideration.

Diagnostic Work-up

The diagnosis of cat-scratch disease is a clinical patient history diagnosis confirmed by serum antibody

identification. The association with cats, the age of the cat, and the clinical quality of the nodes are the most important criteria. There is usually no leukocytosis, and other laboratory data are also within normal limits. Today, a serum cat-scratch antibody test, a test that most laboratories can perform, is used to confirm the diagnosis. If the cat-scratch antibody test either cannot be accomplished or is equivocal, the diagnosis should be established by a lymph node biopsy, which should include Warthin-Starry staining in an attempt to identify the organism.

Histopathology

The histologic changes associated with cat-scratch disease represent a regional lymphadenitis. The spectrum of change within this inflammatory process can be broken down into three stages. Early changes show a nonspecific reactive follicular hyperplasia with prominent follicles of varied size. The sinuses may be distended, but there is little distortion of architecture. The follicles have peripheral small lymphocytes with prominent germinal centers within which mitotic and phagocytic activity are seen. Inflammatory cells such as plasma cells and eosinophils are found between the follicles and are accompanied by endothelial proliferation.

This stage may be followed by granulomatous inflammation in which epithelioid granulomas with occasional Langhans giant cells may be found within the cortex and medulla.

Ultimately, the granulomas may undergo central necrosis. In this case, a focus of neutrophils, nuclear debris, and fibrin surrounded by palisaded epithelioid cells is seen. Granulomas and abscesses may be found in the capsule and may break out into the surrounding fat.

Identification of the small pleomorphic bacteria within damaged vessels and microabscesses of the lymph nodes can be accomplished by means of a Warthin-Starry stain.

Treatment

If the diagnosis is confirmed by a cat-scratch antibody test, no biopsy or surgery is necessary. If the diagnosis is confirmed by lymph node biopsy, further surgery is unnecessary. Eighty percent of cases will resolve spontaneously without treatment, making the value of antibiotic therapy questionable.

In about 10 percent of cases, the lymph node will undergo central necrosis and begin to show clinical fluctuance. If this course becomes evident, incision and drainage is to be avoided in favor of complete lymph node excision. In such cases, postexcision antibiotics, either tetracycline or erythromycin, should be given. When incision and drainage is carried out, the disease is often prolonged while the entire lymph node continues a slow necrosis and drainage, which eventually produces a large, retracted scar.

Prognosis

Although very rare cases of erythema nodosum, papular rashes, and even encephalitis have been reported as complications from cat-scratch disease, spontaneous involution or resolution after lymph node excision is the rule.

TULAREMIA (RABBIT FEVER)

Tularemia is a disease caused by the gram-negative bacillus *Francisella tularensis*, also known as *Bacterium tularense* and *Pasteurella tularensis*. This infection is contracted through contact with infected rodents and rabbits. This exposure and subsequent Infection may occur during skinning and dressing, freshly killed infected animals, through ingestion of contaminated meat and water, or through the bite of an infected deer fly or tick. This disease is highly communicable from infected mammals to human (Figs 4.16 and 4.17).

Clinical Presentation

May be classified into several types, and these include the cutaneous, ophthalmic, pleuropulmonary, oral and abdominal forms. After a variable incubation period of upto 7 days, the child usually suffers a sudden headache, nausea, vomiting, chills and fever. A single cut or sore on the skin develops into a suppurative ulcer. The lymphatic vessels become swollen and painful and the lymph nodes are

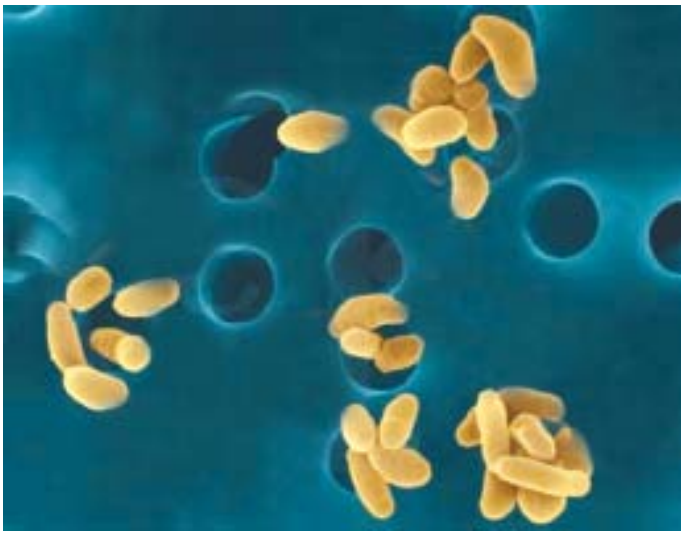


Fig. 4.16: *Coccobacillus bacterium. Franciscella tularensis* causes tularemia

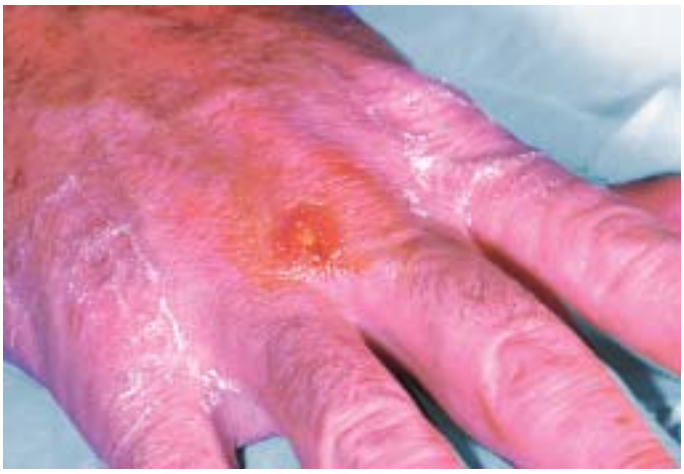


Fig. 4.17: A typical tularemia lesion

remarkably enlarged. This general sequence of events is the most common course of the disease and is called ulceroglandular tularemia. The eyes also become involved with conjunctivitis developing through localization of the disease in the conjunctival sac; oculoglandular tularemia. Tularemic pneumonia and pleuritis are also complication of the disease, which may eventuate in gangrene and lung abscesses. Children are sometimes affected.

Oral Manifestations

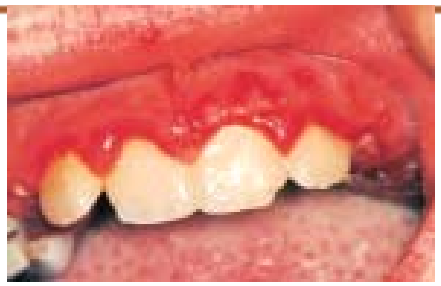
The oral lesions account for 3 to 4 percent of all cases and are manifested as necrotic ulcers of the oral mucosa or pharynx, usually accompanied by severe pain. In some cases it has been reported that the generalized stomatitis develops rather than isolated lesions, single nodular masses eventually developing into abcesses have also been described. Regional lymphadenitis may arise in the submaxillary and cervical group of nodes.

Treatment

The disease responds to antibiotic therapy. Streptomycin is the drug of choice.

5

Viral Infections



Viruses have been defined as submicroscopic entities which reproduce only within specific living cells. Viruses have been known to cause certain infectious diseases and many of them produce a long lasting immunity against reinfection by the same virus. Diagnostic confirmation of viral infection by laboratory investigations is slow and difficult. Thus, most viral infections are diagnosed by their clinical presentation.

HERPES SIMPLEX INFECTIONS

Herpes simplex, an acute infectious disease, is probably the most common viral disease affecting man, with the exception of viral respiratory infections.

PRIMARY HERPETIC GINGIVOSTOMATITIS

Clinical Presentation and Pathogenesis

Primary herpetic gingivostomatitis develops mostly in children and young adults. Painful vesicular lesions develop on all mucosal surfaces and rupture to produce foul smelling ulcers (Fig. 5.1). The patient is usually febrile, drools, has significant malaise, "feels miserable," and will have tender cervical lymphadenopathy. The lesions and acute illness last about 10 days and resolve with scar formation.

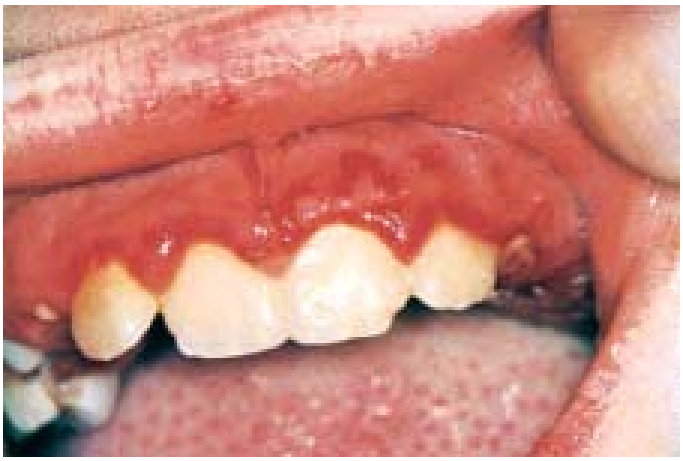


Fig. 5.1: Herpes gingivostomatitis—vesicles on mucosal surfaces

The herpes simplex virus I (HSV-1) gains access to the patient via direct or airborne water droplet transmission from an infected individual. The mucous membrane lesions represent direct viral infection at the site of inoculation. The clinical course is limited by the synthesis of viral specific antibodies (IgM, days 3 to 5; IgG, days 5 to 21). The virus is not completely eradicated because the residual viruses ascend proximally along the epineurium of the trigeminal nerve to the gasserian ganglion. In the gasserian ganglion, the virus is protected from further antibody attack by the blood brain barrier and, therefore, develops a viable dormant existence within ganglion cell bodies.

RECURRENT HERPES INFECTIONS

Clinical Presentation and Pathogenesis

Recurrent herpes lesions may begin with a prodrome of burning, tingling, or pain without a visible lesion. Next, a vesicle may appear that will soon rupture into a moist ulcer, or an ulcer will emerge directly. Such secondary lesions have a predisposition for the vermilion and vermilion skin edge of the lips; in the past, the condition has been termed recurrent herpes labialis. The lesions otherwise have a predisposition for the keratinized surfaces of the palate and gingiva.

Such recurrent lesions represent reactivation and migration of the virus. Stimulants such as sun exposure, cold temperatures (cold sores) (Fig. 5.2), and fevers from other diseases (fever blisters) evoke HSV-1 activity by some unknown mechanism. Some viruses migrate distally down the epineural sheath of the trigeminal nerve, proliferate, and infect the epithelial tissue at the terminal nerve ending to generate vesicles and ulcers.

In immunosuppressed individuals, particularly bone marrow transplant and HIV infected patients, recurrent herpes is more serious. It tends to be more painful and destructive, and lesions may become secondarily infected,

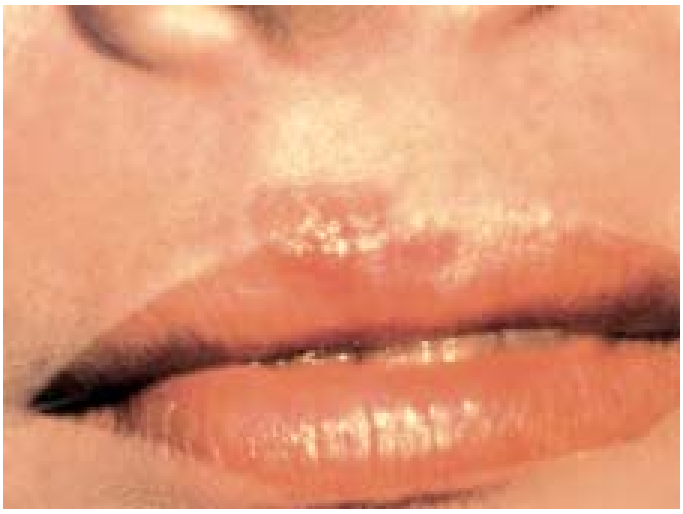


Fig. 5.2: Recurrent herpes simplex—cold sore blisters, or herpes labialis, on the upper lip of the patient

causing further destruction. The lesions are not limited to the lips, palate, and gingiva as they are in recurrent herpes in immunocompetent individuals.

Differential Diagnosis

The painful vesicular ulcerative lesions of acute herpetic gingivostomatitis may resemble necrotizing ulcerative periodontitis or pemphigus vulgaris. The oral lesions by themselves might be suggestive of erythema multiforme, but without concomitant skin lesions true erythema multiforme is not likely. In adults, erosive lichen planus is another consideration as is streptococcal pharyngitis mucositis in younger patients.

Lesions of recurrent herpes simplex, particularly on the palate and gingiva, can be confusing. Intermittent episodes of "burning" lesions will occur. Their duration may be so brief that the practitioner and the patient miss the acute stage. Aphthous ulcers and focal atrophic candida lesions are other prime considerations. Early herpes zoster is also possible.

Diagnostic Work-up

Laboratory evaluation to detect HSV circulating antibodies may be useful in children with suspected primary herpetic gingivostomatitis. However, it is not reliable in recurrent lesions or perhaps even in primary lesions because of the near universal exposure (over 90 percent) to HSV. Lesions can be scraped and smeared for cytologic studies, which may identify viral particles and multinucleated epithelial cells. In addition, tissue biopsy specimens may show suggested viral particles on routine H&E staining. Otherwise, murine monoclonal antibody immunohistochemistry can identify the presence of intracellular HSV in formalin fixed routine specimens.

Histopathology

The essential histologic changes within skin and mucous membrane are the same for the three infections—herpes simplex, varicella, herpes zoster—caused by herpes virus. As in all vesiculobullous lesions, the specific features may be seen only in early lesions; biopsy of long standing and ruptured lesions should be avoided.

In these herpetic infections, the vesicle initially forms in the prickle cell layer secondary to degenerative changes induced by the virus. This takes two forms. Ballooning degeneration, which is seen mainly in the floor of the vesicle, causes expansion of the cell. The cell has an eosinophilic cytoplasm and a single nucleus or multiple nuclei. The nucleus is usually enlarged and may have an irregular contour. With H&E, it has a washed out, steel gray appearance and shows margination of the nuclear material. These cells lose their intercellular bridges, and this acantholytic process creates the vesicle. These cells may be identified by cytologic smears. The vesicle may "bottom out," so that it has a subepithelial rather than an intraepithelial location.

In reticular degeneration, which occurs essentially in the superior and lateral aspects of the vesicle, there is intracellular edema, such that the epithelial cells rupture, leaving strands from the cell walls to form a multilocular vesicle.

Eosinophilic inclusions (Lipschutz bodies), about 3 to 8 um in diameter, may be seen within the nucleus. The underlying connective tissue shows an inflammatory reaction of varying intensity.

Treatment

The two drugs most effective against HSV are systemic acyclovir and ganciclovir (Cytovene, Roche). Topical 5% acyclovir is not very useful in shortening the duration of secondary lesions or in aborting their course once developed. Unless the patient is immunocompromised, topical acyclovir should be withheld because of its potential to stimulate resistant viral strains in the face of very little therapeutic gain. Primary herpetic gingivostomatitis is self limiting and should require only supportive care consisting of hydration, antipyretics, nutrition, and possibly antibiotics, if secondary bacterial infections arise.

Recurrent oral herpes also does not necessarily warrant treatment. Mild clinical expressions are also self-limiting and their course can be endured over 7 to 10 days. In those cases that present with multiple debilitating recurrent lesions and/or frequent extensive recurrences, oral acyclovir, 200 mg five times daily, is given for 10 days at the first sign of new lesions. To prevent frequent severe outbreaks, maintenance at 400 mg twice daily is recommended. If recurrences are infrequent but severe

enough to warrant therapy, oral acyclovir, 200 mg five times daily, is used at each recurrence to shorten its course and limit disability.

Immunocompromised patients warrant acyclovir therapy at each episode. Some may require intravenous therapy, usually in divided dosages for a total of 30 mg/kg per day. As an alternative, ganciclovir, 500 mg orally three times daily, may be used as well. Continued prophylactic oral acyclovir is recommended in immunocompromised patients, usually at 400 mg twice daily.

Prognosis

Acyclovir for those who warrant it is effective, particularly if started early in the disease course. Long-term acyclovir therapy in the immunocompromised patient is effective and safe. However, it does not prevent viral shedding in the symptomatic or asymptomatic patient and will, therefore, not prevent transmission of either HSV-1 or HSV-2 disease.

HERPANGINA

Herpangina is a specific viral infection, which was described by Zahorsky in 1920.

Clinical Presentation and Pathogenesis

Herpangina is seen in children in the summer months with the primary findings of abrupt onset high fever (104 to 105°F range), a diffuse pharyngitis, 1-to 2 mm gray white vesicles, and petechiae and ulcers of the soft palate and tonsillar fossa. The oral mucosa anterior to the anterior tonsillar pillars usually is not involved. Fever and dysphagia are usually the chief complaints. The lesions stand out as gray white, discrete fibrinous lesions against a diffuse erythematous mucosa.

Like hand foot and mouth disease, herpangina is a coxsackie virus disease caused by coxsackie virus A and B (A2-6, A8, A10, and unspecified B-type viruses); it is transmitted via direct salivary contact, aerosolized droplets, and possibly oral fecal contamination. The viruses establish an infection by systemic viremia, hence the abrupt onset of fever and a selection for the oropharynx probably due to its optimal temperature.

Differential Diagnosis

The finding of fever with lesions limited to the posterior oral cavity and oropharyngeal area should rule out diseases with prominent skin lesions such as varicella (chickenpox), and hand foot and mouth disease. These findings should also distinguish it from diseases that are predominantly limited to the true oral cavity, such as primary herpetic gingivostomatitis. However, the presentation does initially resemble a streptococcal pharyngitis and tonsillitis and may be similar to early diphtheria.

Diagnostic Work-up

Most cases are diagnosed by their clinical presentation. Equivocal cases may need confirmation by serum anti coxsackie virus determinations or by viral cultures from fresh lesions. It is important, however, to take bacterial throat cultures to rule out a primary streptococcal pharyngitis or a secondary streptococcal infection, which places the child at risk for rheumatic fever.

Histopathology

Because this is a mild disease of short duration affecting the most posterior aspects of the oral cavity, histology does not play a role in the diagnosis of herpangina. The oral lesions do form intraepithelial vesicles.

Treatment

Herpangina requires no specific treatment other than parental reassurance and supportive care in the form of hydration, antipyretics, analgesics, and rest. If the disease is complicated by a streptococcal pharyngitis, oral phenoxymethyl penicillin (Pen-Vee K, Wyeth-Ayerst), 250 mg four times daily, is required for 10 days. In penicillin allergic patients, oral erythromycin ethyl succinate (EES, Abbott) is a good substitute at 200 to 400 mg four times daily for 10 days. An alternative to penicillin, oral cefuroxime (Ceftin, Glaxo Wellcome), 125 mg twice daily for 10 days, is also effective.

Prognosis

Herpangina usually resolves as a result of host immune responses within 2 weeks.

HAND-FOOT-AND-MOUTH DISEASE

Hand foot and mouth disease is an epidemic infection caused by the enterovirus Coxsackie A16.

Clinical Presentation and Pathogenesis

Hand-foot-and-mouth disease will present in a child younger than 5 years during the summer. Uncomfortable but usually not severely painful oral lesions often will be the reason the parent seeks attention. The oral lesions begin as vesicles but may not be evident because of early rupture. More likely, yellow oral ulcers that will show a fibrinopurulent base surrounded by a red erythematous ring will be present. Similar target like lesions already will be present or soon will develop on the fingers and hands

as well as the toes and feet. Because skin epidermis is thicker than mucosa, the skin lesions will form visible vesicles of up to 1 cm in diameter before rupture. Constitutional symptoms are mild. The child is not usually as irritable as are those with most other childhood diseases.

Hand-foot-and-mouth disease is transmitted via airborne particles and possibly oral-fecal spread. The virus seems capable of penetrating mucous membranes, establishing a viremia, and becoming disseminated with a preference (probably due to cooler temperatures) for the hands, feet, and mouth.

Differential Diagnosis

Early varicella (chickenpox), rubeola (measles), and herpangina will also present with concomitant oral lesions and skin lesions. In addition, one must be concerned about a developing Stevens-Johnson syndrome variant of erythema multiforme, although the course of hand-foot-and-mouth disease would be less rapid and the lesions less painful.

Diagnostic Work-up

Hand foot and mouth disease is a diagnosed based on the history and clinical findings. The pattern of lesions, the patient's young age, and the time of year (summer or warm weather periods) contribute to the diagnosis.

Histopathology

Initially, intraepithelial vesicles are formed, and reticular degeneration may cause multilocular vesicles. In the deep epithelium, ballooning degeneration may occur. Intraepithelial vesicles may become subepithelial. Multinucleated giant cells and inclusion bodies are absent. A dense inflammatory infiltrate of neutrophils and mixed chronic inflammatory cells is present within the connective tissue and vesicles.

Treatment

No specific treatment is required. Supportive care and reassurance to parents about the self-limiting nature of the disease are helpful.

Prognosis

Lesions and their symptoms dissipate within 2 weeks. Mild scarring may remain.

MEASLES (RUBEOLA)

Measles is an acute, contagious, dermatropic viral infection, primarily affecting children and is caused by paramyxovirus.

Clinical Presentation and Pathogenesis

The most typical presentation of measles is a child who abruptly develops high fever (in the range of 104 to 105°F) with nasal stuffiness, sneezing, and sore throat (called coryza). The child usually has a nonproductive cough, photophobia due to conjunctivitis, and often a discharge or crusting around the eyes. This set of signs and symptoms is often called the prodrome because it precedes any skin rash. Oral lesions called Koplik spots also appear during this prodrome and are pathognomonic of the disease. Koplik spots appear as flat, erythematous macules with tiny white "salt crystal" centers. They will characteristically precede the skin rash by 1 or 2 days. Koplik spots may also be seen on the conjunctiva.

The child generally will appear ill and irritable. There is usually a diffuse pharyngitis and bilateral cervical lymphadenitis. The rash will appear on the facial skin and behind the ears before spreading to the chest and trunk and then to all extremities. The skin rash will begin as pinhead sized papules and then spread to form irregular red blotches, which may further coalesce to a more uniform erythema over a large area.

The measles virus is a DNA paramyxovirus transmitted by air water droplet vectors. The clinical prodrome occurs about 10 to 14 days after exposure. The infected individual is contagious from just before the prodromal stage until 4 days after the appearance of the rash. One clinical infection confers permanent immunity.

When a nonimmunized individual is exposed to measles, the live virus vaccine can prevent the disease if given within 5 days of exposure. Pregnant women and immunosuppressed individuals should not receive the live virus vaccine except in rare individual circumstances.

Differential Diagnosis

The clinical picture of an acutely ill child who develops oral lesions followed by a skin rash suggests varicella (chickenpox) and the Stevens-Johnson syndrome variant of erythema multiforme. If the oral lesions were overlooked, the clinical picture would resemble that of rubella (German measles) and possibly scarlet fever, both of which have an oral and pharyngeal erythema but no true Koplik spots.

Diagnostic Work-up

The diagnosis is made from the history and presenting clinical characteristics. Laboratory confirmation can be gained by identifying a rise in antibody titers over several specimens taken 2 days apart. The most commonly used tests are immunofluorescent antibody and complement fixation tests.

Histopathology

In the eruption of skin and mucosa, which represents a reaction to the development of antibody, infected epithelial cells show intracellular vacuolization, hyperkeratosis, and ultimately necrosis. The connective tissue is hyperemic and edematous, with perivascular lymphocytes and macrophages. Koplik spots show more epithelial necrosis and infiltration by neutrophils. The characteristic multinucleated giant cells of Warthin-Finkeldey are seen in hyperplastic lymphoid tissues, including tonsils and adenoids. They are usually present in the prodromal phase and disappear as antibody titers rise. These large cells have eosinophilic cytoplasm and centrally placed clusters of darkly stained nuclei.

Treatment

Measles is self-limiting and runs a 2-week clinical course. However, the child needs to be isolated as the disease is highly transmissible to all who do not have either natural or vaccine acquired immunity. Supportive care consisting of rest, hydration, analgesics, and antipyretics is important. Vitamin A, 400,000 U orally each day during the illness, has been shown to reduce complications. If secondary bacterial infections, such as otitis media, cervical lymphadenitis, or pneumonia, develop (15% of cases), appropriate antibiotic administration is required.

Prognosis

Measles is well known to result in post disease complications, some of which can be debilitating and life-threatening. Encephalitis develops in 1:1000 to 1:2000 cases, with 10 to 20 percent of these cases eventuating in death and another 50 percent of these cases in mental retardation. Pneumonia occurs in 1 to 7 percent of patients, and other bacterial infections occur in 15 percent of patients. Measles during pregnancy can result in premature labor, spontaneous abortion, and low birth weight. Unlike rubella (German measles), rubeola does not have a high incidence of birth defects.

RUBELLA (GERMAN MEASLES)

Clinical Presentation and Pathogenesis

The individual presenting with rubella (German measles) is usually a child or young adult who presents with fever, mild malaise, and cervical lymphadenitis. The general intensity of symptoms in rubella is less than that in rubeola (measles). The posterior lymphatic chains are usually more involved than are the anterior chains. In fact, suboccipital lymphadenopathy is common.

The face will develop a fine reddish maculopapular rash, and the palate and throat will develop an erythema. However, there will be no true Koplik spots as is seen in rubeola. The rash begins on the face, progressing down the trunk and upper extremities in 1 or 2 days. Characteristically, the rash will disappear behind its advancing front. It will fade from each area after 24 to 36 hours.

The disease, caused by a togavirus, is transmitted by air-water droplets. The virus stimulates humoral immunity of the IgM class and the IgG class, which confers postinfection permanent immunity. The MMR vaccine also confers permanent immunity. Because live attenuated rubella virus is used, it is not given to pregnant women, and birth control must be practiced for at least 3 months after vaccination.

Differential Diagnosis

The facial rash and palatal erythema will suggest rubeola (measles). The clinician must examine the oral lesions carefully to assess the presence or absence of true Koplik spots. In addition, scarlet fever, infectious mononucleosis, and adenovirus pharyngitis will present with a similar general picture.

Diagnostic Work-up

Rubella is one of the most worrisome diseases because of the high incidence of congenital rubella (85% in women infected during their first trimester) and the high probability that the baby will have some type of malformation. Therefore, confirmation of suspected rubella is essential. A definitive diagnosis of rubella is made with a fourfold rise in antirubella antibody levels. The rubella virus fluorescent antibody test is most often used.

Histopathology

Rubella is a mild, transient disease in which histology does not have a diagnostic role.

Treatment

The patient requires no specific therapy. Rubella is a short duration, self limiting viral disease. Supportive care consisting of hydration, antipyretics, analgesics, and rest is recommended. It is important to isolate those infected from nonimmunized women of childbearing age for 1 week after the rash has dissipated and to recognize that transmission may have occurred in the 1 week before the appearance of the rash.

Prognosis

The individual's prognosis is excellent, but transmission to a first trimester embryo can be devastating. Such

infection has been associated with congenital heart defects, cataracts, deafness, and growth retardation among other outcomes.

MOLLUSCUM CONTAGIOSUM

It is a disease caused by a virus of the pox group. The lesion, which only occur on the skin or mucosal surfaces, are often considered tumor like in nature because of the typical localized epithelial proliferation caused by the virus.

Clinical Presentation and Pathogenesis

This viral-related skin disease presents with a single or perhaps several round, dome-shaped, waxy papules 2 to 5 mm in diameter. The lesion will be raised with circular rings (umbilicated) and will often contain a caseous plug. Early lesions are firm and flesh colored. As they mature, the lesions become light gray in color and develop their caseous center. Lesions will be seen on the face, hands, lower abdomen and genitals.

Immunocompromised individuals, particularly those with HIV infection, have a high incidence of molluscum contagiosum. Some will present with numerous lesions, particularly on their facial skin and genitals. Because these individuals are immunocompromised, the natural course of the disease—spontaneous resolution and healing—does not occur. Instead, the lesions persist as chronic ulcers.

Molluscum contagiosum is caused by an unclassified pox virus. It is transmitted by direct contact with others, then spread by hand face, hand genitals, or hand abdomen autoinoculation. The site of inoculation is the site of the lesion, but the incubation time is long (2 to 3 months).

Differential Diagnosis

Individually, the skin lesions bear a resemblance to cystic acne. They may also mimic the course of a keratoacanthoma. Multiple lesions may even suggest Torre's syndrome, one component of which is multiple keratoacanthomas. In addition, multiple keratoacanthomas are found in children (Ferguson-Smith type) and in adults (Grybowski type). Similarly, the individual lesions can appear like a skin squamous cell carcinoma or a basal cell carcinoma. Multiple lesions may even suggest basal cell nevus syndrome.

Diagnostic Work-up

Diagnosis is made by microscopic examination of a single lesion or a representative lesion among many.

Histopathology

Low power views show a crateriform or cup-shaped lesion in which the folded, acanthotic epithelium is pushed down into the underlying connective tissue. In addition to this striking architecture, the cellular component is remarkable in that viral intracytoplasmic inclusions. These inclusions develop in the lower prickle cell layer as small ovoid eosinophilic structures. As they progress through the epithelium, they enlarge. When they reach the keratinized layer, they may measure as much as 35 um in diameter. At this level, the eosinophilic inclusion is more basophilic, and the nucleus is compressed at the periphery of the cell. These cells, or molluscum bodies, are released, resulting in the formation of a crater. The connective tissue shows little inflammation. If the lesion ruptures and extrudes into the connective tissue, a marked inflammatory reaction will result. Regression is accompanied by mononuclear infiltration, suggesting a cell mediated immunologic reaction.

Treatment

Lesions will be self healing except in the immunocompromised host. However, treatment to more quickly eradicate the lesion and prevent further spread by autoinoculation is common. Curettage of the central core will theoretically shorten the course and may be the preferred therapy if numerous lesions are present. If a single or small number is present, excision is preferred. As alternatives, liquid nitrogen freezing, electrodessiccation, and topical corrosive chemicals such as 25% podophyllum, applied once weekly for 3 weeks, may be used. More recently, imiquimod (Aldara, 3M), an inducer of local interleukin-2 production, has been used. It is applied 3 to 7 times weekly for 4 to 8 weeks.

Prognosis

Self healing or treatment results in resolution without recurrence over 2 months. In the HIV infected individual, immune restoration with proteinase inhibitors or other therapies will stimulate a spontaneous regression of the molluscum contagiosum.

CONDYLOMA ACUMINATUM

It is an an infectious disease caused by a virus which belongs to the same group of human papilloma virus (HPV).

Clinical Presentation and Pathogenesis

The most common oral presentation of condyloma acuminatum, a viral, sexually transmitted disease, is that of a young man with soft, wart like exophytic lesions of the oral commissure and tongue. Other oral lesions may also be present in the floor of the mouth, gingiva, or upper

lip. The lesions will be asymptomatic but noticed by the patient. There is usually a concomitant penile lesion on either the shaft or the glans. In women, who represent only 8 to 10 percent of oral condyloma acuminatum cases, there will be concomitant lesions on the labia and/or vulva. In either sex, there may be similar anal lesions. Homosexual men have a particularly high incidence of anal lesions.

Condyloma acuminatum is also called "venereal warts" or "genital warts." This DNA virus is highly transmissible. It penetrates the outer parakeratin or orthokeratin surfaces of moist, warm mucosa and skin areas. It infects the nucleus of squamous cells and produces a proliferation recognized as a condyloma or wart.

Differential Diagnosis

Individual lesions will resemble a squamous papilloma or a verrucous vulgaris (oral wart). Multiple lesions may resemble a premalignant verrucous hyperplasia, a verrucous carcinoma, or even an exophytic squamous cell carcinoma. Condyloma acuminatum also bears a clinical resemblance to the focal epithelial thickenings seen in focal epithelial hyperplasia (Heck's disease).

Diagnostic Work-up

The diagnosis of condyloma acuminatum is made primarily by the appearance and location of characteristic lesions. Biopsy of the condyloma will rule out the other entities on the differential list and may or may not show enough evidence of intranuclear changes to confirm the diagnosis.

Histopathology

This verrucous lesion is characterized by marked acanthosis with elongation and broadening of the rete ridges. Hyperkeratosis or hyperparakeratosis is not usually present. Mitoses are frequent. Cells with pyknotic nuclei and perinuclear halos are typical and suggest viral involvement. However, mucosal epithelium often shows vacuolization under normal circumstances.

Treatment

The oral and perioral lesions must be treated after the genital and anal lesions have been treated in order to prevent reinfection from hand to mouth transmission. In addition, the sexual partners of the patient must be treated concomitantly or a second round of transmission will occur. Oral and anal lesions are best treated with surgical excision. Some surgeons prefer cryotherapy, the CO_2 laser, or electrodesiccation over scalpel excision. Each can be effective if all the lesions are removed.

The lesions are superficial and are, therefore, excised with peripheral margins at their base and to a depth within the submucosa. Penile and other genital lesions may also be excised but are more frequently treated with 25 percent podophyllum resin in a tincture of benzoin. Podophyllum resin is a 25 percent concentrate that may be applied every 2 to 3 weeks. The purified active compound of podophyllum, podofilox (Condylox, Oclassen), is available for application twice daily for three consecutive days per week for 4 to 6 weeks. Longer applications risk necrosis of normal tissues. In addition, podophyllum is not indicated in pregnant women.

An alternative topical application is 50% trichloroacetic acid (TCA), which can be effective, but treatment is painful and may damage surrounding tissues. Imiquimod (Aldara, 3M) is a 5% cream that induces local interferon as an antiviral cytokine. It is 75% effective in women but only 40% effective in men, presumably because of better tissue absorption through the thinner and moisture tissue of the vulva and labial mucosa. It is applied once daily for three alternating days per week. Because of its high response rate in women, it is recommended for use in pregnancy over the riskier podophyllum.

Prognosis

Recurrent lesions are common with all treatment modalities. Some recurrent lesions arise from infected areas that are clinically normal appearing during treatment, since the virus incubates within cells. Other recurrences are due to reinoculations from infected sexual partners or from unrecognized and untreated genital or anal lesions.

VARICELLA (CHICKENPOX)

Chickenpox is an acute, ubiquitous, extremely contagious disease usually occurring in children and is characterized by an exanthematous vesicular rash. It is most common in the winter and spring month (Fig. 5.3).

Clinical Presentation and Pathogenesis

Classic chickenpox is one of the usual childhood diseases for which vaccinations were not available until the late 1990s. A live attenuated viral vaccine is now recommended for all children over 12 months of age who have not had clinical chickenpox. It is also recommended that children receiving the vaccine not take aspirin for the following 6 weeks because of the possibility of Reye's syndrome, a rare complication that may produce progressive hepatic failure and encephalopathy with a 30% mortality rate. While Reye's syndrome may occur unrelated to any specific event, vaccinations are a recognized risk that increases with aspirin ingestion.

The child who develops varicella is usually between 4 to 10 years of age. Painful red pustules and vesicles develop

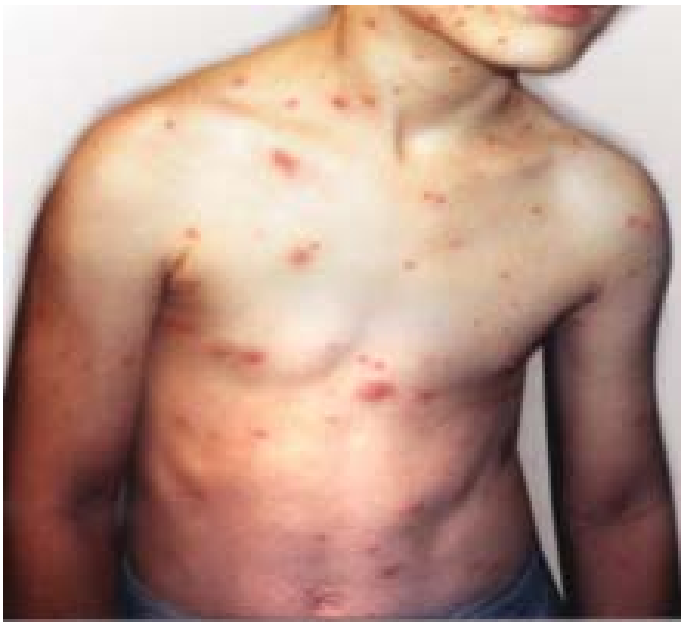


Fig. 5.3: Varicella (chickenpox) red pustules and vesicles

mainly on the trunk and facial skin. The vesicles quickly rupture and form crusting lesions as they mature. The child is usually acutely ill with fever, chills, agitated behavior lapsing into malaise, and a complaint of headache. Successive formations of new lesions occur because of intermittent viremias, producing lesions in all stages of maturity. The oral mucosa may also show lesions, but they are fewer in number. The lesions are both pruritic and painful. Children often scratch them, creating secondary bacterial infections.

In adults, the lesions are identical, but complications are more frequent. Rare complications such as viral encephalitis and pneumonia have been noted. Varicella virus does cross the placenta and may cause fetal malformation.

Chickenpox is caused by the varicella zoster virus (VZV), which is a type of herpes virus. The VZV, like the HSV, is transmitted initially by direct water droplet transmission. The VZV penetrates the epithelium and becomes engulfed by macrophages and other phagocytes. The virus proliferates within the phagocytes and egresses from them to be disseminated via the circulation, which is often called the incubation phase.

The subsequent viremia associated dissemination implants viruses throughout the skin, producing the characteristic skin lesions.

As the host defenses consisting mainly of IgM and IgG antibody production and T cell-mediated reactions with interferon production gain ground on the vast viral numbers, the lesions begin to heal and the constitutional symptoms dissipate. Like HSV, VZV will escape to the protection of the blood-brain barrier via proximal migration along the epineurium of sensory nerves to their respective ganglia. There they remain in a latent or dormant form and will, on certain stimuli or reductions in the level of immune surveillance, migrate outward toward the same nerve endings to produce the lesions of herpes zoster.

Differential Diagnosis

The main differential diagnoses of concern in a child with painful skin lesions with accompanying fever are the other childhood diseases such as rubeola (measles) and rubella (German measles). A developing Stevens-Johnson form of erythema multiforme is another possibility. Less common today, scarlet fever and, if in the summer, hand-foot-and-mouth disease may also show skin rashes, associated fever, and constitutional symptoms.

Diagnostic Work-up

Diagnosis is made by history and clinical examination only. Varicella is diagnosed by the onset, appearance, and locations of characteristic lesions.

Histopathology

The essential histologic changes within skin and mucous membrane are the same for the three infections caused by herpes virus: Herpes simplex, varicella, herpes zoster. As in all vesiculobullous lesions, the specific features may be seen only in early lesions; biopsy of long standing and ruptured lesions should be avoided.

In these herpetic infections, the vesicle initially forms in the prickle cell layer secondary to degenerative changes induced by the virus. This takes two forms. Ballooning degeneration, which is seen mainly in the floor of the vesicle, causes expansion of the cell (Fig. 5.4). The cell has

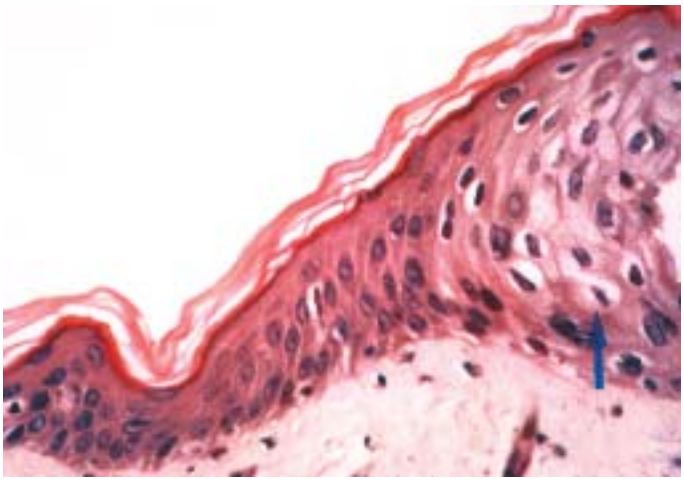


Fig. 5.4: Varicella zoster—balloon degeneration of epithelial cells

an eosinophilic cytoplasm and a single nucleus or multiple nuclei. The nucleus is usually enlarged and may have an irregular contour. With H&E, it has a washed out, steel-gray appearance and shows margination of the nuclear material. These cells lose their intercellular bridges, and this acantholytic process creates the vesicle. These cells may be identified by cytologic smears. The vesicle may "bottom out," so that it has a subepithelial rather than an intraepithelial location.

In reticular degeneration, which occurs essentially in the superior and lateral aspects of the vesicle, there is intracellular edema such that the epithelial cells rupture, leaving strands from the cell walls to form a multilocular vesicle.

Eosinophilic inclusions (Lipschutz bodies), about 3 to 8 um in diameter, may be seen within the nucleus. The underlying connective tissue shows an inflammatory reaction of varying intensity.

Treatment

Varicella is a self-limiting disease in the immunocompetent individual because of the formation of antivaricella antibodies. Supportive care consisting of hydration, analgesics, antipyretics, and rest is recommended during the course of the disease, which lasts from 10 to 21 days. Patients should be isolated until they are afebrile, the crust from skin lesions has disappeared, and the healing areas are dry. Immunocompromised individuals and HIV infected individuals are at particularly high-risk. In immunocompromised patients and pregnant women in the third trimester, acyclovir, 30 mg/kg per day in three intravenous doses for 7 to 10 days, is the treatment of choice. For cases refractory to acyclovir, foscarnet (Foscavir, Astra Zeneca) may be administered at a loading dose of 20 mg/kg intravenously followed by 120 mg/kg intravenously three times daily for 2 weeks.

Varicella zoster immune globulin (VZIG) is effective in preventing varicella in exposed, susceptible individuals with no natural or vaccine derived immunity. It is given at a dosage of 125 U/kg up to a maximum of 625 U with consideration for a repeat dose in high-risk individuals with continued exposure. However, VZIG is not to be used to treat an active case of varicella. Because VZIG binds directly to live attenuated virus in the varicella vaccine, they should not be used together.

Prognosis

In the immunocompetent individual, varicella is a self resolving disease that may leave some residual scarring. In the immunocompromised individual, it can be a desperate situation requiring trials of potent antiviral drugs at high doses and may contribute to the individual's death.

HERPES ZOSTER (SHINGLES, ZONA)

Herpes zoster is an acute infectious viral disease of an extremely painful and incapacitating nature which is characterized by inflammation of dorsal root ganglion, or extramedullary cranial nerve ganglion, associated with vesicular eruptions of the skin or mucous membrane in areas supplied by affected sensory nerves.

Clinical Presentation

Herpes zoster is a disease of reactivated latent varicella zoster virus (VZV), which frequently occurs in older adults who have had some compromise in their immune status. Lesions that are pustular and vesicular, form after a short prodrome of pain and itching sensations. The lesion will follow a peripheral nerve distribution precisely and stop abruptly at the midline. The lesions will quickly ulcerate and become necrotic with crusting. Pain is usually intense and constant. The most common immune status alterations are those related to lymphomas (particularly Hodgkin lymphoma and T-cell lymphomas) and leukemias. It is also seen in chronically ill patients and patients who are receiving chemotherapy, radiotherapy, or immunosuppressive drugs. It may also occur in otherwise normal individuals.

The dermatomes of the chest wall is the most common site for herpes zoster, but the areas of trigeminal nerve distributions, particularly the ophthalmic division, is the next most common site. If herpes zoster lesions involve a trigeminal nerve distribution plus one other cranial nerve distribution (most commonly the facial nerve producing a facial paralysis, the condition is termed the Ramsay Hunt syndrome (after James Ramsay Hunt), and the lesions characteristically begin in the external ear and mimic a painful otitis externa.

Differential Diagnosis

Herpes zoster is a diagnosis of clinical recognition rarely confused with other diseases. In the oral cavity and in its early stages, the presentation of burning and pain may be confused with recurrent herpes simplex lesions or perhaps a focal atrophic candidiasis.

Diagnostic Work-up

In equivocal cases, immunoperoxidase testing using anti-VZV antibodies to identify VZV in fixed biopsy specimens may be needed. Otherwise, herpes zoster is a clinical diagnosis.

Histopathology

Changes beyond those within skin and mucosa may be seen and can be significant in this disease. With reactivation of the virus in the ganglion, the ganglion becomes edematous

and there is infiltration by lymphocytes, plasma cells, and macrophages. Focal areas of necrosis may occur, and intranuclear inclusions may be found in the neurons. Following the attack, the ganglion returns to normal except for loss of neurons secondary to fibrous scarring. The varicella- zoster virus may also cause a lymphadenitis, which may resemble lymphoma because of its diffuse pattern, capsular involvement, and atypical immunoblasts.

Treatment

Herpes zoster is a painful and debilitating disease that is destructive of tissue. Skin necrosis with severe scar formation often occurs, as does pain after the lesions have healed (a condition called postherpetic neuralgia). Lesions frequently become secondarily infected by bacteria, and there is a high incidence of encephalitis complications if the ophthalmic division is involved. Treatment should begin as soon as possible and it should be aimed at shortening the disease course, preventing tissue loss, and reducing postherpetic neuralgia. Acyclovir, as much as 800 mg five times daily, is recommended, along with carbamazepine (Tegretol, Novartis), 200 mg three or four times daily, to reduce neuralgic pain. If oral lesions predominate, patients often will not be able to eat. In such cases, intravenous fluid management or nasogastric feedings may be needed.

In the immunocompromised patient, herpes zoster is even more serious. Intravenous acyclovir, 30 mg/kg per day in three divided doses, is used. Immunocompromised individuals exposed to herpes zoster are considered for the varicella-zoster immune globulin (VZIG).

Immunocompetent patients respond to acyclovir very well. Lesions remit, leaving scars and, in up to 40% of cases, postherpetic neuralgia. Postherpetic neuralgia is at its most intense early after a herpes zoster infection and will diminish with time. During this time, carbamazepine, 200 mg one to three times daily, will alleviate most of the pain.

HIV DISEASE AND AIDS

AIDS is caused by the human immunodeficiency virus (HIV) and is characterized by immunosuppression, which leads to a spectrum of clinical manifestations that include opportunistic infections, secondary neoplasms and neurologic manifestations.

Clinical Presentation and Pathogenesis

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) represent two ends of a spectrum of one infectious disease that first became known to medical scientists in 1980. Between 1980 and 2000, the infectious agent, its mode of transmission, its mode of cellular entry, and its transmissibility were thoroughly documented, and potent antiretroviral medications were developed to control the effects of this disease. During the same period, a combination of preventive measures and lifestyle modifications reduced both individual risk and the rate of disease transmission (Fig. 5.5).

Today, HIV infection is confirmed either by the identification of HIV antibodies in the serum or, more commonly, by measurement of viral load, which identifies the level of HIV RNA in copies/mL. The progression of HIV infection to AIDS is defined by CD4 cell counts of less than 200/mm^3, or about 14 percent of the usual number of CD4 T-helper lymphocytes.

HIV/AIDS Infection and the Natural Disease Course

After gaining access to the bloodstream, viable HIV viruses initially become entrapped in the regional lymph nodes. In terms of size, the viral particles are 100 nm (or 0.1 µm), much smaller than bacteria, which are about 1 µm (10 times larger) or human lymphocytes, which are 15 µm (150 times larger). The presence of the virus evokes an antigenic stimulation, which activates the CD4 T-helper cell lymphocytes and macrophages. These cells secrete growth factors and other cytokines, such as tumor necrosis factor (TNF) and interleukin-6, leading to a multiplication of the CD4 cells. Paradoxically, this increases the number of cells

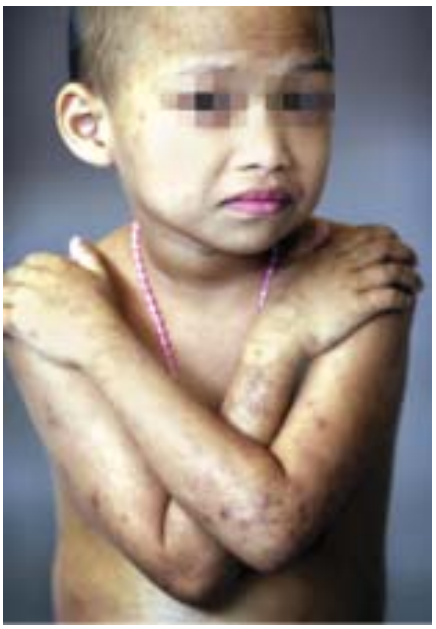


Fig. 5.5: AIDS patient displays arms, covered with skin infections associated with the AIDS virus

vulnerable to the HIV virus, thereby increasing the viral load itself.

To infect the CD4 lymphocyte, the HIV virus adheres to its surface via interaction between the viral gp120 surface glycoprotein and a CD4 cell surface membrane receptor, which serves as the point of entry for the viral RNA.

Within 2 weeks, the HIV virus will have repeatedly replicated itself in the many CD4 cells that will have proliferated by means of the antigenic stimulus and migrated throughout the body. At first the CD4 cells will mount a humoral and cellular attack on the HIV virus, reducing its numbers in serum and partially controlling the infection. However, the continued replication of viruses in the lymph nodes will continue subclinically. Initially thought to represent a latency period, during which time the flu-like symptoms of HIV inoculation and lymphadenopathy cease, it is now known that viral numbers (viral load) actually increase during this period.

Viruses present in the plasma come from recently infected circulating CD4 cells that replicate HIV viruses in great numbers. They produce 93 percent of circulating viruses and are the driving force behind the disease. In addition, however, many noncirculating and slow turnover cells, such as macrophages in lymph nodes, the central nervous system, testicles, and other tissues, also harbor viruses but are not stimulated to replicate, thereby serving as reservoirs of HIV. These so called immunologic sanctuaries are an important factor in the treatment of HIV because of the difficulty of most antiretroviral drugs to penetrate such tissues.

After several years, the continuously high rate of HIV replication eventually destroys the lymph nodes, which until then had kept the virus relatively contained by means of the controlling effects of humoral (antibody) and cellular (cytokine and engulfment) responses that subdued viral reproduction. At this point the virus will reproduce itself unchecked, leading to an explosion of viral numbers (viral load increases) and a reduction in the number of CD4 cells. When the CD4 cell blood count falls below 200/mm^3, the individual is diagnosed with AIDS, at which point secondary opportunistic infections, such as candidiasis, hairy leukoplakia, pneumocystis carinii pneumonia (PCP), and neoplasias begin to emerge. When left untreated, the course from HIV inoculation to AIDS takes about 7 to 10 years.

Position of Individuals in the HIV/AIDS Continuum

Normally, the oral and maxillofacial specialist will not be directly involved in the initial diagnosis or complex treatment of HIV-infected individuals. However, he or she will often manage HIV-related complications by providing therapies or accomplishing surgeries. This requires an assessment of the stage and degree of control of the HIV infection and can be accomplished with knowledge of two specific laboratory values—the viral load and the CD4 count—in addition to those commonly used to assess surgical/anesthetic risk. As stated earlier, the viral load refers to HIV RNA in copies/mL of blood and serves as an index of the rate of HIV progression. Viral load values should be assessed every 2 to 4 months to monitor any changes, since increasing viral loads imply a faster progression of HIV to AIDS, a lack of response to antiretroviral treatment, or a resistance to antiretroviral treatment, each of which will increase the risk of complications and death if surgery is accomplished. The CD4 cell count refers to the absolute number of CD4 cells and serves as a yardstick of the individual's progression toward AIDS and its related opportunistic infections and neoplasms, and of the severity of AIDS (if the count is under 200/mm3). The lower the CD4 count, the higher the risk of complications and death should surgeries become necessary. To better understand these values, they can be conceptualized by imagining the HIV-infected individual running toward a cliff. The speed at which the individual runs is represented by the viral load; when he or she reaches a CD4 cell count of 200 cells/mm3, a mile marker in the individual's path indicates actual AIDS. The point at which the individual reaches the cliff and falls to his or her death occurs soon after he or she passes the 200/mm^3 milestone, somewhere around 50/mm^3.

Oral Manifestations of HIV and AIDS

The oral and maxillofacial specialist must be trained to recognize the oral and head-neck manifestations of HIV infection and AIDS. The following is a brief overview of the more common oral manifestations of AIDS and some palliative measures that can be taken. However, it is important to remember that the best controlling measure is systemic antiretroviral therapy to reduce the HIV viral load.

Candidiasis

Oral candidiasis is common in HIV infection and may be caused by several species. Active oral candidiasis is best treated with oral nystatin suspension, 500,000 U three times a day swish and spit or swish and swallow, combined with fluconazole (Diflucan, Pfizer), 100 mg by mouth daily. Diflucan can be discontinued if or when the oral lesions improve and if those at other sites are resolved.

HIV Lymphadenitis

A generalized lymphadenopathy may be seen early or late in the HIV continuum. Later in the course of the disease

lymph node biopsies may be necessary to rule out lymphoma or scrofula.

Kaposi's Sarcoma

In HIV/AIDS, oral Kaposi's lesions most commonly appear on the palate. They may first appear in the submucosa as a bluish macular area or develop into a reddish purplish mass. While a reduction in the viral load will often reduce the size of the Kaposi's lesions, direct therapy with intralesional injections of vinblastine (0.1 to 0.5 mg/mL) will produce this effect more directly. In addition, local radiotherapy of 1,800 cGy is effective, as well as local excision if the lesions are accessible to surgery. Systemic chemotherapy is a last resort, but graded responses are known with varying doses of doxorubicin.

Hairy Leukoplakia

Hairy leukoplakia represents another opportunistic infection, in this case by the Epstein-Barr virus. The lateral border and dorsum of the tongue are the most commonly affected sites, although the floor of the mouth and the buccal mucosa may be involved as well. The lesions appear as short, white strands that project from the surface epithelium. Once thought to be an early sign of AIDS, hairy leukoplakia is now understood to be only one of many opportunistic infections that may develop as the CD4 count approaches 200/mm^3. There is no specific treatment for hairy leukoplakia other than systemic antiretroviral therapy.

Oral Infections

Various oral infections may be seen, and a more rapid advancement of each type has been reported. Those most commonly seen in HIV/AIDS are aphthous ulcers, so-called HIV gingivitis and HIV periodontitis, recurrent herpes simplex lesions, herpes zoster, cytomegalic virus infections, and even osteomyelitis. All are treated as they are in the non HIV patient, but treatments may be more intensive and need to continue for longer durations.

HIV Parotitis

This entity represents the development of multiple lymphoepithelial cysts and generalized lymphocytic infiltrations of the parotids. It is usually expansile and painful and is treated with either superficial parotidectomies or with radiotherapy of 1,800 to 2,400 cGy.

Histopathology

In hairy leukoplakia, the surface of the specimen is covered by a thick layer of parakeratin, which may have surface projections. Below the parakeratin are balloon cells with pyknotic nuclei surrounded by clear areas called koilocytes (hollow cells), they tend to be seen in viral infections. Some cells may show peripheral rimming of nuclear chromatin. The epithelium is also acanthotic. The corium is either free of inflammation or contains a minimal number of inflammatory cells. Many cases will also have candidal hyphae within the parakeratin. Ultrastructural and immunopathologic studies have confirmed the presence of Epstein-Barr virus.

Current HIV/AIDS Therapies

At the time of this writing, a catch phrase for treating HIV/AIDS is to treat with a lot of HAART, which stands for highly active antiretroviral therapy and refers to combinations of drugs that include a protease inhibitor and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI). The goal of this therapy is to reduce the viral load to undetectable levels so that, at most, only those viruses in the immunologic sanctuaries remain. Combinations of three drugs—zidovudine (ZDV or AZT), lamivudine (3TC), and indinavir (IDV)—have produced undetectable viral loads in 75 to 80 percent of individuals, and this therapy remains encouraging.

The antiviral HIV drugs currently in use are:

Nucleoside Analogs

These were the first drugs used to treat and prevent HIV infection. Represented by ZDV or AZT, zalcitabine (DDS), didanosine (DDI), and 3TC, these drugs competitively inhibit viral replication by competing with natural nucleosides when the HIV virus synthesizes proviral DNA using its reverse transcriptase enzyme. As a result, the faulty proviral DNA does not transcribe HIV RNA, and replication is blocked. However, their effectiveness is reduced by competitive inhibition, whereby the viral speed of reproduction incorporates natural nucleosides so quickly that it overcomes the drug. Effectiveness is also reduced by specific mutations to resistant forms.

Protease Inhibitors

The protease inhibitors represented a revolution in antiretroviral therapy when they were introduced in 1995, and they remain a focal point of therapy today. Represented by saquinavir (SAQ), ritonavir (RIT), IDV, nelfinavir (NFV), and amprenavir (APV), these drugs are both competitive and noncompetitive inhibitors of HIV replication, acting on the HIV protease enzyme. The HIV protease enzymes are necessary for viral infectivity; they act in the later phases of virion maturity, when various glycoproteins necessary for infection are assembled. The protease inhibitors work by creating an immature noninfective virus that the immune system can destroy, and since the structure of HIV

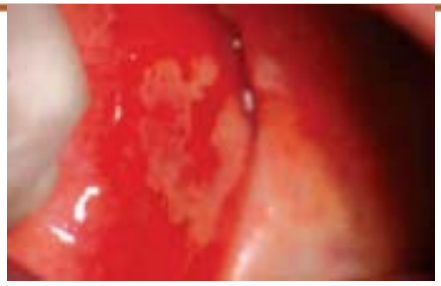
proteases is unique to retroviruses and differs significantly from that of human proteases, human toxicity is minor or nonexistent. However, used alone, even these potent antiretroviral drugs are not completely effective. Various mutations in the HIV proteases have already conferred resistance to some drugs, which explains initial responses followed by an increase in viral load.

Non-nucleoside Reverse Transcriptase Inhibitors

The NNRTIs have received FDA approval only for the treatment of HIV infection in combination with other drugs of a different type, owing to the rapid emergence of drug resistance to NNRTIs when used alone (This well-known microorganism response to a single drug recalls to mind the rapid emergence of resistant mycobacteria to isoniazid (INH) when used alone to treat tuberculosis). Represented by nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV), this group acts as noncompetitive inhibitors of the reverse transcriptase enzyme. Essentially, these agents bind directly and irreversibly to the active site of the enzyme to deactivate it and thus prevent the synthesis of proviral DNA.

6

Fungal Infections



Mycology, the study of fungal infections, has gained remarkable impetus in the past few decades, owing at least in past to the fact that fungal diseases are far more common than was previously suspected.

CANDIDIASIS (CANDIDOSIS, MONILIASIS, THRUSH)

It is the most opportunistic infection of the world caused by a yeast-like fungus *Candida albicans.*

Pseudomembranous Candidiasis

The most common form of oral candidiasis is the pseudomembranous form often referred to as thrush. The most common predisposing factor is the concurrent or recent administration of systemic antibiotics or even a short course of antibiotics used for prophylaxis to cover a surgery. The affected mucosa becomes tender with red and white areas. The white areas are gelatinous plaques of cellular debris mixed with *Candida* organisms. The red areas are caused by organism invasion into the upper layers of the mucosa, resulting in loss of parakeratinization, atrophy, hyperemia, and inflammation. The white plaques characteristically can be scraped off, leaving small hemorrhagic areas behind. This pseudomembranous form is also seen in the very young and very old: Infants often have immature host defenses, and the elderly often have immune exhaustion or chronic disease impairment of their host defenses. Similarly, patients with oral cancer and other more distant types of cancer develop candidiasis, presumably as a result of exhaustion of the cell-mediated arm of their immune system.

Patients with radiation xerostomia, a recent history of chemotherapy, a Sjögren's syndrome-type of xerostomia, and leukemia develop candidiasis with an incidence approaching 70%. In addition, HIV-infected patients and those who have progressed to AIDS frequently develop candidiasis, indicative of their T-cell impairment (Fig. 6.1).

Oral thrush is commonly found in bottle-fed infants.

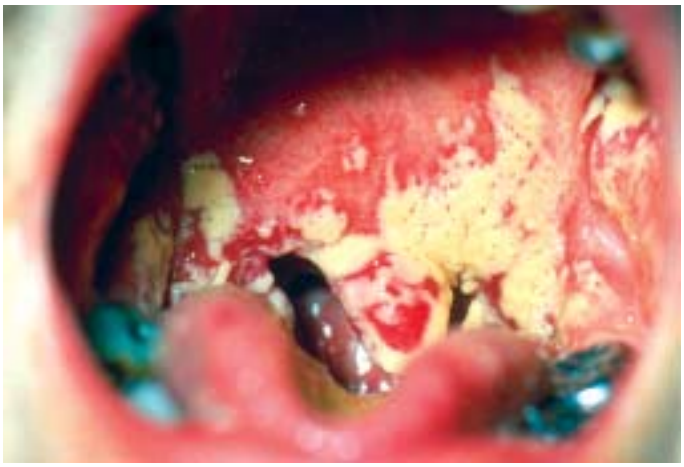


Fig. 6.1: Pseudomembranous candidiasis

Mucocutaneous Candidiasis

Mucocutaneous candidiasis is the most serious form of candidiasis. It suggests a systemic distribution and a more extensive degree of host defense compromise. It will present with a pseudomembranous oral presentation but will also show skin, esophageal, and nail involvement. The nail involvement will be particularly prominent: The nailbed will be destroyed and the nails disfigured.

Several etiologies of this form of candidiasis are recognized. One is a predisposition for the infection, which is the result of an autosomal -recessive inheritance; 50% of these are associated with an endocrinopathy consisting of either hypoparathyroidism, hypothyroidism, Addison type of adrenal cortical insufficiency, or diabetes mellitus. The remaining inherited forms include those related to cellular immune deficiencies and rarely to deficiencies of iron metabolism. The candidiasis seen in AIDS patients and those with HIV infection not yet progressed to AIDS is essentially a mucocutaneous form, which is often first seen on the oral mucosa but may become disseminated to involve skin and even internal organs (Fig. 6.2).

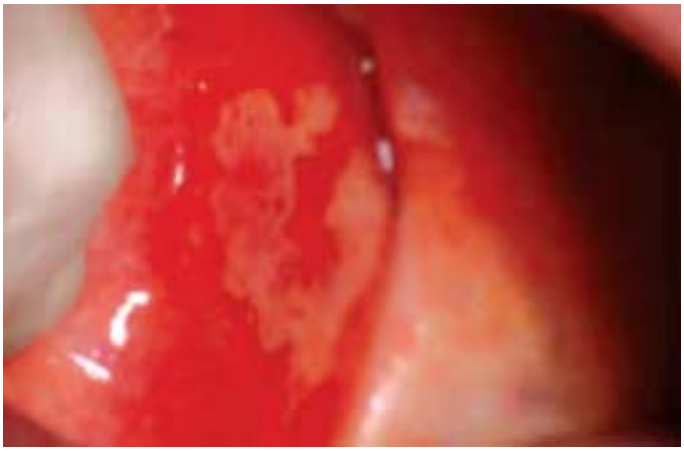


Fig. 6.2: Mucocutaneous candidiasis

Mucocutaneous form of candidiasis will resemble the mucous patches of secondary syphilis, mucosal chemical or heat burns, and the spectrum of lesions of clinical leukoplakia such as verrucous hyperplasia, verrucous carcinoma, and squamous cell carcinoma. The median rhomboid glossitis presentation is also suggestive of lichen planus. The atrophic form, in which a pebbly, velvet-like, soft tissue enlargement of the palate develops, will at times suggest a non-Hodgkin lymphoma. It is also often termed inflammatory hyperplasia of the palate. The disseminated form will appear as a bacterial septicemia often with thrombophlebitis.

Diagnostic Work-up

The most straightforward and least equivocal diagnostic approach is a tissue biopsy stained with a PAS stain. A PAS -stained tissue specimen will better outline the organisms and show evidence of tissue invasion.

Candida organisms can and should be cultured as part of the diagnostic work-up, although the diagnosis is primarily achieved by microscopy. The organisms can be readily cultured on Sabouraud's media or routine blood agar plates. The culture has less diagnostic value than it has for treatment selection, since C albicans is very sensitive to fluconazole (Diflucan), whereas other species of Candida are usually not as sensitive.

Histopathology

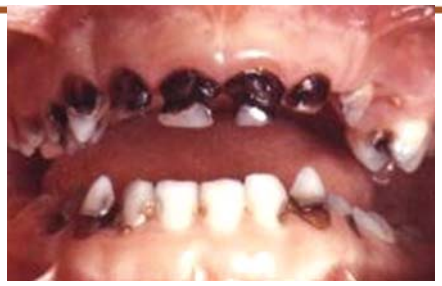
In acute pseudomembranous candidiasis, the plaque represents a thickened parakeratinized layer, separated by edema and infiltrated by neutrophils. The neutrophils collect as microabscesses at the base of the plaque, enabling its ready separation. It also contains numerous hyphae, many of which lie perpendicular to the surface. The organisms are readily identified with PAS or silver stain. They are capable of invading the epithelial cytoplasm and existing as intracellular parasites. Beneath the plaque, the epithelium is acanthotic and usually free of inflammation. The underlying connective tissue, however, is infiltrated by lymphocytes, plasma cells, and macrophages.

Treatment

In all forms of candidiasis, an important pre-requisite to treatment is reversal or withdrawal of the concomitant underlying factor when possible. Specific therapy for mild oral disease is nystatin oral suspension (Mycostatin, Westwood Squibb), 100,000 U/mL to be taken. 5 mL (one teaspoon) at a time as an oral swish and spit or swish and swallow four times daily. For chronic, well-established candidiasis limited to the oral cavity and upper digestive tract, nystatin as noted above combined with clotrimazole troches (Mycelex, Alza), 10 mg five times daily, or the vaginal suppositories used as an oral troche three times daily, is very effective. It should be noted that the clotrimazole troches contain sugars that in xerostomic patients, in particular, may stimulate active caries. For this reason, some clinicians prefer the nystatin vaginal suppositories combined with nystatin oral suspension.

7

Dental Caries



Dental caries is an irreversible microbial disease of the calcified tissues of the teeth, characterized by demineralization of inorganic portion and destruction of organic substance of the tooth which often leads to cavitation. It affects persons of both genders in all races, all socioeconomic strata and every age group.

ETIOLOGY OF DENTAL CARIES

Role of Carbohydrates

The presence of readily fermentable carbohydrates has been thought to be responsible for the loss of caries resistance. A cariogenecity of a dietary carbohydrate varies with the frequency of ingestion, physical form, chemical composition, route of administration and presence of other food constituents. Sticky, solid carbohydrates are more caries producing than consumed as liquids. Polysaccharides are less easily fermented by plaque bacteria than monosaccharides and disaccharides. Plaque organisms produce little acid from the sugar alcohols, sorbitol and mannitol. Glucose or sucrose fed entirely by stomach tube or intravenously does not contribute to any decay as they are unavailable for microbial breakdown. Refined, pure carbohydrates are more caries producing than crude carbohydrates complexed with other food elements capable of reducing enamel solubility or possessing anti bacterial properties.

Role of Microorganisms

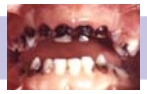
Miller demonstrated the presence of microorganisms within the tubules of decayed teeth mainly cocci and leptothrix and laid the foundation for the role of acids elaborated by bacteria in caries production. It played a role in decalcification of both enamel and dentin. From the carious dentin a bacteria called bacillus acidophilus odontolyticus was isolated. A new streptococcus *Streptococcus mutans* was invariably isolated from carious lesions in the teeth. Microorganisms isolated from the deeper carious cavities were mainly acidogenic streptococci and concluded that there was an apparent relationship of lactobacilli with initial caries and of streptococci with more advanced lesions of dentin.

Microbial Flora and Dental Caries

Type of Caries	Microorganisms
Pit and fissure	*S.mutans* *S.sanguis* *Lactobacillus sp*
Smooth surface	*S.mutans* *S.salivarius*
Root surface	*A.viscosus* *A.naeslundii* *S.mutans* *S.sanguis*
Deep dentinal caries	*Lactobacilli sp* *A.naeslundii* *and other filamentous rods*

Role of Acids

Mechanism of carbohydrate degradation to form acids in oral cavity by bacterial action probably occurs through enzymatic breakdown of sugar and the acids formed are chiefly lactic acid. Carbohydrates and more specifically sugars have been implicated in caries etiology and acid production from these food substances have been studied. Anaerobic catabolism of carbohydrates called fermentation or glycolysis predominates in plaque. The end products of glycolysis have the same empirical formula as the starting substrate in that one molecule of glucose breaks into two molecules of lactic acid. Organisms such as streptococci and many lactobacilli ferment sugars which produce 90% or more lactic acid as end product and are called homofermentative. Heterofermentatives produce a mixture of metabolites including organic acids such as propionic, butyric, succinic and ethanol.



Tooth Factor

The structure and composition of teeth undoubtedly influence the initiation and rate of progression of a carious lesion, which determines its caries susceptibility or caries immunity. Studies on chemical composition of enamel indicate that surface enamel is more resistant to caries than subsurface enamel. Surface enamel is more highly mineralized and tend to accumulate greater quantities of fluoride, zinc, iron than underlying enamel. On the other hand, the concentration of carbonate, magnesium and sodium is lower in the surface layer and increases near DEJ.

Anatomic Characteristics of Teeth

Certain teeth of many patients particularly permanent teeth seem vulnerable to dental caries as they emerge and, in caries active mouths, they may show evidence of attack almost coincident with their eruption into the oral cavity.

Arrangement of Teeth in the Arch

Crowded and irregular teeth are not seen readily cleansed during natural masticatory process. This condition may attribute to dental caries. Partial dentures, space maintainers, orthodontic appliances, encourage retention of food debris and plaque material and they result in increase in bacterial population.

Other Factors Influencing Dental Caries

Saliva

Any patient with salivary deficiency from any cause is at higher risk for caries activities as the dental caries process is controlled to a large extent by a natural protective mechanism inherent within the saliva. The saliva manifests a variety of anti-bacterial and other anti-infectious properties. Saliva is secreted by three pairs of major salivary glands—the submandibular, parotid and sublingual glands. Small accessory glands are also scattered over the oral mucous membranes, each of these has its own duct. The secretion resulting from parasympathetic stimulation is profuse and watery in most animals. Sympathetic stimulation causes a scanty secretion of a thick mucinous juice. Stimulation of the parasympathetic fibers to the parotid gland causes a profuse, watery secretion.

Salivary deficiency: A pronounced reduction or complete absence of saliva will result in a septic mouth with rampant caries. In addition to rapid destruction of the teeth, there may be dryness and cracking of lips, with fissuring at corners of the mouth, burning and soreness of mucous membranes, crusting of tongue and palate and sometimes paresthesia of tongue or mucous membrane. During the acute stages of mumps a temporary reduction in salivary flow may occur. Immune disorders such as Sjögren's syndrome, genetic conditions such as hypohidrotic ectodermal dysplasia, often exhibit chronic xerostomia. Many oncology patients receive head and neck or total body irradiation also resulting in salivary gland dysfunction.

An interruption in the central pathways of the secretory nerves has been suggested as the cause of salivary failure but this is usually over shadowed by definite neurologic signs and symptoms. Similarly, a deficiency of vitamin B complex has been reported as a cause of salivary gland dysfunction. Dryness of the mouth may occur after the use of variety of anti histamines and tranquilizers. It has been observed that dry mouth and rampant caries may accompany a systemic condition such as myasthenia gravis. In this disease the acetylcholine that is necessary for the proper transmission of nerve impulses is destroyed, as a result the salivary glands do not receive adequate stimulation.

If the salivary glands have not undergone degenerative or metaplastic change and if the nerve path is between CNS and salivary glands are still intact, salivary stimulants may be recommended. If dryness of the mouth is attributable to dehydration, increased fluid intake is recommended. Use of gustatory stimulus (sugar free candy) are masticatory stimulants(xylitol gum) has been suggested as an adjunct to encourage salivation. Use of salivary substitutes are useful in preventing soft tissue problems associated with dry mouth. Fluoride and chlorhexidine rinses are reported to enhance remineralization and promote resistance to demineralization of tooth surfaces and may help preventing radiation in used caries.

Socioeconomic Status

It is noted that children and adolescents living in poverty suffer twice as much as tooth decay as their more affluent peers and that their disease is more likely to go untreated. The available data confirmed that from a demographic perspective, economically poor children are at high risk for dental caries.

Hereditary Factors

Certain genetic influences on caries process are relatively minor in comparison with overall effect of environmental factors. It may be influential in promoting or preventing dental caries activity, available effective preventive therapies along with proper dietary and plaque control measures can override the hereditary factors that contribute to caries development.

CARIES PREVALENCE IN PRESCHOOL CHILDREN

Researchers have found dental caries in 4.2% of children in a community of 441 of age 12-17 months, 19.8% in 24-29 months of age, 36.4% in 30-36 months of age. Children in middle and middle low socio-economic groups showed a trend towards higher caries frequencies. 30.5% of 200 preschool children had caries detectable by visual or radiographic examination. In a longitudinal evaluation of caries pattern in 317 children followed an average of 7.8 years in private dental practices found 84% of children who were caries free in the primary dentition remained in mixed dentition also. Children with pit and fissure caries in primary dentition developed smooth surface caries more frequently than caries free children. 57% of children with proximal lesions in primary molars, in primary dentition developed additional primary molar proximal lesion in mixed dentition. Children with nursing caries were at highest risk of any group for developing additional carious lesions.

TYPES OF CARIES

Pit and Fissure Caries

Based on relative susceptibility of surfaces of teeth, pit and fissure caries of primary type develops in the occlusal surface of molars and premolars, in buccal and lingual surface of molars and palatal surface of maxillary incisors. Teeth having steep walls, narrow bases are prone to develop caries due to their mechanical characteristics which result in poor self-cleansing features. Sometimes these pits and fissures are considered as development faults. Deep narrow pits and fissures favor the retention of food debris along with microorganisms and caries may result from fermentation of this food and formation of acid. Pits and fissures affected by early caries may appear brown or black with slight feeling of soft and "catch" a fine explorer point. The enamel directly bordering the pit or fissure may appear opaque bluish white as it becomes undermined. This occurs through lateral spread of caries at dentino-enamel junction (DEJ) and may be a rapid process if the enamel in the base of pit or fissure is thin (Fig. 7.1).

Smooth Surface Caries

This type develops on proximal surface of teeth and on gingival third of buccal and lingual surface. It is generally preceded by formation of microbial plaque. This ensures the retention of carbohydrate and microorganisms on the tooth surface in an area not habitually cleansed, and the subsequent formation of acid to initiate caries process. Proximal caries usually begins below the contact point, and appears in the early stage as a faint white opacity of the enamel without apparent loss of continuity of enamel surface. Early white chalky spot becomes slightly roughened, owing to superficial decalcification of enamel. As caries penetrates the enamel, the enamel surrounding the lesion assumes a bluish white appearance similar to that seen around carious pits or fissures (Fig. 7.2).

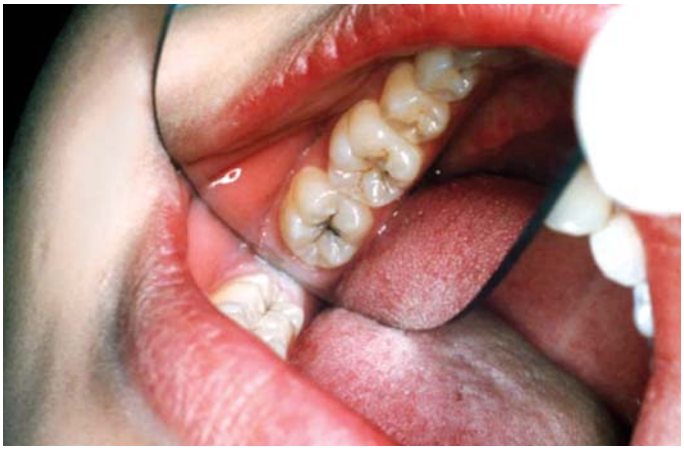


Fig. 7.1: Pit and fissure caries

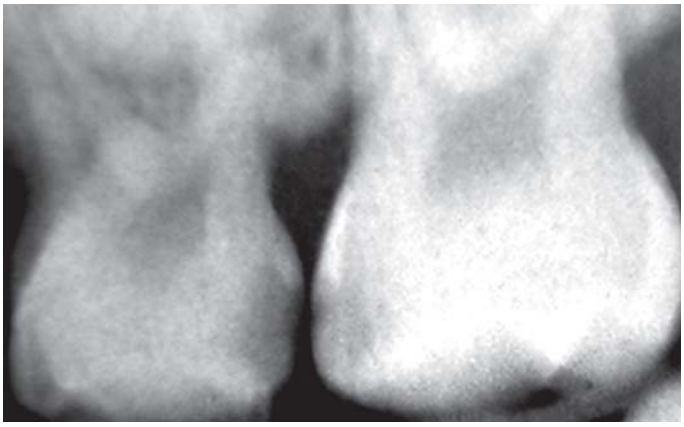


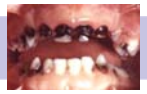
Fig. 7.2: Interproximal caries

Early Childhood Caries

American Academy of Pediatric Dentistry defines early childhood caries as the presence of one or more decayed, missing, filled tooth surfaces in any primary tooth in a child 71 months of age or younger. The academy also specifies that children younger than 36 months of age, any sign of smooth surface caries is indicative of severe early childhood caries.

There is an early carious involvement of maxillary anterior teeth, the maxillary and mandibular first primary molars and sometimes the mandibular canines. The mandibular incissors are usually unaffected.

A discussion with parents often reveals an inappropriate feeding pattern; the child has been put to bed at afternoon



nap time or at night with nursing bottle holding milk or sugar containing beverage. The child falls asleep and liquid becomes pooled around the teeth. The lower anterior teeth tend to be protected by the tongue. It seems that carbohydrate containing liquid provides an excellent culture medium for acidogenic microorganisms. Salivary flow is also decreased during sleep, and clearance of the liquid from oral cavity is slowed. It is prudent to counsel parents to practise good oral hygiene measures for the child and to avoid inappropriate feeding habits (Fig. 7.3).

Rampant Dental Caries

There is no complete agreement on definition of rampant caries or on clinical picture of this condition. It has been generally accepted that the disease referred to as rampant caries is relatively new. Rampant caries has been defined recently by Massler as a suddenly appearing wide spread rapidly burrowing type of caries resulting in early involvement of the pulp and affecting those teeth usually regarded as immune to ordinary decay.

Rampant caries can occur suddenly in teeth that were previously sound for many years. The sudden onset of the disease suggests that an overwhelming imbalance of oral environment has occurred, and some factors in the caries process seems to accelerate it so that it becomes uncontrollable. There is considerable evidence that emotional disturbances may be a causative factor in some cases of rampant caries. Repressed emotions and fears, dissatisfaction with achievement, rebellion against a home situation, feeling of inferiority, traumatic school experience, continuous general tension and anxiety have been observed in children and adults with rampant dental caries. Adolescence is often considered to be a time of difficult adjustment, increased incidence of rampant caries is observed in this age group. An emotional disturbance may initiate an unusual craving for sweets or habit of snacking

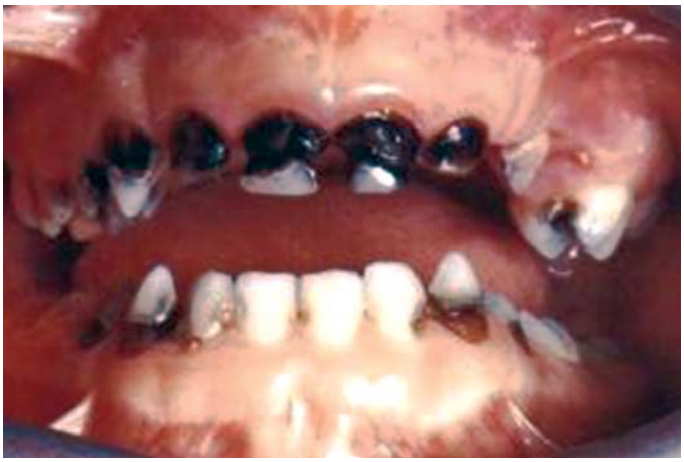


Fig. 7.3: Early childhood caries

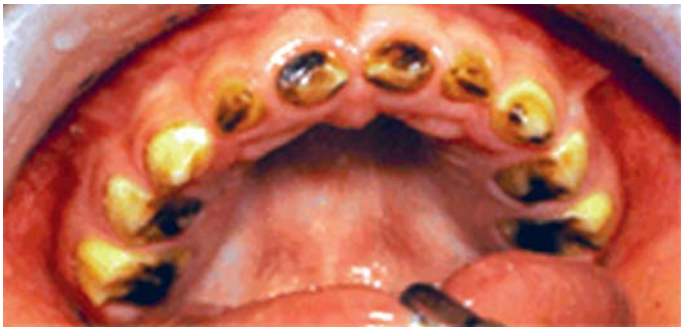


Fig 7.4: Rampant caries

which in turn might influence the incidence of dental caries. On the other hand, a noticeable salivary deficiency is a common finding in tensed, nervous and disturbed persons. Various forms of stress in children and adults, as well as medications such as tranquilizers and sedatives commonly taken to cope with stress are associated with decreased salivary flow and decreased caries resistance caused by impaired remineralization. Radiation therapy to head and neck often results in significantly diminished salivary function and may place the patients at higher risk for severe caries development (Fig. 7.4).

Linear Enamel Caries

An atypical form of dental caries observed in primary dentition of children in Latin American and Asian countries. The lesion predominates on the labial surface of the anterior maxillary teeth, in the region of neonatal line, which results from metabolic disturbances such as hypocalcemia or trauma of birth. A variant of linear enamel form of caries in the primary teeth in children has been named odontoclasia in far east. The morphological aspects of this type of caries are atypical and results in gross destruction of labial surfaces of incisor teeth.

EARLY DETECTION OF DISEASE ACTIVITY

Visual identification of demineralized areas typically white spots or suspicious pits and fissures and the use of dental explorer to determine the presence of loss of continuity or brakes in the enamel and assist the softness or resilience of the enamel. Carious lesions located on interproximal tooth surfaces have generally been detected with use of bitewing radiographs.

Infrared Laser Fluorescence (Diagnodent)

An instrument designed to facilitate the detection of dental caries, diagnodent has recently become available in several countries. This instrument was developed for detection and quantification of dental caries of occlusal and smooth surfaces. It uses a diode laser light source and a fiberoptic

cable that transmits the light to a hand held probe with fiber optic eye in the tip. The light is absorbed and induces infrared fluorescence by organic and inorganic materials. The emitted fluorescence is collected at the probe tip, transmitted through ascending fibers and processed, presented on a display window an an integer between 0 and 99. The results of various *in vitro* studies have indicated that the diagnodent instrument is capable of detecting relatively advanced carious lesions and they show a very good correlation with histologic evidence of caries but not with the depth of lesions into dentin. The instrument is very good at indicating the presence of deeper lesions in enamel but may not be apparent on radiograph and unreliable to indicate a dentinal lesion. The diagnodent instrument appears to be particularly useful for confirming the presence of occlusal caries.

Digital Imaging Fiber Optic Transillumination (DIFOTI)

It provides an intense light beam that is transmitted through a fiber optic cable to a specially designed probe to permit the use of transillumination on the proximal surfaces of posterior teeth. It is a further advancement of this technology in which the visually observed images are captured using a digital Charged Coupled Device (CCD) camera and sent to a computer for analysis using dedicated algorithms.

Quantitative Light Fluorescence

The most extensively investigated technique available for the early detection of dental caries. It makes use of a laser light of selected wavelength markedly enhance the visibility of early noncavitated lesions. The fluorescent filtered images are captured using a color CCD camera and a frame grabber. Data are collected, stored and analyzed by custom software.

CONTROL OF ACTIVE CARIOUS LESIONS

When rampant caries occurs, the first step's is to initiate treatment of all carious lesions to stop or at least slow the progression of the disease and to identify the most important causes of existing condition. Simultaneously, the practitioner begins to work with parents and patients to achieve appropriate behavioral modifications required to prevent recurrence.

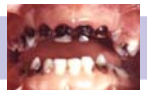
If the initial restorative treatment is to be done in one appointment under GA or in one or two appointments with sedation, control of existing lesions will be definitive at that time. If the restorative care is performed over several visits, gross caries excavation is an initial approach in the control of rampant caries which has several advantages. Superficial caries removal and filling with GIC or IRM will temporarily arrest the caries and prevent its rapid progression to the dental pulp. This may be accomplished even in one appointment. An alternative approach for some compliant children old enough to rinse and expectorate and for compliant adolescents is to initiate intensive and multiple antimicrobial and topical fluoride therapies in conjunction with necessary behavioral lifestyle modifications and then to proceed systematically with restorations and other indicated therapies. Reduction in intake of freely fermentable carbohydrates.

There is a relationship between diet and dental caries and evidences confirm that in between meal snacking, frequency of eating, drinking are related to dental caries incidence. A well controlled study of dental caries considered a classic, observed that a group of patients whose diet was high in fat, low in carbohydrates, practically free of sugar had low caries activity. When refined sugar was added to the diet in the form of meal time supplement, there was a little or no caries activity. When caramels were given in between meals statistically significant increase in number of new carious lesions occurred. Sweetened liquids produced nursing bottle caries enormously in children. The clinical control of dental caries could be a determination of eating habits by having the patient keep a 7-day record of all food eaten at meal time and in between meals. The record should be evaluated to determine the adequacy of the diet and the amount of freely fermentable carbohydrates. The number of servings of food in each basic five food groups should be determined and compared with recommended number of servings.

Dry fruits including resins, prunes, peaches, apricots, dates have high sugar content should be included in diet analysis. There are foods commonly eaten by children between meals, there is no reason to believe that they are any less cariogenic than refined foods. Although honey is considered as natural food, its sugar equivalent should be considered in addition to the syrups and other spreads for bread. The purpose of limiting a diet to the basic five food groups is two fold. An adequate diet is fundamental to general good health, essential to the period of tooth formation to help ensure development of normal tooth structure. If children and adults closely follow the recommended basic diet and consume a diet containing adequate amounts of protein, fresh fruit, vegetables, the appetite for snacks between meals will be decreased.

CONTROL OF DENTAL PLAQUE

Children whose dental cleanliness was consistently good had lower caries increments. Supervised tooth brushing with instruction produces significantly and consistently



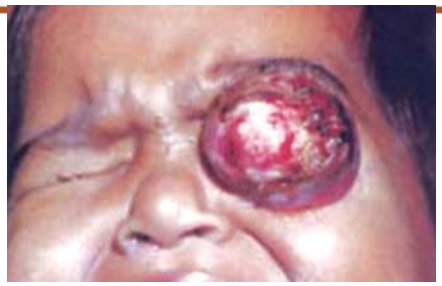
lower plaque scores even in preschool children. Investigators concluded that constant reinforcement is necessary to maintain effective plaque control in pre school children. Frequent inter-dental flossing of proximal dental caries produce less caries incidence.

USE OF FLUORIDES AND TOPICAL ANTI MICROBIAL AGENTS

Clinical investigations have consistently demonstrated the cariostatic properties of fluorides. The ingestion of fluoride results in its incorporation into dentin and enamel of unerupted teeth, this makes the teeth more resistant to acid attack after eruption. Ingested fluoride is secreted into saliva. Although present in low concentration, fluoride is accumulated in plaque, it decreases microbial acid production and enhances remineralization of underlying enamel. Fluoride from saliva is also incorporated into the enamel of newly erupted teeth, thereby enhancing enamel calcification. As a topically applied therapeutic agent, fluoride is effective in preventing future lesion development, in arresting or at least slowing the progression of active incipient lesions. The exposure of teeth to fluoride through professional applications of fluoride solutions, gels, foams, varnishes plus exposure from dentifrices and other fluoride preparations used at home engages almost all of the foregoing mechanisms. It greatly enhances the rate of remineralization. Tooth structure remineralized in the presence of fluoride contains increased concentrations of fluorohydroxyapatite, which makes the remineralized tissue, more resistant to future attack by acids than original structure.

8

Benign and Malignant Tumors of Oral Cavity



PERIPHERAL OSSIFYING FIBROMA

Clinical Presentation and Pathogenesis

The peripheral ossifying fibroma is one of a triad of lesions that present as a gingival mass, usually emerging from interdental gingiva and seemingly from the periodontal ligament. The other two lesions are the pyogenic granuloma, which may represent an early immature form of the peripheral ossifying fibroma, and the peripheral giant cell proliferation. The peripheral ossifying fibroma will be more firm and have a less friable nature than the other two lesions (Fig. 8.1).

The mass will usually have a broad base, but it may also have a pedunculated appearance. It is slightly more common in young adults, in women, and in the anterior quadrant of either arch. A close examination of the base will identify an emergence from the periodontal ligament space. The associated teeth are usually not mobile. The fact that this lesion emerges from the periodontal ligament and is not seen in edentulous areas suggests its origin to be the connective tissue elements of the periodontal ligament. The fact that ossifications are found in these lesions is, therefore, not surprising since cementum and lamina dura are part of the periodontal ligament complex. The variant that shows odontogenic epithelium within it, i.e. the peripheral odontogenic fibroma, is also not surprising, since rests of Malassez are rather abundant in the periodontal ligament and can easily become incorporated into lesions arising from the periodontal ligament.

Differential Diagnosis

A peripheral ossifying fibroma must be distinguished histologically from a pyogenic granuloma or a peripheral giant cell proliferation. In addition, gingival masses, particularly those arising from deeper tissues, should suggest a possible primary malignant lesion or even a metastatic malignancy.

Radiographic Findings (Fig. 8.2)

A periapical radiograph may or may not detect the small foci of ossifications in these lesions. In those with a great amount of ossification, radiopaque flecks will be apparent on routine periapical radiographs and may even appear on a panoramic radiograph. In the more usual case, the lesion will contain only small amounts of ossifications and will not be visible on a periapical radiograph because of the other mineral dense structures in the field, such as teeth, restorations, and alveolar bone. Therefore, in cases where a peripheral ossifying fibroma is high on the differential list, a radiograph of the excised specimen is recommended. It will show subtle radiopacities that would otherwise not be evident.

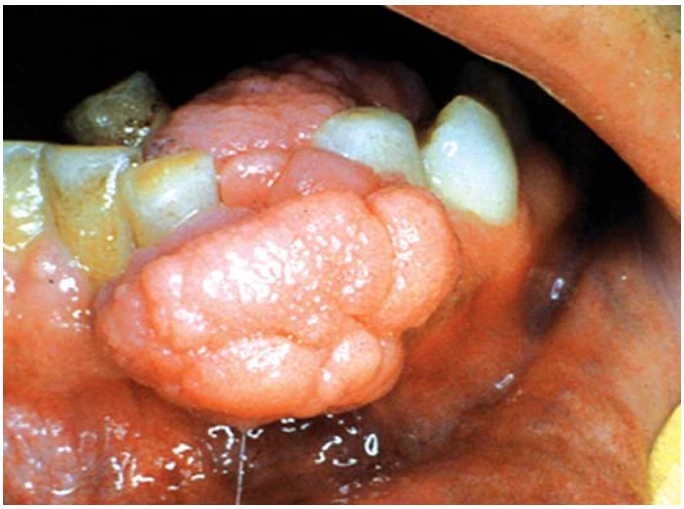


Fig. 8.1: Peripheral ossifying fibroma

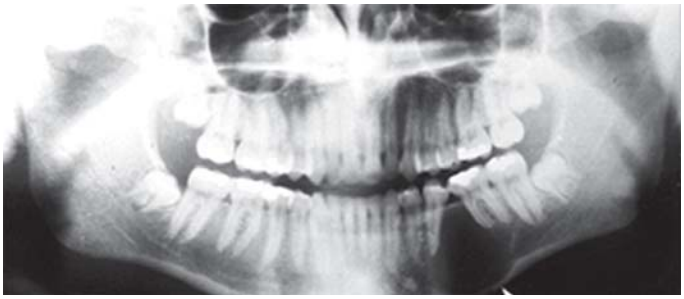


Fig. 8.2: Peripheral ossifying fibroma in left mandible

Histopathology (Fig. 8.3)

The peripheral ossifying fibroma is yet another reactive lesion found on the gingiva, despite the nomenclature that suggests a neoplasm. The lesion consists of very cellular fibrous tissue with areas of more delicate fibrovascular tissue that often contain an inflammatory component rich in plasma cells. Within the cellular areas, ossifications are usually present. These vary considerably both in quality and quantity. Small, rounded calcific deposits may be seen, or, at the other extreme, broad osseous trabeculae lined by active osteoblasts may be formed. Sometimes ossification is such that the specimen requires decalcification before sectioning. Multinucleated giant cells may sometimes be present but are not a prominent component. The mass is not encapsulated.

In a differential diagnosis of surgically excised gingival masses, the pyogenic granuloma, peripheral giant cell proliferation, and peripheral ossifying fibroma are considered together, although each appears to be a distinct clinicopathologic entity. They may overlap, and the histologic features of more than one entity may occur within a single lesion. Present knowledge indicates that these are all reactive lesions.

Treatment

The peripheral ossifying fibroma is treated by local excision with surgical margins at the periphery of the lesion and deep margins to include its periodontal ligament origin. Failure to excise the periodontal ligament origin will predispose to recurrence, which has been reported to be as high as 20%.

PERIPHERAL GIANT CELL PROLIFERATION

Clinical Presentation and Pathogenesis

A peripheral giant cell proliferation will present as a soft, fleshy, broad-based, and easily bleeding mass. Like the pyogenic granuloma, it will arise from the gingiva, but unlike the pyogenic granuloma, it may also arise from an edentulous ridge and not from extragingival sites such as the lips, tongue, or buccal mucosa. Also, like the pyogenic granuloma, some peripheral giant cell proliferations are associated with failing dental restorations, sharp tooth edges, or foreign bodies. Some will attain sizes of 5 to 7 cm and may develop superficial ulcerations with a fibrin base, mimicking a fungating tumor. There is a slight female predilection.

The peripheral giant cell proliferation is an enigmatic lesion that seems to arise from the periosteum or periodontal ligament and contains granulation tissue with osteoclasts. The presence of such giant cells (osteoclasts) and its designation as a giant cell lesion should not raise concerns about hyperparathyroidism. There is no known association between these lesions and primary, secondary, or tertiary hyperparathyroidism (Fig. 8.4).

Radiographic Findings

Seen best in edentulous areas, a peripheral giant cell proliferation will characteristically show a cupped out resorption of the alveolar crest and sometimes of root surfaces. The resorptive pattern is well demarcated and is not suggestive of a destructive or an infiltrating lesion (Fig. 8.5).

Differential Diagnosis

Where lesions associated with teeth arise, the peripheral giant cell proliferation bears the closest resemblance to the pyogenic granuloma followed by the peripheral ossifying fibroma. The clinician must also differentiate such presentations from a primary or metastatic malignancy.

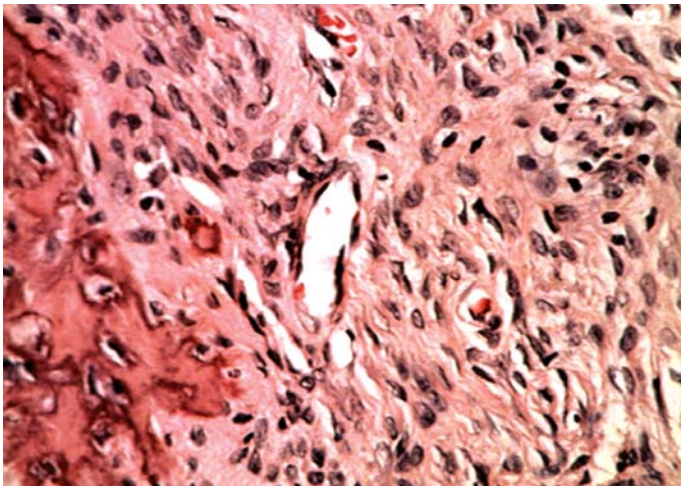


Fig. 8.3: Histopathology of peripheral ossifying fibroma

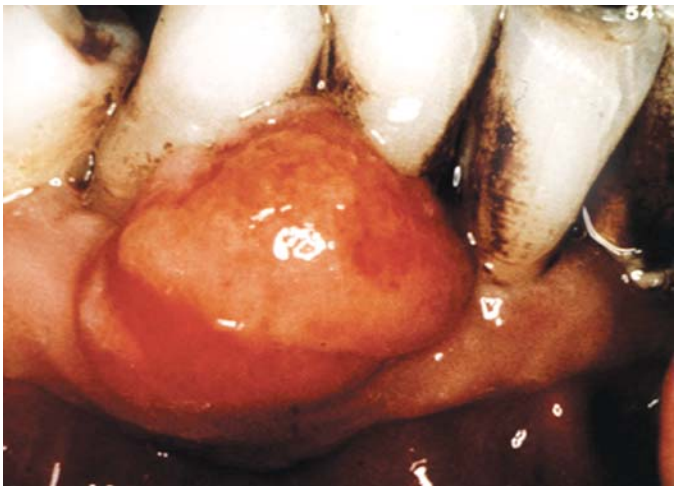


Fig. 8.4: Peripheral giant cell granuloma

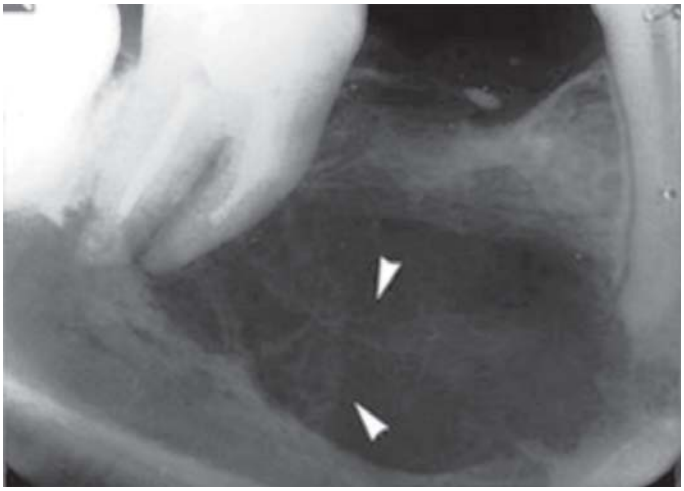


Fig. 8.5: Radiographic findings of peripheral giant cell granuloma

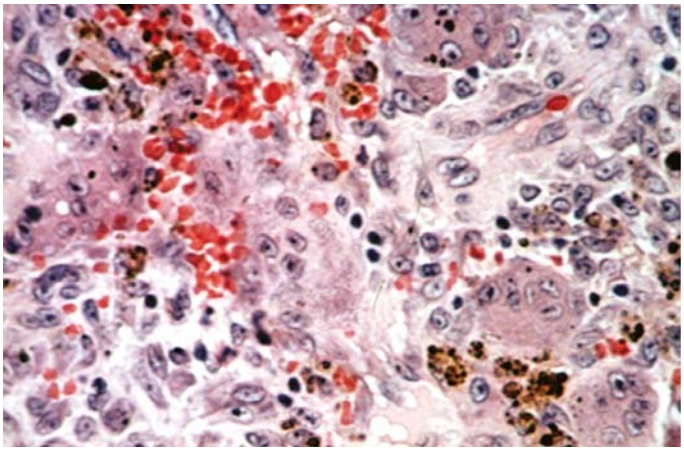


Fig. 8.6: Histopathology of peripheral giant cell granuloma

Histopathology

Histologically, a discrete tumor mass is usually seen. The covering mucosa may sometimes be ulcerated. Whether or not this is the case, there will be numerous capillaries and an inflammatory infiltrate with prominent plasma cells. The mass itself is very cellular and consists of spindle cells with numerous multinucleated giant cells of varying size and some extravasated blood. Hemosiderin, usually more prominent at the periphery, may be present (Fig. 8.6).

The histogenesis of the component cells has been controversial. Based on the elegant studies of Flanagan et al, it would seem that the multinucleated giant cells are indeed osteoclasts. They may be brought in through the circulation or formed on site. The stromal cells may be a mixed population that includes macrophages. Some stromal cells are alkaline phosphatase-positive and form woven bone, which indicates that they are osteoblasts.

Treatment

Peripheral giant cell proliferations should be excised with surgical margins at the periphery of the clinical lesion, and the excision should include the periosteum and/or periodontal ligament from which they are thought to arise. If there is an apparent stimulating etiology such as a failing restoration, foreign body, etc. it should be removed with the lesion. The resultant defect is left to heal by secondary intention if a primary approximation of tissues is impossible.

Prognosis

Excision of the lesion and removal of any stimulators resolves the lesions without recurrence.

CONTACT DRUG REACTIONS

Clinical Presentation

Contact drug reactions are of three types. The first type is a direct drug toxicity, whereby the pH or an active chemical site produces a physical injury to the tissue. "Aspirin burn" caused by the acidic pH of aspirin and the chemical burn of capsicum in sharp peppers are examples of direct drug toxicity (Fig. 8.7). Such reactions are direct physical injuries, not actual immune based reactions. The lesions are usually a localized, white painful area with a fibrinous base or slough surrounded by a small zone of erythema.

The second and most predominant type is a T cell mediated immune reaction. Initially, the offending drug is topically absorbed through intact skin or mucosa. During absorption, the drug contacts the Langerhans cells, which exist in the middle zone of the prickle cell layer in both skin and mucosa. The Langerhans cell, which seems to be a type of histiocyte, processes the drug as an antigen. It will present the drug on its cell membrane to T

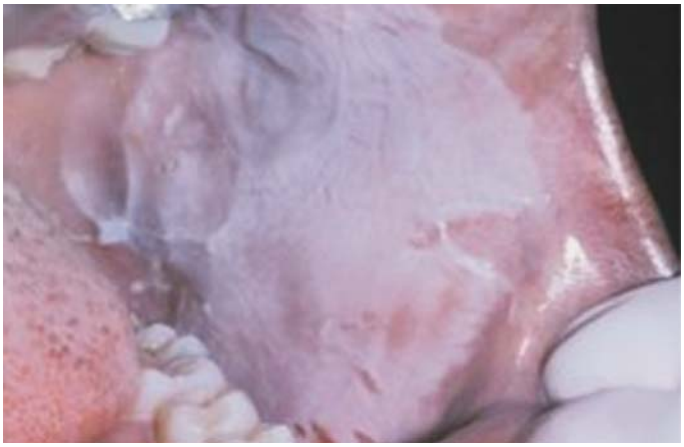
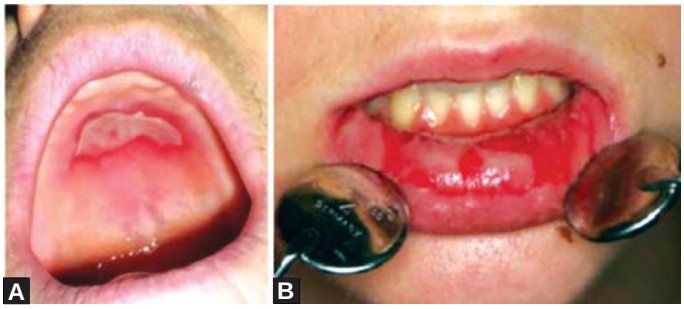


Fig. 8.7: Aspirin burn



Figs. 8.8A and B: Contact stomatitis

lymphocytes, creating antigen sensitized T lymphocytes. When the drug is topically absorbed a second time, the sensitized T lymphocytes will react by secreting an array of lymphokines that produce inflammation and tissue injury characteristic of contact reaction "allergies." This may affect skin (contact dermatitis) or oral mucosa (contact stomatitis) (Figs 8.8A and B). Such reactions will mostly be areas of boggy erythema corresponding to the drug contact and the pattern dispersal by tongue, lip, and swallowing movements. If the reaction is more severe, actual vesicles or ulcers may form.

The prime offending agents have been cosmetics, including lipsticks and lip balm, and dental preparations, such as toothpaste and some of its ingredients. In particular, mint and cinnamon flavorings have been implicated in oral contact stomatitis. Cosmetic and skin care preparations have been such prominent offenders that complete lines of hypoallergenic products have been developed. Included in this group is hypoallergenic surgeon gloves, which were developed because the powdered starch in many gloves induced a typical contact dermatitis. One supposed cause of contact stomatitis that has been grossly overstated for years is that related to denture acrylic. There is little if any direct evidence to support a true "denture contact stomatitis". Most so called denture reactions represent other diseases, such as candidiasis, pemphigoid, lichen planus, or mere chronic injury from an ill fitting denture.

The third type of contact drug reaction is a B cell mediated immune reaction whereby antibodies are produced. In a fashion similar to the mechanism noted for T cell mediated immune reaction, Langerhans cells may present processed antigen to B lymphocytes, which in turn manufacture specific antibody to the absorbed drug. On a subsequent absorption, antibodies attack the antigen at the epithelial or sub epithelial level to produce inflammation and tissue injury. In plasma cell gingivitis, for example, the plasma cells are prominent because they produce specific antibody in the area of antigen (the contact drug) absorption. Plasma cell gingivitis was common in the late 1960s and early 1970s but is rare today. It is believed that the peak of incidence was related to formula changes and ingredients in several dental preparations, which have since been eliminated by the manufacturers.

Clinically, contact drug reactions produce a soft, spongy, red attached gingiva. They may also affect to a lesser degree the labial mucosa, tongue, and commissures. The gingiva and tongue are reported to have a dull, burning sensation.

Differential Diagnosis

The clinical picture of diffuse, red, burning lesions on the oral mucosa without concomitant skin lesions is the classic "burning mouth syndrome" that frequently confronts practitioners. Indeed, many of these represent some type of contact drug reaction that should be meticulously sought out from the patient's history. However, systemic drug reactions, candidiasis, recurrent herpes, pemphigoid, pemphigus, and erosive lichen planus also produce a complaint of burning mouth (Fig. 8.9).

Diagnostic Work-up

If the offending drug is apparent, no further work-up is required. If not, a biopsy including PAS staining to assess for invasive candidiasis, routine H&E staining, and possibly direct immunofluorescence studies to rule out pemphigus and pemphigoid may be required.

Histopathology

The histologic picture is variable. Some will be indistinguishable from lesions of lichen planus, although lymphoid aggregates are often found in deeper areas of connective tissue in addition to the interface pattern. Plasma cells also may be more prominent, and eosinophils may be present. Plasma cell gingivitis, in addition to a dense

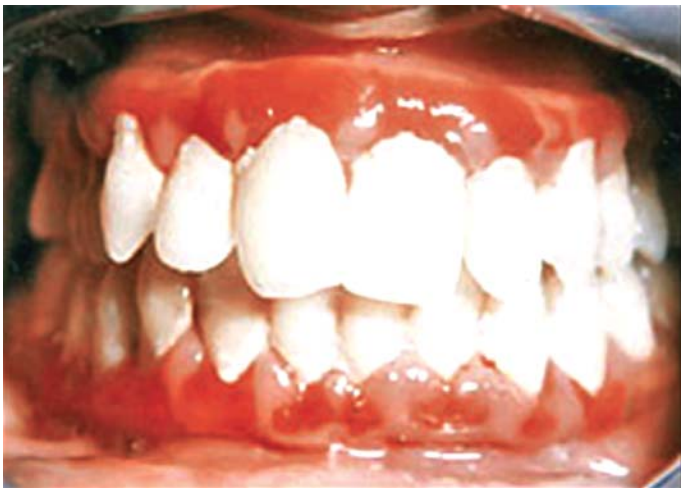


Fig. 8.9: Plasma cell gingivitis

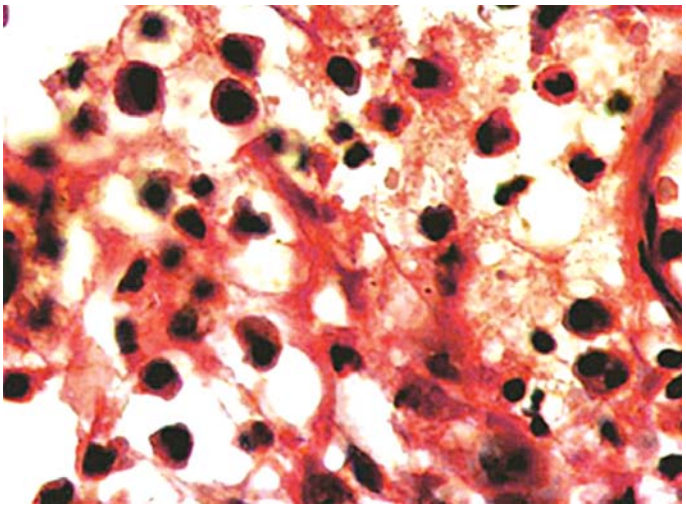


Fig. 8.10: Histopathology of plasma cell gingivitis (H & E 400X)

plasmacytic infiltrate in the connective tissue, shows spongiosis of the epithelium, often with a neutrophilic infiltrate. Langerhans cells are increased in number (Fig. 8.10).

Treatment

Discontinuation of the offending drug is the obvious treatment of choice. However, the patient should be cautioned that improvement may be slow and may take up to 3 months. The delay seems to be caused by the fixation of antigen (drug) to cell membranes, slowing the clearance of the drug. Topical corticosteroids, 0.05% fluocinonide cream for skin (Lidex cream, Medicis Dermatologics) or 0.05% fluocinonide gel (Lidex gel) for mucosa will reduce the symptoms and erythema during the course of antigen clearance.

ENCEPHALOTRIGEMINAL ANGIOMATOSIS (STURGE-WEBER ANOMALY) (FIG. 8.11)

Clinical Presentation and Pathogenesis

Encephalotrigeminal angiomatosis (ETA) is not a genetic inheritable defect but a disturbance of fetal development in utero, an anomaly that is present from birth. The most notable clinical manifestation (infant or adult) is an ipsilateral facial angioma that ends abruptly at the midline in most areas and thus seems to follow the distribution of the trigeminal nerve. This and the other angiomas are the result of a persistent fetal vascular plexus that has failed to involute. By the sixth week of normal fetal development, a vascular plexus forms between the neural tube ectoderm destined to become brain and the skin ectoderm destined to become facial skin. This plexus normally involutes by the ninth week. In ETA, failure of involution results not only in a visible dermal-level angioma, but in angiomas of the meninges as well. The facial pattern of the angioma has nothing to do with the trigeminal nerve per se, except that it shares the same developmental and anatomic location.

Meningeal angiomas are venous in type with low-flow characteristics. They, therefore, frequently calcify, which makes them visible radiographically and produces a seizure disorder in 75 to 90% of individuals. If the meningeal angiomas hypertrophy or extensively calcify, mental deficiency states (30% of individuals) and in some cases overtretardation can arise. Occasionally, the meningeal angiomas affect a motor area and produce a hemiplegia. Commonly, the angiomas will extend into the choroid plexus of the eyes, where they are mostly an incidental finding but rarely have been reported to produce glaucoma.

Oral angiomas either in bone or in soft tissue correspond to the facial lesions and may be more troublesome. They frequently enlarge and become bulbous, causing bleeding episodes and interfering with the occlusion. Characteristically, the bone size is increased (usually the maxilla) on the involved side, and tooth eruption is accelerated compared to the unaffected side, presumably because of the increased blood supply.

Differential Diagnosis

Encephalotrigeminal angiomatosis must be distinguished from congenital hemangiomas and vascular malformation

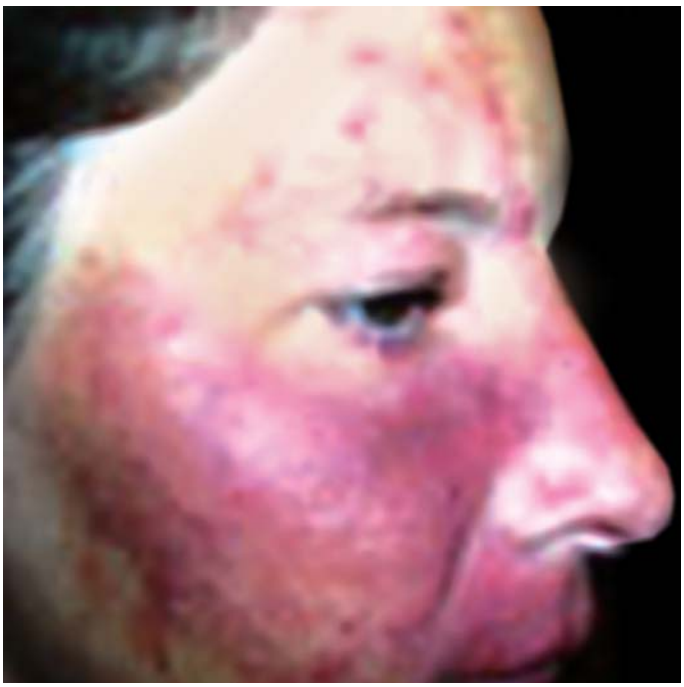


Fig. 8.11: Sturge-Weber syndrome

not associated with ETA. Each will show no midface midline demarcation or cerebral calcifications. Another syndrome, Klippel-Trenaunay-Weber syndrome (angio osteohypertrophy), also manifests ETA like facial and oral angiomas. It differs from ETA in that it lacks meningeal angiomas and calcifications and also has overt limb enlargement. In fact, because the angiomas of Klippel-Trenaunay-Weber syndrome involve the trunk and enlarged limbs and no genetic inheritance is known, it may very well represent an ETA like anomaly in a different location. Beckwith-Wiedemann syndrome also has a facial vascular component, but it occurs symmetrically across the midline in the glabellar region and will disappear within the first year. Beckwith-Wiedemann syndrome will of course be identified by its other features such as prognathism, macroglossia, and omphalocele.

Diagnostic Work-up

If ETA is suspected in the first 2 years of life, the meningeal angiomas can be mapped by internal carotid angiography. Beyond 2 years, cerebral calcification negates most of its diagnostic value. Otherwise, plain skull radiographs and a panoramic radiograph are useful.

Histopathology

The angiomas (nevus flammeus) of this disorder show dilation of blood vessels, which increases with age. Endothelial proliferation is not present.

Treatment

Most patients to date have not been treated for their facial angiomas because of the limited prognosis. Recently, subdermally focused laser ablation has shown promise in removing at least some of the angiomatous tissue without affecting the skin surface. Oral manifestations, which involve bulbous and inflamed gingival tissue due to plaque accumulation and bleeding episodes, may be treated by gingivectomy. Because the angiomatous tissue is venous and venous pressure is not great, bleeding is controllable.

SQUAMOUS PAPILLOMA (FIG. 8.12)

Clinical Presentation and Pathogenesis

Squamous papillomas are common lesions of the oral mucosa with a predilection for the mucosa of the hard and soft palate, including the uvula and the vermilion of the lips. It is an innocuous lesion that is neither transmissible nor threatening. As an oral lesion, it raises concern because of its clinical appearance, which may mimic exophytic carcinomas; verrucous carcinomas; or condyloma acuminatum, a viral disease that is transmissible.

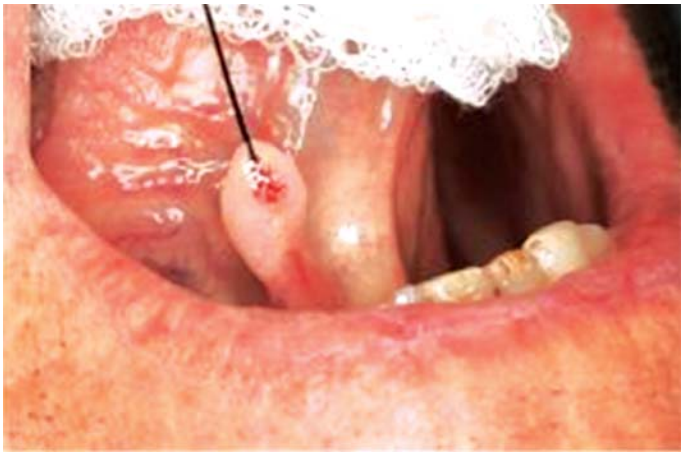


Fig. 8.12: Squamous papilloma

The squamous papilloma is also noteworthy for its uncertain pathogenesis. Many oral and maxillofacial specialists accept its pathogenesis as being from the human papillomavirus (HPV). This is based on its similar appearance to cutaneous warts and the identification of HPV subtypes 2, 6, 11, and 57 in some oral squamous papillomas. However, despite extensive research, a definitive cause and effect relationship has not been established. If a DNA virus such as HPV were the stimulus, one would expect a direct contact transmission such as that seen with condyloma acuminatum and herpes. The squamous papilloma also shows no histopathologic signs of viral infections, such as internuclear inclusion bodies and vacuolated nuclei. Furthermore, HPV is not identified in most squamous papillomas. However, HPV types 1, 2, 4, 6, 7, 11, 13, 16, 18, 30, 32, 40, and 57 have been identified in other lesions containing oral squamous cells, suggesting that HPV may be merely an incidental finding unrelated to the development of a squamous papilloma. This is further suggested by the failure of tests to show HPV DNA in the squamous cells or basal cells of squamous papillomas. Regardless of its pathogenesis, the squamous papilloma will usually present in one of the four sites of predilection, although it may occur on any oral mucosal surface. Usually appearing as asymptomatic single lesions without induration (clusters and multiple lesions occasionally develop), they generally have a sessile base but may sometimes have a stalk.

Differential Diagnosis

Single squamous papillomas may resemble verrucous carcinomas or even exophytic squamous cell carcinomas if they have a sessile base. Certainly the finding of induration or ulceration would lead the clinician to suspect these two concerning lesions more strongly than a

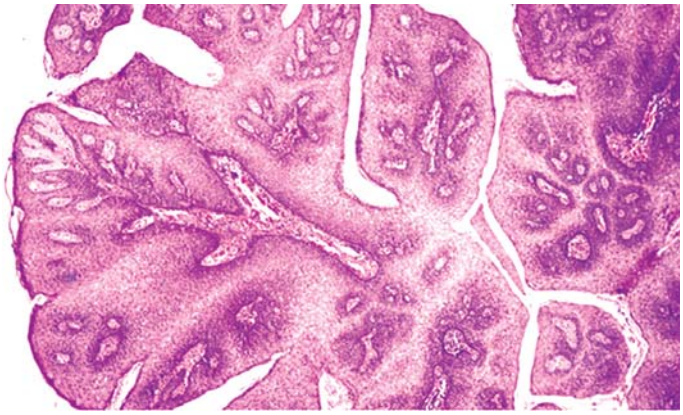


Fig. 8.13: Histopathology of squamous papilloma

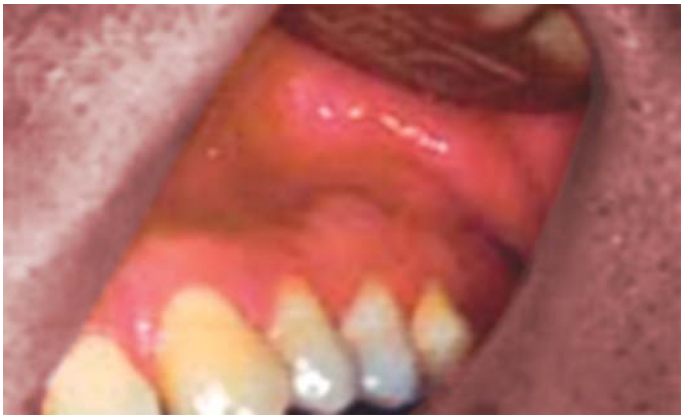


Fig. 8.14: Verrucous xanthoma

squamous papilloma. In addition, clustered or multiple squamous papillomas would suggest focal epithelial hyperplasia (Heck disease). In addition, a verruciform xanthoma will clinically resemble squamous papilloma, but it is mostly seen on the gingiva or the edentulous alveolar ridge.

Histopathology (Fig. 8.13)

The papilloma is a benign proliferation of squamous epithelium. With the epithelium's dependence for nutrition on the underlying fibrovascular tissue, the most efficient growth pattern is one of exophytic papillary projections, each with a fibrovascular core. The epithelium may show orthokeratosis, parakeratosis, and/or acanthosis. Mitoses may be numerous but are usually confined to the basal area. The prickle cells may have a clear glycogen-filled cytoplasm, particularly in lesions of the soft palate. Koilocytic cells (epithelial cells with pyknotic nuclei surrounded by a clear halo), which are often associated with viral disease, also may be present, but they can also be found in nonvirally infected oral mucosa. Their presence is not sufficient to confirm a viral etiology for any particular papilloma. The lamina propria frequently contains a chronic inflammatory infiltrate.

Treatment

Because of the varied lesions on the differential diagnosis, most of which have a more concerning prognosis than that of the squamous papilloma, all lesions resembling a squamous papilloma are recommended for excision at the base (1 mm margin) to the depth of the submucosa. This excision should be curative. Recurrence or new lesions should raise suspicions of a possible retransmission of a condyloma acuminatum or of carcinoma.

VERRUCIFORM XANTHOMA

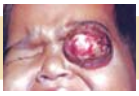
Clinical Presentation and Pathogenesis

The verruciform xanthoma is a specific but rare lesion most commonly found on the attached gingiva, edentulous alveolar ridge, and sometimes the palate. Individuals are usually older than 45 years, and there is no sex or race predilection. The lesions are generally asymptomatic and will range in size from 2 mm to 2 cm. Their most common appearance is that of a slightly raised pebbly surface with a slightly pale or red color. However, variations of this presentation include a white surface, a depression rather than an elevation, and even ulceration (Fig. 8.14).

The pathogenesis of the verruciform xanthoma is uncertain. One theory suggests that it is a focal proliferation of Langerhans cells, and it is supported by the immunohistochemical identification of Langerhans cells as part of these lesions. Another theory suggests that it is a local accumulation of lipid that subsequently becomes ingested by macrophages, which in turn secrete epithelial growth factors (EGFs) to stimulate a limited epithelial hyperplasia. The lack of an association with systemic hyperlipidemia states and the positive identification of Langerhans cells clearly favor the first theory over the second.

Differential Diagnosis

Verruciform xanthoma is not usually the first consideration on the differential diagnosis. The more common squamous papilloma and the more concerning exophytic squamous cell carcinoma or verrucous carcinomas are more serious considerations. If the lesion is larger or more than one is present, consideration of either condyloma acuminatum or focal epithelial hyperplasia is appropriate.



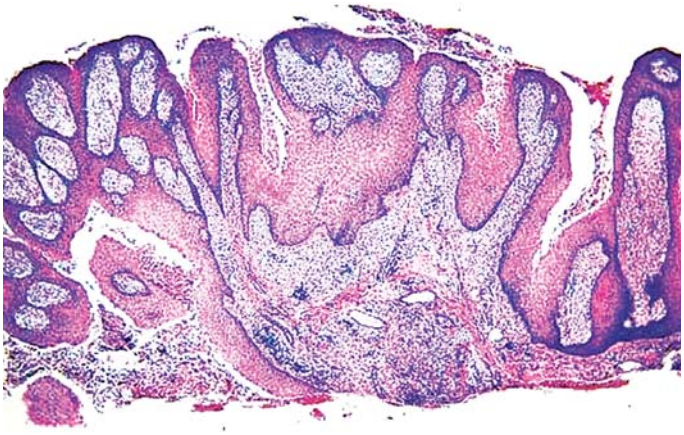


Fig. 8.15: Histopathology of verrucous xanthoma

Histopathology (Fig. 8.15)

This lesion has a very distinctive histology. It presents a verrucous surface covered by parakeratin, which extends into the epithelium in thick seams. The epithelium also exhibits acanthosis with equal elongation and extension of the rete ridges into the connective tissue. Within the connective tissue papillae, numerous foamy cells are seen, which almost invariably are contained only within the papillae and rarely extend below the level of the rete ridges. These xanthoma type cells are macrophages that contain lipid and periodic acid Schiff (PAS) positive, diastase resistant granules. There is evidence to suggest that the source of this material may be necrotic epithelial cells.

Treatment

Local excision at the base of the lesion (1 mm margin) to the depth of the submucosa or to the supraperiosteal plane over bone is curative. There is no association with systemic lipid alterations, arteriosclerosis, or cardiovascular disease, and therefore blood studies related to this diagnosis are not required. Recurrence should be looked upon as suspicious for other diseases such as carcinoma or for a reinfection of condyloma acuminatum.

BASAL CELL CARCINOMA

Clinical Presentation and Pathogenesis

Basal cell carcinoma (BCC) is the most common skin neoplasm (Fig. 8.16). The ratio of basal cell carcinomas to squamous cell carcinomas of skin in sun-damaged skin is 5:1. Like squamous cell carcinoma of skin, BCC is found on the sun exposed areas of the face, shoulders, and extremities. However, it is not seen on the lower lip, and it is less common on the forehead or pinna of the ear compared to squamous cell carcinoma of skin.

Correlation of BCC to ultraviolet light (particularly UVB 290 to 320 nm) as the primary carcinogen is related both to time and degree of exposure. Therefore, an increased incidence is found with advancing age, particularly after the age of 40 years. However, greater numbers of young people are developing BCC, ostensibly related to increased populations in the sunbelts (some have attributed the trend to depletion of the ozone layer, but this has not been proven).

Basal cell carcinoma is considered a malignant lesion by convention, yet it does not have metastatic potential. Nevertheless, it remains a dangerous lesion because of its subtle and relentless growth potential that may cause it to present as either a small scaly ulcer or as a large destructive lesion destroying an entire side of the face. There are several histopathologic subtypes of basal cell carcinoma. However, the one that is most deeply infiltrative and destructive is the basosquamous cell subtype, which has features of both a basal cell carcinoma and a squamous cell carcinoma.

Today, there are five recognized clinical types of BCC, each with its own growth pattern and implications for treatment.

NODULAR ULCERATIVE BASAL CELL CARCINOMA

Nodular-ulcerative BCC is the most common type of BCC (Fig. 8.17). It will appear as a pearly, dome~ shaped papule. It may have small telangiectatic vessels within it, and it may ulcerate in the center. Usually irregular in shape, the ulceration has been termed the rodent ulcer because of its appearance of having been chewed by rodents. The growth pattern is irregular, and the lesion may form a multilobular mass. When ulcerations occur, the area often heals with some scarring, giving the false impression of a noncancerous condition. This cycle of ulceration, healing,

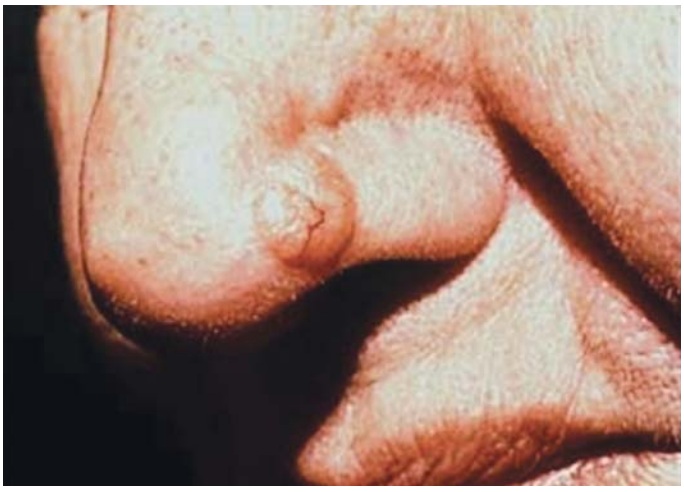
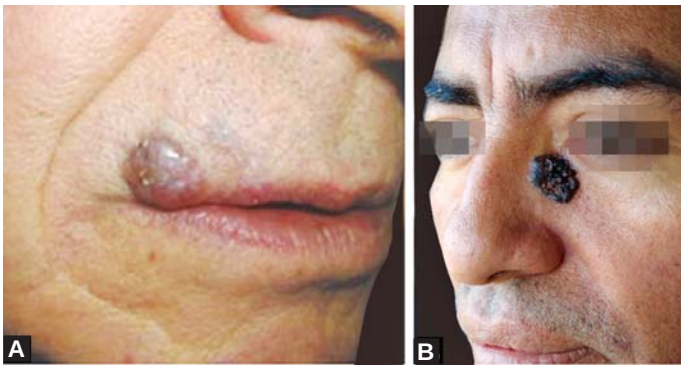


Fig. 8.16: Basal cell carcinoma

Fig. 8.17: Nodular ulcerative basal cell carcinoma



Figs 8.18A and B: Pigmented basal cell carcinoma

growth, and reulceration has been known to create enormously destructive lesions.

PIGMENTED BASAL CELL CARCINOMA (FIG. 8.18A AND B)

Nodular BCC may also contain melanin from local melanocytes stimulated by the BCC and from dispersed melanin that is taken up by macrophages, which are then called melanophages. This imparts a black, brown, or blue color to the lesion depending on the depth of the melanin deposition (more superficial melanin appears black, deeper melanin transitions into brown and then blue). Because this may make the lesion appear to be a melanoma, biopsy should be performed. However, close examination will show pigmented BCC retaining a pearly white, translucent surface and margin.

CYSTIC BASAL CELL CARCINOMA

Cystic BCC is merely a variant of the nodular-ulcerative type of BCC that has undergone subsurface cellular breakdown (Fig. 8.19). Therefore, rather than creating an ulcer by surface necrosis, it creates a small cystic space through subsurface necrosis.

SCLEROSING OR MORPHEAFORM BASAL CELL CARCINOMA

Sclerosing or morpheaform BCC is a more serious form of BCC because its wide extension and deep invasion are masked by a nonulcerated, innocuous appearance (Fig. 8.20). This lesion will appear as a pale white to yellowish flat scar or area of hypopigmentation. Its borders to normal skin are indistinct, showing gradual blending. The texture is firm, resembling scar tissue, and suggests the dermal extensions, which average 7.2 mm from the lesion's clinical border.

SUPERFICIAL BASAL CELL CARCINOMA

Superficial BCC, the least aggressive form, is at the opposite end of the infiltrative growth spectrum from the sclerosing or morpheaform BCC (Fig. 8.21). Superficial BCC spreads outward for several centimeters at a superficial level but

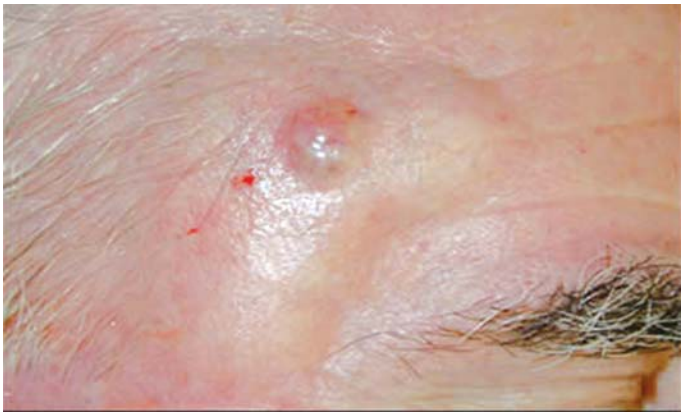


Fig. 8.19: Cystic basal cell carcinoma

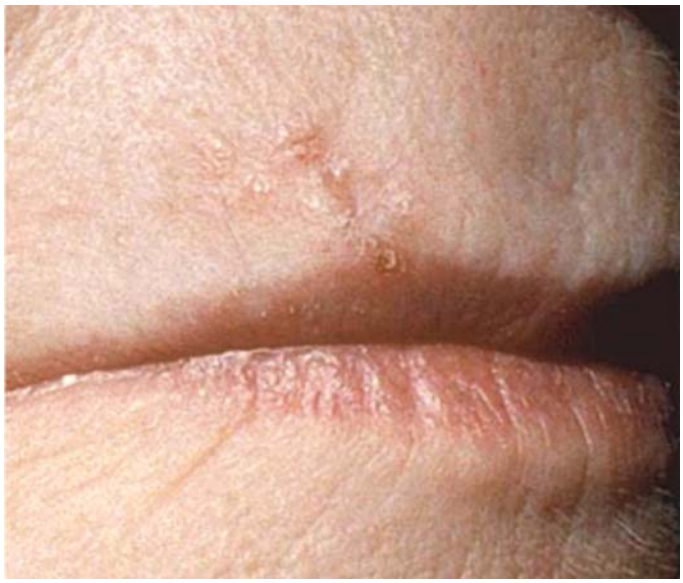
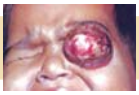


Fig. 8.20: Morpheaform basal cell carcinoma



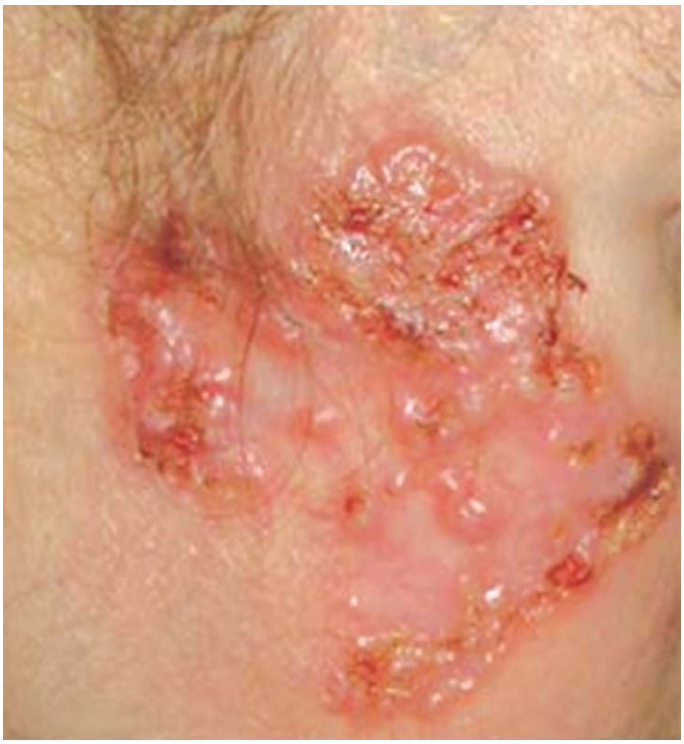


Fig. 8.21: Superficial basal cell carcinoma of the cheek

does not show vertical invasive growth until very late. Therefore, it may cover a large surface area but is usually not indurated or ulcerated. Superficial BCCs usually manifest well demarcated, red, scaly plaques that blanch under finger pressure like a hemangioma.

Differential Diagnosis

Basal cell carcinomas, in general, are one of a subset of skin lesions related to sun damage. The other lesions include actinic keratosis, skin squamous cell carcinoma, keratoacanthoma, and melanoma. The nodular-ulcerative type, in particular, will show the surface irregularity and ulcerations seen in actinic keratosis and skin squamous cell carcinoma. The pigmented BCC resembles a melanoma, but so does the cystic BCC, suggesting a nodular melanoma by its raised nodular quality. The sclerosing/morpheaform BCC may easily be confused with a scar or an area of atrophic hypopigmented skin. The superficial type may resemble a vascular malformation or lymphangioma.

Histopathology (Fig. 8.22)

Basal cell carcinomas are usually well demarcated lesions, but some may be infiltrative, particularly the sclerosing type. The nodular-ulcerative lesion, which is by far the most common form of BCC, usually consists of well-defined nests of basaloid cells within the dermis. Nests may originate from the basal cell layer of the overlying epidermis or from follicular epithelium. The cells have round to oval nuclei and scant cytoplasm. Intercellular bridges are typically absent. The cells at the periphery of the nest are often palisaded. Degeneration secondary to ischemia may occur and give rise to cyst formation, which may be extensive. The resemblance to ameloblastoma may be striking, although the BCC may show individual cell necrosis and mitoses, which are not seen in the ameloblastoma.

The stroma of the BCC is an important component of the tumor. The area adjacent to the tumor islands is often mucinous, and retraction of the stroma from the islands is often seen. It had been thought that this is a result of fixation artifact, but this does not seem to be the case. The absence of bullous pemphigoid antigen in these areas may be a factor. This phenomenon can be helpful diagnostically. Collagenases and proteases within the tumor are thought to contribute to the expansion of the lesion. Their absence in seborrheic keratosis is thought to be responsible for the exophytic growth of the basaloid cells in that lesion.

Many histologic variations may occur, some expressing differentiation to skin appendages. Clear cells, due to the presence of glycogen, recapitulate the outer root sheath of hair follicles. Squamoid changes and keratin cysts also are an expression of differentiation toward hair follicles and, when extensive, are called keratinizing BCCs. The adenoid BCC suggests a glandular pattern, and small cystic spaces surrounded by small basaloid cells are seen. The pigmented BCC differs histologically only in the presence of numerous pigment-laden melanocytes and melanophages.

Of greater clinical significance are the superficial and sclerosing types of BCC, which are ill-defined, diffuse tumors and thus more subject to recurrence. The superficial type occurs predominantly on the trunk, but the sclerosing

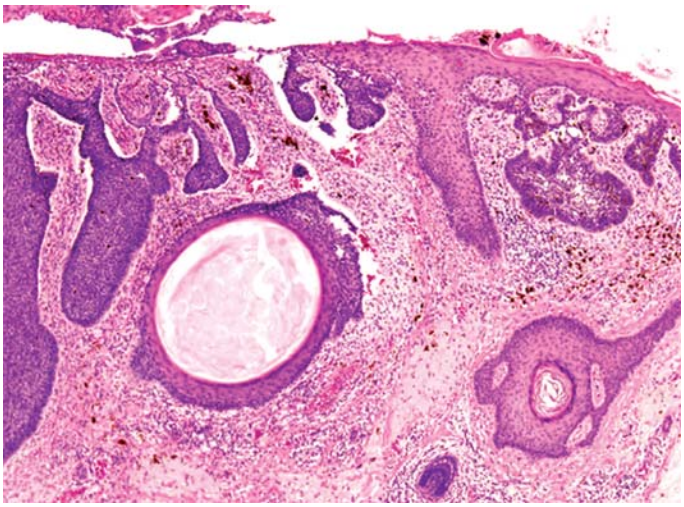


Fig. 8.22: Histopathology of basal cell carcinoma

type has a predilection for the face. In the sclerosing tumor, there is a proliferation of cuboidal to fusiform basal cells as ill-defined cords within a cellular stroma. Consequently, identification of the tumor cells within the stroma is difficult, and to define the margin of the tumor it may be necessary to resort to immunohistochemistry for cytokeratin identification.

The basosquamous cell carcinoma is essentially a basal cell carcinoma in which there is a significant squamous proliferation. Whether this represents a single entity is unclear. Some may represent a basal cell carcinoma with squamous metaplasia, while others may represent a collision tumor of a basal cell carcinoma and a squamous cell carcinoma.

The BCCs within the basal cell nevus syndrome are usually well differentiated tumors. The base of the keratin pits in this syndrome demonstrates basaloid hyperplasia and sometimes even small basal cell carcinomas.

Treatment

Most BCCs are clinically recognized and treated for cure at the first opportunity. If there is uncertainty about the diagnosis or type, an incisional biopsy from within the confines of the lesion is recommended.

The common nodular-ulcerative BCC that is less than 2 cm and not around the eyes or ears may be treated by electrodessication and curettage, excision, cryosurgery, or Mohs micrographic surgery with equal outcomes. A 98% cure rate is recognized for surgeryof lesions of this size if 4-5 mm margins are employed. Selection of treatment modality is often related to the clinician's training and experience. Some of the principles that must be considered include the following:

Cryosurgery

Cryosurgery is limited by the depth of freezing achievable. Unless specialized thermocouples are used, it is limited to the superficial BCC with less than 3 mm of invasion.

Electrodessication and Cautery

Electrodessication and cautery are limited to the nodular-ulcerative type and the superficial type of BCC because of absolute need for margin assessment by frozen sections of the other types.

Mohs Micrographic Surgery

Mohs micrographic surgery enables fine control of the margins of excised tissue, providing greater assurance of complete excision with minimal excision of normal tissue. Mohs micrographic technique is particularly advantageous in the sclerosing/morpheaform type and all types of BCC around the eyelids and canthal areas. It was first described in 1941 by Fredrick Mohs, who used zinc chloride ($ZnCl_2$) as an in situ tissue fixative. Mohs concept involved mixing $ZnCl_2$, which was being used in dentistry of the era, to accomplish a chemical gingivectomy as a treatment for periodontal disease. It was placed in a vehicle paste (stibinite) and applied to skin lesions over 24 hours. Because of its dehydrating effects, the $ZnCl_2$ fixated the tissue to a depth of 2 to 3 mm. Mohs then excised the lesion in layers and examined each layer microscopically. Each visit excised the lesion to bleeding edges or to the patient's report of pain. He progressed with several such outpatient visits until he obtained tumor-free margins and a tumor-free base. The procedure has since been modified to a 1 day procedure using unfixed fresh tissue and cryostat-generated frozen sections. The lesion is accurately mapped by scalpel excision in thin layers, which are cut into quadrants before frozen section preparation. Elimination of persistent tumor may be observed in any location by means of serial layers oriented to the same quadrants. Drawings may facilitate construction of a three dimensional model indicating the excisional block and the tumor with all of its projections within it.

The Mohs technique can be tissue sparing and, when strictly applied, is associated with a high cure rate. However, since the wound is left to heal by secondary intention, it often leaves an unacceptable scar (Fig. 8.23).

Local Excision

Surgical excision with frozen section assessment is not greatly different from Mohs micrographic surgery. Each is indicated primarily for larger tumors and for recurrent tumors, although they can be used to eradicate the other types as well.

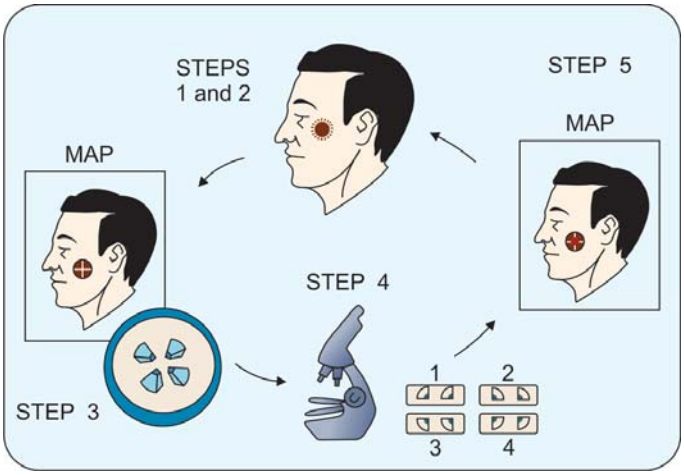
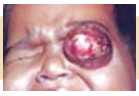


Fig. 8.23: Steps involved in Mohs micrographic procedure



Local excision has not been entirely replaced by Mohs micrographic surgery and remains a reliable and time-honored method for treating BCCs. Local excision with routine frozen section control may be more practical in recurrent BCC, in larger or deeper lesions, and in sclerosing/morpheaform types of lesions. Smaller lesions and those located in areas that can be readily closed should be closed primarily. Larger excisions can be practically managed with split-thickness skin grafts. For best results, the skin graft should be adapted with an overlying pressure bolste. Other large excisions may require local rhomboid or rotation flaps or more rarely myocutaneous or free vascular flaps.

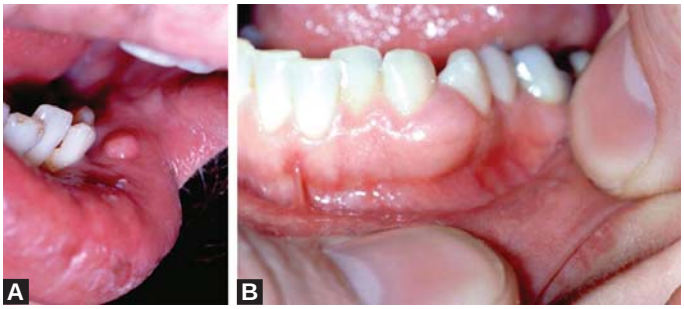
Radiotherapy

Radiotherapy is a necessary and useful treatment modality for elderly patients or for those who cannot tolerate the required surgery or anesthesia. It may also be a consideration in areas around the eyelids and canthus, where surgery of any type can cause dysfunction of eyelid closure or epiphora. Usually, BCCs treated by radiotherapy receive 5000 to 6500 cGy of electron beam radiotherapy, which is preferred over the usual beta particle source for its reduced depth of penetration.

Prognosis and Follow-up

Generally, the prognosis for BCC is excellent. Recurrences are related to several factors: (1) Identification of tumor cells at the margins of an excision is strongly associated with recurrence. When tumor cells are found at an excision margin, the recurrence rate rises to 30% from the overall rate of 3%. Therefore, for all patients with questionable margins, techniques using frozen section margin assessment, as well as re-excision, are preferred over a "wait and see" approach. (2) Recurrent lesions develop after a second treatment 18% of the time, compared to 3% for a first treatment approach. Therefore, aggressive initial treatment is recommended. It is also noted that many of the disfiguring types of BCC started as small, recurrent lesions. (3) The sclerosing/morpheaform type has a high recurrence rate due to its diffuse lateral and deep infiltration. These lesions require more aggressive initial therapy and close follow-up. (4) Recurrences are related to depth of invasion and location. Basal cell carcinomas around the nose, eyes, and ears, where tumor cells readily migrate along the tarsal plate or perichondrium, are the most recurrent.

It must also be recognized that new primary BCCs will arise in sun-damaged skin. Sun exposure precautions, the use of sunscreens, and frequent examinations are part of overall management (see also the section on actinic keratosis treatment.



Figs 8.24A and B: Oral fibroma

FIBROMA (Figs 8.24A and B)

Clinical Presentation and Pathogenesis

The fibroma is not a true neoplasm because its growth potential is limited. Since it ceases to grow once it reaches about 2 cm in diameter, it probably represents a reactive hyperplasia of fibroblasts or a hamartoma. It presents as a painless, firm mass that protrudes from the submucosa. The overlying mucosa is intact with mature epithelium unless some form of trauma has caused surface ulceration secondarily. It is generally rounded, does not blanch, and is not painful to palpation. Most are found on the buccal mucosa in the areas adjacent to the occlusal plane and are thus believed to be related to tooth abrasion, cheek biting, or sucking trauma. In the past, these have been referred to as traumatic fibromas or irritation fibromas; however, a traumatic stimulus is not always apparent. Other locations include the lateral border of the tongue and the labial mucosa.

Differential Diagnosis

A mass with benign characteristics within the submucosa can be almost any benign tumor arising from native cells within the submucosa. Therefore, a schwannoma, lipoma, or benign minor salivary gland tumor such as a pleomorphic adenoma, canalicular adenoma, or basal cell adenoma is possible. A neurofibroma is not likely to clinically present as a fibroma because of its unencapsulated nature, which usually imparts an irregular and, if severe, a "bag-of-worms" consistency. On the other hand, a schwannoma is well encapsulated and will present as a submucosal bulging mass.

Diagnostic Work-up and Treatment

These lesions and most of the serious considerations on the differential list are diagnosed and treated by local excision. The mass with its overlying mucosa is excised with 1 to 2 mm margins to the depth of the underlying muscle fascia. The resultant wound can be closed by undermining and advancing the edges. If the lesion is in

the buccal mucosa close to the commissure, it is best to excise it with the long axis oriented anteroposteriorly. A vertical excision may scar in such a manner as to restrict the oral opening.

Histopathology (Fig. 8.25)

A fibroma usually appears as a well-defined mass of hypocellular collagenized tissue. Cellularity is variable, however, as is the degree of vascularity. If an inflammatory component is present, it is usually found adjacent to the overlying epithelium or perivascularly. The epithelium is often attenuated and may be hyperkeratinized. Most of these lesions are reactive rather than neoplastic, and only their circumscription separates them diagnostically from fibrous hyperplasia.

Prognosis

Local excision is curative. If left untreated, fibromas will remain with little change. However, excision is recommended to rule out more serious neoplasms.

GIANT CELL FIBROMA (FIG. 8.26)

Clinical Presentation and Pathogenesis

Occasionally the clinician may be confused by a pathology report diagnosing a "giant cell fibroma" in what seemed to be a routine intraoral fibroma. Indeed, the two are nearly identical except for the histopathologic finding of multinucleated but stellate shaped giant cells in the giant cell fibroma. Both the intraoral fibroma and the giant cell fibroma represent a focal fibrous hyperplasia that has limited growth potential and is usually static when first seen. Both are curable by local excision around their clinical periphery and into the submucosa.

This lesion should not be confused with the giant cell fibroblastoma, a term often used by general pathologists and dermatopathologists. This lesion, a true benign neoplasm, is a distinctive subcutaneous/dermal mass of 2 to 6 cm seen mostly in young boys. It is not related to the giant cell fibroma of the oral cavity.

Histopathology

These fibromas may have smoothly rounded or verruciform surfaces. Within a fibrous mass are large stellate and angulated cells, some of them multinucleated. The stellate cells often have dendritic processes. Ultrastructurally, these cells appear to be atypical fibroblasts and may contain melanin.

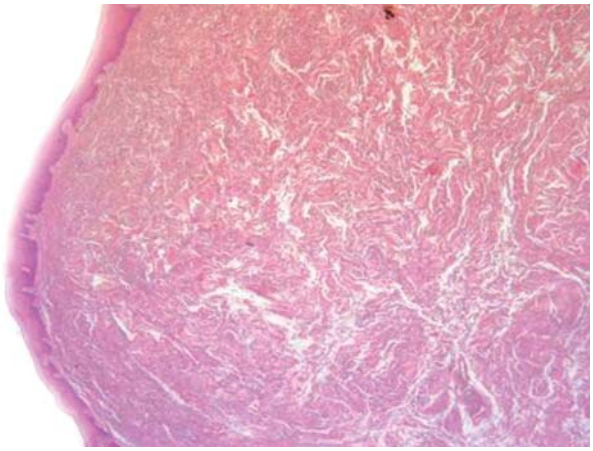


Fig. 8.25: Histopathology of fibroma

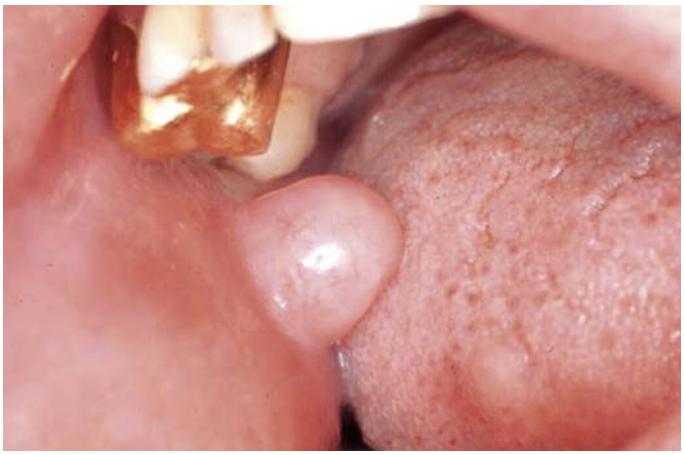


Fig. 8.26: Giant cell fibroma

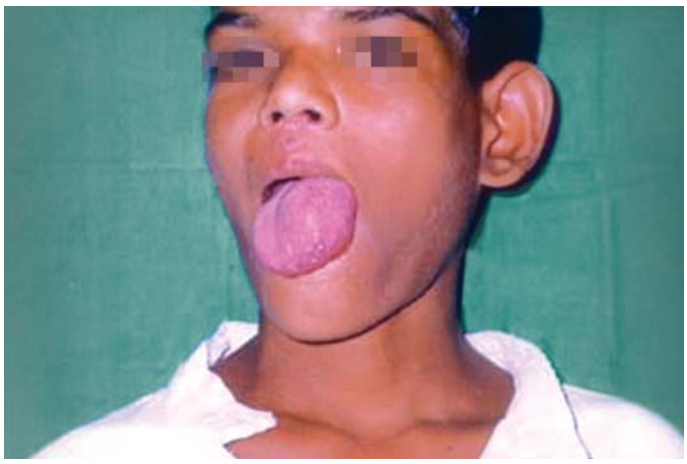
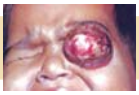


Fig. 8.27: Solitary neurofibroma of tongue

SOLITARY NEUROFIBROMA (FIG. 8.27)

Clinical Presentation and Pathogenesis

A solitary neurofibroma is a single neurofibroma that occurs in an individual who does not have hereditary



neurofibromatosis. The condition may at first be difficult to identify because a single neurofibroma may be the first sign of neurofibromatosis, and the hereditary history of neurofibromatosis may be lacking because of the high incidence of new cases due to spontaneous mutations. Nevertheless, solitary neurofibromas account for 90% of cases of neurofibroma (the other 10% are associated with neurofibromatosis).

A neurofibroma will present as an asymptomatic mass within the subcutaneous or submucosal tissues. The mass will be diffuse. The edges will gradually blend into normal tissue without a clear distinction. Similarly, the mass will infiltrate into and incorporate normal tissues such as muscle, glands, and lymph nodes. Its palpable quality will be that of a lobulated surface, the so called bag of worms feeling.

Occasionally, neurofibromas will develop centrally within the jaws or within difficult to access spaces, such as the infratemporal space, the lateral pharyngeal space, or the pterygomandibular space.

Differential Diagnosis

The diffuse and soft nature of the neurofibroma will give the same tactile impression as that of a lipoma, a vascular malformation, a lymphangioma, and a rhabdomyoma. Vascular malformations and lymphangiomas especially are seen more commonly in the same young age group as are neurofibromas.

Diagnostic Work-Up and Treatment

A neurofibroma is usually diagnosed by incisional biopsy. Once a neurofibroma is confirmed, a computed tomography (CT) scan is recommended to assess its relationship to nearby anatomy. If the tumor is small and accessible, it should be excised with 1 cm margins and frozen section control of the margin. If the tumor is large, it may be unresectable or resectable but associated with a greatly increased morbidity. Such large tumors present a treatment dilemma, which is further compounded by the vascular nature of neurofibromas. This compromises visualization, which in turn compromises the surgery and also adds expectations of increased blood loss, which may require transfusions. Neurofibromas are unencapsulated tumors, making their complete removal more difficult, and since they bear a close histologic resemblance to normal connective tissue, frozen section assessments at the margins are not reliable. Radiotherapy is not an option because of the possibility of radiation sarcomas developing in future years. Therefore, some neurofibromas are not treated or are treated with intentionally incomplete removal in a debulking type of procedure. Other large tumors undergo radical excision, for which reconstructive surgery is required.

In contrast to the schwannoma, a neurofibroma arises from the internal portion of a nerve clinically. In most cases, the parent nerve is not identifiable. In some cases the nerve can be seen to enter the proximal end of the tumor. Because the nerve is incorporated into and is actually part of the neurofibroma, it cannot be preserved.

Histopathology (Fig. 8.28)

The lesions are unencapsulated, consisting of interlacing bundles of spindle cells that typically have wavy or "serpentine" nuclei. The stroma is often fibrillar and eosinophilic but may have mucoid areas. Mast cells and scattered lymphocytes are usually present, and neurites may be found within the tumor. The solitary neurofibroma and the usual neurofibroma of neurofibromatosis do not differ histologically. Cellular atypia may be seen in benign neurofibromas, but mitotic activity indicates malignant change. This phenomenon is more likely to be seen in neurofibromatosis. Although Schwann cells appear to be a major component of neurofibromas, other cells, such as fibroblasts, are also present.

Prognosis

For patients with small lesions excised with tumor-free margins, the prognosis is excellent. Even in tumors that are incompletely excised, the residual lesion grows back so slowly that a lasting gain is attained. Solitary neurofibromas do not exhibit a spontaneous transformation to malignancy. It seems only those that are irradiated or those that are part of hereditary neurofibromatosis have a known malignant potential.

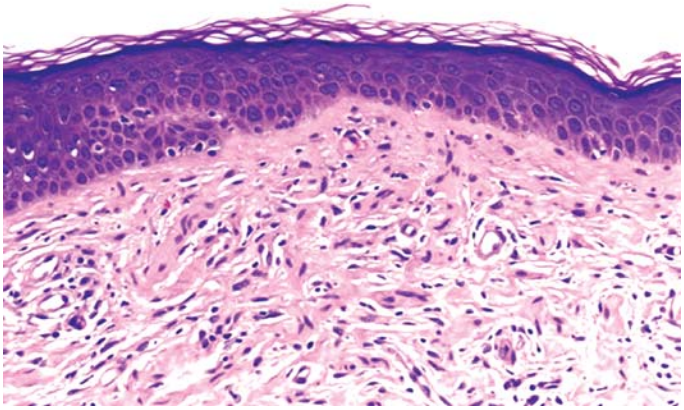


Fig. 8.28: Histopathology of neurofibroma

CONGENITAL GRANULAR CELL TUMOR

Clinical Presentation and Pathogenesis

The congenital granular cell tumor is a specific lesion representing a hamartomatous proliferation of granular cells rather than a true neoplasm. It is present at birth as a mass arising from the anterior maxillary or mandibular gingiva. It is more common in females than in males (9:1) and more common in the maxillary gingiva than in the mandibular gingiva (3:1). The lesions seem to be painless and will almost always arise from a narrow stalk. Even so, some can reach very large sizes (that of an adult's fist) and interfere with feeding. Most will be 2 to 4 cm and brought to the clinician's attention by neonatal nursing personnel or the parents. Occasionally, two (or more) will appear in the same area or one may appear on each jaw (Fig. 8.29).

Although the granular cells of this tumor are identical to those of the granular cell tumors of adults and those of some ameloblastomas under light microscopy, they seem to be of a different origin. The granular cells in this congenital tumor fail to show the suggestive neural elements ultrastructurally or the S-100 protein immunohistochemically as do adult granular cell tumors. Therefore, it is suspected that the congenital lesion arises from vascular pericytes or smooth muscle rather than Schwann cells as is believed to be the histogenesis of adult tumors.

Differential Diagnosis

Several serious tumors can arise from the anterior jaws (particularly the maxilla) in neonates. However, the congenital granular cell tumor is a clinically recognizable tumor if the clinician identifies a stalk and an intact surface epithelium and confirms that the tumor was present at birth. The melanotic neuroectodermal tumor of infancy (MNETI) is the primary differential that can easily be eliminated if the parents or obstetrician can confirm the presence of the mass at birth. The MNETI is not a congenital lesion; it will arise between 2 and 11 months of age. The MNETI will also show clinically black to blue pigmentation and destruction of the anterior maxilla. Malignancies such as a rhabdomyosarcoma or a neuroblastoma are also serious considerations, but each will be destructive masses and will not have an associated stalk. Benign lesions common to newborns, such as hemangiomas and lymphangiomas, are also considerations, but these also will not emerge from a single stalk.

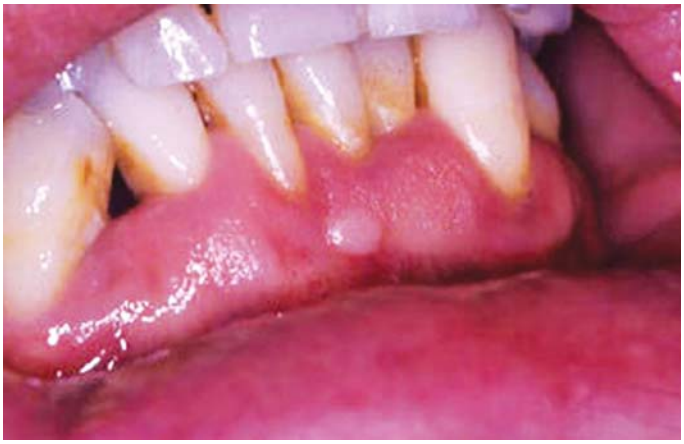


Fig. 8.29: Lower gingival granular cell tumor

Diagnostic Work-up and Treatment

There are some anecdotal reports that these lesions will regress, but regression is not a constant finding. Small lesions can be excised in the neonatal period and closed with a simple suturing. Before the excision, it is well to educate the neonatal staff and reassure parents that the tumor is not a dangerous one and that the child should not be permanently affected in any way. It is also wise to inform the neonatal staff and parents that the baby will cry during the procedure because of fear, not because of pain, and that a small amount of local anesthesia will assure that.

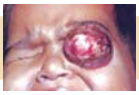
Large lesions (greater than 4 cm) have a significant blood supply, all of which flows into the mass and out of the mass through its stalk. Excision through the stalk may create a rapid blood loss in a neonate such that transfusion is required. Such blood loss can easily be prevented. Before the lesion is excised, the stalk should be stretched slightly and two hemostats placed on the stalk. The stalk should be cut between the hemostats, the tumor mass delivered on one hemostat and the other hemostat used to gain a tissue vascular tie. In this manner, the tumor can be removed with no blood loss.

Histopathology (Fig. 8.30)

The histologic appearance of the cells composing this tumor is identical to that of the granular cell tumor because the cells have a granular eosinophilic cytoplasm due to the presence of enlarged lysosomes. Certain differences do exist, however. The congenital tumor does not show pseudoepitheliomatous hyperplasia. It is also more vascular. Ultrastructurally, it lacks angulate bodies but shows smooth muscle features not present in the granular cell tumor. In addition, it is negative for S-100 protein.

Prognosis

Excision is curative without recurrence.



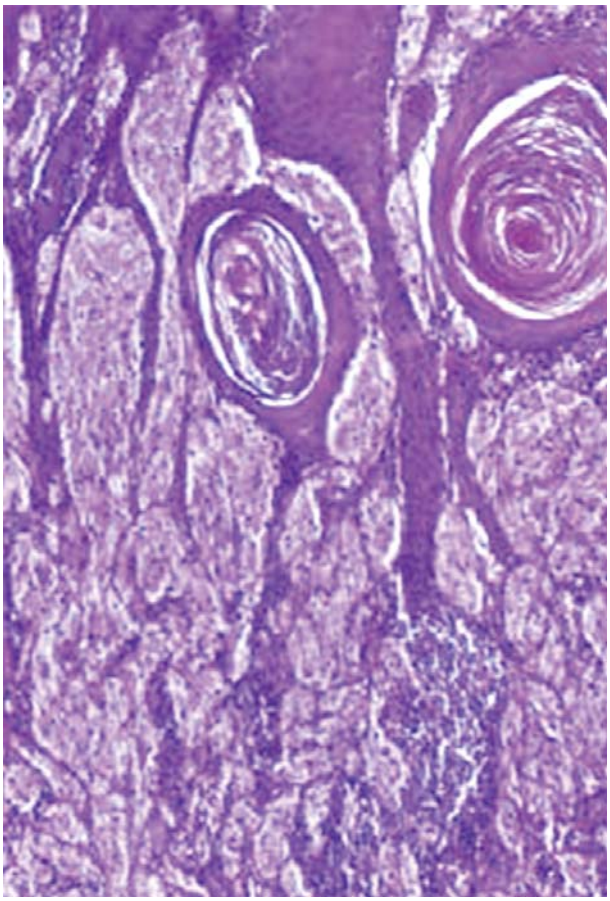


Fig. 8.30: Severe pseudoepitheliomatous hyperplasia in a granular cell tumor

LYMPHANGIOMA

Clinical Presentation and Pathogenesis

Lymphangiomas represent hamartomas of malformed lymphatics. They are sometimes termed lymphangiectasias because they are actually cystic dilations of malformed lymphatic channels that fail to communicate with or drain into other lymphatic channels or veins, and therefore will collect lymph. The fact that a lymphangioma may be seen on ultrasound in utero and that it clinically manifests in early childhood supports the explanation of its origin as an error in embryogenesis. Moreover, its predilection for the head and neck and the axilla, where the embryonic lymph sacs are located, lend further support to this explanation.

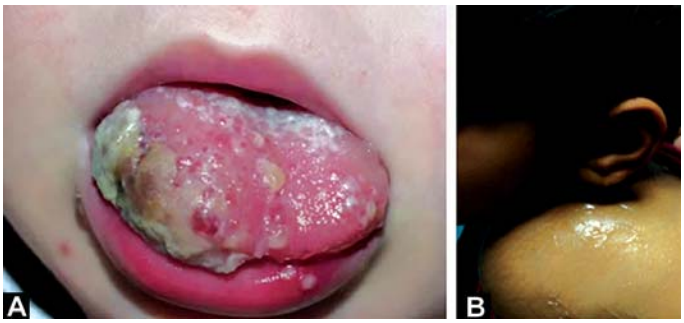
The lymphatic system appears alongside the venous drainage of an area at the sixth week of embryo development. Like veins, lymph channels are lined by endothelium, but unlike veins they contain no adventitial support and no basement membrane. This is important to the normal function of the lymphatic system because it allows for direct contact with the interstitial fluid space. The normal lymphatic channels collect the metabolic products and fluid from the interstitial space by direct pinocytosis through the endothelial cell and by means of an opening-closing cycle at the junctions between endothelial cells. Neither process is inhibited by the barrier effect that a basement membrane would pose. This already delicate developmental structure is further weakened by developmental endothelial malformations, which may result in the well-known large cystic hygromas or in multicystic deep and superficial lymphangiomas.

Three types of lymphangiomas have been described: The superficial multicystic type; the deep cavernous type; and the cystic hygroma. However, these actually represent a single type of defect in lymphatic development manifesting different degrees of severity. Generally speaking, lymphangiomas are less common than hemangiomas. Most of those occuring in the head and neck area (50 to 65%) are present at birth, while 90% are clinically apparent by age 3 years; the majority of these are the deep cavernous type.

The most common presentation is that of a painless soft mass that gradually enlarges and then remains static over a long period. Although occasional enlargements and shrinkages occur, a residual mass remains. The superficial multicystic type is the most static of the three types; it will develop slowly in a young adult as a soft enlargement or fullness of the involved area and will usually present with a pebbly surface that may appear to contain fluid-filled vesicles or blood.

The deep cavernous type tends to expand outward, creating a generalized enlargement of the area. Individuals will often complain of a swollen face or a swollen tongue (Fig. 8.31A). This type is more often reported to undergo episodes of expansion and shrinkage than are the other types.

The cystic hygroma type can reach enormous sizes and lead to the death of the infant (Fig. 8.31B). Otherwise, it will remain over a long period of time as a static mass that is either unresectable or can only be incompletely removed.



Figs 8.31A and B: (A) Lymphangioma of tongue, (B) Cystic hygroma

Differential Diagnosis

Because of their soft quality, lymphangiomas will most closely resemble lipomas, salivary retention phenomena, and hemangiomas. Since many lymphangiomas actually have some blood in their lymphatic channels, they are most often confused with hemangiomas; thus the term hemangiolymphangioma has been applied to such lesions. However, these basically represent lymphangiomas with communications to normal blood vessels.

Diagnostic Work-up

No definitive studies other than an exploration and biopsy will confirm the diagnosis of a lymphangioma. However, ultrasonography will detect the cystic nature and fluid component of a lymphangioma, and angiography will rule out a vascular lesion such as an arteriovenous or cavernous hemangioma. A CT scan will raise suspicions of a lymphangioma if it shows multiple areas or large spaces that are homogeneous and do not enhance with contrast injections.

Histopathology (Fig. 8.32)

Lymphangiomas are unencapsulated lesions consisting of dilated, endothelially lined channels that may contain lymphocytes. The stroma consists of delicate collagen within which lymphoid aggregates are sometimes encountered. Some lymphangiomas also have a vascular component and may therefore contain some red blood cells. Cystic hygromas differ only in that they are usually composed of very large, interconnecting, endothelially lined, cyst-like spaces.

Treatment and Prognosis

Lymphangiomas may be described as benign because they are hamartomas that may become large but will not continue to grow indefinitely and will not metastasize. Nevertheless, they can be life-threatening as a result of their size or secondary infection. Since they do not respond to sclerosing agents, pressure therapy, radiotherapy, or any known chemotherapy, almost all are either tolerated by the patient or treated surgically.

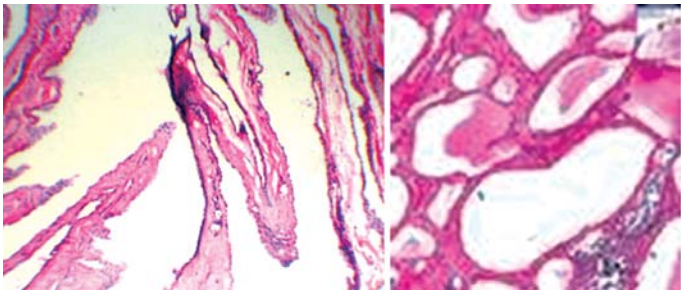


Fig. 8.32: Histopathology of cystic hygroma

The cystic hygroma that is compatible with life is best removed between the ages of 18 and 24 months. If the cystic hygroma has compromised the airway, a tracheostomy may be required before this time. Cystic hygromas are usually well circumscribed, but they have only a thin connective tissue capsule at best. In such cases, a precise pericapsular excision and removal of any lymph nodes or identifiable lymphatic structures in the neck are recommended. A complete removal of the entire lymphangioma/cystic hygroma may not be possible. However, since it represents a hamartoma rather than a true benign neoplasm, the remaining lymphangioma will not reproliferate, but what remains may dilate and reexpand.

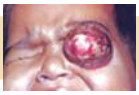
The localized cavernous types and the superficial multicystic types are either allowed to remain untreated or excised with 5 mm margins. However, since many lymphangiomas extend deeply into the muscle of the lip or tongue, such surgery risks deformity, some functional loss, and possibly nerve injury. It is not uncommon to excise a lymphangioma in one, two, or three stages to minimize these risks.

It is important to emphasize that sclerosing agents, chemotherapy, and radiotherapy are not effective therapies and therefore are not recommended. Moreover, radiotherapy is a known risk for malignant transformation.

HEMANGIOMAS

Hemangiomas are benign proliferations of vessels closely resembling normal vessels. Their similarity to normal vessels is so great that it is unclear whether they represent vessel malformations, true neoplasms, or hamartomatous overgrowths. One school of thought suggests that lesions that have greater numbers of endothelial cells than are required to line their lumen represent neoplasms; the remainder represents hamartomas. Under this definition, hemangioendotheliomas would represent true neoplasms, but so would reactive lesions such as papillary endothelial hyperplasia, while arteriovenous malformations and what are now termed juvenile capillary hemangiomas would represent hamartomas.

Another school of thought contends that malformations present at birth or those that appear shortly after birth are all congenital and represent vascular malformations. However, many vascular lesions may be congenital but subclinical at birth, only to appear years later (e.g. telangiectasias seen in hereditary hemorrhagic telangiectasia and several facial hemangiomas). Indeed, many arteriovenous hemangiomas that emerge in the late teens and early 20s are associated with other abnormal vessels identified only by angiography.



In the absence of a uniformly accepted classification and in light of the wide range of biologic behaviors, the authors of this text prefer the term hemangioma used with the acknowledgment that almost all of these lesions represent vascular malformations that may be expressed at any time from fetal life to old age. They will be distinguished from proliferating cellular entities including hemangioendotheliomas, hemangiopericytomas, and angiosarcomas, which are true neoplasms owing to their continuous cell division without true vessel formation.

ARTERIOVENOUS HEMANGIOMA

Clinical Presentation and Pathogenesis

Arteriovenous hemangiomas (AVHs) are the most serious of all the hemangiomas and is life-threatening. Those occuring in deep locations or centrally within the bone of the jaws and face are associated with a variable number of direct arteriovenous communications. They may also have a large soft tissue component that is most often located within the overlying skin and the lip (Fig. 8.33). Most will occur within the mandible, the maxilla, or the tongue in the teenage and early adult years. The patient is often able to detect a "whirring sound" or will claim to hear their heartbeat within the lesion. Indeed, some will demonstrate a visible palpation or a palpable thrill, and occasionally some of these will be able to be auscultated with a stethoscope (i.e., a bruit). Most can be heard as an increased pulsatile sound with turbulence by Doppler examination. Some AHVs will produce vague paresthesias in the lip, apparently due to pulsatile pressure on the inferior alveolar nerve. In high-flow lesions, jugular venous distension can be seen; in those within the tongue, engorgement of the lingual veins on the tongue's ventral aspect becomes apparent.

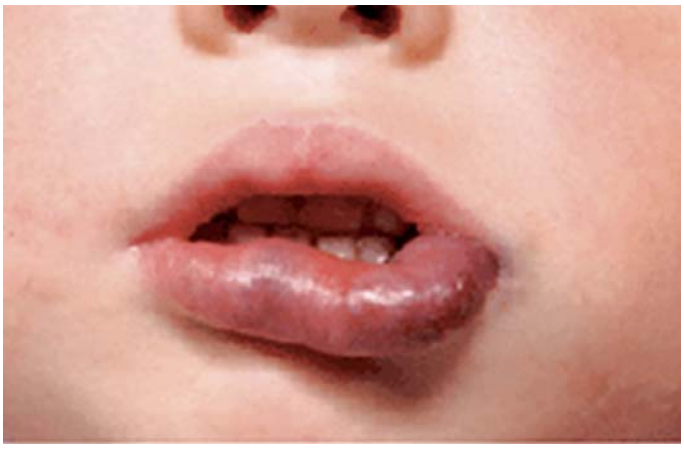


Fig. 8.33: Arteriovenous hemangioma of lip

If this type of hemangioma is located in the mandible or maxilla, the bone will be expanded and a fine multilocular radiolucency will often be present. The radiographic picture will vary from distinctly radiolucent; to a well-defined multilocular appearance, often described as a "soap bubble"; to a fine, mixed radiolucent-radiopaque appearance that resembles fibrous dysplasia. It is also common to see periosteal new bone formation perpendicular to the cortex, which on occlusal radiographs will have the so called sun-ray appearance more often associated with osteosarcoma. A careful radiographic inspection frequently reveals periodontal bone loss around one or more teeth, which will appear to be elevated in their sockets. Clinically, these teeth will be mobile and compressible in their sockets. Removal of such teeth has given rise to dramatic high pressure (arterial) bleeding from traumatic rents in what usually amounts to large arteriovenous dilations.

The soft-tissue components of an AVH frequently occur in the skin of the midface and around the lips. Unlike cavernous or capillary hemangiomas, this type is not present in infancy but emerges independently, usually during the teenage years. The lesion will develop into a solitary blue-red nodule located at the submucosal or subcutaneous level. Although arteriovenous communications are apparent in these soft tissues, they do not pose as significant a bleeding risk because the vessels remain small, as does the degree of shunting. Although some will elicit a palpable thrill, they do not present the uncontrollable bleeding potential associated with those in bone.

The pathogenesis of AVHs originates with fetal endothelial cell precursors. During development, one or a few of these cells lose their ability to produce or secrete platelet-derived growth factor (PDGF) and transforming growth factor beta-1(TGF-β1), which are required to recruit adventitial cells around developing vessels. Consequently, the daughter cells and eventually the vessels that arise from these original cells develop as single cell-lined vessels (arteries, arterioles, veins, and venules). During prepuberty there is usually insufficient pressure to cause these structurally unsupported vessels to expand and produce symptoms. However, beginning at 10 years of age, the maturity of the cardiovascular system and the increased systemic pressure causes these single cell-lined vessels to expand. As they expand, they create turbulence and a negative pressure that reverses the local flow dynamics to feed blood into this expanded lumen and even recruit new feeder vessels. This process is known as the black hole phenomenon.

The black hole phenomenon explains the clinical presentation of patients who are mostly in their early

teenage years and the absence of any limitation to a known vascular anatomy. The earlier in fetal development that the loss of these growth factors occurs, the larger the vascular territory that will be involved. Therefore, some will be smaller and some larger in area; most will cross the midline. This pathogenesis also identifies the arteriovenous hemangioma as a developmental malformation rather than a neoplasm. Therefore, its apparent growth during its active phase is not due to a neoplastic process but to either a further manifestation of developmentally unsupported vessels or to recruitment of vessels into its central nidus.

Differential Diagnosis

Arteriovenous hemangiomas that occur in the jaws may be subclinical (other than a radiolucent expansion). They will resemble odontogenic tumors such as ameloblastomas, odontogenic myxomas, and ameloblastic fibromas. Those with some fine bone trabeculations may instead resemble fibro-osseous diseases such as fibrous dysplasia, ossifying fibroma, central giant cell tumors, or even the infectious disease chronic sclerosing osteomyelitis.

Diagnostic Work-up

A lesion that is suggestive of an AVH, whether via clinical examination, radiography, or Doppler sounds, should undergo a CT or MRI scan to determine its extent of involvement and its relationship to other tissues and a diagnostic angiogram of both common carotid systems. A lesion that is not initially thought to be an AVH but returns blood under pressure from aspiration should also undergo scanning and angiography. Both common carotids should undergo angiography separately because possible crossover feeders from the opposite side and/or from the internal carotid circulations need to be assessed. The clinician should be present during the angiography or arrange to review videotapes of the procedure to understand the dynamics of this malformation.

In reviewing the static angiograms, it is important to understand that images are taken one second apart beginning just before dye injection and ending when the dye completely clears from the field. One should, therefore, assess the number of feeders, their size, their location and parent feeding vessels, the time required until the venous phase begins, and the time required for the central lesion to empty. The sooner the venous phase is seen, the greater the arteriovenous shunt and the higher the flow. Prolonged retention of residual dye within the lesion (3 to 5 minutes) is associated with larger lesions, increased flow rates, and turbulence, which creates eddies that retain the dye longer.

Histopathology (Fig. 8.34)

Histologically, dilated vessels, comprising only a single row of endothelial cells, are present. In close proximity, feeder arteries and veins may be seen. Often there is thickening of the intima of the vein because of increased pressure, but no adventitial cells are present.

Treatment

The ideal therapy for these lesions, particularly when located within the jaws, is selective embolization followed by surgeries. The goal is to obstruct or reduce the blood flow to the lesion so that it can be excised with minimal blood loss. This approach is very effective for lesions that are resectable, and little blood loss is the rule. Overaggressive embolization is discouraged because embolization affects the normal as well as the abnormal vessels, and there have been several reports of tissue slough and dehiscences due to skin and other tissue ischemia.

Embolization techniques and materials vary. As of this writing, embolizations are usually achieved with coils, 100% alcohol, or polyvinyl alcohol (PVA) beads. Coil embolizations generally embolize feeder vessels at the small artery level. They are initially effective, but small

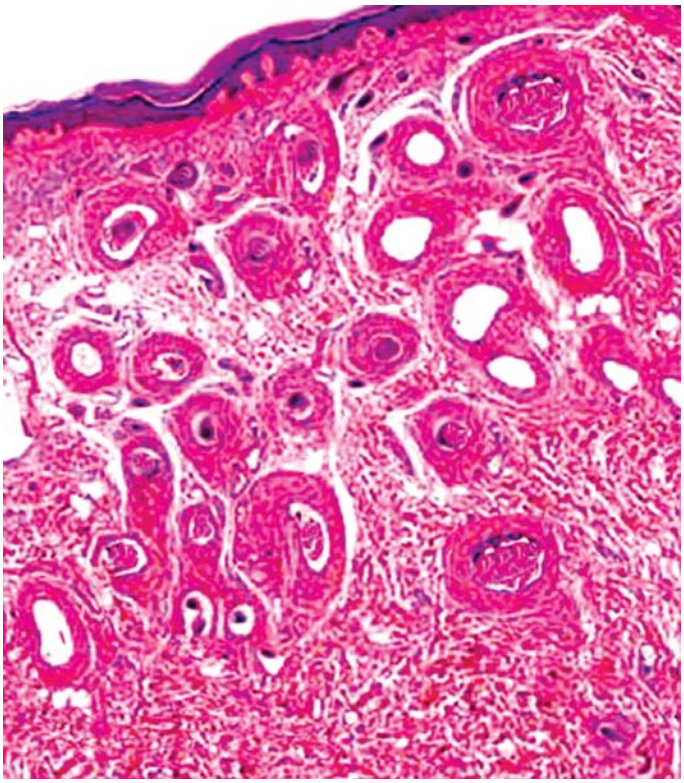
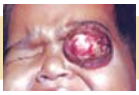


Fig. 8.34: Histopathology of arteriovenous hemangioma



unembolized and often collapsed feeders enlarge rapidly (within 24 hours) to become dominant feeders, and recanulation of the clot and growth of bypass vessels quickly negate its effects. The surgeon should discourage the invasive radiologist from using coils because their reduction of blood flow is too shortand too small. In addition, these coils will block access to these same vessels in future embolizations, which are often required. Absolute alcohol can be injected into the small artery precapillary arteriolar level by what is called "superselective" embolization. The caustic effects of 100% alcohol are, therefore, exerted close to the center of the lesion, which results in fibrosis of many of the lesion's multiple feeders. PVA beads of varying sizes are released in the main feeders and progress downstream to lodge in and embolize at the precapillary arteriolar level or within the lesion itself. Both PVA beads and alcohol are believed to be selectively guided to the more abnormal vessels by the fluid dynamics (higher flow rates than normal) of abnormal vessels.

The timing of surgery following embolization depends on the material used for embolization. If solid or bulky materials, such as coils, fat, muscle, or Gelfoam (Pharmacia) are used, the surgery should follow soon after; that is, the same day or the next day (12 to 24 hours). Because these materials obstruct vessels too proximal in the feeder system, after this time collapsed collateral vessels fill to supply the AVH and restore high pressure flow. If small PVA beads (250 µm or less) or liquid agents such as 100% alcohol or cyanoacrylate are used, the surgery is best delayed for about 72 hours to gain the maximum reduction of blood flow to the central portion of the AVH. In the case of PVA beads, they will initially lodge at the arteriole level and then flow further downstream toward the center of the AVH, at which level they will clot. Because the clot is closer to the AVH, they encompass more distal feeders in the feeder system. In the case of liquid agents, these flow initially into the distal portions and then hopefully into the central portions of the AVH. However, unlike solid materials, they do not lodge to act as a plug. Instead, they initiate endothelial damage by inducing clotting and eventual fibrosis, which takes time.

Today the standard approach to a serious, life-threatening AVH in bone is resection, which is often large and necessitates later reconstruction. Although it leaves residual AVH in the soft tissues, this approach is effective, and it eliminates the life-threatening bleeds from the bone. An AVH resection requires a wide access via a visor incision in the neck to reduce the blood loss beyond that achieved by preoperative embolization. The external carotids should be isolated and temporarily clamped to reduce the blood flow. As the dissection approaches the mandible, numerous thin, dilated vessels may be encountered in the soft tissue. Each is isolated, clamped, and ligated as it is approached. The approach to either jaw should separate the bone from the attached soft tissue with a supraperiosteal dissection. Attempting a subperiosteal reflection to preserve the periosteum will not promote better healing but will increase the surgical blood loss instead. This is due to multiple high pressure perforating vessels from the bone to the periosteum that will be opened and difficult to control because they will contract into the cortex. Transsection of these same vessels at the supraperiosteal level makes them more easily controlled with electrocautery. Should bony bleeds occur under high pressure (pumpers), the best control measure is bone wax applied to the cortex. Once the mandible or maxilla is circumscribed with a supraperiosteal dissection in the area of resection, the bony resection can be completed with a readiness for electrocoagulation and/or bone wax at each bone end.

In addition to the technical surgical approach described, as part of this type of resection, typed and cross-matched blood (8 units) should be available and hypotensive anesthesia techniques should be used. A tracheostomy will also be necessary because the degree of surgery and the vascular nature of the AVH will predictably create a significant degree of swelling that may compromise the airway. The significant size of most AVHs in the mandible will necessitate reconstruction with a rigid titanium plate. Immediate bone grafting is not recommended because of the time length of most resections and the potential for contamination from oral communications. Instead, the rigid plate will maintain the jaw contours and tissue projection until a well-planned cancellous marrow graft can be accomplished 3 months later.

As of this writing, another surgical approach, one that avoids jaw resection and has shown promising results in several cases, is being tested. This approach exposes the mandible or maxilla with the same soft tissue surgical approach to the bone, and, as before, dilated vessels encountered in the soft tissue dissection are isolated and ligated as they appear. This may amount to many vessels, but their removal will further reduce the blood flow to the vessels within bone. In this approach the jaw is not resected, but with the external carotids temporarily clamped and hypotensive anesthesia achieved, the lateral cortex is quickly removed and the endothelial lining of the AVH quickly curetted. The bony cavity is then packed with Surgicel (Ethicon), Avitene (Davol), and platelet-rich plasma (PRP). A dense compaction of the Surgicel has been effective in stopping any residual AVH bleeding. To date, this approach has shown bone regeneration in the defect without a return of the AVH in bone. However, it is still a relatively new approach that is considered only in cases occuring in bone that have an accessible, single, large

radiolucency. The theory supporting the effectiveness of this approach is the removal of the central AVH nidus, which literally sucks in blood from adjacent vessels via its negative pressure and recruits new feeders.

Some lesions in soft tissue may be unresectable. In particular, large lesions of the tongue may require total glossectomy in young adults, creating obvious swallowing, speech, and aspiration difficulties. Such "unresectable lesions" in soft tissue may be managed with serial embolizations, usually performed annually. A few lesions resolve completely after several embolizations; most persist but no longer continue to pose a bleeding threat; and a few others continue to develop new high pressure vessels, leading to a risky resection or to eventual death.

Prognosis

Arteriovenous hemangiomas that are embolized and resected tend not to recur. Therefore, the focus of management is to embolize and resect those that are resectable and to manage the unresectable AVHs with serial embolizations. Those that undergo serial embolizations have about a 10% chance of resolution, a 60% chance of preventing progression and life-threatening bleeds, and a 30% chance of progressing to uncontrollable disease.

MANAGEMENT OF EMERGENCIES AND COMPLICATIONS

The two most common AVH-related emergencies that the oral and maxillofacial specialist may need to manage are a life-threatening bleed and a rapid proliferation of the AVH that may obstruct the airway.

The emergency bleed is a time honored scenario in oral and maxillofacial surgery education. It may start with a single extraction of a tooth that has its roots in an unrecognized AVH. The surprised practitioner is startled to see a rapid high pressure bleeding. In the past, the clinician has been taught to replace the tooth in the socket with pressure. However, experience has found this maneuver to be inadequate, as rapid bleeding continues around the tooth. Instead, the socket should be directly packed with Surgicel or plain gauze and digital pressure should be applied until bleeding is stopped; afterward, a tie-over suture maintaining pressure on the packing material is placed using a nonresorbable suture. In the authors' experience, direct packing is universally effective, rendering other more dramatic hemorrhage control measures, such as external carotid ligation and panicked emergency embolizations, unnecessary. This approach is also effective when the patient develops a spontaneous bleed and is brought into the emergency room. In each case, after packing has controlled the rapid bleeding, fluid resuscitation is provided, ORh negative blood is given, and blood is typed and cross-matched. There should be no reluctance to give ORh negative blood in such urgent cases. This "universal donor" type of blood has an excellent track record, supported by the use of over a million units during the Vietnam War without a reaction. From this controlled situation, a diagnostic angiogram and initial embolization can be accomplished.

A less common emergency is upper airway obstruction, usually caused by proliferation or expansion of the AVH. In particular, those that occur in the tongue often require emergency intubation or tracheostomy. After an airway is secured, an attempt may be made to manage the AVH by embolization and surgery. However, a total glossectomy is not recommended because of the obvious speech, swallowing, and aspiration difficulties it would create. Therefore, radiotherapy, which would otherwise not be a strong consideration because of the potential for sarcoma transformation, is used in this rare situation. A dose of up to 6,000 cGy will induce a fibrosis and physical shrinkage of the AVH, restoring the airway and allowing discontinuation of the tracheostomy.

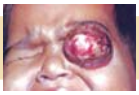
Another complication that the oral and maxillofacial specialist must keep in mind is high output cardiac failure. Even many young patients will have demonstrable cardiomegaly due to the increased blood volume within the AVH. This should decrease somewhat with embolization and surgery and is another indication for treating the AVH directly.

JUVENILE CAPILLARY HEMANGIOMA (Fig. 8.35)

Clinical Presentation and Pathogenesis

Juvenile capillaryhemangiomas are distinctive lesions that commonly occur in the superficial skin area of the chin and upper neck and slightly less commonly occur in the parotid area. The lesion appears as a red-blue multinodular mass with a thin overlying skin. Although painless, it may ulcerate if the thin overlying skin is ruptured. It is much more common in young girls than in boys, and it is not rare, occurring in 1 of every 200 live- births.

The lesion may be described by the parents or obstetrician as congenital, but it usually becomes apparent about 2 to 6 weeks after birth and then rapidly enlarges to its maximum size (usually 4 to 8 cm) by 6 to 9 months of age. Most will then remain static for 2 to 6 months before undergoing a slow but steady involution. As the lesion regresses, it loses its red to violaceous color and takes on a pale appearance. As it involutes it leaves an irregular, almost wrinkled looking skin surface. By the age of 7 years, 75 to 90% of the lesion will have involuted. Because the



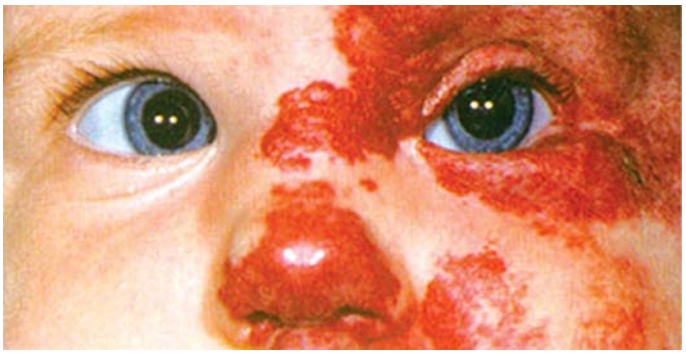


Fig. 8.35: Superficial capillary hemangioma

involutional process is one of interstitial and vessel fibrosis, it leaves behind a firm, fibrotic, multinodular texture.

This classic appearance and evolution have given this lesion the designation strawberry nevus. Nonetheless, this hemangioma is a vascular malformation of a series of abnormal vessels fed by a single normal arteriole and therefore is not under abnormally high pressure and does not pose a bleeding threat.

Diagnostic Work-up

The juvenile capillary hemangioma is a clinically distinctive entity diagnosed by its appearance and history. No known diagnostic studies will add useful information. An angiogram is not indicated.

Histopathology (Fig. 8.36)

Hemangiomas may be classified as either capillary or cavernous; however, both types consist of proliferative vascular channels that are lined by endothelium and lack a muscular coat. Erythrocytes are in the lumen. The arrangement is often lobular, since capillaries proliferate around a feeder vessel. Capillary hemangiomas may initially be extremely cellular lesions composed of endothelial cells and poorly canalized vessels. Mitoses may be present. In early stages, these have been called juvenile hemangiomas. Mast cells, which may be a source of angiogenic factors, can be seen. As these lesions mature, the vessels are canalized, and the endothelial cells flatten to form the typical capillary hemangioma. When they undergo regression it is through interstitial fibrosis.

Treatment and Prognosis

The best therapy in most cases is time and the avoidance of overaggressive therapy during the hemangioma's active growth phase. Parental education and reassurance about involution are of great value. In addition, it is reasonable to prepare parents for cosmetic/reconstructive surgery, which may be required in later years (ages 8 to 12 years).

Although cryosurgery, sclerosing agents, and surgical excision have all been used, these methods often create more scarring and disfigurement than the lesion itself or its involution. Irradiation also once was used, but today it is not advised because of its possible carcinogenic effects and its scarring and drying effects on skin. Systemic prednisone is a valid and commonly used therapy today. A dose of 1 mg/kg per day at 2 week intervals (interrupted by 2 week intervals) for 3 months at a time will hasten involution and is associated with few side effects or complications.

A more recent alternative therapy for certain juvenile capillary hemangiomas has been developed in the laboratory of Judah Folkman at Boston Children's Hospital. His discoverythat interferon alpha 2a is anti-angiogenic has already led to its use in the treatment of Kaposi sarcoma and to ongoing studies of its use in treating hemangiomas. For example, it is used in large and unresponsive hemangiomas, especially in patients who demonstrate increased levels of basic fibroblast growth factor (βFGF) in a 24 hour urine collection. Increased levels of βFGF, which stimulates angiogenesis, is a marker for response to interferon alpha 2a, and the use of interferon alpha 2a, in turn, is predicated on its action to down regulate βFGF, which is overexpressed by certain hemangiomas. Its use in selected hemangiomas is not universal but offers a nonsurgical treatment approach that is less prone to complications. Dosages vary according to the patient and the size of the hemangioma but range from 1 million to 4 U per day for an indeterminate time.

When natural involution is complete, the residual nodular, irregular skin surface may be improved, requiring only makeup or dermabrasion. However, more severe cases may require excision and advancement of local flaps, which are preferred over distant pedicled or free vascular flaps

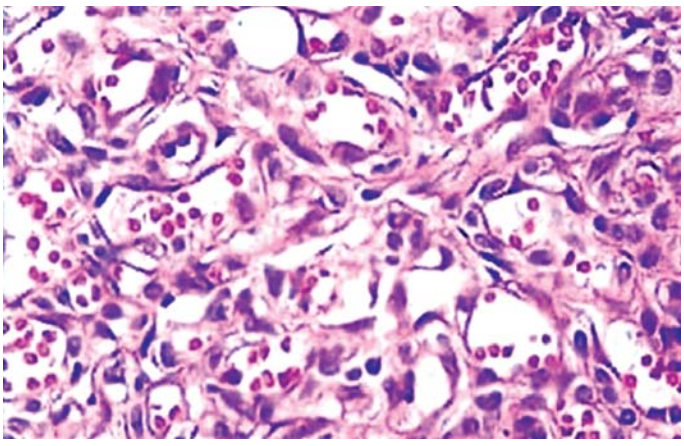


Fig. 8.36: Histopathology of juvenile capillary hemangioma

to match skin thickness and color. If the excised skin surface area is large, it is reasonable to consider placement of a tissue expander adjacent to the area so that the expanded local skin can be rotated or advanced to cover the defect without stretching it or creating tension at the site of closure.

CAVERNOUS HEMANGIOMA (Fig. 8.37)

Clinical Presentation and Pathogenesis

Cavernous hemangiomas are less common than juvenile capillary hemangiomas in all areas of the body except the oral cavity. Like juvenile capillary hemangiomas, they occur most frequently at or just after birth. Cavernous hemangiomas differ from capillary hemangiomas in that they are larger, more diffuse, usually located somewhat deeper, and only partially involute. Therefore, they persist into adult life unchanged or somewhat fibrosed.

The classic presentation is a soft, diffuse, puffy mass in the parotid and in the skin over the parotid region as well as within bone, mostly in the posterior mandible. They may also present as a large, soft, blue-red, painless blanching mass in the oral mucosa. Soft tissue cavernous hemangiomas will often produce a cupped out type of resorption of the bony cortex. Although these lesions do not undergo involution, they develop calcifications via phlebolith formation. These dystrophic calcifications in organized thrombi are often first seen on a radiograph. Those that occur in the parotid region are well-known to show multiple small, round radiodensities superimposed over the ramus and posterior body.

Less commonly, cavernous hemangiomas will occur centrally within bone. They will usually cause a painless expansion and a mixed radiolucent radiopaque appearance due to their stimulation of reactive bone. Like their soft tissue counterparts, their blood-filled spaces are not under high pressure and therefore do not pose a significant bleeding threat.

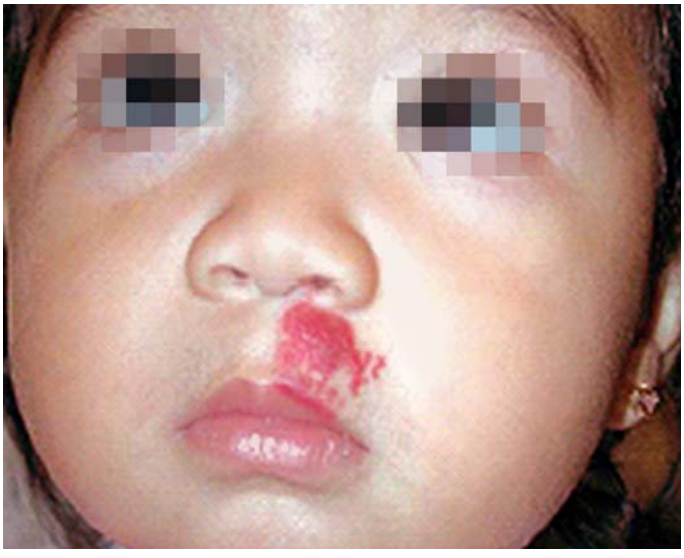


Fig. 8.37: Cavernous hemangioma

Differential Diagnosis

Because of their deep location, the red-blue vascular nature of cavernous hemangiomas is less apparent and therefore initially may not be correctly recognized. Lymphangiomas can bear a strong resemblance to cavernous hemangiomas because they too are soft and diffuse and can imparta red-blue appearance by virtue of their hemangiomatous components, some blood in their abnormal lymphatic spaces, and the bluish color of lymph when viewed through skin. Neurofibromas and lipomas will also clinically have a soft, diffuse, and irregular quality to their presentation, mimicking that of a soft tissue cavernous hemangioma.

Cavernous hemangiomas centrally located in bone will mostly resemble fibro-osseous disease or bone tumors. They will produce a radiographic appearance most similar to an ossifying fibroma or an osteoblastoma. In the jaws, some may be confused with a developing odontoma, a calcifying odontogenic cyst, or a calcifying epithelial odontogenic tumor.

Diagnostic Work-up

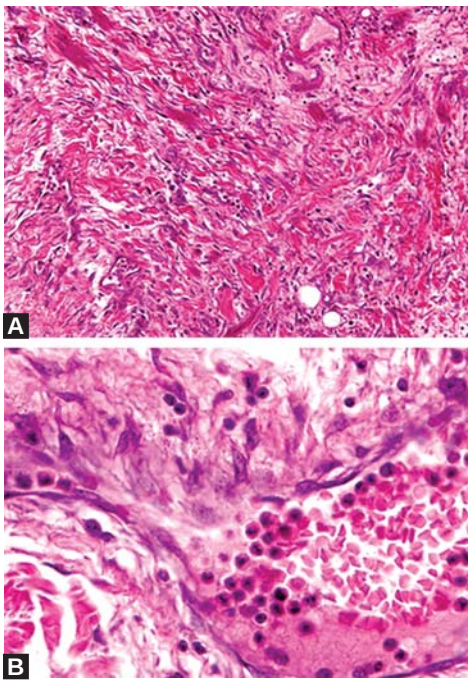
A cavernous hemangioma may require no specific work-up if the lesion is clinically apparent and/or it radiographically demonstrates phleboliths. If there is a suspicion that the lesion represents an arteriovenous hemangioma (also called an arteriovenous malformation), it should be palpated to detect a possible thrill and auscultated for a possible bruit. Although auscultation with a stethoscope is the standard, a more precise auscultation can be accomplished with a Doppler unit and is highly recommended. If bruits are heard by either examination, a diagnostic angiogram is required.

Histopathology

Cavernous hemangiomas are less circumscribed than capillary hemangiomas and have dilated vascular channels with flattened endothelium. Calcifications and formation of phleboliths occur through dystrophic calcification of organizing thrombi, but regression does not occur (Figs 8.38A and B).

Treatment and Prognosis

Cavernous hemangiomas in soft tissue usually require some type of treatment because of their impingement on adjacent structures. Because these lesions are not true



Figs 8.38A and B: (A) Cavernous hemangioma at 10X magnification, (B) Cavernous hemangioma at 40X magnification

neoplasms with continual growth, they do not necessarily require complete removal or wide margins. The goal of therapy is alleviation of their impingement on native structures or their interference with function. Therefore, if they are accessible, soft tissue cavernous hemangiomas should be completely excised if feasible. They do not pose a severe bleeding potential and can be managed in many cases by a peripheral resection around their edges. If the lesion is so large that the excisional wound is unmanageable or major reconstructive surgery would be required, ablation with cryosurgery or laser surgery offers some distinct advantages if performed by experienced practitioners. Sclerosing therapy is less desirable than either excision, cryosurgery, or laser surgery, but it has been used in the past. Sclerosing agents, such as sodium morrhuate, sodium psyllate, or a slurry of 250 mg tetracycline in 5 mL of saline, are useful in inducing fibrosis in most cavernous hemangiomas. However, repeated injections are required, and unpredictable outcomes (from minimal effect on the hemangioma to overfibrosis of the tissues) are common.

Cavernous hemangiomas in bone will be very well demarcated and some what radiopaque. They will resemble the radiographic picture of an ossifying fibroma or an osteoblastoma and are treated in much the same way with a peripheral resection using 2 to 3 mm margins. Since the tumor itself contains lined vessels that are dilated and thinned, the perfusion may produce some extracortical bone formations, giving it a so called sun ray appearance. The tumor does not pose a significant bleeding threat because of the absence of high pressure or high flow rates. Therefore, the resection may be accomplished with saws and osteotomes as needed. When the bone graft can be placed into a contamination-free tissue bed and immobilized, the graft can be done immediately; otherwise the graftshould be staged for 3 to 4 months.

NASOPHARYNGEAL ANGIOFIBROMA (Fig. 8.39)

Clinical Presentation and Pathogenesis

Nasopharyngeal angiofibromas are benign tumors that are life-threatening because of their vascularity and location. The tumor develops almost exclusively in adolescent boys.

It will present with the patient complaining of progressive nasal obstruction over the past 1 to 2 years and episodes of epistaxis. Some of the bouts of epistaxis will be prolonged and severe because the small vessels within the lesion lack vasoconstrictive capacities. A nasal speculum examination or a transoral mirror examination will usually identify a red-blue polypoid mass, which may protrude into the pharynx or into the anterior nasal cavity. The tumor does not cause pain, but its size and erosion into adjacent structures will produce a variety of signs. Orbital invasion will often cause protrusion of the globe and visual changes, particularly diplopia. Obstruction of the eustachian tube often creates a secondary otitis media, and obstruction of sinus drainage may cause sinusitis in any of the paranasal sinuses.

The nasopharyngeal angiofibroma represents a benign but true neoplasm as evidenced by its continued growth and recurrence if incompletely excised. Its bleeding nature

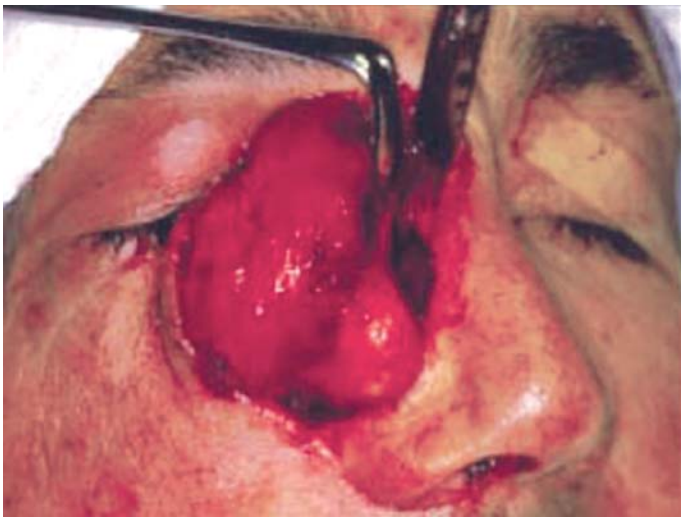


Fig. 8.39: Nasopharyngeal angiofibroma

is due not only to its vascular density, but also to a thin or absent smooth muscle component and the lack of an elastic membrane within the vessel wall. Because of these missing elements, the vessels cannot vasoconstrict or form a platelet plug, which is the first phase of hemostasis.

Differential Diagnosis

The clinical presentation of a nasopharyngeal angiofibroma is very distinctive. Occasionally, a vascular nasal polyp will produce a mass related epistaxis, or an allergic rhinitis will produce swollen bleeding nasal membranes, which may be mistaken for a nasopharyngeal angiofibroma. Vascular malformations and hemangiomas are other clinical possibilities.

Diagnostic Work-up and Treatment

A CT scan is essential for assessing the extent and location of this tumor. Because the clinical presentation and male predominance are so specific, an incisional biopsy, which may produce profuse bleeding, is often deferred if the CT scan is consistent with a nasopharyngeal angiofibroma. In some cases, a diagnostic angiogram is useful, but usually this procedure is also deferred until just before surgery and includes embolization (Fig. 8.40).

The treatment goal is to accomplish a complete excision with wide access and minimal blood loss. An angiogram is performed 1 to 3 days before surgery. The angiofibroma is embolized, usually with PVA beads, alcohol, or other particulate materials. The surgical access is through a Le FortI down-fractured maxilla and nasal mucosal incision. The embolized tumor bleeds much less, and the wide access provided by the Le FortI approach allows for a more complete excision. The down-fractured maxilla is returned to its original position as defined by the dental occlusion and the indexing of rigid fixation plates on the maxillary cortex prior to the Le Fort I osteotomy. It is then rigidly fixated so that the patient can return to function without requiring maxillomandibular fixation.

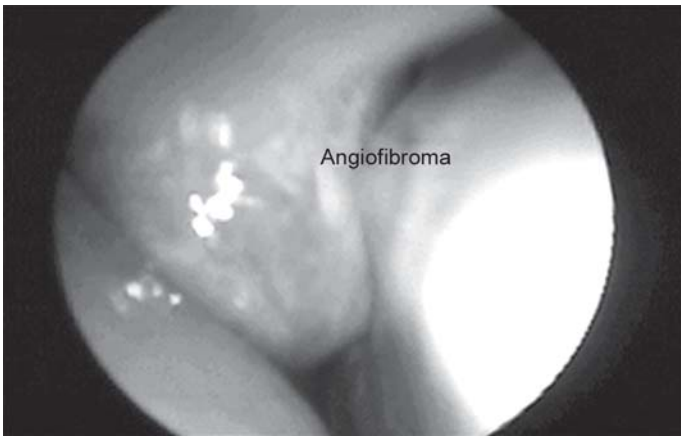


Fig. 8.40: Nasofibroscopy showing angiofibroma in right nasal cavity

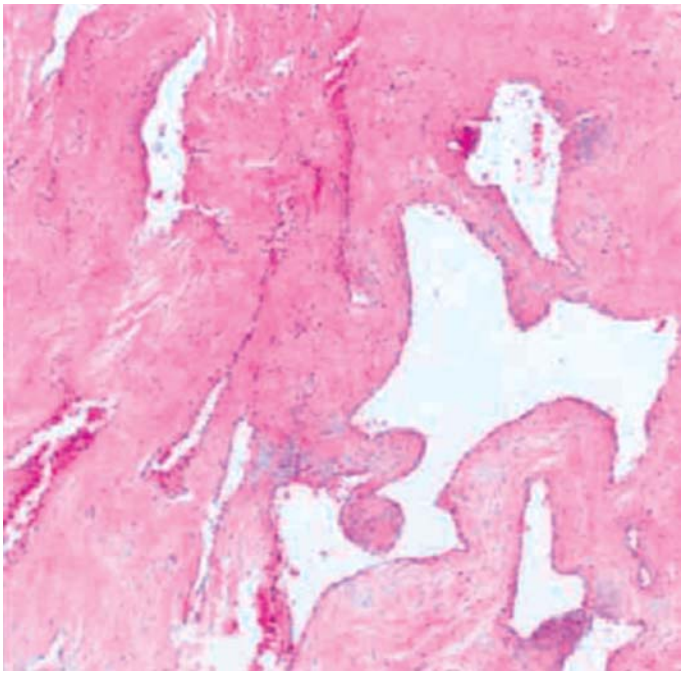


Fig. 8.41: Histopathology of nasopharyngeal angiofibroma

Histopathology

Histologically, these firm, rubbery, lobulated masses are fibrovascular. The stromal collagen fibers are often in parallel arrangement, and there may be areas of hyalinization and myxoid degeneration. The vessels may be slit-like, but they are characteristically angulated or staghorn in shape. They have a normal endothelial lining but lack elastic fibers, and smooth muscle is sparse or absent. Mast cells are prominent (Fig. 8.41).

Prognosis

Use of the Le Fort I approach has caused a dramatic reduction in the intraoperative blood loss and the recurrence rate of nasopharyngeal angiofibromas. Recurrence rates with the older transnasal approach were around 40 to 60% because of incomplete excision. Recurrence with the Le Fort I approach is 5 to 8% because of higher rates of complete removal.

Because of high recurrence rates in the past, many cases were treated with radiotherapy, which relieved bleeding and nasal obstruction and induced tumor regression. However, a small number of patients developed sarcomas after 10 years or more. Such treatment today is used only as an alternative for cases that cannot be treated surgically.

HEMANGIOPERICYTOMA

Clinical Presentation and Pathogenesis

Benign hemangiopericytomas arise from a vascular supporting cell, the pericyte. They are part of a spectrum of tumors that range from benign to intermediate types to overtly malignant. Those of the intermediate type have features of both the benign and malignant forms and probably represent a low-grade malignancy. However, the overtly benign form is the most common.

It will present as a deep-seated mass within muscle or within deeper fascial spaces. It tends not to occur at superficial levels such as the subcutaneous level or submucosa. Men and women are affected equally. The peak incidence is between the ages of 30 and 50 years. The tumor grows very slowly and will often have a reported duration of several years. Most are of significant size at the time of diagnosis.

The tumor mass is painless but often contains pulsations or audible bruits. This is due to the development of functional vascular spaces and prominent feeding vessels with arteriovenous shunting.

The oral and maxillofacial area is an uncommon location for hemangiopericytomas, accounting for only 16% of cases. Most of these occur within the orbit.

Differential Diagnosis

The deep-seated location of the mass is strongly suggestive of salivary gland tumors such as the pleomorphic adenoma. If pulsations are noted, it may suggest an arteriovenous hemangioma or, if the nasal cavity or medial orbit is involved, a nasopharyngeal angiofibroma.

Diagnostic Work-up

Despite its vascular nature, the tumor can undergo an incisional biopsy with normal hemostatic controls. The incisional biopsy should be of sufficient size for adequate histopathologic assessment. Determining the cellularity and number of mitotic figures on the basis of examination of 10 to 20 high-power fields (HPFs) is critical in determining whether the tumor is benign or malignant. Because of its deep location, a CT or MRI scan is recommended to determine its size and anatomic relationships. A Doppler examination is also suggested. If the tumor displays audible bruits with the Doppler, an angiogram should follow.

Histopathology (Fig. 8.42)

Hemangiopericytomas have a thin, vascular pseudocapsule. They consist of ovoid to spindle cells, which surround endothelially lined vascular spaces. The vessels may be distended and often have a staghorn contour. A silver stain will stain the basement membrane of the endothelial cells so that the proliferating cells are seen outside the vessel, thus clearly distinguishing these tumors from those of endothelial origin.

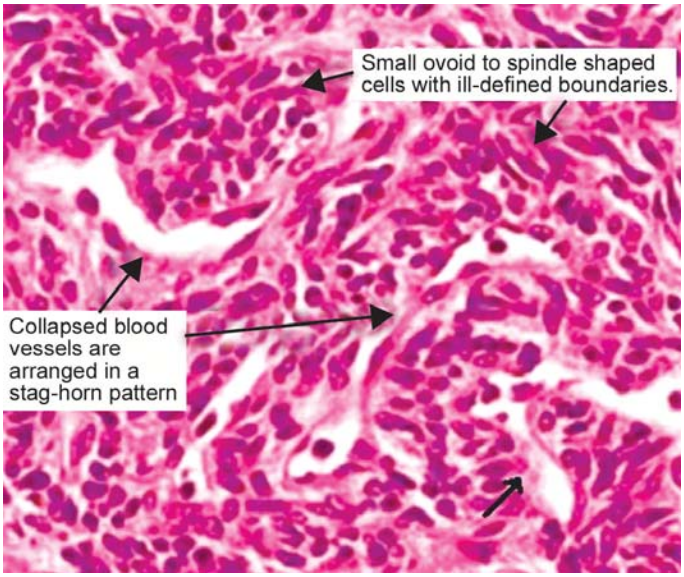


Fig. 8.42: Histopathology of hemangiopericytoma

Treatment

If histopathology confirms a benign hemangiopericytoma, treatment is local excision with margins of 0.5 to 1.0 cm. Because many have feeder vessels and the lesion itself is vascular, ligation of all feeding vessels in the immediate area is advised.

Prognosis

The prognosis of this tumor is excellent; no recurrences are expected when it is excised with clear margins.

FIBROBLASTIC MALIGNANCIES
FIBROMATOSES

Clinical Presentation and Pathogenesis

Fibromatoses found in the oral and maxillofacial region have been categorized as the deep musculoaponeurotic type. They have been given many terms, including extra-abdominal desmoids, desmoid tumors, grade 1 fibrosarcomas, nonmetastasizing fibrosarcomas, and aggressive fibromatosis. This abundant nomenclature is indicative of the tumor's vague position in the spectrum of benign to malignant neoplasms. Nonetheless, fibromatoses remain a benign fibrous tissue proliferation with an

intermediate biologic behavior between a benign fibroma and a fibrosarcoma; that is, like fibrosarcomas they exhibit destructive infiltrative growth and frequently recur, but like fibromas they do not metastasize.

The oral and maxillofacial region is an uncommon location for a fibromatosis. Most occur in the shoulder (22%), chest and back (17%), thigh (13%), and mesentery (10%). Those that arise in the oral and maxillofacial area (2%) are somewhat unique compared to those that occur in the more common locations around the shoulder girdle and trunk. The oral and maxillofacial locations (mostly the mandible, maxilla, and mastoid area) show a younger peak age range (5 to 20 years compared to 25 to 35 years), more infiltrative and faster growth, and a much greater propensity to invade underlying bone or to arise seemingly from within bone.

The patient is usually a preteen or teenager with a poorly circumscribed, painless fibrous growth apparently arising from the periosteum or from the fascia of muscles attached to the jaws or mastoid. The history is one of rapid emergence over a 2 to 6 week period. There is no sex predilection. The mass will seem to be adherent to bone and will extend close to the surface mucosa or skin in most cases.

Radiographs frequently show a poorly demarcated, irregular bony destruction. If the lesion is located on the surface of the jaws, it may show an irregular resorption of the adjacent cortex only. If the location is central, it will usually show a destructive pattern in all directions.

Uncommonly, pain or even paresthesia has been reported. The pain seems to be located at the periosteal level during the rapid growth phase or related to jaw motion if the tumor is attached in an area of muscle contraction. Paresthesia is related to the tumor encompassing a sensory nerve but is a slow to develop finding and does not occur in all cases.

The pathogenesis of fibromatoses remains unexplained. Both trauma and endocrine influences have been proposed but remain unsatisfactory explanations. Yet, many cases have occurred in an area of previous injury such as that of a surgical scar, radiation, burn scar, or fracture, and a small percentage of lesions have been shown to contain markedly elevated amounts of estrogen-receptor protein.

Differential Diagnosis

A fibromatosis must be distinguished from a fibrosarcoma and a reactive fibrous proliferation by means of histopathology and history. A fibromatosis will be distinguished from a fibrosarcoma primarily by its uniform growth pattern, maturity of cells, and paucity of mitotic figures. A fibromatosis is distinguished from a reactive fibrous proliferation by its absence of an apparent stimulus and its lack of inflammatory cells and focal hemorrhages. Clinically, the destructive and infiltrative nature of a fibromatosis will also resemble that of a neurofibroma or a malignant peripheral nerve sheath tumor as well as that of nodular fasciitis. These three entities can be distinguished only by their histopathologic features.

Diagnostic Work-up

The diagnosis requires a deep incisional biopsy in the center of the mass. The biopsy should extend to bone and include periosteum to enable assessment of the infiltrative growth pattern of the mass. It is important not to biopsy the edge of the mass or to take too small a specimen. A biopsy at the edge of the mass will induce scar tissue that is histologically similar to the tumor itself, thereby confusing the margins at the time of excision. If too small a specimen is taken, a subsequent biopsy specimen will contain inflammatory cells and a scar tissue pattern, which may make the mass resemble a reactive fibrous proliferation or nodular fasciitis.

Histopathology (Fig. 8.43)

These are infiltrating tumors composed of fibroblasts and myofibroblasts. They consist of uniform, elongated, slender spindle cells with abundant collagen arranged in broad, elongated fascicles. There is variable cellularity and mitotic activity. Some areas may be hypocellular or hyalinized. At the periphery of the tumor where it infiltrates muscle, there may be atrophy of the skeletal muscle resulting in the formation of multinucleated giant cells. This may give the impression of malignancy, but this impression is counterbalanced by the fact that the nuclei do not show atypia and there is considerable collagen production. These tumors may appear innocuous on a cellular level even though they are highly infiltrative. These lesions may be difficult to separate from low grade fibrosarcomas.

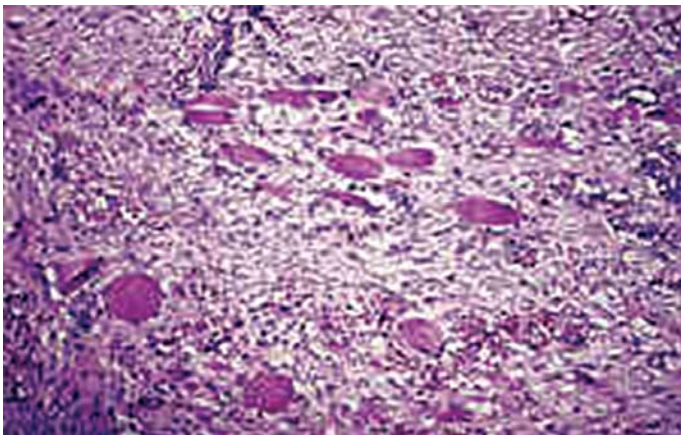
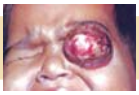


Fig. 8.43: Histopathology of fibromatosis



Treatment

The focus of treatment is a wide local excision of the tumor and any involved bone. Margins are 1.0 to 1.5 cm with frozen section assessment at the time of surgery. Treatment of regional lymph nodes is not necessary.

Reports from some centers suggest good results with initial chemotherapy protocols using agents often used for sarcomas, such as adriamycin, actinomycin D, cyclophosphamide, and daunorubicin, followed by surgery. This approach may be advantageous in those very large tumors that approach the base of the skull, making complete resection difficult, or those tumors associated with significant functional loss and morbidity. Additionally, radiotherapy may have a role to play in some large unresectable tumors and in recurrent or incompletely excised tumors. Response to radiotherapy in such situations has been documented, but it is slower than it is for epithelial malignancies. Radiation induced sarcomas have been reported but are very rare.

Prognosis

If a recurrence is to develop, it usually becomes apparent within the first year. The recurrence rate for oral and maxillofacial fibromatoses is unknown because of the paucity of cases, but for fibromatoses in other locations it ranges from 25 to 68%. The recurrence rate is inversely proportional to the attainment of surgically clear margins of clinically uninvolved tissue.

FIBROSARCOMA

Clinical Presentation and Pathogenesis

Fibrosarcomas are rare lesions in general and in the oral and maxillofacial area in particular (only 10% of fibrosarcomas occur in the head and neck region). Between 1950 and 1975, they were believed to be the most common soft tissue malignancy. However, the identification and separation of malignant fibrous histiocytomas, fibromatoses, nodular fasciitis, fibrous osteosarcomas, and undifferentiated epithelial malignancies, all of which were previously regarded as fibrosarcomas, has unmasked the rarity of true fibrosarcoma. Fibrosarcoma is less common than liposarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma.

Today, fibrosarcomas are defined as malignant tumors of fibroblasts that show no other evidence of cellular differentiation and are capable of recurrence and metastasis. They are often graded with a grading scale of grade 1 through grade 3. Grade 1 and 2 fibrosarcomas tend to be more differentiated and therefore less clinically aggressive. Grade 3 fibrosarcomas are usually faster growing and very aggressive; they also have a greater tendency to metastasize (Fig. 8.44).

Fibrosarcomas in the oral and maxillofacial area usually arise from bone, periosteum, or muscle fascia. They are usually painless fibrous, fleshy masses that are destructive of bone and will cause mobility of teeth if they are located in alveolar bone. Compared to fibromatoses, they are slower to develop and often somewhat smaller. Fibrosarcomas frequently have a duration of several months to years before presentation and are usually 3 to 5 cm in size. They may occur at any age, but peak incidence in the oral and maxillofacial area is the 20s and early 30s, older than for fibromatoses in this same area (5 to 20 years) and younger than for fibrosarcomas elsewhere (30 to 55 years).

Much has been written about fibrosarcomas arising in sites of previous trauma, and many have indeed been reported to arise from the scar tissue of an old injury site. However, no clear evidence exists to ascribe an etiologic role of trauma. Other than scar tissue being an abundant source of fibroblasts, there is no cause-and-effect relationship. Considering the prevalence of trauma and at least some scar tissue, the simultaneous occurrence of fibrosarcoma and scar is likely only coincidental.

Differential Diagnosis

In the oral and maxillofacial area, fibrosarcomas either arise from bone or invade into bone from their deep soft tissue origin. Therefore, osteosarcomas are prominent on the differential list, as are malignant fibrous histiocytomas, fibromatoses, neurofibromas, and malignant peripheral nerve sheath tumors. Each one must be distinguished by its unique histopathologic features.

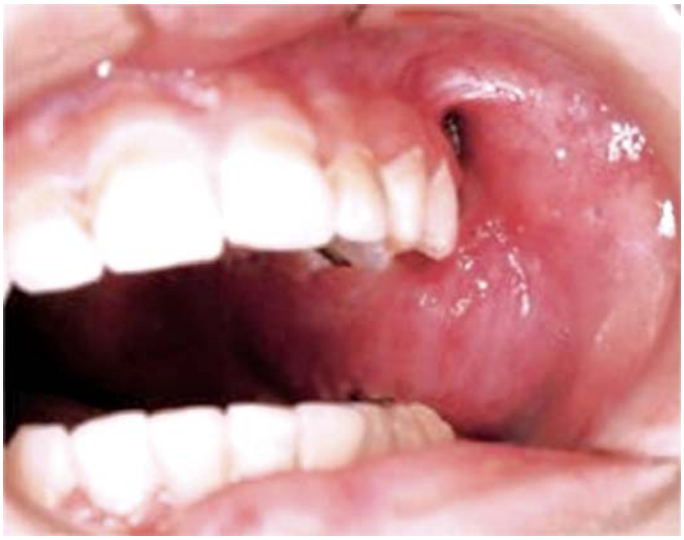


Fig. 8.44: Fibrosarcoma

Diagnostic Work-up

Diagnosis of a fibrosarcoma requires a deep incisional biopsy within the lesion's center. Too superficial a biopsy may lead to a diagnosis of a reactive fibrous lesion, since periosteal and fascial reactions to many tumors are manifested by the deposition of collagen. Plain radiographs, computed tomography (CT) scans, or a magnetic resonance imaging (MRI) scan to delineate the extent of the disease is also recommended. Assessment of metastatic activity is best accomplished by a chest radiograph and a technetium-99 methylene diphosphate (99Tc-MDP) bone scan, as metastasis is most frequent to lungs and bone.

Histopathology (Fig. 8.45)

Fibrosarcomas are invasive tumors with no distinct margins. The cells are rather uniform and spindle-shaped and lie in fascicles, often forming a Herringbone pattern. Mitoses are present, but multinucleated and bizarre giant cells are not a feature of this tumor.

Tumors that are poorly differentiated form less collagen and thus have more densely packed nuclei. The pattern is less organized. Mitoses are numerous, but marked cellular pleomorphism is not seen. Tumors that are highly pleomorphic or contain bizarre giant cells are more suggestive of malignant fibrous histiocytoma.

Malignant neoplasms are often given a histologic grade. Parameters between different grading systems may vary, but in general the grade relates to factors such as invasiveness, cellularity, pleomorphism, mitotic rate, atypical mitoses, necrosis, and the quantity of matrix that may be produced. The importance of some of these factors may depend on the tumor type.

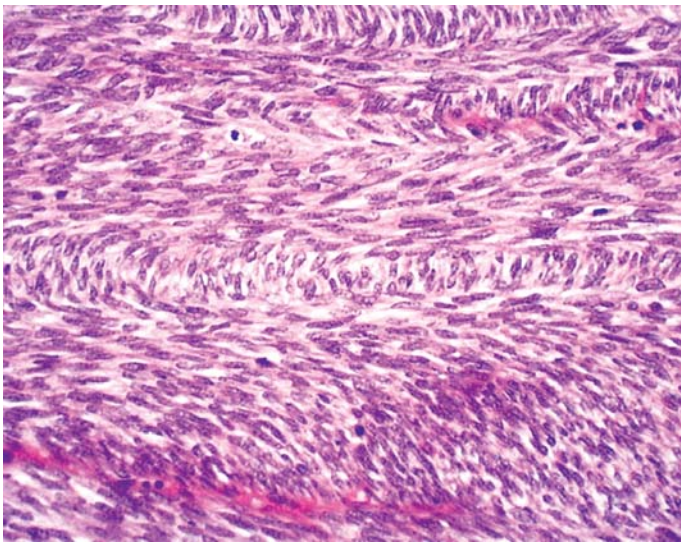


Fig. 8.45: Histopathology of fibrosarcoma

In the case of fibrosarcomas, grades I and II show the features described above. They are more uniform with distinct fascicles and a Herringbone pattern. There is a greater production of matrix (collagen). Grade III (high grade) is more cellular, produces less collagen, and has greater mitotic activity. Distinct fascicles and a Herringbone pattern are lacking.

Treatment

The focus of treatment is very wide local excision using 3 cm clinical margins in soft tissue and bone as well as assessing margins with frozen sections at the time of surgery. Lymph node dissection is not required. In fibrosarcomas that cannot be completely excised because of their location or extreme size, postoperative radiotherapy of 6000 to 7000 cGy is appropriate. In grade 3 fibrosarcomas, postoperative adjunctive chemotherapy is recommended, ostensibly to treat potential subclinical or microscopic metastasis. When chemotherapy is employed, agents used successfully for sarcomas are preferred, including adriamycin, actinomycin D, oncovin, cyclophosphamide, prednisone, and daunorubicin.

Prognosis

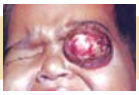
Like most sarcomas, fibrosarcomas are malignancies for which the prognosis correlates most closely with histologic grade. Conversely, most epithelial malignancies, such as squamous cell carcinoma, correlate better to clinical staging. Using a three grade system of advancing histologic grade, reported 5 year survival rates are 82% for grade 1, 55% for grade 2, and 36% for grade 3 tumors. In addition, margin integrity and width of excisional margins correlate with recurrence and survival. The simple truth is that the wider the excision, the lower the recurrence rate and the greater the survival rate. Tumor size, duration, and location do not influence recurrence or survival.

Local recurrence (persistence of the original tumor) by incomplete excision is the most common cause of failure to cure. Metastasis is less frequent. When metastasis occurs, it does so via bloodborne routes. Venous tumor emboli most commonly spread to the lungs as they are swept into the right heart chambers by normal venous return and implanted into the lungs via the pulmonary artery system. Other venous tumor emboli spread to bone, especially to the vertebrae and skull, because of their rich venous system of valveless veins.

RHABDOMYOSARCOMAS (Fig. 8.46)

Clinical Presentation and Pathogenesis

Rhabdomyosarcomas are malignant tumors of primitive mesenchymal cells that undergo partial rhabdomyoblast



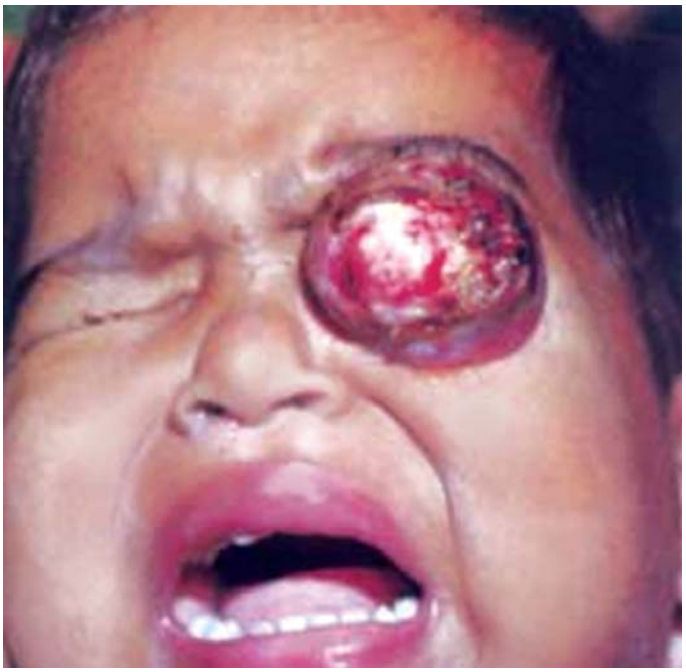


Fig. 8.46: Orbital rhabdomyosarcoma

differentiation. Unlike other soft tissue sarcomas, which generally occur in adults and are more common in sites other than oral and maxillofacial regions, rhabdomyosarcomas are most common in this region (44% of all rhabdomyosarcomas) and occur mostly in children and teenagers. In fact, 2% of rhabdomyosarcomas are present at birth, and 5% occur in individuals younger than 1 year.

There are three basic histologic types: Embryonal, alveolar, and pleomorphic, with the embryonal type bearing the best prognosis and being by far the most common type found in the oral and maxillofacial area. Males are affected a little more commonly than females (1.5:1). Tumors have a peak incidence at age 4 years and another at age 17 years.

In the oral and maxillofacial area, the orbit is the most common location, followed by the nasal cavity, mouth, sinuses, cheek and neck. The tumor presents as a rapidly growing, fleshy mass, which readily invades and destroys bone. In the orbit, the medial upper quadrant is the preferred location with prominent nasal and orbital bone destruction as well as invasion into the eyelids producing marked eyelid edema. Proptosis is another frequent feature of orbital tumors, along with diplopia and epiphora, but visual acuity usually is not affected. Those that arise in the cheek, maxillary sinus, or masseter area readily invade into adjacent bone and the orbit.

Pain is not a prominent feature of rhabdomyosarcoma despite the tumor's bony destruction and often large size. However, sensory nerve loss (anesthesias and paresthesias) is common, and, if motor nerves are involved, paresis or paralysis may occur.

Rhabdomyosarcomas are not radiographically distinctive but will show primarily the anticipated soft tissue mass and bony destruction.

Although rhabdomyosarcomas are frequently described as tumors of muscle origin or of muscle cells, their histogenesis is, like that of other sarcomas, from primitive mesenchymal cells, which are specific for these tumors and undergo rhabdomyoblast differentiation. They may also arise from residual fetal rhabdomyoblasts, which might explain their predilection for children and their occasional occurrence in fetal life. It is nearly impossible for them to arise from muscle cells proper since these cells do not dedifferentiate, and even injured muscle cells fail to mitose but instead repair via scar tissue formation.

Differential Diagnosis

A tumor with rapid growth and destructiveness in a child or young adult should suggest a rhabdomyosarcoma. Other rapidly destructive lesions in this age group are Ewing sarcoma, neuroblastoma (the third most common malignancy in children), an acute Langerhans cell histiocytosis, and less commonly, a malignant peripheral T-cell lymphoma. All of these are also known to invade bone in a destructive manner.

Diagnostic Work-up

The diagnosis is established by means of a deep incisional biopsy within the center of the tumor. Plain radiographs, a CT scan, or an MRI scan is required to understand the tumor's size, spatial anatomic relationship, and extent of bony destruction. The CT or MRI scan should include detailed cuts of the base of the skull to assess potential invasion into this area and include the entire skull to rule out brain extension or metastasis. A chest radiograph is taken to rule out lung metastasis, and because rhabdomyosarcomas have a propensity to metastasize to bone marrow, a bone marrow aspiration is also a strong consideration.

Histopathology

Rhabdomyosarcomas are classified according to their histologic appearance into one of three categories.

EMBRYONAL RHABDOMYOSARCOMA

The embryonal rhabdomyosarcoma develops from undifferentiated mesenchymal stem cells, which can resemble different stages in the development of skeletal muscle. Thus, the histologic picture can be quite varied. In many instances the tumors may contain small round cells,

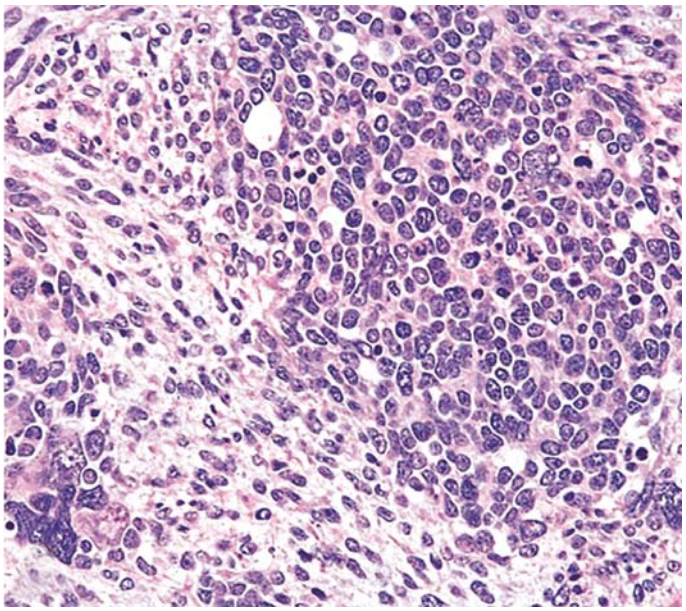


Fig. 8.47: Anaplastic variant of embryonal rhabdomyosarcoma

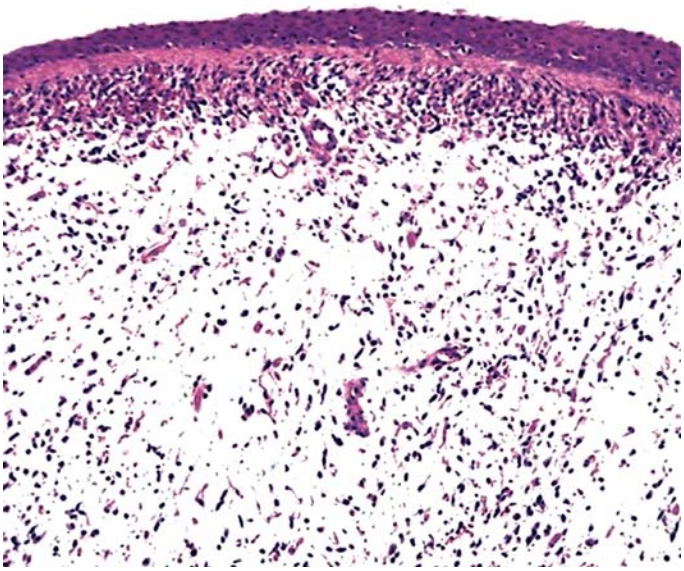


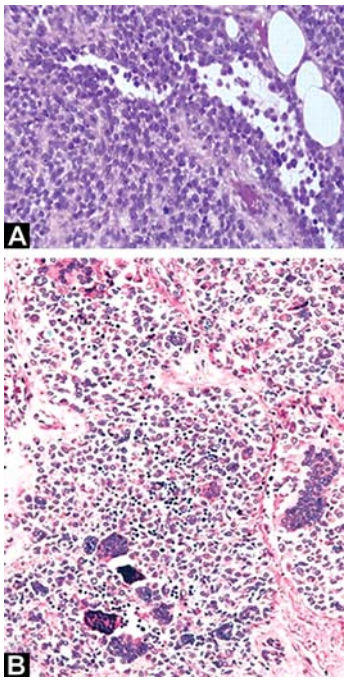
Fig. 8.48: Botryoid variant of embryonal rhabdomyosarcoma

but they may also contain spindle cells. Depending on their differentiation, the cytoplasm may be scant and indistinct or more abundant and strongly eosinophilic. The cytoplasm may be vacuolated because of the deposition of glycogen. Tadpole-shaped cells may be present, and cross-striations can sometimes be identified in more well-differentiated tumors. Nuclei are usually hyperchromatic and on occasion may be eccentrically situated. Mitoses may be numerous. Stromal collagen is scant. A characteristic pattern shows areas of hypercellularity with densely packed cells alternating with less cellular myxoid areas. These tumors are infiltrative. They may be difficult to distinguish from other round cell tumors of childhood, such as neuroblastoma, Ewing's sarcoma, and malignant lymphoma (Fig. 8.47).

A variant of embryonal rhabdomyosarcoma is the botryoid type (Fig. 8.48), which is usually seen within mucosa-lined cavities such as the nasopharynx and nasal and oral cavities. Because of their unrestricted growth, these polypoid tumors have a mucoid stroma and myxoid appearance with relatively few cells. Below the covering epithelium, a dense zone of undifferentiated cells, which has been termed the cambium layer of Nicholson, is often found.

ALVEOLAR RHABDOMYOSARCOMA (Figs 8.49A AND B)

The alveolar rhabdomyosarcoma is characterized by the presence of clefts or alveolar spaces, which are formed through loss of cohesion within the tumor cell aggregates.



Figs 8.49A and B: Histopathology of alveolar rhabdomyosarcoma

The spaces are lined by a single layer of tumor cells, which are attached to fibrous septae. Some of the cells may protrude into the space in pseudopod-like fashion. Most of the tumor cells are rounded. Multinucleated giant cells and mitoses are common. Cross striations may sometimes be identified.

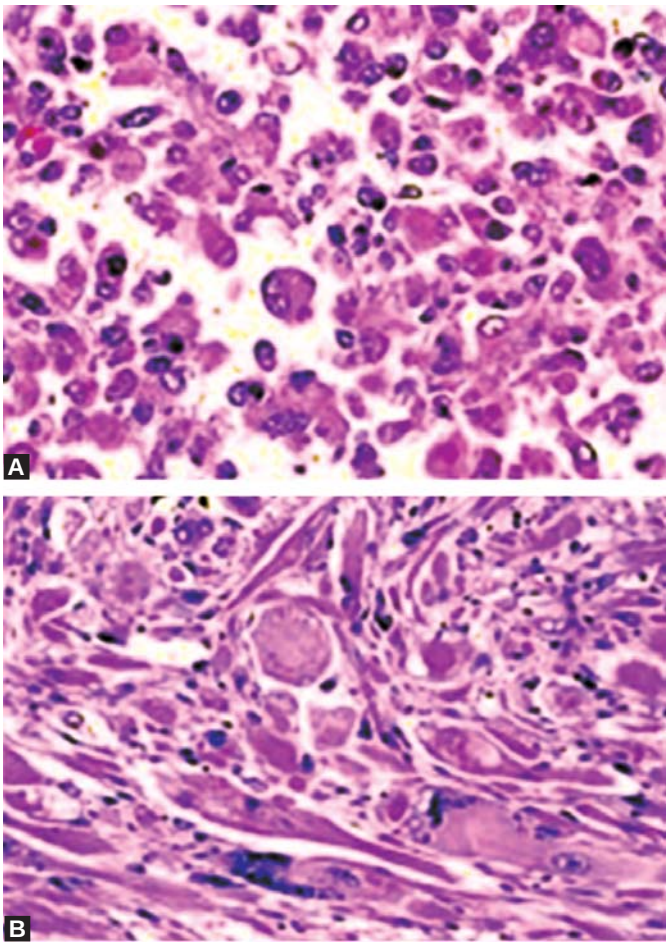
PLEOMORPHIC RHABDOMYOSARCOMA

Pleomorphic rhabdomyosarcoma may be difficult to separate from other pleomorphic sarcomas such as malignant fibrous histiocytoma. There is great variation in the size and shape of the cells. Racquet-shaped cells, tadpole - shaped cells, strap cells, and giant cells may be present, and bizarre mitoses are not uncommon. Cross striations are not usually observed.

The histologic diagnosis of rhabdomyosarcoma is often difficult and usually requires ultrastructural examination and immunohistochemistry. Immunohistochemistry in particular is of considerable help. While there are many markers available, myoglobin and desmin are probably the most useful. Cytogenetic studies can be diagnostic for alveolar rhabdomyosarcoma, which typically shows a chromosomal translocation (Figs 8.50A and B)

Treatment

The treatment of rhabdomyosarcoma has been a great success story dating back to 1960, when the Intergroup Rhabdomyosarcoma Study (IRS) created staging and combination treatment protocols. Until that time, rhabdomyosarcoma survival rates were dismal. For oral and maxillofacial tumors, the 5 year survival rate was only 6% and the average survival time was only 16 months. Today, the outcome is vastly improved.



Figs 8.50A and B: Histopathology of pleomorphic rhabdomyosarcoma

The staging is based on local excision rather than on radical surgery and takes into account tumor size as it relates to the degree of excision. Therefore, the initial therapy is local excision without radical ablation of normal tissues. This is a decided deviation from normal oncologic surgical principles, but one that is acceptable in these cases because of the responsiveness of residual tumor cells at the margins to chemotherapy and radiotherapy. Examination of the resected specimen for residual disease at the margins then becomes critical because tumor staging will depend on this assessment.

The surgeon's assessment of visible disease remaining after surgery as well as the identification of any distant metastasis will dictate the staging. From this information alone, the choice and degree of additional therapy is made. Group I refers to localized disease and microscopic margins free of tumor. Group II indicates grossly negative but microscopically positive margins. Group III indicates grossly visible disease leftat the time of surgery. Group IV indicates identification of distant metastasis irrespective of the tumor resection margins. In general, group I and group II tumors are treated with three chemotherapeutic agents: Vincristine, adriamycin, and cyclophosphamide (Cytoxan) (VAC). Group II tumors receive, in addition, radiotherapy of 4000 to 6000 cGy over 6 weeks. Group III and group IV tumors receive the same chemotherapy, but with the addition of actinomycin D (VACA) and radiotherapy of the same dose to the primarysite and to any metastatic focus. For tumors of the oral and maxillofacial area, surgery does not include regional lymph node dissection. Chemotherapy is continued for 1 year, or up to 2 years if there remains a suspicion of residual disease.

Prognosis

The strict protocol of the IRS staging has allowed for reliable survival statistics. The 5 year survival rate is 83% for group I tumors, 70% for group II tumors, 52% for group III tumors, and 20% for group IV tumors. Inherent in these data is the conclusion that the size of the tumor and its resectability are the most important prognostic factors. Therefore, a speedy diagnosis and work-up are recommended; prompt surgery followed by clinical staging with follow-on therapy is the challenge.

When cure is not obtained, it is usually because of uncontrollable disease at the primary site. Metastasis, when

it occurs, is to lung or bone marrow and will frequently be associated with a local recurrence as well.

Because the therapy advanced by the IRS group is very effective, many children live into adult life. However, they must accept and at times be treated for the long-term complications of their therapy. Complications possibly related to early life chemotherapy are leukemia, neutropenia, anemia, and chronic diarrhea. Those seemingly related to radiotherapy are xerophthalmia, xerostomia, hypoplastic facial bones and mandible, hypoplastic dentition, dysphasia with a propensity for aspiration, radiation fibrosis limiting jaw opening, and osteoradionecrosis. In fact, the ongoing damage of radiation cellular injuryhas caused a significant number of patients to develop osteoradionecrosis of the mandible 20 to 30 years later.

MALIGNANT HEMANGIOPERICYTOMA

Clinical Presentation

Although some hemangiopericytomas are obviously benign and others are obviously malignant, there are also a number that are intermediate; these are included in the malignant hemangiopericytoma category to avoid the possibility of undertreatment. Nevertheless, benign hemangiopericytomas far out number the rare malignant ones, and the oral and maxillofacial area is an uncommon site, accounting for only 16% of all types of hemangiopericytomas.

Truly malignant hemangiopericytomas are diagnosed and graded by their cellular nature and mitotic figures per high-power field (HPF). Clinically, both benign and malignant hemangiopericytomas present as painless, deep-seated tumors (often arising within muscle or deep fascia). Males and females are affected equally. The lesions are richly vascular with functional vessels that may produce a pulsatile thrill or an audible bruit.

The incidence increases with advancing age up to a peak in the 30 to 50 year age range. However, a separate infantile form occurs more commonly in the superficial subcutaneous fat rather than deep within muscle as does the adult type, and it grows in a rapid infiltrative pattern, forming satellite lesions. By contrast, the adult type is slower growing and develops into a lobulated mass, sometimes reaching large sizes. Most adult types are present for several months or even years before the individual seeks medical attention.

Differential Diagnosis

Because of its rarity, a malignant hemangiopericytoma is usually not an initial consideration. Deep-seated tissue masses in the oral and maxillofacial area in mid-adult life may suggest several salivary gland neoplasms, particularly the more common ones such as the pleomorphic adenoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. The deep location and large size are also consistent with benign and malignant fibrous histiocytomas. If pulsations are present or a bleeding history is elicited, an arteriovenous hemangioma is appropriate, and if it is located in the nasal area, a nasopharyngeal angiofibroma should be considered.

Diagnostic Work-up

The tumor's deep location requires a CT or MRI scan to delineate its true size and anatomic relationships. It is also recommended that angiography be performed because many tumors have a rapid circulation pattern with feeders and considerable arteriovenous shunting. The diagnosis requires an incisional biopsy of sufficient size to take several sections for histopathology. Because the differentiation between benign and malignant (and thus the treatment approach) is based on the mitotic figures and the cellular pattern, the biopsy is exceedingly important.

Histopathology (Fig. 8.51)

These circumscribed tumors arise from pericytes. They consist of closely packed cells arranged around ramifying, thin-walled, endothelial lined, vascular channels of greatly varying size. Small vessels may be obscured by tumor cell proliferation and compression. The cells have round to oval nuclei and may sometimes be spindled. They can resemble endothelial cells, fibroblasts, and histiocytes. The vessels often have a "staghorn" configuration. Because it acts as an arteriovenous shunt, the periphery of the tumor tends to be under increased venous pressure with resultant vascular dilation, so that there is the potential for considerable hemorrhage during surgical removal.

The behavior of the malignant hemangiopericytoma can be difficult to predict, but it is most closely associated with

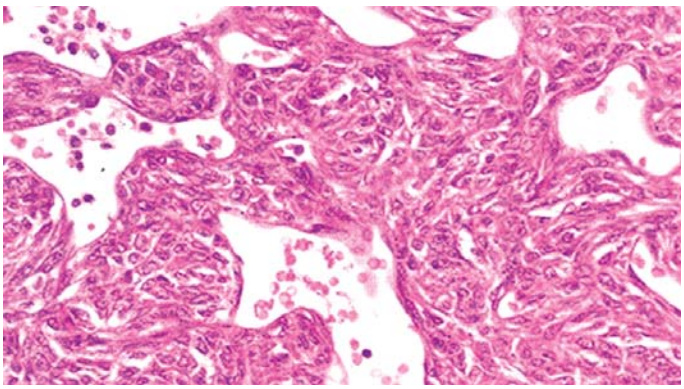


Fig. 8.51: Histopathology of malignant hemangiopericytoma

mitotic activity. Fewer than 2 per 10 HPFs indicates a favorable prognosis, whereas 4 or more per 10 HPFs correlates with recurrent disease and metastasis. Greater aggression may also be seen with tumors that show increased cellularity, pleomorphism, and/or necrosis and hemorrhage. Malignant hemangiopericytomas occurring in the upper aerodigestive tract typically lack these aggressive histologic features and metastatic potential.

The diagnosis depends on the architecture of the lesion. Immunocytochemistry is nonspecific.

Treatment

Truly malignant hemangiopericytomas are usually treated with preoperative embolization and surgical excision followed by postoperative radiotherapy in doses between 3500 and 5500 cGy. Even with preoperative embolization, it is wise to approach the lesion with identification and ligation of the known feeding vessels as identified by the angiogram.

Prognosis

The prognosis of malignant hemangiopericytomas depends on the tumor's size and the number of mitotic figures per HPF. Metastasis, usually to lungs or bone, can occur as much as 10 years after initial therapy. Metastasis incidence is difficult to ascertain because of this tumor's rarity, but it ranges from 20 to 50%. Five year survival rates for those with fewer than 4 mitotic figures per 10 HPFs is about 85%; for those tumors with more than 4 mitotic figures per 10 HPFs, the 5-year survival rate is 45%.

ALVEOLAR SOFT PART SARCOMA

Clinical Presentation and Pathogenesis

The alveolar soft part sarcoma is an uncommon tumor of uncertain histogenesis. The most prevalent location is the thigh and buttocks, but the head and neck, particularly the tongue and orbit, are often the involved sites in children. The usual age range is 15 to 35 years, and there is a female preponderance. These tumors are typically asymptomatic. An important characteristic is the marked vascularity with the potential for severe hemorrhage at surgery (Fig. 8.52).

Histopathology (Figs 8.53A and B)

The alveolar soft part sarcoma is a poorly circumscribed, friable tumor, typically with a uniform histology in which the tumor cells have a nest-like arrangement. The cell clusters are divided by thin-walled blood vessels. The cells are large, usually polygonal, with single or multiple nuclei. The abundant cytoplasm is eosinophilic and granular.

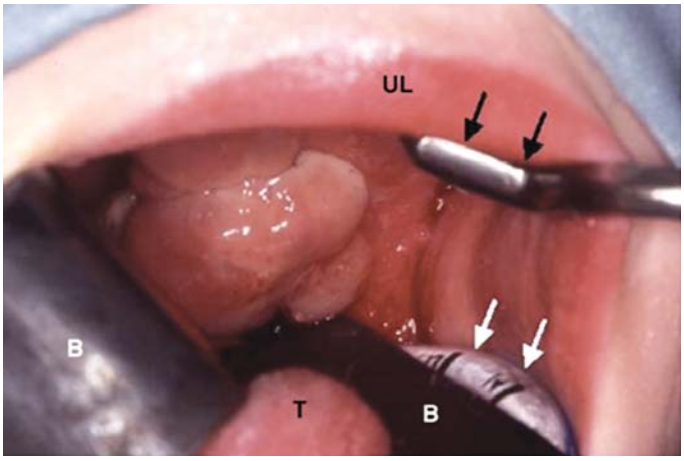
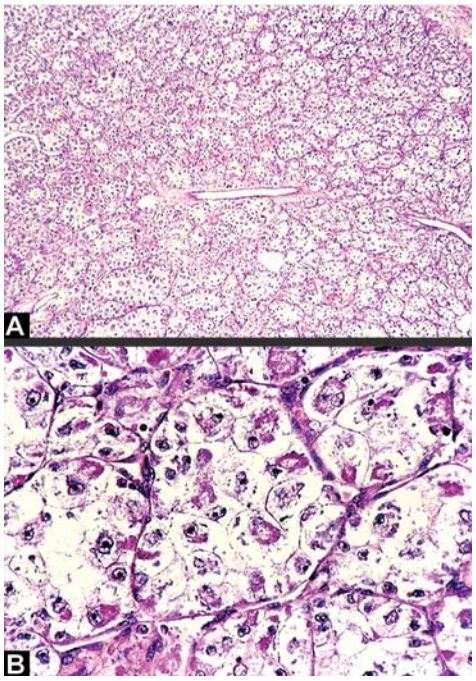


Fig. 8.52: Alveolar soft part sarcoma—tumor occupying whole of hard palate with extension of soft palate



Figs 8.53A and B: Histopathology of alveolar soft part sarcoma

Mitoses are rare. In the center of the nests, there is frequently necrosis with loss of cell adhesion, giving a pseudoalveolar pattern. A characteristic feature is the presence of PAS positive, diastase resistant crystals that are rhomboid or rod-shaped and are visible ultrastructurally. Dilated veins, often showing tumor invasion, are seen at the periphery. Occasionally, but particularly in children, the tumors have a more uniform appearance and lack the nesting arrangement. These often have a better prognosis.

MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY

Clinical Presentation And Pathogenesis

The melanotic neuroectodermal tumor of infancy (MNTI) is a clinically distinctive benign neoplasm of neuroectodermal origin. With only rare exceptions, the tumors arise from the anterior maxilla (the rare exceptions are in the anterior mandible, skull, scapula, and epididymis). They are never congenital but will emerge sometime within the first year of life and usually at less than 6 months of age. They often first appear as a blue gingival mass that is mistaken for an eruption cyst. The mass will grow rapidly, raising the concern of a malignancy. It is not uncommon to see the mass double in size in 1 week.

The mass characteristically will be round with a bluish-black coloration and will carry one of the primary central incisor teeth outward with it. It will not carry both central incisors since these tumors arise from one side of the midline. The central incisor is visible in most cases, seeming to erupt from the mass. More rarely, the central incisor is within the mass just beneath the surface and will be readily apparent on an occlusal radiograph. Larger lesions are often secondarily ulcerated by trauma from the hands of the infant, but the lesion itself does not ulcerate.

The lesion is destructive. Occlusal radiographs show an irregular resorption of the anterior maxilla and displacement of developing tooth buds. The lesion has no radiopaque components except for the developing teeth, particularly the ipsilateral central incisor, which is often displaced and located within the tumor.

The MNTI, which originates from neural crest cells, represents an overgrowth of these cells rather than their usual involution. Normally, neural crest cells originate from a mantle around the developing spinal cord and project out to the peripheryalong sympathetic nerves. In other parts of the body, they populate the primordia of sympathetic ganglia and the adrenal medulla to become neurosecretory cells of these respective structures. In the maxilla and most peripheral sympathetic neural pathways, they involute. Those that develop into the MNTI are the rare failures of involution, which instead proliferate into a tumor (Fig. 8.54).

Differential Diagnosis

The rapid development and, at times, frightening growth of the MNTI suggest a malignancy. In particular, the neuroblastoma is a distinct and serious consideration. The few cases of so-called "malignant MNTI" that have recurred or metastasized have probably represented neuroblastomas, which are the most common early childhood malignancy and the fourth most common malignancy in the head and neck area. Other infancy tumors with aggressive behavior and possible blue colorations are rhabdomyosarcomas, which have a predilection for the head and neck area in children, and hemangiomas or lymphangiomas, which may indeed present with a bluish color and often appear within a few months after birth with rapid development. The congenital granular cell tumor, which also frequently arises from the anterior maxilla (65%) and is seen in infants, is not a consideration because it is always congenital (present at birth) whereas the MNTI is never congenital. Questioning the parent or the birthing team about the presence of an oral mass at birth will distinguish between the two.

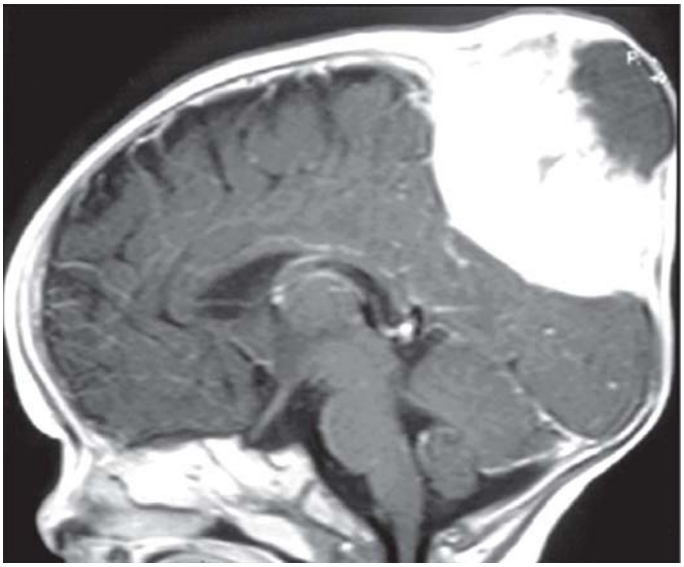
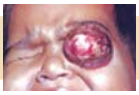


Fig. 8.54: MRI shows a highly enhancing tumor dislocating the superior, transverse and straight sinus anteriorly and inferiorly

Diagnostic Work-up

The most important diagnostic step is a confirmatory incisional biopsy. However, an occlusal radiograph that shows the central incisor displaced to the periphery of a mass that itself shows destruction of the anterior maxilla is pathognomonic. About 10 to 15% of MNTI will elaborate vanillylmandelic acid (VMA or 3-methoxy 4-hydroxy mandelic acid), which is a soluble metabolic breakdown product of norepinephrine. It is indicative of the neuroectodermal cell origin of this tumor. VMA levels from a 24 hour urine collection may be compared to normal values but have no real diagnostic value. This is because increased VMA levels may imply a neuroectodermal cell origin, but normal VMA levels do not rule out a neuroectodermal cell origin because not all the cells are involved in neuroepinephrine synthesis.



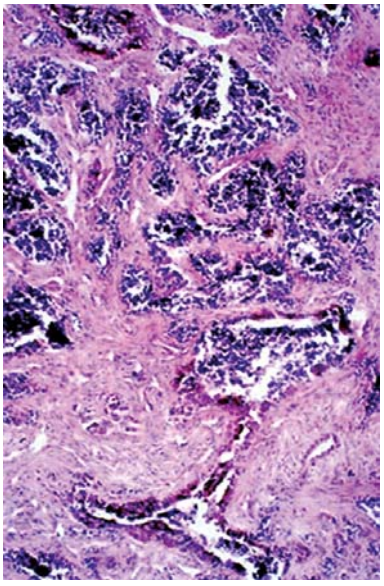


Fig. 8.55: Histopathology of melanotic neuroectodermal tumor of infancy

Histopathology (Fig. 8.55)

These infiltrating, unencapsulated tumors have irregular alveolar spaces and a dense, fibrous stroma. The spaces contain two types of cells. The larger cuboidal cell usually lines the space and has a pale nucleus and abundant cytoplasm, which often contains melanin. These cells are S-100 negative, however. The more centrally located cells are smaller and round with a deeply staining nucleus and scant cytoplasm, resembling neuroblasts. Mitoses are not seen. These tumors appear to be of neural crest origin, and neuroblastic and melanocytic cell lines have been identified ultrastructurally. Both cell types are positive for neuron - specific enolase and synaptophyisn and negative for S - 100. The larger cells are cytokeratin positive and HMB (human melanoma block)-45 positive, features that are noted in pigmented retinal epithelium. In the rare instances in which these tumors have behaved in a malignant fashion, their histologic appearance and clinical behavior have paralleled those of the neuroblastoma.

Treatment

The melanotic neuroectodermal tumor of infancy should be treated by a peripheral excision with 2 to 5 mm margins. Although the destructive nature of this tumor and its growth rate are significant, total maxillectomies and maxillary resections with margins greater than 5 mm are unnecessary. Early excision is of great value. Limiting the destruction that the tumor causes in the anterior maxilla will lessen the deformity and preserve developing teeth. The excision should include the overlying mucosa. The resultant wound may be packed with a tie-over pressure dressing for 5 to 7 days to reduce oozing. The wound itself heals rapidly by granulation tissue and secondary epithelialization.

Prognosis

The excised MNTI in which gross tumor is not allowed to remain should not recur. Recurrent MNTI should be looked on as suggestive of an unrecognized malignancy and followed by a review of multiple sections of the excised specimen and a systemic review for neuroblastoma elsewhere.

The maxillary defect becomes relatively smaller as the child grows. Nevertheless, primary and permanent teeth will be missing and a permanent concave defect in the canine to midline area will be present. Most children adapt to this very well, but some will require speech therapy and serial removable appliances. The resultant scarring will usually eventuate in an anteroposterior deficiency of the maxilla as well as a crossbite relationship more severe on the affected side. Therefore, as the child develops, orthodontic care and possibly orthognathic surgery may be required.

MELANOCYTIC NEVI

Clinical Presentation and Pathogenesis

Nevi, also called moles, are benign collections of nevus cells that are derived either from melanocytes or from the same neural crest precursors as melanocytes. Nevi on skin are very common; nearly every person has at least one. Nevi on the oral mucosa are very uncommon, with less than 1% of individuals possessing a true mucosal nevus. About 1% of newborns have a nevus. The number of individuals with nevi increases and the number of nevi on each individual increases to a peak at puberty. Although nevi can occur on any skin surface, greater numbers appear on sun-exposed surfaces.

The concern of both the patient and the practitioner is differentiating a nevus from a melanoma (so-called black-mole cancer). Nevi are far too numerous and melanoma far too uncommon to biopsy all nevi. Therefore, only those with suspicious deviation from the usual appearance are excised. The nevus may be either brown, black, or blue, but the color is uniform throughout. Although nevi have different outlines, the outlines are regular and basically symmetric. Additionally, unlike melanomas, nevi do not change color, shade, or texture overtime. Despite these characteristics, uniformity cannot always be relied on to differentiate a nevus from a melanoma. Early melanomas may appear quite uniform with an oval shape and a uniform brown color. In such cases, repeat examinations,

often using a magnifying glass or loop magnifications and noting changes in color, shape, and texture, will draw suspicion to a developing melanoma.

Nevi are classified into three types—junctional, compound, and dermal—based on the location of nevus cells in the skin. The three types reflect the evolution of the nevus to some degree. During childhood, the nevus cells are located in the area of the basement membrane both suprabasilar and infrabasilar. Clinically, these nevi appear flat. Over time, some of the nevus cells migrate into the dermis, resulting in a compound nevus. Migration of all the nevus cells into the dermis results in a dermal nevus. When this occurs, the nevus cell collection results in smooth-surfaced elevated nodules. Because this process takes several years, nearly all dermal nevi are found in adults.

JUNCTIONAL NEVUS (Fig. 8.56)

Junctional nevi are flat or only slightly elevated. Most are hairless and small, varying in size from 1 to 10 mm. They are only rarely seen as a congenital nevus. Most arise at about age 2 years and evolve into compound nevi in the teen years. Junctional nevi on the palms, soles, and genital areas remain junctional and never seem to convert to a compound nevus. Transformation into a melanoma is very rare.

COMPOUND NEVUS (Fig. 8.57)

Compound nevi tend to be elevated with a uniformly round or oval shape. Many are natural skin color, others are somewhat darker. Hair is often present arising around a compound nevus. With increasing age, nevi become more elevated and may develop a warty appearance. Melanoma transformation is also rare.

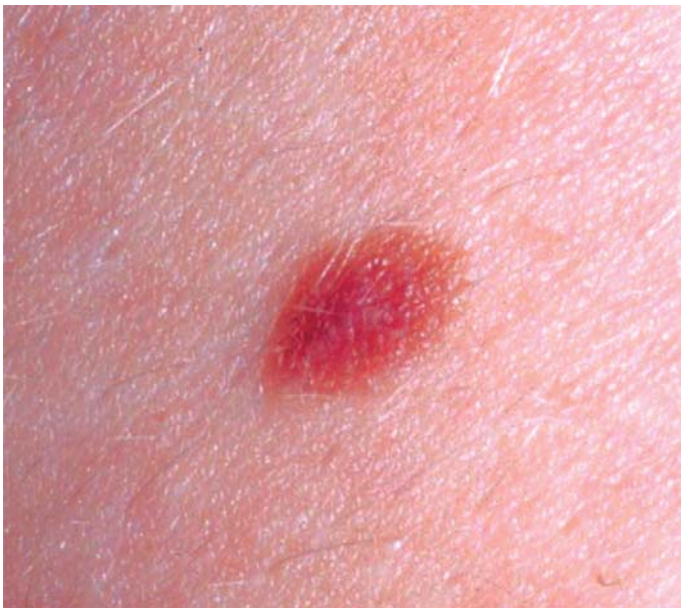


Fig. 8.56: Junctional nevus

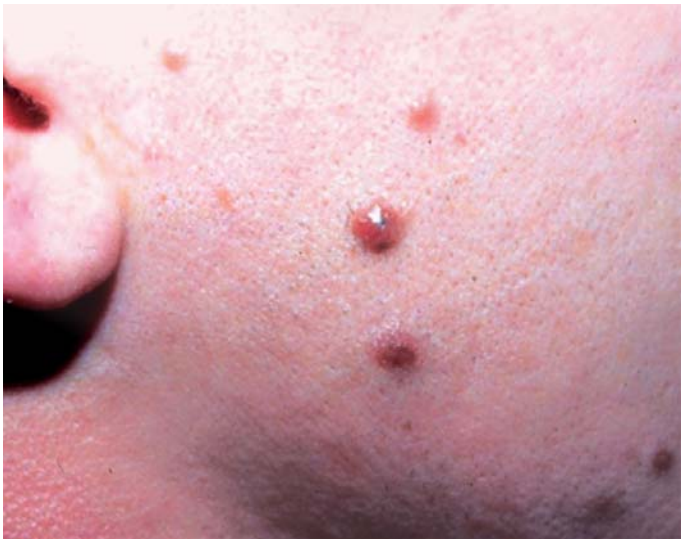


Fig. 8.57: Compound nevus

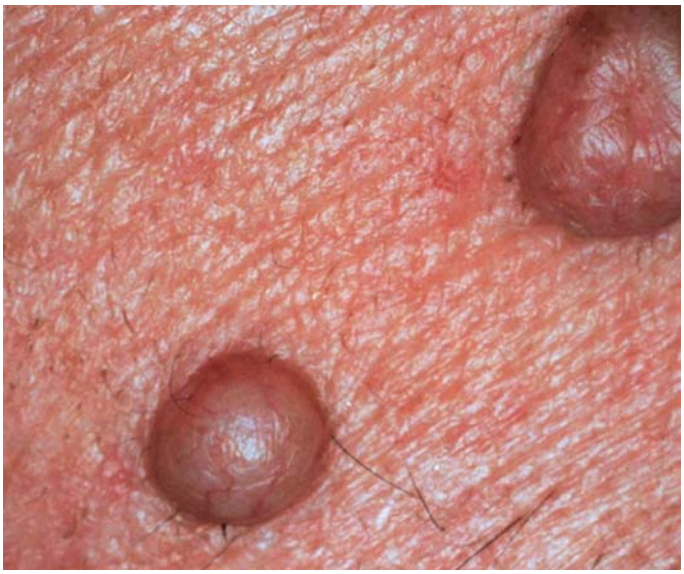
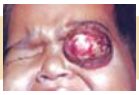


Fig. 8.58: Dermal nevus

DERMAL NEVUS (Fig. 8.58)

Dermal nevi may also be of natural skin color or darker. All are elevated nodules and become firm as fibrous tissue replaces degenerated nevus cells. Most are described as dome-shaped, but others may be warty. Like the warty surface texture of some compound nevi, the warty surface is regular and symmetric throughout the lesion. Some



dermal nevi will also develop a stalk and produce a pedunculated lesion resembling a skin tag, particularly in the groin, axilla, and neck. Transformation into a melanoma is very rare, but the dermal nevus itself may resemble a nodular melanoma. The unchanging appearance of the nevus is the best way to differentiate the two.

Differential Diagnosis

Any nevus can resemble a melanoma. Junctional and compound nevi may resemble superficial spreading melanomas, and dermal nevi may resemble nodular melanomas. On sun exposed skin, nevi may also be confused with actinic keratosis, seborrheic keratosis, and pigmented basal cell carcinomas. Cutaneous hemangiomas appear blue as do some deep dermal nevi. Some dermal nevi will appear blue (blue nevus) due to the phenomenon whereby only the higher energy blue range of the light spectrum penetrates to this depth; the otherwise brown melanin will appear blue by the absorption of all other colors, leaving only the higher-energy blue spectrum to be reflected. A cutaneous hemangioma may also resemble a nevus by appearing brown because of accumulation of hemosiderin.

Treatment and Prognosis

Any skin nevus with signs suggestive of a melanoma requires excision down to and including the subcutaneous level. All mucosal nevi require excision down to and including the submucosal level. Excision of such nevi eradicates the lesion and may lead to diagnosis of an early melanoma. Static nevi without features suggestive of a melanoma do not require excision and may be followed.

Histopathology

Melanocytic nevi form a spectrum that begins as a melanotic macule (lentigo simplex). Nondendritic, enlarged, and rounded melanocytes are seen in linear and contiguous arrangement along the basal layer. The melanocytes and keratinocytes are heavily pigmented. There is elongation of rete ridges secondary to proliferation of keratinocytes. Melanophages and lymphocytes are often present within the dermis.

The junctional nevus resembles lentigo simplex except that nests of melanocytes are seen at the epidermal~dermal junction, often at the tips of the elongated rete ridges. These lesions tend to be less heavily pigmented than those of lentigo simplex, and there are fewer melanophages and lymphocytes in the dermis. Contiguous rounded melanocytes are usually present in linear arrangement in the basal layer. Lesional cells are not present within the dermis (Fig. 8.59).

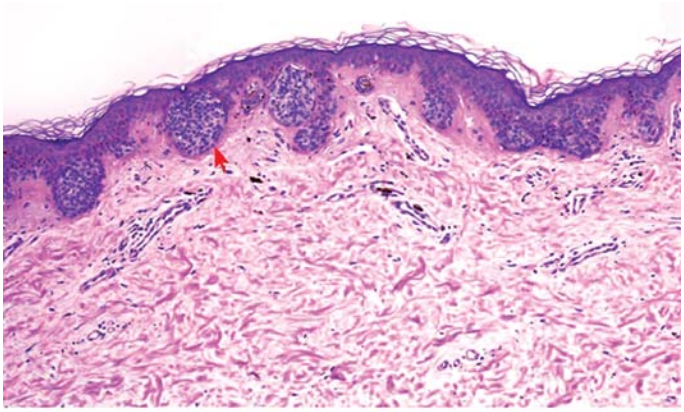


Fig. 8.59: Histopathology of junctional nevus

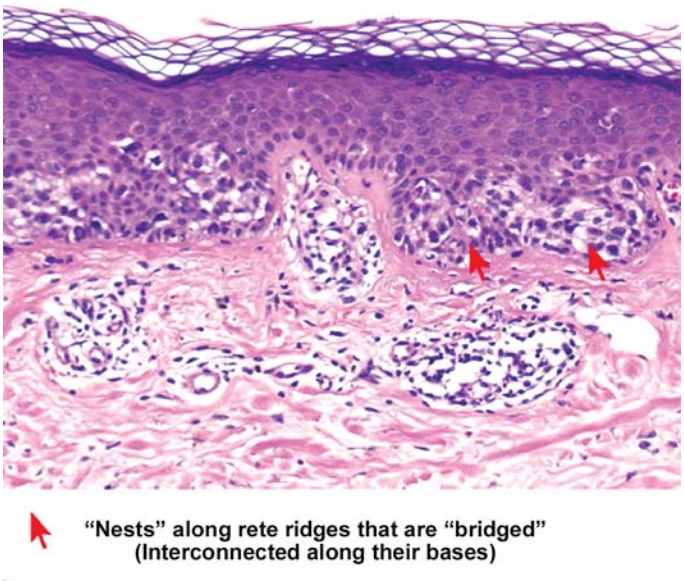


Fig. 8.60: Histopathology of compound nevus

The compound nevus maintains the pattern of the junctional nevus, but additionally there is extension of the nevus cells into the papillarydermis and sometimes into the reticular dermis as nests and anastomosing cords. A pattern of maturation may be seen within these nevus cells. The more superficial, known as type A, are large and rounded and contain melanin (epithelioid). The deeper cells, known as type B, are smaller and lack pigment (lymphoid). Older lesions may contain type C cells at their base; these are spindled and have a neurogenic appearance (Fig. 8.60).

The dermal nevus has nevus cells only within the dermis and lacks an epidermal component. Rete ridges are not elongated. The preponderance of nevus cells is more likely to be of types B or C. Sometimes only the spindle cells

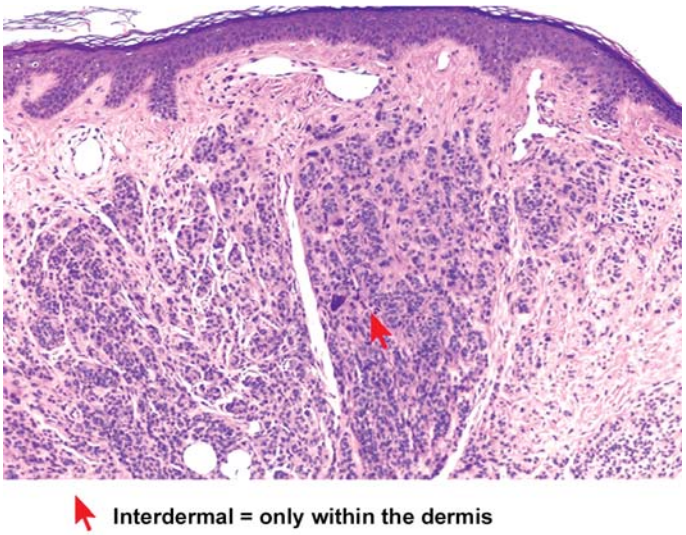


Fig. 8.61: Histopathology of dermal nevus

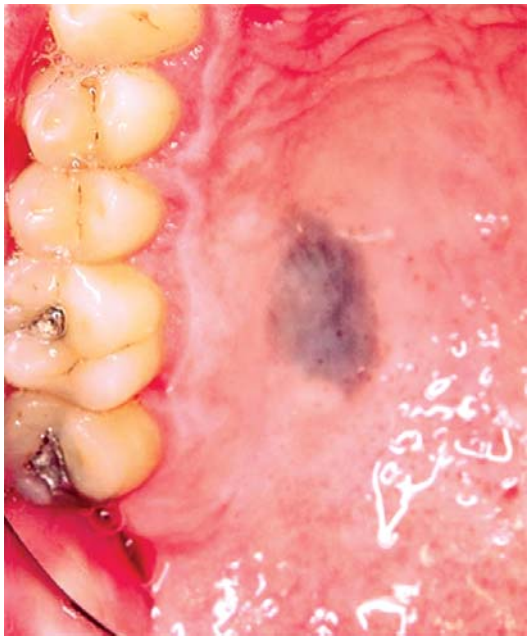


Fig. 8.62: Blue nevus

remain so that the nevus has a completely neurogenic appearance. The dermal nevus may undergo involution, in which case nevus cells are absent and are replaced by fibrous tissue and fat. The appearance of these lesions is the same when they occur on mucous membranes (Fig. 8.61).

BLUE NEVUS (FIG. 8.62)

Clinical Presentation

The blue nevus, a blue dermal nevus, is usually small (less than 5 mm) and appears as a regular, round elevated nodule. It appears blue because the melanin pigment, which is naturally brown, is located deep within the dermis. The brown pigment and the thickness of skin absorb the longer wavelengths of light (e.g., reds, oranges, yellows) and reflect the more penetrating, shorter wavelengths, such as blue (i.e., the Tyndall effect).

The blue nevus will appear in childhood on the dorsum of hands, extremities, and scalp. It has a low potential for malignant transformation. However, a larger, rare variant, called the cellular blue nevus, has a higher melanoma transformation rate. It is frequently larger than 1 cm and most often located on the buttocks.

Differential Diagnosis

The blue nevus will closely resemble a small hemangioma, a venous varix, or even a lymphangioma. Compressing the lesion (diascopy) will blanch such vascular lesions but will not change the appearance of a blue nevus.

Diagnostic Work-up and Treatment

Unless there are signs suggestive of melanoma, blue nevi may be followed without excision. However, if the clinical diagnosis is uncertain or such changes as blackening, induration, surface irregularity, outline irregularity, or ulceration occur, excision including the subcutaneous level is required.

Histopathology (Fig. 8.63)

Blue nevi consist of groups of elongated dendritic or spindle cells, which sometimes have a wavy appearance and often lie parallel to the epidermis. They contain abundant melanin granules, which often obscure the nucleus. The cells are usually within the reticular dermis and lie between the collagen fibers, which are often thickened. A reactive

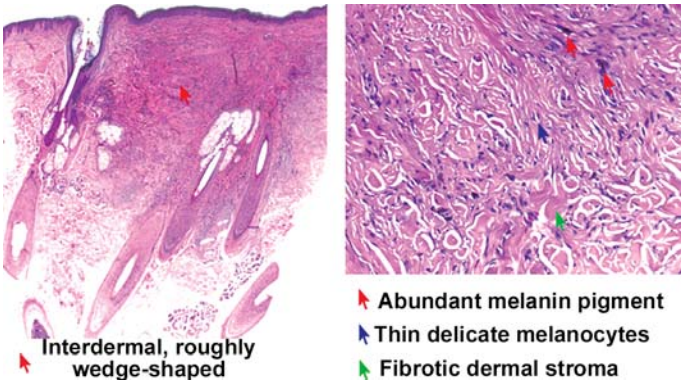
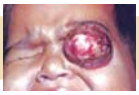


Fig. 8.63: Histopathology of blue nevus



fibroblastic proliferation may also be seen. The melanocytes are sometimes found within nerve or vessel walls. Melanophages may be present. The epidermis is unremarkable unless the lesion is a combined nevus, in which case there may be a concomitant junctional, compound, or dermal nevus.

The cellular blue nevus typically is biphasic with pigmented cells alternating with clear cells. Mucosal blue nevi have the same histologic appearance as those on the skin.

NEVUS OF OTA (Fig. 8.64)

Clinical Presentation and Pathogenesis

The nevus of Ota is a unique nevus that represents a melanocytic disorder following the distribution of one or more divisions of the trigeminal nerve. About 48% are congenital or appear within a few weeks of birth, and 36% arise at puberty, thereby creating a bimodal incidence peak. The nevus will appear as a diffuse brownish discoloration or a cluster of small, blue-black, well-demarcated spots. The skin over the maxillary division of the trigeminal nerve seems to be involved more frequently than the other divisions, and corresponding nevi simultaneously appear on the oral mucosa, nasal mucosa, and sometimes on the conjunctiva of the ipsilateral eye. The nevus of Ota is most common in Asians and dark-skinned individuals and has a marked predilection for women (80%).

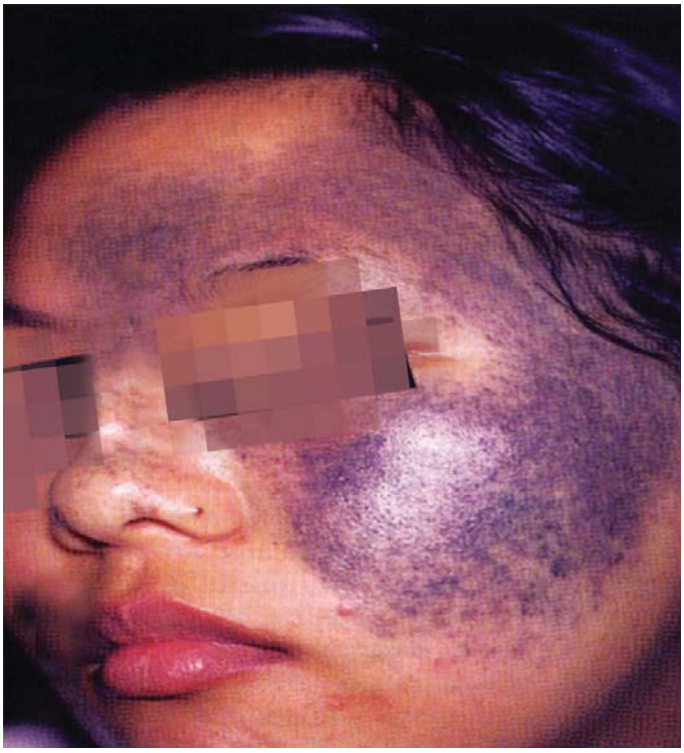


Fig. 8.64: Nevus of ota

Neither the cutaneous component nor the oral mucosa membrane component of the nevus of Ota is associated with melanoma. The nevus of Ota is thought to represent a developmental anomaly of excess melanocytes residual from neural crest cells that migrated along a trigeminal nerve distribution. In those arising during puberty, it may be a hamartomatous proliferation of these residual cells stimulated by hormonal increases.

Differential Diagnosis

Facial hyperpigmentation occurring unilaterally in children or teenagers of Asian descent is characteristic of the nevus of Ota. Other entities that may appear similar are encephalotrigeminal angiomatosis (Sturge-Weber anomaly), progressive systemic sclerosis (scleroderma), and a melanoma.

Diagnostic Work-up and Treatment

The nevus of Ota is merely a matter of cosmetic concern; rarely does it undergo transformation to melanoma, nor does the nevus usually progress throughout life. However, patients with ocular involvement have a high incidence of secondary open-angle glaucoma due to melanocytes collecting at the angle, causing obstruction of drainage. They also have a higher incidence of retinal, iridic, and cerebral melanomas. Therefore, patients with cutaneous lesions suggestive of nevus of Ota should undergo an ophthalmologic evaluation.

Various cosmetic procedures are used to remove these nevi. The argon laser is used to ablate the nevi, but this procedure often results in a lighter colored area of equal cosmetic distraction due to permanent loss of pigment and scarring. Alternatively, the Q-switched ruby laser, which uses short pulses of high energy (8 to 10 j/cm^2 at 40 nanoseconds and 694 nanometers wavelength), has been used to damage melanocytes and melanosomes more than surrounding tissue. Partial clearing of nevi is reported in 50% of patients, complete clearing in 25%, and residual nevi in another 25%. Other approaches use microsurgical excision of each focal spot or dry ice packing combined with argon laser ablation. Many lesions are left untreated.

Histopathology (Fig. 8.65)

A proliferation of elongated dendritic and stellate melanocytes containing melanin is seen between the collagen bundles of the reticular dermis. These lesions are less cellular than the blue nevus, but the cells may also lie parallel to the epidermis. There is no epidermal component. The nevus of Ota will appear as a blue or darkened patch over one or more distributions of the trigeminal nerve. It will resemble an area of ecchymosis.

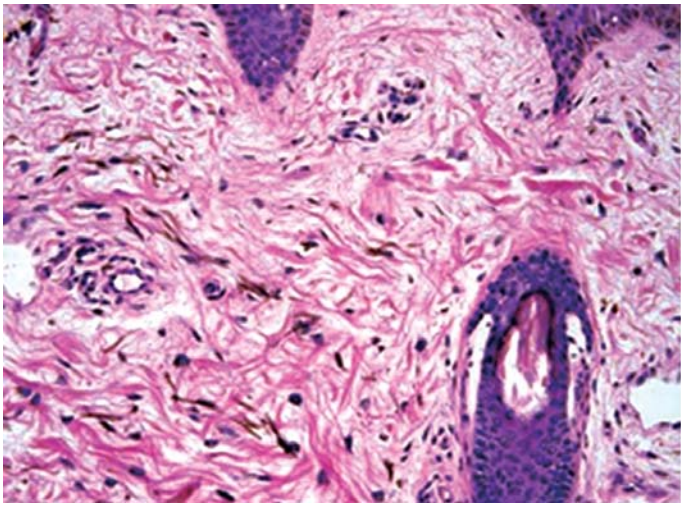


Fig. 8.65: Histopathology of nevus of Ota

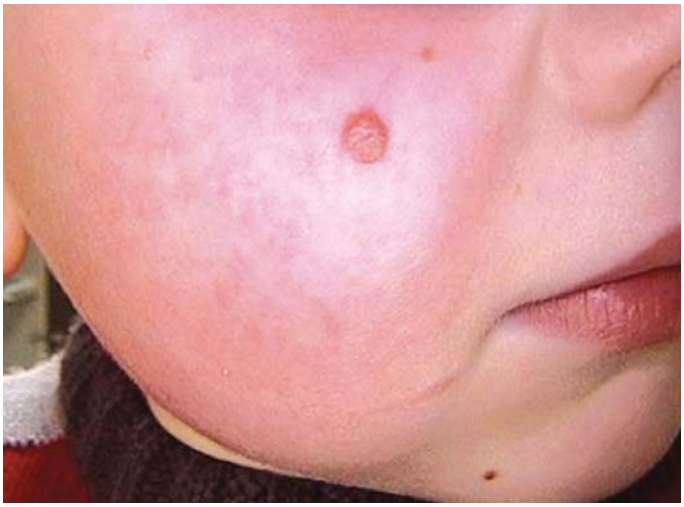


Fig. 8.66: Spitz nevus

NEVUS OF ITO

The nevus of Ito is similar to the nevus of Ota; however, it mostly occurs in the deltoid region. It may be seen on the upper chest, back, or supraclavicular area as well. Like the nevus of Ota, this nevus forms along peripheral nerve fibers. Clinically, it will present as a bluish hyperpigmentation, which on fine sensory testing may be associated with a local paresthesia. On occasion, the nevus has been associated with reduced sweating presumably because of its association with small sympathetic fibers, which innervate facial sweat glands.

The nevus of Ito is primarily an adult nevus but is rare. Because it mostly occurs in the deltoid region and other areas of low cosmetic index, it may be managed by local excision and primary closure or by laser ablation. Because it represents a benign nevus, its recurrence potential is low, and only very rare cases undergo melanoma transformation.

SPITZ NEVUS (Fig. 8.66)

Clinical Presentation

The Spitz nevus has clinical and histologic features mimicking those of a melanoma. The nevi present as red or reddish-brown, smooth-surfaced nodules, usually between 0.5 and 1.5 cm. Clinically, Spitz nevi may suggest a melanoma because they emerge suddenly, unlike other nevi that develop slowly as macular lesions and evolve into nodular dermal nevi. They may also be suggestive of a melanoma because of their vascular nature, which may lead to bleeding following minor trauma.

Most Spitz nevi occur in children as single, fast-developing nodules. However, multiple nevi can also occur, and adults may develop them as well.

Differential Diagnosis

The rapid development of a small nodule on the skin of a child or a young adult suggests common acne lesions, sebaceous cysts, or furuncles. In addition, their reddish color and vascularity may suggest a small hemangioma or lymphangioma. Melanoma remains a serious consideration due to the lesion's color and rapid emergence.

Treatment and Prognosis

Spitz nevi usually require excision to rule out melanoma and other diseases on the differential list. Excision is accomplished with 1 to 2 mm margins and includes the entire subcutaneous level. If the pathologist identifies the lesion as a Spitz nevus, no further excision or treatment is required. The Spitz nevus does not recur, not even in the case of incomplete excision. Therefore, in equivocal cases in which the histopathologic distinction between melanoma and a Spitz nevus is uncertain, follow up is recommended. Any evidence of clinical recurrence is interpreted as evidence of melanoma.

Histopathology (Fig. 8.67)

Spitz nevi have the overall architecture of an intradermal or compound nevus. The overlying epithelium may show considerable hyperplasia with elongated rete ridges, and the papillary dermis may be edematous and contain dilated capillaries and lymphocytes. This vascularity contributes to the red color clinically. There are usually well-circumscribed nests of large cells, which may be plump spindle cells or large, round epithelioid cells. They are believed to represent a single cell population. The epithelioid cells have eosinophilic cytoplasm and may be multinucleated and atypical in appearance. Spindle cells are usually seen in whorls but may permeate the reticular

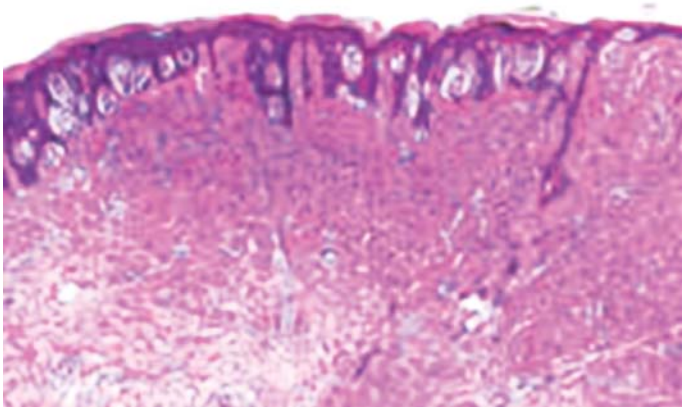


Fig. 8.67: Histopathology of Spitz nevus

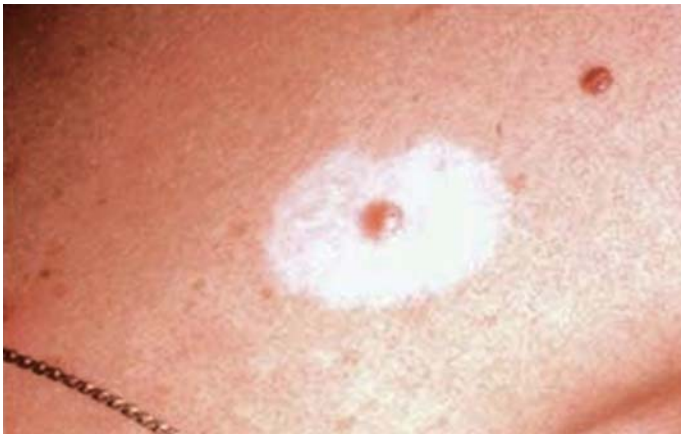


Fig. 8.68: Halo nevus

dermis and show a single-file pattern at the base. Mitoses may be seen. Because of the pleomorphism, mitoses, and infiltrative pattern, as well as the presence of lymphocytic infiltrates, these nevi may be extremely difficult to distinguish from melanoma. Unlike melanoma, however, the Spitz nevus usually will show maturation (cells decrease in size in the deeper areas) and single-file infiltration rather than infiltration by nests and fascicles of cells. In addition, the presence of eosinophilic globules within the epidermis, which are periodic acid-Schiff (PAS) positive and diastase resistant, are seen in a high percentage of Spitz nevi, but are very uncommon in melanoma. These are known as Kamino bodies and probably represent apoptotic cells. Melanin pigment is not usually prominent. Artifactual clefts often separate the cell nests from the keratinocytes. The Spitz nevus will present as a reddish-brown nodule with a rapid onset. These features, together with its vascularity and occasional bleeding, suggest a melanoma. A Spitz nevus with the arrangement of a compound nevus. As is typical of this lesion, there is little melanin, inflammatory cells are present, and artifactual clefts are seen above the clusters of nevus cells.

HALO NEVUS (Fig. 8.68)

Clinical Presentation

The halo nevus is a type of compound or dermal nevus that develops a regular, symmetric white border. The white halo, which represents an area of depigmentation, is well demarcated from a normal skin edge. Halo nevi develop spontaneously from pre-existing nevi, most commonly during the teenage years. Most occur on the trunk, some occur more rarely on the neck, but none has ever been reported on the palms or soles. Most occur singly, but on occasion several nevi may show halo characteristics around the same time. Most halo nevi retain their halo. Some will show repigmentation of the white halo and in some others the halo will envelope and eradicate the nevus, resulting in a white circle.

Differential Diagnosis

The main differential is a melanoma with halo formation. Halo areas do indeed form around some melanomas, but these halos are asymmetric and have jagged borders with the adjacent, normally pigmented skin. If the nevus is small or the halo has replaced most of the nevus, it may resemble an area of vitiligo. However, vitiligo lesions are also irregular, usually larger, and have several areas of depigmentation.

Treatment and Prognosis

Removal of a halo nevus is unnecessary unless the nevus or halo shows irregularity or variations of pigmentation suggestive of melanoma. Atypical lesions require excision of the halo area as well as the nevus, including the subcutaneous level. The halo nevus, per se, does not have a high potential for melanoma transformation. In fact, an immune system that is attacking and destroying nevus cells is associated with a reduced melanoma potential. In the past, the incidence of halo nevi transforming into melanoma has been overestimated because of the cases of melanoma that have shown halo formation. These melanomas with halos, however, arise de novo rather than from a pre-existing halo nevus.

Histopathology (Fig. 8.69)

The appearance of the halo nevus is essentially one of a compound nevus heavily infiltrated by lymphocytes, which tend to mask the nevoid pattern. Melanophages may be

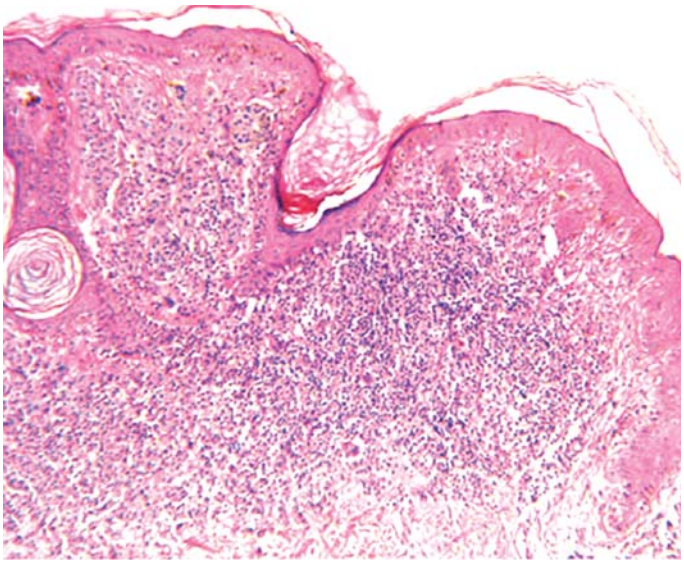


Fig. 8.69: Histopathology of halo nevus

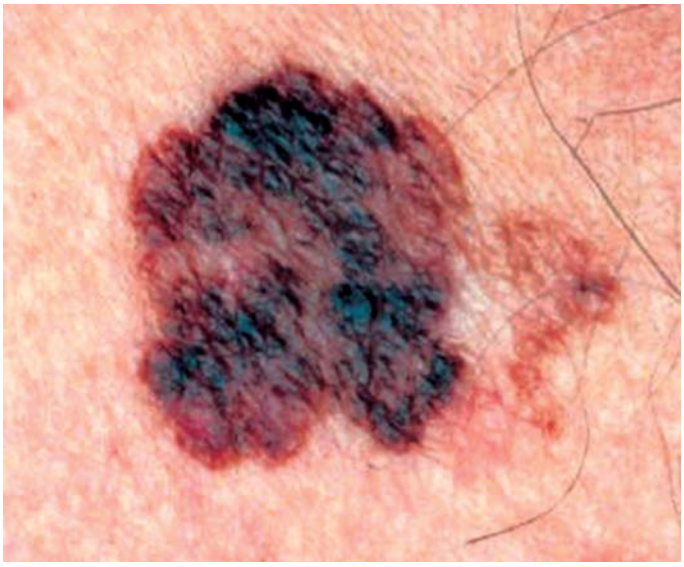


Fig. 8.70: Dysplastic nevus

present. Over time, the dermal nevus cells are destroyed. In the area of the clinical halo, there is reduced melanin production. The halo nevus is very recognizable. It will usually develop during the teenage years from a pre-existing nevus with a white depigmented area at its peripheral circumference. A halo nevus showing destruction of the nests of nevus cells by lymphocytes.

DYSPLASTIC NEVUS (NEVUS WITH ARCHITECTURAL DISORDER) (Fig. 8.70)

Clinical Presentation and Pathogenesis

The dysplastic nevus is a clinically and histologically atypical nevus representing the single most important precursor to a cutaneous melanoma. More than the congenital nevus, it is the primary pigmented lesion that transforms into a melanoma. Dysplastic nevi appear either sporadically or in an autosomal-dominant inherited condition called dysplastic nevus syndrome (DNS).

Clinically, the dysplastic nevus differs from the ordinary nevus. It is usually larger, and many are greater than 1 cm, whereas the common nevus rarely exceeds 0.6 cm. Its borders are irregular, with the color fading gradually into the surrounding skin, in contrast to the well-demarcated and regular borders of the ordinary nevus. It is variegated in color, usually a mixture of brown, black, and red, whereas common nevi are uniform in color. Common nevi have a site preference for sun-exposed areas, while dysplastic nevi tend to occur at unusual sites such as the scalp, buttocks, and breast.

The frequency of sporadic dysplastic nevi is unknown. However, 8% of melanomas unassociated with a familial inheritance have at least one concomitant dysplastic nevus, and serial examinations have revealed the progression of dysplastic nevi into melanoma of the superficial spreading type.

Dysplastic nevi associated with dysplastic nevus syndrome have an exceedingly high melanoma potential. Dysplastic nevi are found concomitantly on the skin of 90% of melanoma patients who have a family historyof melanoma. The lifetime incidence of cutaneous melanoma among whites in the United States is about 0.6%. Those with sporadic (nonfamilial) dysplastic nevi have a tenfold greater risk and therefore an incidence of 6%. Those with a family historyof DNS or melanoma who have a dysplastic nevus have an incidence of melanoma of 15%. The risk of melanoma approaches 100% for those who have a dysplastic nevus and two or more first-degree relatives with a cutaneous melanoma.

Dysplastic nevi of either the sporadic type or the familial DNS are not congenital but appear in mid-childhood as a common mole. They begin to take on the clinical features of dysplastic nevi in the early teens, and new nevi continue to appear even past the age of 40 years.

Dysplastic nevus syndrome and/or familial melanoma is estimated to affect 32,000 people in the United States, accounting for about 85.5% of all melanomas. The autosomal-dominant inheritance is localized to the distal end of the short arm of chromosome 1. This gene locus seems to be related to skin pigmentation regulation only. There is no association with or greater risks for other dysplasias or carcinomas.

Differential Diagnosis

Dysplastic nevi must be distinguished from common melanocytic nevi on one end of the spectrum and from melanoma on the other end. In addition, the overall presentation of multiple brown-black macular lesions may suggest syndromes associated with café-au-lait macules or other hyperpigmented lesions, including Albright syndrome, hereditary neurofibromatosis, Peutz-Jeghers syndrome, and Leopard syndrome.

Diagnostic Work-up and Treatment

Individuals who have two or more lesions clinically consistent with dysplastic nevi require a complete topographic skin examination, as do their family members. The purpose is to identify others who may have dysplastic nevi or melanomas and are therefore also at risk, as well as to assess the familial tendency. Photographs of lesions are highly recommended, as not all nevi can or should be excised. Baseline photographs enable comparisons and an assessment of change during future examinations.

The general approach is to excise two to four of the most suspicious nevi to establish a histopathologic diagnosis. The excision uses 2 to 5 mm margins to and inclusive of the subcutaneous level. If the diagnosis confirms dysplastic nevi, the general rule is to excise all new nevi that arise thereafter and all of those in the scalp because of the difficulty of monitoring scalp lesions. Prophylactic excision of all remaining nevi is neither practical nor indicated if there are more than 10. Such lesions should be followed with serial examinations and compared to baseline photographs.

Histopathology (Fig. 8.71)

Histologic features associated with dysplastic nevi include architectural, cytologic, and stromal changes. Architecturally, there is a fairly regular elongation of the rete ridges and a lentigo simplex-like proliferation in the basal layer of single or nested nevus cells. The nests may coalesce or form bridges between adjacent rete ridges. A "shouldering"pattern may be seen in which the epidermal melanocytes extend singly or in nests beyond the dermal component.

Cytologically, most cells have the appearance of a regular nevus, but scattered atypical cells are present. These are epithelioid cells, which are larger, have more abundant cytoplasm, and may contain fine, dusty pigment. These cells can show variation in size and shape of the nuclei, and nucleoli may be prominent. The degree of atypism may range from mild to severe. Mitoses are rare. Stromal changes include a patchy perivascular lymphocytic infiltrate and eosinophilic fibroplasia, which is a condensation of collagen around the rete ridges.

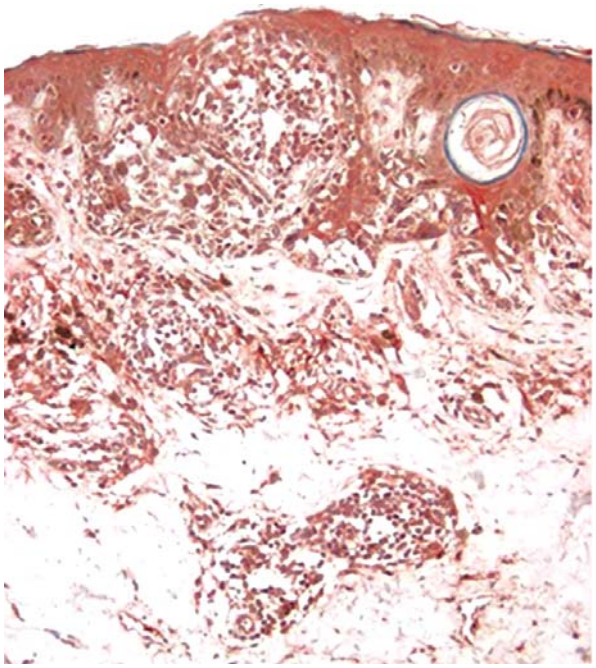


Fig. 8.71: Histopathology of dysplastic nevus

Prognosis

Dysplastic nevi require continued surveillance. Those with a nonfamilial sporadic dysplastic nevus have a tenfold increased risk of melanoma; the greater the number of family members who have dysplastic nevi or melanomas and the greater the number of such lesions on each family member, the greater the risk.

CONGENITAL NEVI (Fig. 8.72)

Clinical Presentation

Congenital nevi account for only 1% of all nevi. More usual is a junctional nevus developing at age 2 years and progressing to a compound nevus through the teenage years and then to a dermal nevus in adulthood. Congenital nevi are significant because of their much higher incidence of melanoma transformation.

Congenital nevi, also called birthmarks, may occur in any location but most commonly are seen on the buttocks and trunk. Some contain hair, which is usually coarse in texture. Rarely, an individual will present with an extremely large nevus, called a giant hairy nevus, which imparts a focal, so called were-wolf appearance. Most are flat, smooth, and uniform in color (brown to black). As the child ages, the nevus tends to become thicker and the

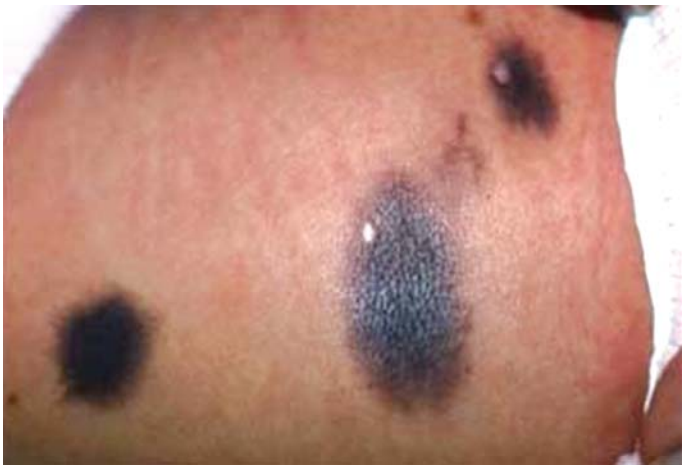


Fig. 8.72: Congenital nevus

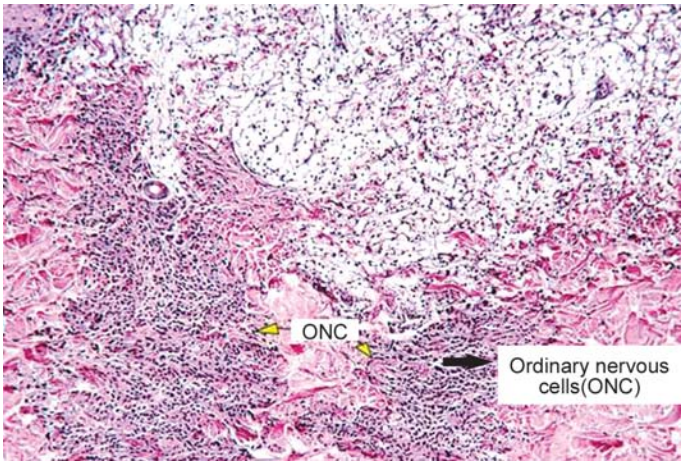


Fig. 8.73: Histopathology of congenital nevus

surface verrucous or nodular. The potential for melanoma development even as early as childhood increases with the size and thickness of the congenital nevi.

Differential Diagnosis

Most congenital nevi are recognizable clinically, but café-au-lait macules associated with Albright syndrome and hereditary neurofibromatosis may also occur congenitally. Rare syndromes such as Leopard syndrome (lentigines, electromyographic disturbances, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retarded growth, and deafness) and lipatrophic diabetes with acanthosis nigricans will manifest large areas of brown hyperpigmentation congenitally.

Diagnostic Work-up and Treatment

Small congenital nevi require only observation. Larger, thicker lesions should be excised. Some authors have recommended excision of all congenital nevi because of the high melanoma transformation rate. This view, however, is not universally accepted; some reports show that only 8% of melanomas have features suggesting that they arose from congenital nevi. However, careful and watchful follow-up of all congenital nevi is recommended.

Histopathology (Fig. 8.73)

Congenital nevi may be indistinguishable from acquired nevi. However, they often involve the lower third of the reticular dermis and the skin appendages. Giant nevi typically involve reticular dermis, subcutaneous tissue, and fascia. A splaying of cells is seen between the collagen bundles in the reticular dermis. Within the fat, the nevus cells often resemble fibroblasts. Abnormalities of neural crest - derived tissues, including schwannian proliferations and cartilage formation, may be seen within the giant nevi.

OSTEOMA (Figs 8.74 AND 8.75)

Clinical Presentation and Pathogenesis

Osteomas are referred to as benign neoplasms, but they are actually hamartomas that occur almost exclusively in membranous bone. Single osteomas are rare in the jaws and uncommon in the facial bones. In the oral and maxillofacial region, the skull is where most single osteomas occur, the frontal sinus being the site of predilection.

An osteoma will present as a slow-growing, painless, discrete bony mass that is palpable unless it develops within the medullary space. It will often be observed only in incidental radiographic findings as a well-defined round or oblong radiopacity. Men seem to be affected more frequently than women, and children are almost never affected unless they have Gardner's syndrome, which is an autosomal dominant trait that features osteomas, fibromatosis of the skin and fascia, and polyposis of the

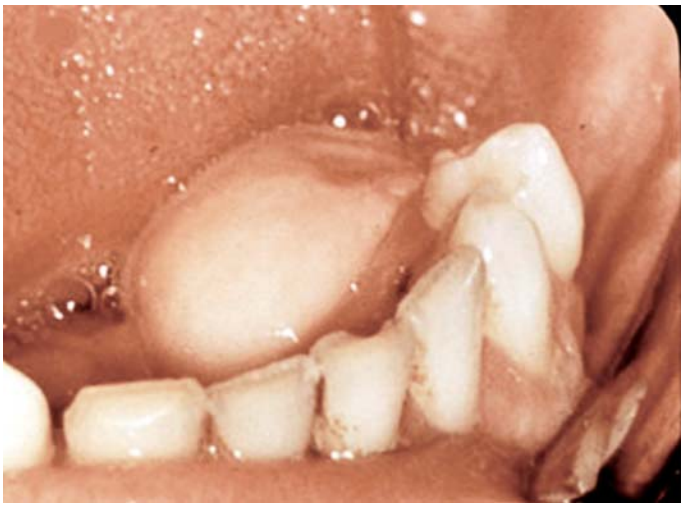
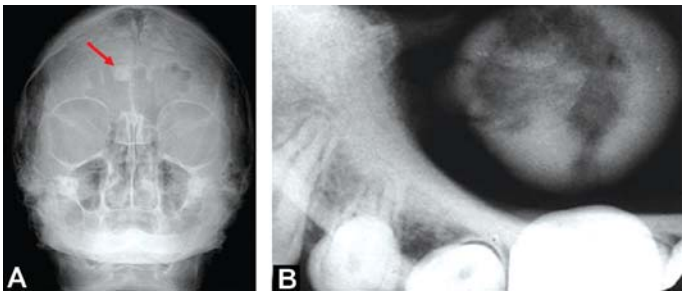


Fig. 8.74: Osteoma



Figs 8.75A and B: (A) Osteoma of the frontal sinus, (B) Osteoma

large intestines with a high degree of malignant transformation. In fact, the finding of a true osteoma (not an exostosis or a palatal torus) of the jaws in a child should prompt an evaluation for Gardner syndrome. On rare occasions an osteoma will be found in the tongue musculature; this represents a benign choristoma arising from mesenchymal stem cells in the tongue.

Differential Diagnosis

Osteomas should be distinguished from tori and exostosis, which are developmental overgrowths rather than neoplasms or discrete hamartomas. Both are clinically recognizable by their broad base, which emerges from the superficial cortex of the mandible or palate. Most are lobulated or multiple. Osteomas tend to have a narrow base and appear as single lesions. Osteoblastomas and radiopaque ossifying fibromas also may mimic an osteoma. However, osteoblastomas are associated with deep, dull pain and will exhibit more rapid growth, and an ossifying fibroma will be less radiopaque than an osteoma when it is small, or, when it becomes sufficiently radiopaque, too large to be an osteoma. A complex odontoma could also appear radiographically similar to an osteoma.

Histopathology (Fig. 8.76)

An osteoma may consist of dense lamellar bone with little marrow, or it may show trabeculae of lamellar bone with a more prominent fibro fatty marrow and peripheral cortex. Osteoblastic activity is variably present.

Diagnosis and Treatment

Osteomas are diagnosed and treated by local excision. Margins of more than 1 mm are unnecessary. However, the finding of a true osteoma in the jaws should prompt a search for osteomas elsewhere (i.e. skull, sinuses, facial bones) and an examination for dermoid cysts, sebaceous cysts, desmoid tumors, and aggressive fibromatoses, since these may also signal Gardner's syndrome. If gastrointestinal symptoms are part of the patient's history, if a second osteoma is found, or if stools are heme-positive, a colonoscopy also should be performed.

Follow-up

Because osteomas do not recur, the goal of follow-up is to look for new osteomas or other signs indicative of Gardner-syndrome.

CENTRAL GIANT CELL TUMOR (Fig. 8.77)

Clinical Presentation and Pathogenesis

Central giant cell tumors of the jaws are benign but aggressively destructive osteolytic lesions. This tumor, and biologic behavior in the jaws, is identical to that in the long bones, and the terminology related to both of them has become extremely confused. Today, these tumors seem to represent benign tumors of osteoclastic origin. They are not unique to the jaws and are not odontogenic. The giant cells have osteoclast receptors and thus represent osteoclast precursors or are themselves osteoclasts. The tumor is not a true granuloma and is not at all reparative; the use of such outdated terminology should be abandoned because it is misleading. Even the generic term "giant cell lesion" is incorrect and misleading. In addition, there is no difference in histopathologic features or biologic behavior between a central giant cell "lesion" and an aneurysmal bone cyst (which is not a true cyst either). A so-called aneurysmal bone cyst represents a central giant cell tumor that has larger vascular spaces and may attain a larger size. For the purposes of this text, central giant cell tumors will include what has also been described in the literature as an aneurysmal bone cyst. This tumor is histopathologically and behaviorally identical to the benign giant cell tumor of long bones, the most common neoplasm found in long bones; it is not to be confused with what some authors have

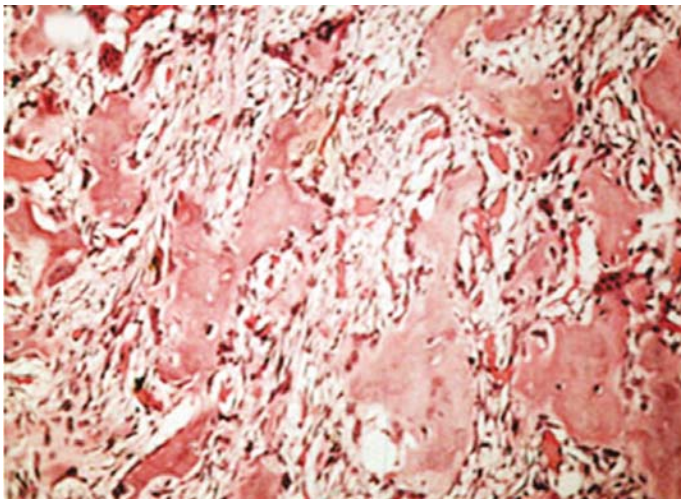


Fig. 8.76: Histopathology of osteoma

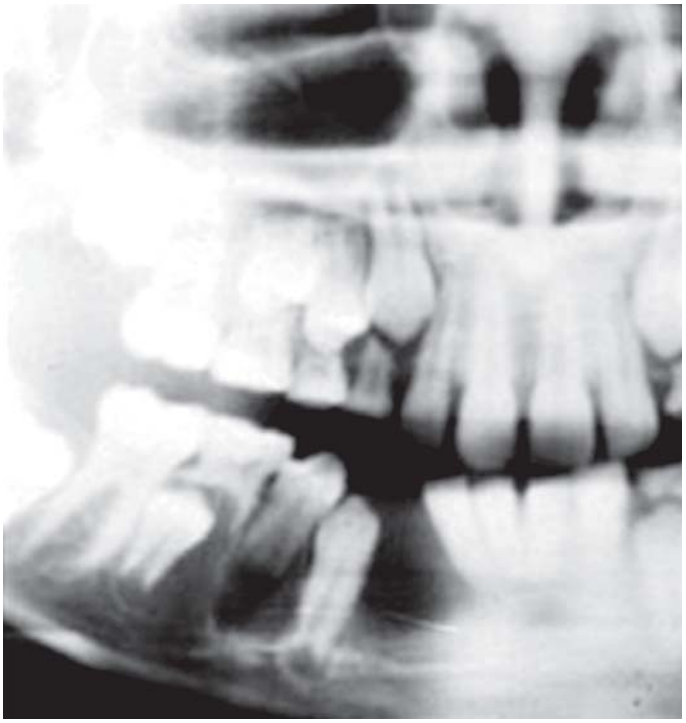


Fig. 8.77: Central giant cell tumor

described as malignant giant cell tumors, which may represent an osteosarcoma with prominent osteoclasts or a true malignant variant of osteoclasts.

In the jaws, a central giant cell tumor presents as a painless clinical expansion that may have a short (2 week to 2 month) ascendancy. The expanded lesion may appear blue because of its cortical and mucosal thinning and internal vascularity. Occasionally, the rapid expansion will stretch periosteum, producing pain. The peak range of occurrence is between 5 and 15 years of age, although some cases develop in the 20s and 30s as well. Women are affected twice as frequently as men. The mandible is involved three times as frequently as the maxilla. Although this lesion is one that is known to cross the midline and to occur in the anterior jaw regions, the posterior regions are affected as well.

Radiographic Findings

The central giant cell tumor will classically present as a multilocular radiolucent lesion that severely thins the cortices, including the inferior border. It is also known to scallop the inferior border, displace teeth, and resorb interradicular bone. It may also resorb tooth roots to some degree.

Differential Diagnosis

A multilocular, expansile, radiolucent lesion in a child or teenager is suggestive of several lesions, most notably an odontogenic keratocyst, an odontogenic myxoma, an ameloblastic fibroma, or Langerhans cell histiocytosis. If the patient is older than 14 or 15 years, an ameloblastoma becomes a statistically more likely consideration as well. In addition, because of the bleeding potential and generally young age of presentation, as well as a multilocular "soap bubble" radiolucency, a central arteriovenous hemangioma must be considered.

Diagnostic Work Up

A clinical presentation such as that of a central giant cell tumor is approached first with the goal of ruling out a high-pressure vascular lesion. Central giant cell tumors are not high~ pressure vascular lesions and will either fail to return blood or will return only a small amount. In most cases, an incisional biopsy is then performed, although it is not unreasonable to thoroughly curet the entire lesion if it is small, the access is good, and it seems consistent with the red - brown friable tissue of a central giant cell tumor (Fig. 8.76). If the lesion is determined to be any type of a giant cell tumor, it is prudent to obtain a serum calcium determination to rule out both primary and secondary hyperparathyroidism. A parathyroid hormone assay is not required because primary hyperparathyroidism of sufficient severity to produce a so-called brown tumor will evidence hypercalcemia, and secondary hyperparathyroidism of sufficient severity to produce a brown tumor will evidence hypocalcemia. An alkaline phosphatase determination also is not required because this age group frequently has growth-related elevations of this enzyme, and even in adults this study adds no further diagnostic information.

Histopathology (Fig. 8.78)

Grossly, these tumors are red to brown in color. The mass consists of a spindle cell stroma that may be quite cellular. There is a variable amount of collagen, and mitoses are sometimes seen. Extravasated erythrocytes are present, and

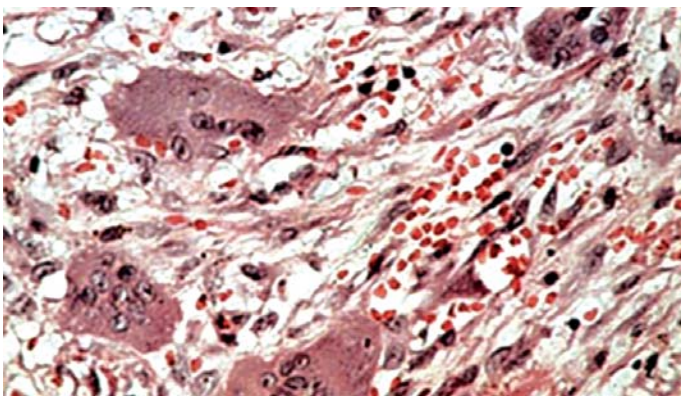
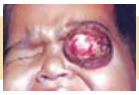


Fig. 8.78: Histopathology of central giant cell tumor



hemosiderin may be noted. The hemosiderin may be contained within macrophages. Multinucleated giant cells are conspicuous and tend to be irregularly distributed throughout the mass, often concentrating in areas of hemorrhage. There may be considerable variation in the size of the giant cells and the number of nuclei present. Osteoid may be deposited, particularly at the periphery of the lesion. Giant cell tumors are unencapsulated but usually delimited and frequently develop locules. They often abut tooth roots and may resorb them. The giant cells have been shown to excavate bone, respond to calcitonin, and bind osteoclast-specific monoclonal antibody, indicating that they are indeed osteoclasts.

Central giant cell tumors cannot be distinguished histologically from lesions of hyperparathyroidism, and therefore this latter possibility must be ruled out. Cherubism also has the same histologic features. Occasionally, fibrous dysplasia contains a sufficient number of giant cells so that it may also enter the histologic differential.

The so-called aneurysmal bone cyst is a condition that frequently develops secondarily within another lesion of bone. Most frequently, it is associated with central giant cell tumors. Large, blood-filled spaces develop that lack an endothelial lining. Solid areas of the lesion consist of central giant cell tumor with cellular fibrous tissue, extravasated blood, and multinucleated giant cells. However, if these dilated, blood-filled spaces have developed within another lesion, the solid areas will consist of that entity.

Treatment

The most common treatment is a thorough curettage of the lesion and its bony cavity. Multiple recurrent lesions or lesions with significant destructive bone resorption to the point of near pathologic fracture may require resection. The lesion itself is confined to and requires bone for its existence. It cannot exist outside of bone, even after possible implantation from a curettage procedure.

The central giant cell lesion does have a recurrence potential with curettage that reaches as high as 50% by some reports. Recurrences are seen more frequently with larger lesions and those that involve significant numbers of teeth. These recurrences are related to incomplete removal of a friable, bleeding lesion, which is more difficult to remove from between teeth and furcations, or to a greater possibility of incomplete excision in a larger sized lesion. The weak points in curettage are thus the areas between teeth, the areas around unerupted teeth, and the neurovascular bundle area; additionally, the vascular nature of this lesion, which produces an oozing type of blood loss, obscures the clinician's view. To reduce the impact of these factors, the following approach to the curettage has been developed: intraoperative reduction of local blood pressure by the anesthetic technique; placement of the patient in a head-up position; local vasoconstrictor usage; and, in the case of large lesions, preparation for possible transfusion. The lesion is approached initially by a wide soft tissue reflection to obtain a direct view of the entire lesion. It is first grossly curetted to debulk its mass. This will reduce the bleeding since the residual lesion in the bone bleeds more than do normal vessels because of the absence of a muscularis around the vessels within the tumor, which normally would vasoconstrict. The remainder of the tumor is then meticulously curetted, giving special attention to the weak points associated with recurrence described earlier.

Because of the known recurrence potential and the unencapsulated vascular nature of this lesion, two other treatment concepts have been advanced. One is the use of Carnoy's solution as a cellular fixative to sterilize remaining tumor cells. However, statistics do not support a reduction in recurrences when Carnoy's solution is used. Another is to perform endodontic therapy of erupted teeth within the lesion. This also does not reduce recurrences because it is the presence of the roots, rather than their vitality, that limits curettage in this area. Endodontic therapy in otherwise healthy teeth is not recommended because the long-term function of these teeth is reduced by the extensive crown destruction created by the access preparation and the dehydration of the tooth after pulpal extirpation. Moreover, endodontic therapy has not been shown to reduce tumor recurrence, and curettage on or around root surfaces does not truly devitalize teeth but only deinnervates them. Even so, reinnervation is common.

More recently, intralesional corticosteroid use has shown some value, inducing complete involution in many cases and partial involution in others. The suggested treatment is triamcinolone, 10 mg/mL, of which 1 mL is injected for each 1 cm of jaw involvement throughout the lesion, once a week for 6 weeks. Each injection sequence is performed with local anesthesia (bupivacaine) added to the injection solution. As yet, sufficient numbers and controlled studies are not available to assess the true resolution rate of this approach. In the authors' experience, 65% of central giant cell tumors have completely resolved with this therapy. The remaining 35% either recurred more aggressively or failed to respond at all, requiring either curettage or resection. Today, most cases of central giant cell tumor are initially treated with the series of intralesional corticosteroid injections. The potential value of resolving these tumors without invasive surgery is compelling. Because the treatment sequence is associated with minimal morbidity and does not preclude further therapy should it be

unsuccessful, it is a reasonable first choice. If the tumor fails to respond or accelerated growth results, a population of altered osteoclasts that do not have cell membrane receptors for corticosteroids is implied. Such tumors are then treated with either curettage or a resection with 0.5 to 1.0 cm margins if they are sufficiently large.

Prognosis

Lesions approached with wide-access, thorough curettage rarely recur. Recurrent lesions may be recuretted before resection is considered. If a recurrence develops, it is usually within the first 12 to 18 months, much sooner than recurrent odontogenic tumors. Patient age does not affect recurrence; however, the size of the lesion does seem to be related to recurrence, which is often the result of limited access caused by the tumor's infiltration between and around teeth. The biologic behavior of the giant cells varies greatly but is unrelated to patient age and the size of the lesion.

OSSIFYING FIBROMA (Fig. 8.79)

Clinical Presentation and Pathogenesis

Ossifying fibromas are slow-growing, benign neoplasms most commonly found in the jaws. Because of their less common but identical presence in other craniofacial bones and long bones that have no cementum (e.g. the tibia is a commonly involved long bone), the term used in this text is ossifying fibromas rather than cemento-ossifying fibromas. The fact that this tumor is most common in the jaws is related to the vast amount of mesenchymal cellular induction into bone (lamina dura) and cementum (a bone layer covering tooth roots) required in odontogenesis; the probability of induction error or genetic alteration leading to a neoplasm is, therefore, greater. In the past, preoccupation with the myriad pseudonyms for this lesion (e.g. osteofibroma, fibro-osteoma, cementifying fibroma, benign fibro-osseous lesion of periodontal ligament origin) created a hopelessly confusing and unnecessary terminology. Because bone and cementum cannot be distinguished by any known method, the origin of the calcified material of this tumor is a moot point, particularly when one considers that the origin of bone and cementum—that is, the mesenchymal stem cells—is the same.

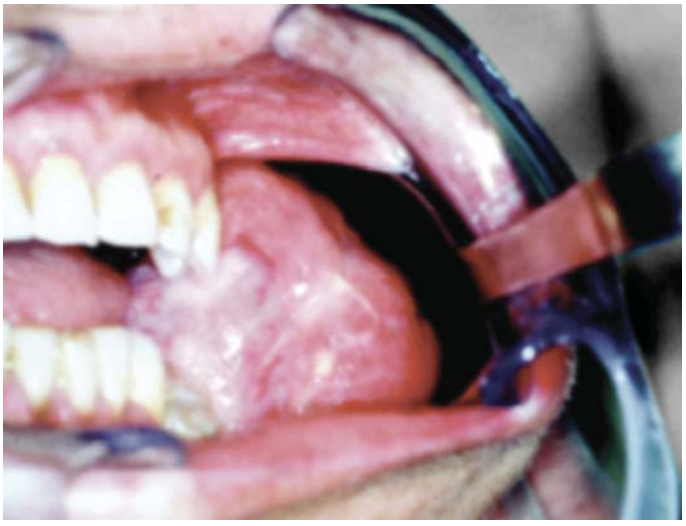


Fig. 8.79: Ossifying fibroma

Early ossifying fibromas are small and may be radiolucent. As they enlarge and mature, they will become mixed radiolucent-radiopaque, then completely radiopaque. These tumors characteristically expand slowly and asymptomatically. Their expansion is symmetric from the epicenter of the tumor, creating a spherical or egg-shaped mass on plain radiographs and CT scans. This tumor is seen most commonly in women in their 20s and 30s, but those younger and older, as well as men, are also affected. In the jaws, the lesions are found mostly in the tooth bearing areas, which is consistent with the higher rate of bone and cementum induction in these areas. Ossifying fibromas also occur in the rami but at a lower incidence.

Of all the benign tumors of the head and neck area, the ossifying fibroma is one of a few allowed by patients to reach the largest and most disfiguring size (ameloblastomas, odontogenic myxomas, neurofibromas, and pleomorphic adenomas are the others), probably because of its persistently steady but slow rate of growth and its painless character. Many will expand to the point of ulceration from occlusion by opposing teeth, but will not otherwise ulcerate. Because the tumor initially expands in bone, it remains encapsulated and therefore well demarcated radiographically. However, when it reaches a certain large size (in the range of 2 to 3 cm in diameter), it loses its encapsulation and infiltrates beyond its margins for a few millimeters. It will also induce a reactivity with the adjacent bone, making it difficult to determine the tumor edge both radiographically and visually at the time of surgery. Most of these large, mature, and very mineralized ossifying fibromas in the past have been termed gigantiform cementomas.

The reader should not consider a peripheral ossifying fibroma as the soft tissue counterpart of this type of ossifying fibroma. Although the term peripheral ossifying fibroma implies a neoplasm, it actually represents a reactive hyperplasia of periodontal membrane fibers that also may induce some bone formation.

Differential Diagnosis

The expansile, mixed radiolucent-radiopaque quality of the ossifying fibroma often makes it resemble fibrous dysplasia. In addition, other benign tumors of bone, such as the osteoblastoma, and some odontogenic cysts and tumors that produce calcified materials, such as the calcifying epithelial odontogenic tumor and the calcifying odontogenic cyst, may radiographically resemble an ossifying fibroma. If the ossifying fibroma occurs around tooth roots, it may also resemble a cementoblastoma or florid cemento-osseous dysplasia. The latter two may be distinguished from an ossifying fibroma by their radiographic appearance. A cementoblastoma will emerge from and obscure the apical half of the involved tooth roots. Florid cemento-osseous dysplasia will exhibit not one but several sclerotic densities in the alveolar bone of one or both jaws.

Diagnostic Work-up

Because benign tumors of bone such as ossifying fibromas cannot be accurately distinguished from several fibro-osseous lesions via histopathology, accurate clinical, historical, and radiographic data are important. A CT scan is a valuable diagnostic tool. Ossifying fibromas are spherical to egg-shaped, expand cortices equally, and are heterogeneous because of an inconsistent distribution of their osseous and fibrous components. Their calcified material will be of the density of bone, not that of dentin or enamel, and there will be no air spaces or fluid spaces within them, as are found in cysts. Therefore, an ossifying fibroma can usually be diagnosed radiographically. In particular, ossifying fibromas must be distinguished from fibrous dysplasia. Because an ossifying fibroma is a benign tumor in bone, whereas fibrous dysplasia is a maturation defect of bone, they will present with distinctly different radiographic and CT scan images (Fig. 8.80). As noted, ossifying fibromas will be spherical, will have expanded and thinned cortical outlines, will displace adjacent structures, and will be well-delineated from surrounding tissues. Fibrous dysplasia, on the other hand, will be fusiform, will expand bone but will remodel the cortex to make it indistinct, will not be well demarcated, and will form around adjacent structures rather than displacing them. This distinction can best be seen when the ossifying fibroma develops within an existing fibrous dysplasia. This is an uncommon occurrence that the oral and maxillofacial specialist should be careful to recognize. In such cases, a spherical mass will develop slowly and protrude from a diffuse fibrous dysplasia involvement. These ossifying fibromas should be excised with the same 5 mm margins. However, the margins will be in fibrous dysplastic bone. If

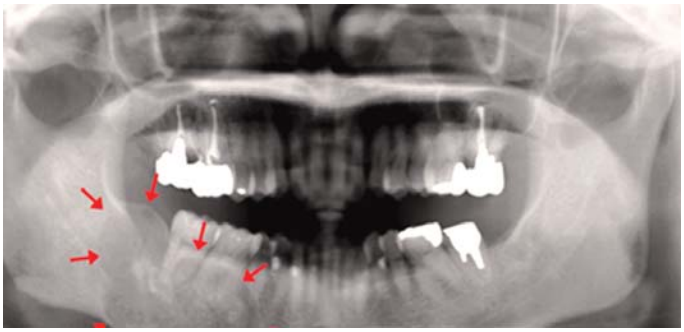
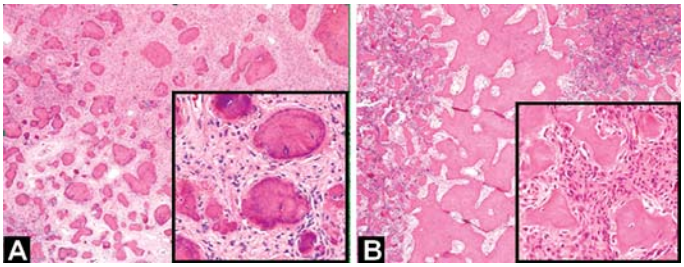


Fig. 8.80: Radiographic view of ossifying fibroma



Figs 8.81A and B: Histopathology of ossifying fibroma

osteosarcoma or Paget's disease is a possibility, an incisional biopsy and/or an alkaline phosphatase determination is necessary.

Histopathology (Figs 8.81A and B)

Ossifying fibromas usually lack a capsule within bone but have minimal local bone infiltration. This finding distinguishes ossifying fibromas from fibrous dysplasia. The tumor itself consists of a proliferative fibrous tissue that is sometimes well vascularized. The cellularity is variable but can be considerable. Trabeculae of woven or lamellar bone are usually present, and osteoblastic and osteoclastic activity is variable. Rounded, cementicle-like masses may be present, either alone or together with the trabeculae. Because of the variation in the configuration of these calcific deposits, such tumors have been referred to as both ossifying and cementifying fibromas. However, because these "cementicle like" deposits actually represent dysmorphic osteoid, the distinction appears invalid. Thus, these tumors should be referred to as ossifying fibromas.

Treatment and Prognosis

Early tumors that are small, well demarcated, and clinically encapsulated are treated by enucleation and curettage. However, because many patients allow this tumor to reach enormous size, resection is usually required. The decision of whether to enucleate or resect is often difficult; however, resection is generally recommended under the following

conditions: involvement of (or within 1 cm of) the inferior border, extension into the maxillarysinus or nasal cavities, and/or loss of encapsulation radiographically or clinically. Often, the outcome of an enucleation procedure is the same as that of a resection. Because this tumor does not infiltrate more than 1 or 2 mm beyond its borders, when it does lose its encapsulation, resection margins need be no larger than 5 mm.

If enucleation and curettage is used, the bony cavity is best left to regenerate normal bone; there is no need to pack the cavity. Packing such cavities with iodoform gauze or other materials only delays healing and will retard and reduce normal bone regeneration. Packing the bony cavity with various hydroxyapatite preparations or bone-inductive agents has not proven to induce more or faster bone regeneration than the organized fibrin blood clot and growth factors arising from platelets within the clot. If a resection is used, stabilization with a reconstruction plate or immediate bony reconstruction may be accomplished. However, immediate bony reconstruction may be complicated by a higher incidence of infection caused by oral contamination and the dead space created by the expansion of the tumor. Resections in the maxilla do not require excision of the overlying mucosa unless it is ulcerated from occlusal injury. Resections in the maxilla may be immediately reconstructed with bone if the tumor is small but are best deferred for second-stage surgery because of the thinning of the overlying mucosa, which often promotes dehiscence over the graft.

Follow-up

By either method of therapy, the recurrence rate is extremely low. Nevertheless, the clinician should follow these patients with yearly examinations and panoramic radiographs for more than 10 years; because of the tumor's slow growth rate, there is an extended period of time during which a recurrence may develop.

OSTEOSARCOMA

Clinical Presentation and Pathogenesis

Osteosarcomas represent malignant neoplasms arising from mesenchymal stem cells and/or their early progeny. Their partial differentiation leading to the production of tumor bone from a malignant cellular stroma is what defines them as osteosarcomas rather than any other malignant mesenchymal tumor that can arise from a mesenchymal stem cell. Recent genetic findings have indicated that osteosarcoma development is related to loss of the P53 tumor suppressor gene, loss of the retinoblastoma tumor suppressor gene, and development of independence from regulation by platelet-derived growth factor (PDGF). No doubt other tumor suppressor gene losses and oncogene expressions may be involved. However, these three are known to be part of the stem cell or its early progeny's escape from its normal differentiation pathway and loss of controlled proliferation, leading to a sarcoma.

Osteosarcomas occur in the jaws at an average age of 37 years, whereas osteosarcomas occur in long bones at an average age of 25 years (Fig. 8.82). However, numerous jaw osteosarcomas occur in the teen years and early 20s as well. In fact, the experience at the University of Miami Division of Oral and Maxillofacial Surgery has been that 4% occur in individuals younger than 10 years and 40% in those between the ages of 10 and 25 years. Nevertheless, it is this later-in-life average occurrence that is often used to explain the better statistical prognosis of osteosarcomas in the jaws.

Osteosarcomas may present with an expansion of bone, an incidental radiographic finding of a radiopacity, a widened periodontal ligament space (Garrington's sign), a mobile tooth, a "numb lip" or other paresthesia, and/or pain. Because some of these signs and symptoms can be produced by a number of different developmental, infectious, benign neoplastic diseases, or malignancies, an osteosarcoma often goes undiagnosed for a significant period of time. No doubt its presentation, similar to that of osteomyelitis with proliferative periostitis, suppurative osteomyelitis, ossifying fibroma, osteoblastoma, and even fibrous dysplasia, has too often caused an osteosarcoma to be delayed in its diagnosis or approached with less concern than its biology would warrant.

Osteosarcomas occur evenly among males and females. Mandibular osteosarcomas are more frequent than those in the maxilla (60 vs 40%). All but a rare few arise from

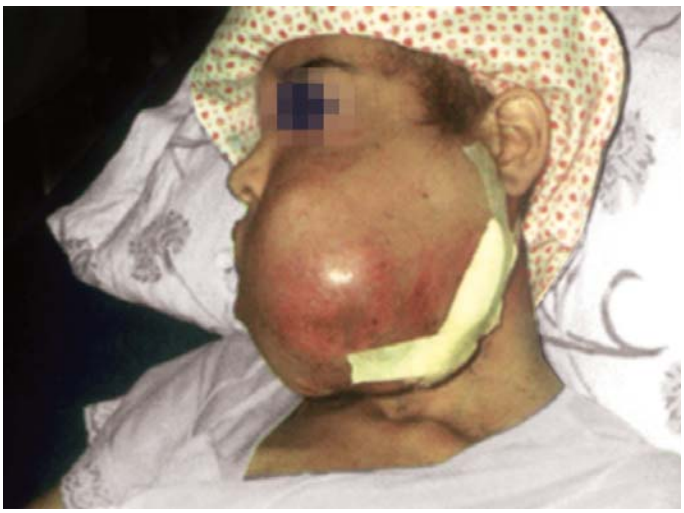
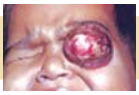


Fig. 8.82: Osteosarcoma



within the bone. Parosteal (also called juxtacortical) osteosarcomas arise from periosteum and occur outside the bone cortex. However, this type accounts for only 4% of those that occur in long bones and less than 1% of those that occur in the jaws.

Radiographic Findings

Osteosarcomas may indeed produce the often described "sun-ray" appearance. However, because of calcified cartilage or distension of reactive periosteum, other malignancies will also produce the sun-ray appearance. Even some benign tumors or infections causing reactive periosteal distension can produce this appearance. A widening of the periodontal ligament space, also called Garrington sign, is seen in several mesenchymal malignancies as an early finding but is most commonly seen in osteosarcoma.

Most radiographs and computed tomographic (CT) scans show a mottled radiopaque or mixed radiolucent-radiopaque appearance in the medullary space. Extracortical bone formation is common and may or may not produce the sun-ray appearance. However, cortical bone destruction is characteristic and should be evident.

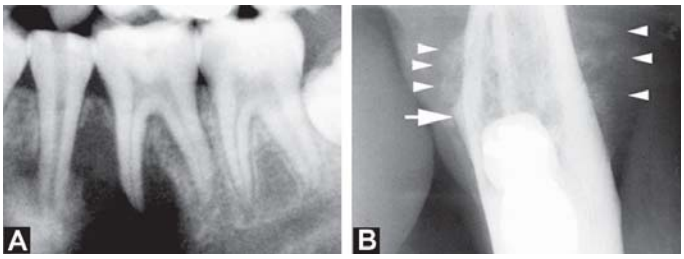
Maxillary osteosarcomas produce a sun-ray appearance and extracortical bone formation less frequently. Because they also grow into the air space of the maxillary sinus as a bulbous radiopaque mass, they may suggest a benign tumor of bone or a fibro-osseous disease rather than an infiltrating malignant bone tumor.

Radiograph shows widening of periodontal ligament space and absence of lamina dura of the distal root of left 1st molar due to osteosarcoma

A sign of radial spicules (arrowheads) and Codman's triangle (arrow) seen in Osteosarcoma of mandible

Differential Diagnosis (Figs 8.83A and B)

The radiographic and clinical picture of an osteosarcoma can be similar to that of infections such as osteomyelitis with proliferative periostitis, chronic sclerosing osteomyelitis, and suppurative osteomyelitis; to benign bone tumors or benign tumors within bone such as osteoblastomas, ossifying fibromas, and cavernous hemangiomas within bone; to odontogenic tumors such as calcifying epithelial odontogenic tumors and ameloblastic fibro-odontomas; and to fibro-osseous diseases or systemic diseases of bone such as fibrous dysplasia and Paget disease.



Figs 8.83A and B: Radiograph shows widening of periodontal ligament space and absence of lamina dura of the distal root of left 1st molar due to osteosarcoma (B) A sign of radial spicules (arrowheads) and Codman's triangle (arrow) seen in osteosarcoma of mandible

An important clinical differential feature is neurosensory loss. Other than a rare osteomyelitis or neural loss from a previous biopsy or surgery, only malignancies can produce objective paresthesias. In addition, radiographs or CT scans at right angles to the cortex should show extracortical bone and a destroyed cortex. Fibrous dysplasia and ossifying fibroma will not have extracortical bone. The extracortical bone seen in osteomyelitis with proliferative periostitis will be associated with an intact cortex. Even when other osteomyelitides produce extracortical bone, it is parallel to the cortex rather than at right angles as is seen in osteosarcoma.

Diagnostic Work-up

A presentation suggestive of osteosarcoma requires a biopsy as soon as possible. A tissue biopsy is the only means of making a definitive diagnosis. The biopsy should be taken from the lesion's center to avoid missing the diagnostic portion of the tumor or including benign reactive periosteal bone in the specimen, which could lead to a misdiagnosis. The remainder of the work up requires at least a chest radiograph and perhaps a chest CT scan. Because early and small lung metastatic deposits are a concern, either will establish absence of disease or early metastasis. In addition, a CT scan of the primary site and adjacent structures is suggested for surgical planning.

Histopathology

The histologic appearance of osteosarcomas is highly variable. What all osteosarcomas have in common is the direct formation of osteoid from a sarcomatous stroma. The quantity of osteoid and bone that is formed varies considerably, ranging from a sclerotic osseous tumor to one in which multiple sections may be necessary to identify some semblance of osteoid. The stromal cells may be osteoblastic, chondroblastic, and/or fibroblastic. However, distinguishing osteoblastic, chondroblastic, and fibroblastic osteosarcomas based on the most prominent pattern does not seem to have any prognostic significance. In general, osteoblastic tumors are most common, but in the jaws the chondroblastic pattern prevails. A myxoid stroma is also frequently seen, and an atypical myxoid proliferation

should alert one to the possibility of osteosarcoma. The majority of tumors are not homogeneous, reflecting the pluripotentiality of the proliferating mesenchymal cell.

Some osteosarcomas are very heavily ossified, and in these cases there may be entrapment of tumor cells within the sclerotic osteoid, such that the cells appear to represent osteocytes. This process is known as normalization because the osteocytic cells are small and no longer retain their malignant morphologic features (Fig. 8.84).

Mitoses may be present, but they are not usually numerous. Multinucleated giant cells may also be present, sometimes in large numbers, although they are unusual in the jaws. Stromal cells may be predominantly rounded, spindled, angulated, or pleomorphic with marked atypia.

Other histologic variants include a telangiectatic type in which there are numerous widely dilated vascular channels and prominent multinucleated giant cells (Fig. 8.85). This type is uncommon in the jaws. The small cell osteosarcoma may resemble Ewing's sarcoma histologically, but unlike Ewing's sarcoma, it forms osteoid. Particularly in tumors with prominent chondroblastic or fibroblastic features, or those in which identification of osteoid is difficult, the recognition of bone-specific alkaline phosphatase in fresh tissue may be helpful diagnostically.

It is important to emphasize that biopsy specimens from the superficial or peripheral aspects of the tumor—that is, from the advancing edge—are least likely to be representative of the tumor and frequently fail to demonstrate osteoid formation. Periosteal osteosarcomas are essentially chondroblastic osteosarcomas that expand into the soft tissue from an intact cortex.

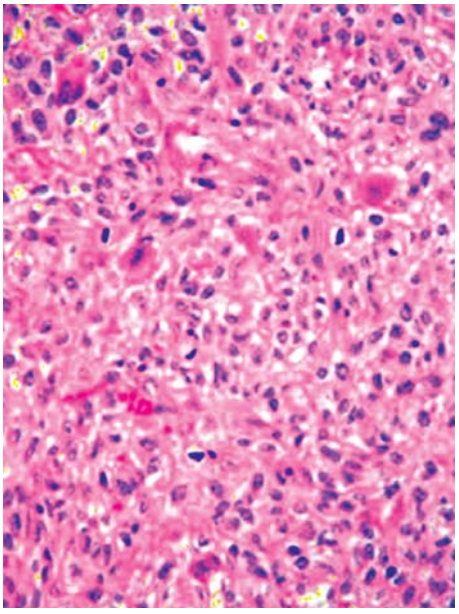


Fig. 8.84: Histopathology of osteosarcoma

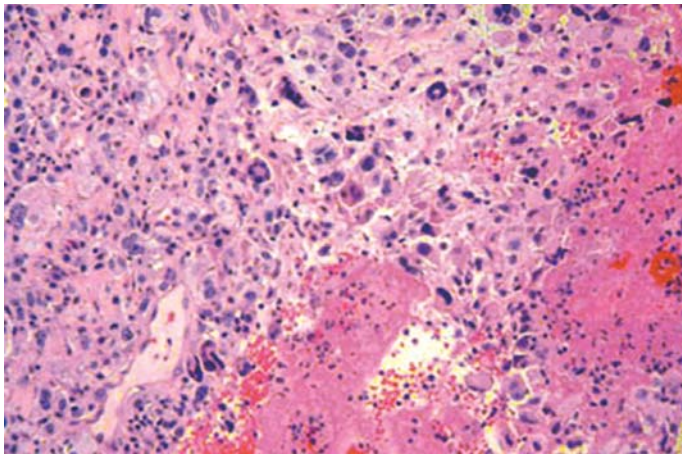


Fig. 8.85: Histopathology of telangiectatic osteosarcoma

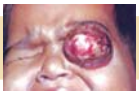
PAROSTEAL OSTEOSARCOMA

Parosteal osteosarcomas develop on the surface of the bone and are well differentiated with a bland appearance. There is a hypocellular, spindle cell stroma with little atypia and irregular trabeculae of woven bone. These tumors may be mistaken for a benign condition. Some tumors may be more histologically aggressive with more atypical stromal cells, and recurrent tumors can have increasingly atypical cytologic features.

Treatment and Biologic Behavior

After squamous cell carcinoma, osteosarcoma is the most common oral malignancy encountered by the dental professional. Unlike squamous cell carcinoma, osteosarcoma treatment does not involve radiotherapy except in late palliative situations, nor does it require cancer neck dissections. Instead, osteosarcomas of the jaws are ideally treated with initial chemotherapy of about five inductions, followed by surgery, which is followed by two or three additional induction doses of chemotherapy.

Treatment involves selected chemotherapy protocols to sterilize micrometastatic deposits that may already be in the lung, to test the tumor's responsiveness to the chemotherapeutic agents by assessing tumor shrinkage, and to decrease tumor bulk. Surgery involves resection of the entire tumor with wide margins. Bony margins should be at least 3 cm from the clinical-radiographic edge or to the joint or the nearest suture if in the midface. A neck dissection is not required because, as is typical of most sarcomas, osteosarcomas do not metastasize via lymphatics except in rare instances. Instead, osteosarcomas readily metastasize via tumor emboli in the bloodstream and are most commonly filtered out in the lungs. The soft tissue margins around an osteosarcoma resection should be 2 cm or more and assessed with frozen sections. Therapeutic



failure most often relates to local recurrence in the surgical area. The postoperative chemotherapy is intended to sterilize any tumor foci not excised during the surgical resection. The same chemotherapy agents used in the preoperative phase will be used in the postoperative phase if the tumor was responsive to them.

The chemotherapy protocols used for osteosarcoma will vary with each oncologist. However, doxorubicin (Adriamycin, Pharmacia and Upjohn) is usually used within every protocol, and vincristine, cyclophosphamide (Cytoxan, Mead Johnson), and prednisone are commonly used as well.

In most cases, the initial five chemotherapy inductions are physiologically and psychologically stressful. Marrow suppression will produce an anemia, thrombocytopenia, and leukopenia. A 1-month period between such chemotherapy and surgery will allow marrow recovery as well as a psychologic recovery. Vitamin C, 250 mg three times daily, and iron in the form of ferrous sulfate, 225 mg three times daily, will reduce the anemia. Surgery can be performed if the hemoglobin nears 10 g/dL, the white blood cell (WBC) count is 3,000/uL, and the platelet count has increased to 100 ×103/uL. Family support, a frank discussion of the surgeryand its goals, and, at times, counseling will particularly help young individuals to cope with this diagnosis and its treatments. If the osteosarcoma is in the mandible, the resected area is best reconstructed with a rigid titanium plate. Bone grafting with cancellous marrow or using a free vascular bone flap is not recommended because of the necessity for postoperative chemotherapy and the general inadequacy of free microvascular fibula ilium grafts to functionally reconstruct the mandible. Because osteosarcoma resections require excision of 2 to 3 cm of surrounding soft tissue that often includes overlying skin or approaches the skin surface, myocutaneous soft tissue flaps or other soft tissue flaps may be needed. Once the plate and flap are healed (about 6 weeks), the postoperative chemotherapy can begin. Reconstruction of the bony defect leading to dental rehabilitation can begin after the individual recovers from the postoperative chemotherapy phase.

If the osteosarcoma is in the maxilla, the resection will take the form of a hemimaxillectomy or a variation of it. Because an oral-nasal-antral communication is certain, the surgeon should have an obturator prosthesis ready for placement at the time of surgery. This obturator prosthesis will reduce hypernasal speech and nasal regurgitation of fluids and foods in the early postoperative phase. It will later be replaced by a definitive denture-obturator prosthesis. The defect takes about 6 to 9 months to sufficiently mature and become dimensionally stable.

Prognosis

Osteosarcomas of the jaws are associated with a better prognosis than are osteosarcomas of long bones. There is about a 50% 5-year survival rate with jaw osteosarcomas compared to a 30% 5-year survival rate with long bone osteosarcomas. However, 50% survival is still suboptimal. Therapeutic failure results from local recurrences followed by lung metastasis, followed by brain metastasis, and then metastasis to other bones. All of the distant metastases occur via tumor emboli in veins that either flow "downstream" to the right side of the heart, where they are pumped into and become lodged in the capillaries of the lungs, or via retrograde flow to the brain or other bones.

Prognosis worsens with a delay in diagnosis and treatment, with increased tumor size, and with symptoms of pain and paresthesia. Histologically, no grading system correlates well to prognosis. However, the presence of tumor emboli in the venules within the specimen is an ominous sign. The presence of myxomatous cells, tumor giant cells, and necrosis are also associated with a poorer prognosis. The abundant production of tumor bone should not be looked upon as a favorable sign or as a sign that it is "well differentiated." Osteosarcomas that produce abundant calcified bone are often associated with the poorest prognosis. The presence of numerous cartilaginous cells, however, has been found to be a somewhat favorable sign.

Follow-up

Since the concern is recurrence at the primary tumor site and/or metastasis to the lungs, a clinical oral and head and neck examination and a chest radiograph are recommended every 4 months for the first 2 years and then every 6 months for the next 3 years. Thereafter, such examinations should be carried out on an annual basis. Any suspicious changes seen on a plain chest radiograph should be further evaluated with a CT scan of the chest.

Bloodborne metastasis to the lungs occurs via tumor emboli (often 25 to 100 um in diameter) eroding into small veins that may drain into the pterygoid plexus, inferior alveolar vein, or facial vein, which in turn drains into the internal jugular or external jugular vein. The tumor emboli then flow down current into the innominate (brachiocephalic) veins to the superior vena cava and right atrium. With each systole, the tumor emboli are pumped through the tricuspid valve into the right ventricle and then into the pulmonary artery system. As the tumor emboli are pumped further into the pulmonary vascular system, they wedge in small vessels to clone into metastatic deposits.

EWING'S SARCOMA

Clinical Presentation and Pathogenesis

Ewing's sarcoma is a genetically and histologically distinctive small round cell sarcoma of bone. It is a notoriously aggressive and destructive malignancy of bone arising from marrow mesenchymal stem cells. It is rare in the jaws but accounts for about 8% of malignancies in long bones. It was first described by James Ewing in 1920 as a "diffuse endothelioma of bone." Since then it has been documented as a distinct malignancy of primitive mesenchymal stem cells that have undergone a unique reciprocal translocation of chromosomes 11 and 22. The resultant highly malignant tumor causes extensive destruction of bone and tumor necrosis and has a strong propensity for metastasis.

In both the jaws and long bones, it is mostly seen in patients younger than 20 years (80%). The peak age of occurrence is in the teenage years (50%). It practically never occurs in black individuals. Young men are affected slightly more often than are young women (1.4:1).

In the mandible's posterior body, the angle and ramus regions are most commonly affected. It is rare in the mandible in general and even more rare in the maxilla. Its presentation will frequently involve bony expansion, mobile teeth, and fever presumably due to necrosis within the tumor and its destruction of native bone. It will, therefore, present a picture similar to that of an osteomyelitis. Its growth rate is usually rapid.

Radiographic Findings (Figs 8.86A to C)

Panoramic radiographs and a CT scan will show an ill-defined, irregular resorption of bone with focal areas of residual bone resembling sequestra. Pathologic fractures are common, attesting to the degree of bone destruction. Ewing's sarcoma has often been reported to produce a multilayered periosteal reaction that has been described as an "onion skin" appearance, similar to that commonly observed in an osteomyelitis with proliferative periostitis. However, such a radiographic appearance is almost never seen when Ewing sarcoma arises in the jaws, although it is seen occasionally when Ewing sarcoma arises within the diaphysis of long bones. Ewing's sarcoma in the jaws will produce a destructive radiolucency with resorbed tooth roots and displaced teeth. On rare occasions, a Ewing's sarcoma may produce a periosteal new bone formation perpendicular to the cortex and thereby create the "sun-ray" appearance more frequently seen in osteosarcomas.

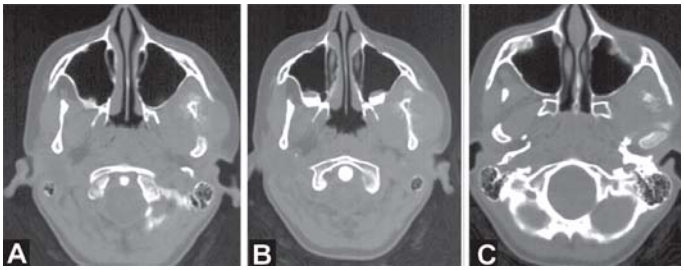
Differential Diagnosis

The presence of pain, fever, and at times leukocytosis will suggest a suppurative osteomyelitis. This will be reinforced if the radiographs show a destructive bone pattern with bone foci resembling a sequestrum. If it is an early Ewing's sarcoma with minimal osteolysis and with a layered periosteal "onion skin" radiographic appearance, it may resemble osteomyelitis with proliferative periostitis.

The usual more destructive and expansile tumors will point to an aggressive malignancy from the outset. Other aggressive malignancies that occur in this young age group include rhabdomyosarcoma, osteosarcoma, fibrosarcoma, and neuroblastoma. In the uncommon situation of an older individual developing Ewing's sarcoma, one would also need to consider a non-Hodgkin lymphoma and a carcinoma metastatic to the mandible. In early presentations and in younger individuals, a seeding of leukemia cells, particularly acute lymphocytic leukemia and acute myelogenous leukemia, is a possibility.

Histopathology (Fig. 8.87)

Ewing's sarcomas are composed of densely packed, rather uniform cells with little intercellular stroma. The nuclei are rounded to oval with defined nuclear borders and a finely granular chromatin pattern. The cytoplasm is indistinct and



Figs 8.86A to C: CT scan images through the face demonstrate the soft tissue mass based on the neck of the mandible and surrounding it laterally, medially and anteriorly. There is "hair on end" periosteal reaction with cortical destruction of the bone. There is bony involvement of the left zygomatic arch

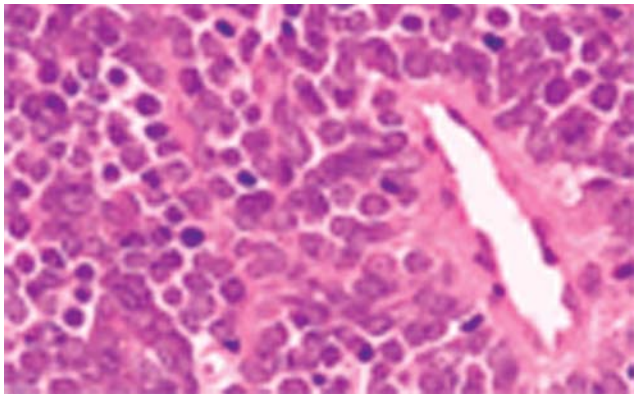
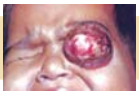


Fig. 8.87: Histopathology of Ewing's sarcoma



may be vacuolated. The cells are two to three times the size of a lymphocyte. Mitoses are infrequent. The tumors tend to grow rapidly and may undergo considerable necrosis, sometimes resulting in a perivascular pattern of viable tumor cells. The friable consistency produced by this tumor necrosis may result in a biopsy specimen with an inadequate number and pattern of viable cells from which to make a diagnosis. While usually arranged in broad sheets, the cells may have a filigree pattern in which infiltrating strands of tumor cells are separated by thin fibrovascular septae. There is some evidence that the filigree pattern may indicate a worse prognosis.

The histologic differential diagnosis includes other small round cell tumors, including neuroblastoma, lymphoma, small cell osteosarcoma, and embryonal rhabdomyosarcoma. Histochemical studies are of limited help. Ewing's sarcoma will usually have intracytoplasmic glycogen granules demonstrated by periodic acid-Schiff(PAS) and diastase staining. However, on occasion, neuroblastoma and embryonal rhabdomyosarcomas may also yield positive staining. In recent years, Ewing's sarcoma has been recognized as part of the spectrum of primitive neuroectodermal tumors (PNETs). The monoclonal antibody HBA-71 is helpful diagnostically, since it reacts with the Ewing~specific antigen MIC2 and has a high sensitivity (approximately 98%). Cytogenetic testing reveals a translocation in 95% of cases that is also shared by PNET, t(11;22) (q24;q12), that is, translocation of chromosomes 11 and 22 at their respective q24 and q12 loci. A fresh tissue specimen is necessary for this type of cytogenetic testing.

Diagnostic Work-up

As with all potential malignancies, a biopsy should not be delayed and it should sample tumor tissue central and deep within the bone. As with biopsies for suspected osteosarcoma, a biopsy that samples superficial aspects of the tumor may show only benign reactive bone created by periosteal distension. A CT scan is useful to determine the local extent of the tumor in bone and soft tissue. A chest radiograph or CT scan is required to assess for metastasis to the lung, which is the most common metastatic site.

Obtaining laboratory values such as a complete blood count (CBC), WBC count, and platelet count is recommended, but the values are not diagnostic. Because the tumor necrosis produces a leukocytosis and the tumor bulk itself may produce an anemia, a baseline set of blood studies is useful. The leukocytosis usually resolves in response to treatment.

It is well for the clinician to recall that tumor necrosis will interfere with efforts to obtain a representative biopsy specimen. Therefore, the tissue to be sampled should have the firmest consistency possible. In addition, if Ewing sarcoma is part of the differential diagnosis, a portion of the specimen should be withheld from formalin fixation and submitted fresh for cytogenetic testing.

Treatment and Biologic Behavior

Today Ewing's sarcoma is treated with multimodal therapy in a manner similar to that for rhabdomyosarcoma. This approach uses all three traditional modes of cancer therapy. Although there are variations in the order of each modality, doses of radiotherapy, and choice of drugs, a commonly used protocol begins with resection of all clinically detectable disease at the primary site, followed by multidrug chemotherapy (usually vincristine, doxorubicin [Adriamycin, Pharmacia and Upjohn], and cyclophosphamide [Cytoxan, Mead Johnson]) and 5,000 to 6,000 cGy of radiotherapy. The resection of this jaw tumor creates a continuity defect using bony margins of 3 cm and often includes a margin of surrounding tissue between 1 and 2 cm. If sufficient soft tissue remains, plate reconstruction is recommended. However, definitive bony reconstruction should be deferred until completion of radiotherapy and chemotherapy. In cases where there is insufficient bone to place a plate or the soft tissue loss would risk plate exposure, it may be better to let the jaw collapse into the defect rather than risk a wound healing complication that would delay the chemotherapy/radiotherapy for more than 6 weeks.

Prognosis

Before the advent of multimodal therapy, 5-year survival rates were approximately 15%. With multimodal therapy, patients who initially present without metastasis have a 70% 5-year survival rate. Even those with identifiable distant metastasis at presentation have a 30% 5-year survival rate. This is significant because 15 to 30% of Ewing sarcoma cases initially present with distant metastasis.

In contrast to the general rule of malignancy prognosis related to age of onset, younger patients with Ewing's sarcoma have a better treatment response and 5-year survival rate than do older individuals. Generally, negative prognostic indications include larger tumor size, pain, leukocytosis, fever, and a high mitotic index. In those cases with lung metastasis, wedge resection of the metastatic deposit extends life and reduces symptoms.

Follow-up

Because Ewing sarcomas will usually recur within the first 2 years, initial follow-up is conducted every 3 months. The follow up will consist of an oral and head and neck examination as well as local plain radiographs and a

chest radiograph. After the first 2 years the frequency of follow-up examinations can be reduced to every 4 to 6 months.

CHONDROSARCOMA

Clinical Presentation and Pathogenesis

Chondrosarcomas arise from mesenchymal stem cells and undergo a partial differentiation to form chondroblastic differentiation and even definable cartilage. A true chondrosarcoma cannot demonstrate bone formation from a malignant mesenchymal stroma. Such entities are actually osteosarcomas, which is especially important since many osteosarcomas of the jaws and facial bones have significant chondroblastic portions within them. However, if tumor bone arises from cartilage rather than from the malignant stroma, it remains a true chondrosarcoma. Chondrosarcomas of the jaws and facial skeleton are much rarer than in other bones presumably because of the scarcity of cartilage in development and in the joint areas. Chondrosarcomas are second to osteosarcomas in their frequency as primary sarcomas of bone. Their overall incidence represents about 25% of all primary sarcomas of bone. However, of these, the face and jaw area represents only 2%.

Most chondrosarcomas of the facial skeleton and jaws occur in individuals older than 30 years with a slightly increasing frequency with advancing age. There is no race or sex predilection.

The presentation is that of a slow-growing mass. Pain may or may not be a presenting symptom. The mass will emanate from bone as an irregular lytic lesion that will palpate as a firm-to-hard lobulated soft tissue mass. Teeth involved with the lesion will be displaced and mobile. The mass is only rarely ulcerated. Most chondrosarcomas will be seen either in the anterior part of the maxilla or in the posterior body region of the mandible. These areas of occurrence have been postulated to arise from remnants of embryonic cartilage precursors from nasal septal development in the anterior part of the maxilla and from Meckel cartilage precursors in the posterior aspect of the mandible.

Approximately 90% of chondrosarcomas will be slow-growing, low grade, nonmetastasizing tumors. The remaining 10% demonstrate aggressive growth, significant local tissue invasion, and metastasis.

Because of their slow growth and their tendency to undergo neural invasion only later in their course, chondrosarcomas are often mistaken for "benign chondromas" or "cartilaginous rests". Several have presented with previous biopsies identifying "cartilage" where the patient was informed that it merely represented "ectopic cartilage". This false impression of a cartilage hamartoma or a benign cartilage forming tumor is often supported by histopathologic features that will appear to be benign because of mature cartilage with little stroma and mostly single nuclei in each lacunae.

Radiographic Presentation

Chondrosarcomas will appear as irregular intramedullary radiolucencies causing cortical expansion and destruction. Punctate radiopacities may be present because of dystrophic calcifications or focal ossifications of cartilage. In the tooth bearing areas, a widening of the periodontal ligament space (Garrington's sign) may be seen as an early sign of chondrosarcoma, just as it is an early sign of osteosarcoma. Reactive extracortical bone may occasionally be seen as well (Fig. 8.88).

Differential Diagnosis

Because of their slow growth and especially their intact overlying mucosa, most cases will initially resemble a benign odontogenic tumor or a benign tumor of bone. If the lesion is entirely radiolucent, the clinician may consider an ameloblastoma or odontogenic myxoma. If some punctate radiopacities are identifiable, the lesion will resemble a calcifying epithelial odontogenic tumor, an ossifying fibroma, an immature osteoblastoma, or a cavernous hemangioma of bone. The more obviously aggressive presentations with irregular radiolucencies and

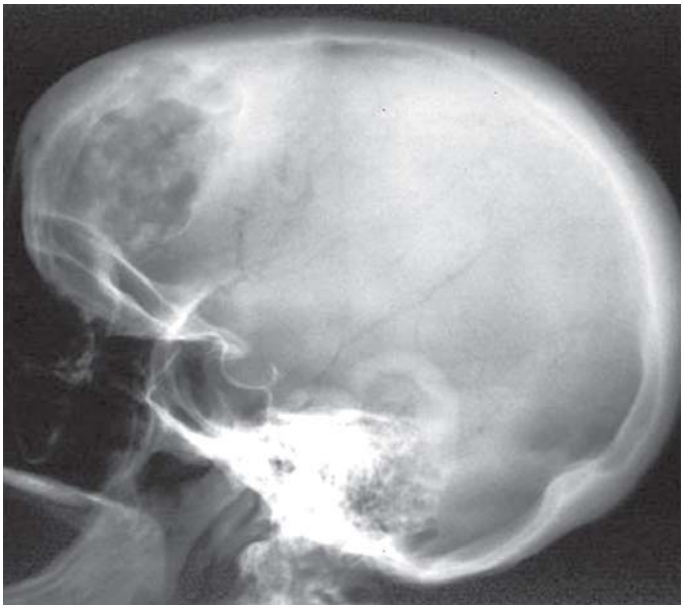
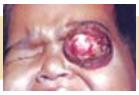


Fig. 8.88: A lateral view of the skull demonstrates a mixed lytic and sclerotic lesion within the right frontal bone with relatively well-defined sclerotic margins—Chondrosarcoma



perhaps neurosensory loss would be consistent with an intraosseous carcinoma, an osteosarcoma, and a malignant fibrous histiocytoma. A benign chondroma or cartilage rests are not considered part of a differential diagnosis with this presentation because each is very rare and perhaps nonexistent. Accepting either of these as the final diagnosis may result in the overlooking of a true malignancy.

Diagnostic Work-up

A deep incisional biopsy within the center of the mass is required as soon as possible. A tissue specimen is the only means of establishing a definitive diagnosis. The remainder of the work-up should include plain radiographs and a CT scan to determine tumor extent for surgical planning. Because cartilage itself and cartilaginous tumors are well demonstrated by magnetic resonance imaging (MRI), this modality may provide a better delineation of tumor extent than a CT scan. Although metastasis of chondrosarcomas is less frequent than with an osteosarcoma or other sarcomas, a chest radiograph is required to rule out this most likely place for a metastatic focus.

Histopathology (Fig. 8.89)

Chondrosarcomas are characterized by the formation of malignant cartilage without deposition of osteoid from a sarcomatous stroma. The cartilage cells have large, plump nuclei and are often binucleated or multinucleated. There is an increase in the number of cells, and lacunae often contain two or more cells. Pleomorphism and hyperchromatism also are present. Histologic grading is important with regard to prognosis in chondrosarcoma. Grade I tumors tend to have a lobular pattern and two or more cells within a lacuna. There is endochondral ossification, and myxoid and cystic areas may develop. Grade II tumors show an increase in cellularity with retention of lobules and ossification, while grade III tumors are markedly cellular with a proliferation of spindle cells. The lobular pattern is lost. In the jaws, grade I tumors predominate.

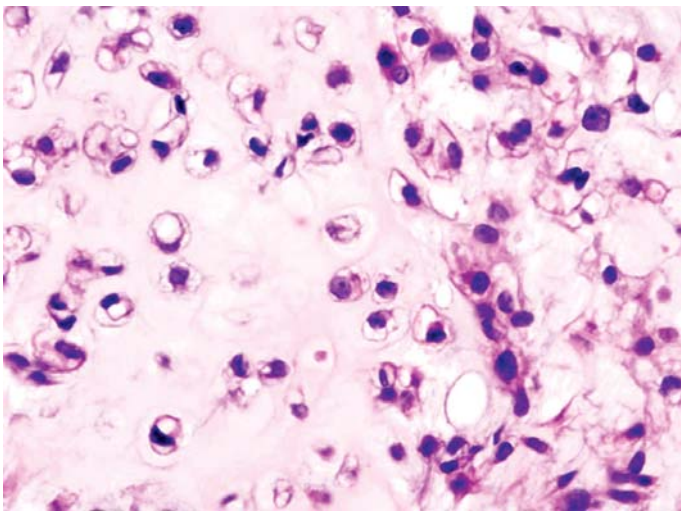


Fig. 8.89: Histopathology of chondrosarcoma

MESENCHYMAL CHONDROSARCOMA

Mesenchymal chondrosarcomas contain islands of cartilage that may be well differentiated and circumscribed. The islands are surrounded by undifferentiated cells with round to oval hyperchromatic nuclei and a variable number of mitoses. In other tumors, the foci of cartilage may be scant. There may be a vascular stroma with branching vessels surrounded by malignant mesenchymal cells. This pattern simulates hemangiopericytoma.

Mesenchymal chondrosarcomas are high-grade tumors that may metastasize to lymph nodes. Although they comprise only about 10% of chondrosarcomas, the jaws are a favored site.

Treatment and Prognosis

The common low grade chondrosarcomas (grades I and II) of the jaws and facial skeleton are best treated with a local resection using 1.5 cm margins for bone and soft tissue. Neither chemotherapy nor radiotherapy is indicated as primary treatment. The uncommon high grade chondrosarcomas (grade III) are treated with an initial aggressive resection of 3 cm in bone and 2 cm in soft tissue followed by chemotherapy. Because high grade chondrosarcomas metastasize to regional lymph nodes more than do other sarcomas, an ipsilateral neck dissection also is recommended. In some cases, a high grade chondrosarcoma can be treated with a protocol similar to that for an osteosarcoma: initial chemotherapy followed by aggressive resection surgery, which is followed by postoperative chemotherapy. However, the response of chondrosarcomas to chemotherapy is much poorer than that of most osteosarcomas.

Resultant defects in the anterior maxilla are usually obturated or reconstructed with a prosthesis. Delayed reconstruction if needed with either soft tissue, usually from a temporalis flap, or bone grafting may be accomplished to provide better support for a prosthesis or to place osseointegrated implants. Defects in the mandible usually are initially reconstructed with a rigid titanium plate and soft tissue flaps if required. A delayed bone graft can be accomplished after initial healing is complete and the diagnosis is confirmed. This usually permits a definitive

bone graft to be accomplished at about 3 to 4 months after extirpative surgery.

The prognosis for the more common low grade chondrosarcoma is excellent. The 5-year survival rates are 90% for grade I and 81% for grade II. However, the less common, high grade (grade III) chondrosarcomas are associated with a 29% 5-year survival rate.

When low grade chondrosarcomas recur, they recur late. Most first recur between 5 and 10 years after initial treatment. At that time, a second surgery (salvage surgery) can result in a cure. However, it is best to resect with even wider margins than those used in the initial surgery. Recommended margins are 3 cm in bone and 2 cm in soft tissue. Even then, an occasional low grade chondrosarcoma may become uncontrollable, eventuating in death despite repeated surgeries and chemotherapy. In some instances, recurrence may be associated with a more advanced histologic grade than the initial tumor. This seeming "dedifferentiation"is instead thought to represent a resistant tumor clone arising from an additional mutation within the original tumor. High-grade (grade III) chondrosarcomas more often fail cure by distant metastasis (66%), most often to the lungs. However, lymph node metastasis also can develop if the initial therapy did not include a neck dissection.

Follow-up

Low-grade chondrosarcomas (grades I and II) may occur any time over several decades. Therefore, follow-up is lifelong and can be limited to an oral and head and neck examination and local radiographic studies. Semi-annual chest radiographs also are recommended.

High grade chondrosarcomas (grade III) usually recur within the first 2 years. Therefore, follow-up consisting of an oral and head and neck examination, local radiographs, and a chest radiograph are recommended every4 months for the first 2 years. For the next 3 years, these examinations are conducted every 6 months, and then annually thereafter.

CHORDOMA

Clinical Presentation and Pathogenesis

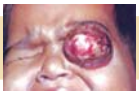
The chordoma is a low to medium grade malignant tumor arising from residual cell rests of the embryonic not ochord. Although it is rarely seen by the oral and maxillofacial specialist, it is regarded as a relatively common malignant tumor of bone. It accounts for 3 to 4% of all primary malignant bone tumors. Over 90% occur in either the saccrococcygeal bone or the sphenoccipital/base of skull bone. Therefore, the oral and maxillofacial specialist may observe one either as an extension from the base of the skull or arising from the cervical vertebrae region. Even then the presentation will be of either a primary or a recurrent painful mass located deep in the neck or within the infratemporal or retropharyngeal spaces.

In human embryonal development, the notochord acts as a template for the development of the neural tube destined to become the spinal cord and becomes surrounded by the sclerotomes destined to become the vertebrae. This occurs during the first month of embryonic development. During the second month, the notochord begins its involution into residual rests located within the nucleus pulposis of the intervertebral disks, which it forms directly, and within the vertebrae, for which it acts as a scaffold to the sclerotomes. At the cephalic and caudal ends of the notochord, greater numbers of rests come to be positioned outside the vertebral bodies, and this accounts for the high incidence of chordomas in the sacrococcygeal and base of skull regions.

Those chordomas that develop in the head and neck area usually present as a painful, deeply located mass. The patient is usually an adult older than 40 years. The peak incidence is about 65 years of age, but certainly a small number of chordomas have been reported in children and teenagers as well. Pertinent to the oral and maxillofacial specialist, chordomas that occur in these young individuals typically arise from the second cervical vertebrae and present as a deep neck mass or as a mass in the pharynx or tonsillar fossa. The older patient, who more frequently develops chordomas within the skull or at the skull base, may present with visual disturbances due to optic nerve compression.

Differential Diagnosis

Because of its rarity, the presentation of a deeply located painful neck or pharyngeal mass is not likely to suggest a chordoma to the oral and maxillofacial specialist. Instead, the more common diseases such as a fascial space infection, a tonsillar abscess, or a metastatic lymph node deposit of a carcinoma would be the more likely considerations. If the individual is within the age range when most chordomas develop, the mass will resemble a non-Hodgkin lymphoma, and at any age one might consider tuberculosis lymphadenitis (scrofula) or cat scratch disease. If a radiograph or a CT scan shows calcification in the chordoma, a benign pleomorphic adenoma or a carcinoma ex-pleomorphic adenoma from the deep lobe of the parotid would be added to the differential list.



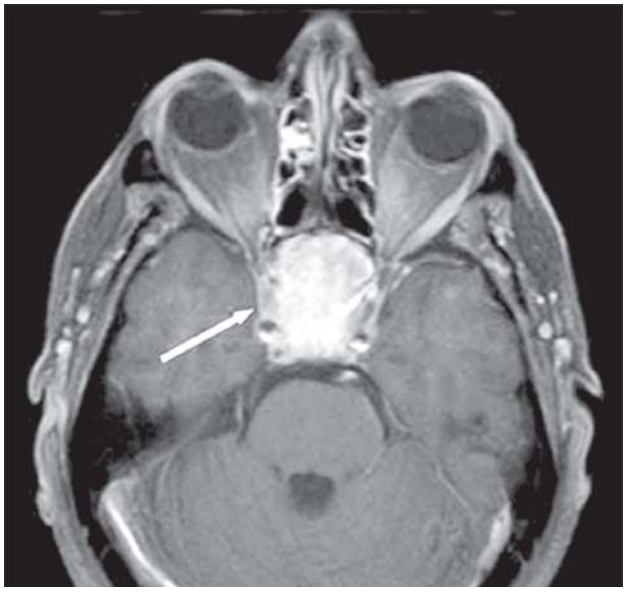


Fig. 8.90: Chordoma

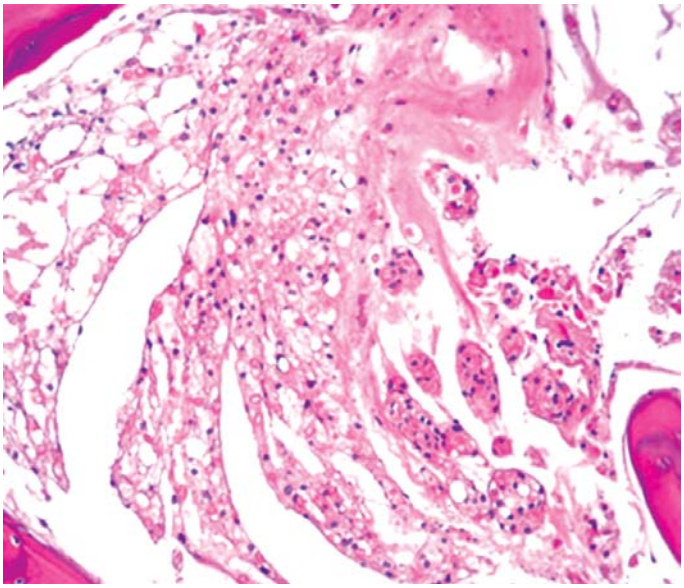


Fig. 8.91: Histopathology of chordoma

Diagnostic Work-up

An MRI scan is the single best tool to diagnose a chordoma. It will best identify the characteristic lobulated nature of a chordoma and its surface bony erosions. Usually, a T2-weighted image of two adjacent vertebrae shows a high signal enhancement. A CT scan and plain radiographs are also useful in delineating the mass, its size, and its association with adjacent structures. Either may show intralesional calcifications, which are very characteristic of chordomas (Fig. 8.90).

Histopathology (Fig. 8.91)

These tumors are lobular with fibrous septae. Though they often appear well contained, they are infiltrative, gelatinous tumors that have a mucoid stroma. The cells may be arranged in cords or sheets, or the pattern may be haphazard. The tumor cells may have eosinophilic cytoplasm, but frequently the cytoplasm becomes vacuolated to form physaliphorous cells. Atypia is rare and mitoses absent.

Myxoid chondrosarcomas may closely resemble chordomas, but chordomas bear epithelial markers and are positive for keratin and epithelial membrane antigen.

Some chordomas contain cartilaginous foci and are thus termed chondroid chordomas. These tumors have a more favorable prognosis.

Treatment

As it is in every other location, treatment of a chordoma in the neck is extremely difficult because of its deep location and unencapsulated lobular character. Surgery, including an attempt to resect the tumor completely, is the frontline therapy. However, microscopically positive margins—even grossly positive margins—are the rule, turning the surgery into an aggressive debulking procedure. In either case, postoperative radiotherapy at doses of 5,000 to 6,400 cGy is recommended.

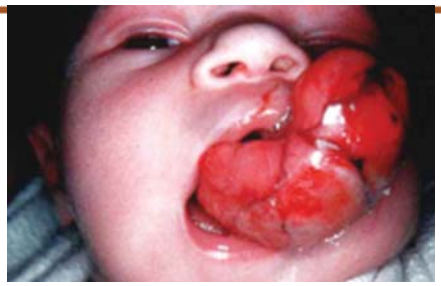
The surgical access for tumors presenting in the neck will vary depending on their location. However, the widest possible access is recommended. The incision design will resemble that of a total parotidectomy approach with a neck dissection extension.

Prognosis

Chordomas are associated with a high late-mortality rate. Tumor control is usually seen for 1 to 3 years, although some can be fulminant and recur to eventuate even more quickly in an early death. The 5-year survival rate is about 65%, but 10-year survival is rare. Local recurrence with and without regional lymph node spread is the main reason for treatment failure. Distant metastasis to other bones or as subcutaneous nodules occurs in about 10% of cases.

9

Tumors of Salivary Glands



INTRODUCTION

Development of Salivary Glands

Developing salivary glands arise from the stomodeum as ectodermal buds that proliferate as cords into the underlying mesenchyme. The ends thicken to form terminal bulbs. These undergo branching, followed by continued advancement into the mesenchyme. This process repeats itself, all the while maintaining continuity with the oral epithelium. This branching process gives rise to the lobular architecture of the gland. The terminal tubular elements differentiate into acinar cells, and between the acinar cells and basal lamina myoepithelial cells form. These are strap-shaped and stellate cells, which may appear as clear cells prior to the development of myofilaments. Intercalated and smaller striated ducts also differentiate from this area (Figs 9.1 and 9.2) . The original cords and their branches become the excretory ducts.

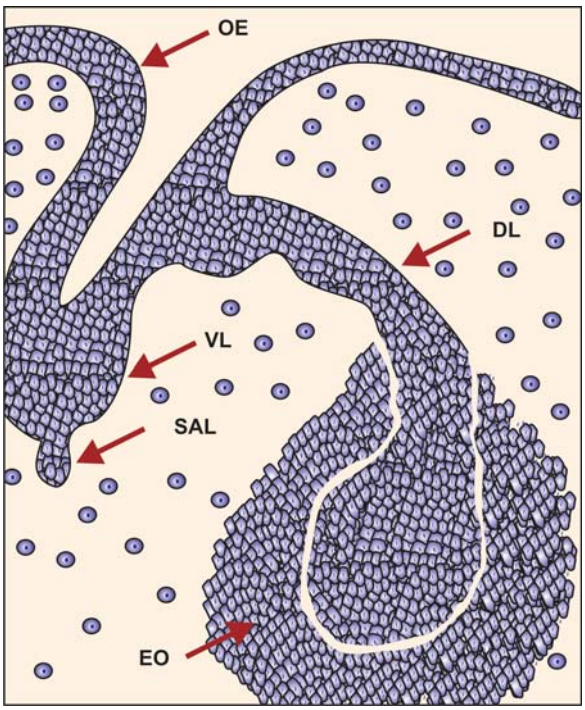


Fig. 9.1: Development of paroitid gland

Histogenesis of Salivary Gland Tumors

The histogenesis of salivary gland tumors has been controversial. Some suggest acinar cells, since these have been shown to have a regenerative capacity. Others however, propose a stem or reserve cell in the salivary duct system. The complexity of salivary gland tumors is due in part to the fact that in most instances more than one cell type is involved. These may be acinar, luminal, myoepithelial, basal, or squamous. Adding to this diversity, extracellular secretory products are a striking component of many tumors. These products include basal lamina, collagen fibers, elastic fibers, and glycosaminoglycans. It is believed that these substances are probably secreted by the neoplastic myoepithelial cells (Fig. 9.3).

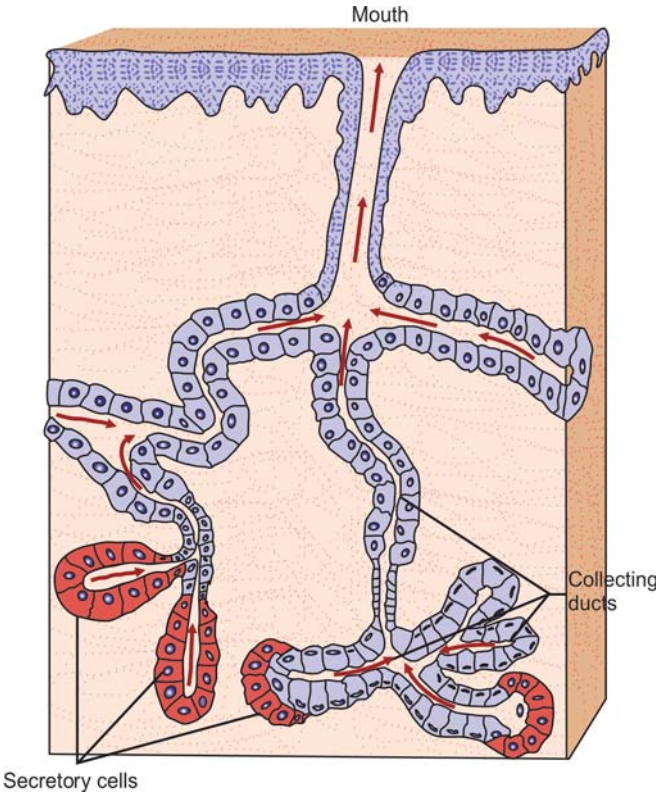


Fig. 9.2: Formation of salivary ductal structures

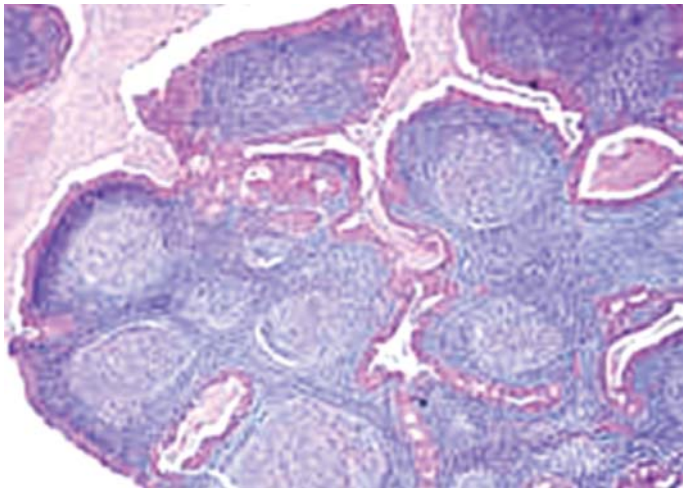


Fig. 9.3: Salivary gland tumor histogenesis

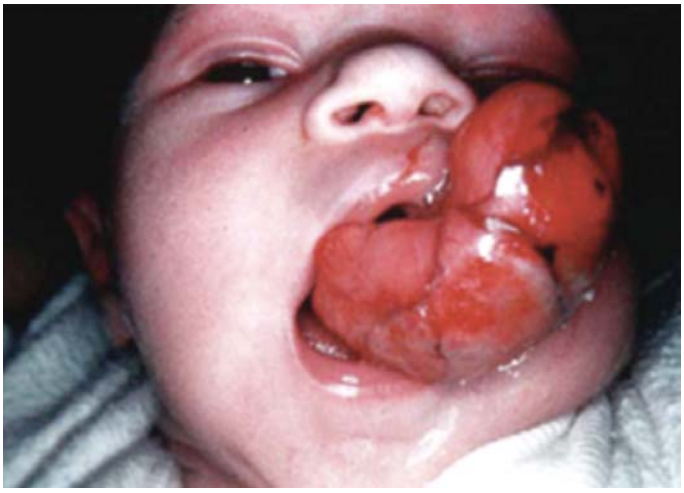


Fig. 9.4: Pleomorphic adenoma

Salivary gland tumors may involve major or minor glands. The largest number of cases are found within the parotid. While most types of tumors may be found in both sites, relative frequency can vary. Thus approximately 80% of parotid tumors are benign. In minor salivary glands, however, the benign-malignant ratio is closer to 1:1, while in the sublingual gland, an uncommon site for neoplasms, the majority are malignant.

Non epithelial neoplasms also may arise within the gland that are not actually of salivary gland or ductal origin. Most of these are found in the parotid gland. Among the more common benign tumors is the hemangioma, which is the most frequently occurring tumor in the parotid gland in children.

PLEOMORPHIC ADENOMA (MIXED TUMOR)

Also called enclavoma, branchioma, endothelioma, enchondroma

It is a benign neoplasm consisting of cells exhibiting the ability to differentiate to epithelial (ductal and nonductal) and mesenchymal (chondroid, myxoid and osseous) cells.

Clinical Presentation

The pleomorphic adenoma is the prototypical benign yet true neoplasm; that is, it will continue to grow—or regrow if not completely removed—but it is incapable of metastasis. Eighty percent of tumors that occur in the parotid gland are benign: of these, 75% are pleomorphic adenomas and 5% are Warthin's tumors (papillarycystadenoma lymphomatosum). Pleomorphic adenomas, and salivary gland tumors in general, are not commonly found in the submandibular and sublingual glands. Nevertheless, they account for about 20 to 30% of all tumors in these glands. Oral pleomorphic adenomas are somewhat common, accounting for about 45% of all oral minor salivary gland tumors. The site of predilection is the mucosa over the posterior hard palate and anterior soft palate; pleomorphic adenomas can occur in any location where minor salivary glands exist. The two most common clinical presentations are a painless firm mass in the superficial lobe of the parotid gland and a painless firm mass in the posterior palatal mucosa. The ratio of F to M is 6:4. Lesion shows intermittent growth. It is the most common salivary gland tumor.

Eighty percent of all pleomorphic adenomas in the parotid gland develop in the superficial lobe, which constitutes 80% of the parotid gland. It presents as a freely movable, firm mass. Peculiarly and rarely, these can fluctuate in size or be painful. Pleomorphic adenomas do not induce facial nerve paralysis. Any facial nerve weakness not attributable to previous surgery should be considered a malignancy until proven otherwise. When a pleomorphic adenoma arises from the deep lobe of the parotid gland, it usually goes unrecognized for a number of years until its size creates symptoms of dysphagia or gagging. These present orally as a bulge arising from the tonsillar fossa area. Pleomorphic adenoma of parotid shows irregular nodular lesion having firm consistency although areas of cystic degeneration may be palpated if they are superficial (Fig. 9.4).

When a pleomorphic adenoma presents in the mucosa of the hard palate-soft palate junction, it will be a firm, painless mass with intact overlying mucosa. If the mucosa is ulcerated and the ulceration is not attributable to trauma or a biopsy, the mass should be considered a malignancy. In the palatal mucosa, the mass will seem to be fixed to the palate. Since the pleomorphic adenoma cannot invade bone, this is not caused by bony invasion but rather by the inelasticity of the palatal mucosa, which becomes distended by the tumor mass and may eventuate in a cupped-out

resorption of bone. In other oral mucosal sites, the pleomorphic adenoma presents as a freely movable, circumscribed mass. Pleomorphic adenoma of intraoral accessory gland is never more than 1-2 cm in diameter. It causes difficulty in mastication, talking and breathing.

Differential Diagnosis

The differential diagnosis of a firm mass in the parotid gland must include a Warthin tumor (papillary cystadenoma lymphomatosum), which is particularly likely in men, and basal cell adenoma, which preferentially develops in the parotid gland. In addition, malignant salivary gland tumors that must be considered include mucoepidermoid, adenoid cystic, and acinic cell carcinomas. Non salivary gland neoplasms that are known to occur in the parotid gland, i.e. hemangiomas, lymphangiomas, lipomas, and lymphomas within parotid lymph nodes—may also present in a similar fashion. The clinician must also be aware that skin nodules such as sebaceous cysts can form a subcutaneous mass in the area that may give an impression of being located in the parotid gland.

The differential diagnosis of a firm mass in the palatal mucosa with intact overlying epithelium is primarily a subset of other salivary gland neoplasms. Another benign tumor that requires some consideration is the canalicular adenoma. In addition, several non salivary gland tumors may present with a similar appearance, such as non-Hodgkin lymphoma and neurofibroma.

Diagnostic Work-Up and Treatment

For a mass in the parotid gland, a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan is valuable to confirm its location in the parotid, specifically in the superficial lobe. This should be followed by a superficial parotidectomy, which represents both the diagnostic biopsy and the definitive treatment. In such a presentation, an incisional parotid biopsy would be contraindicated because seeding of tumor cells throughout the biopsy site is a concern.

For a mass in the palatal mucosa, a CT scan, particularly coronal views, also is recommended to determine its extent and the degree of any resorption of the palate. A deep incisional biopsy of the mass is recommended in its center to establish a firm permanent section diagnosis prior to planning definitive surgery. This is different from the parotid gland approach, in which biopsy and definitive surgery are one and the same, because an oral incisional biopsy can be accomplished without seeding tumor cells.

If a pleomorphic adenoma is confirmed, it is excised with 1 cm clinical margins at its periphery and includes the overlying surface epithelium and the periosteum of the palate. Excision or scraping of the palatal bone is not required because the periosteum is an effective anatomic barrier and pleomorphic adenomas do not elaborate osteoclast activating factor to invade bone. If the tumor extends to the area of the soft palate, the excision includes the fascia over the soft palate musculature. The muscles of the soft palate need not be excised unless frozen sections indicate tumor at this margin.

For pleomorphic adenomas in other mucosal sites, a peripheral excision with 1 cm margins is recommended. This will include overlying mucosa but should not include overlying skin if the mass is located in the lip or buccal mucosa. In these instances, the muscle fascia of the orbicularis oris or buccinator is an effective anatomic barrier.

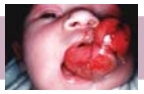
In any site, enucleation, or a "shelling out" of a pleomorphic adenoma, is contraindicated. The pseudocapsule of a pleomorphic adenoma will certainly give the clinical impression of a complete removal of an "encapsulated nodule or mass" with these approaches, but the extracapsular tumor projections left behind may lead not only to recurrence but to multicentric recurrences caused by the remaining tumor projections and foci within the tissue at the circumference of the resections.

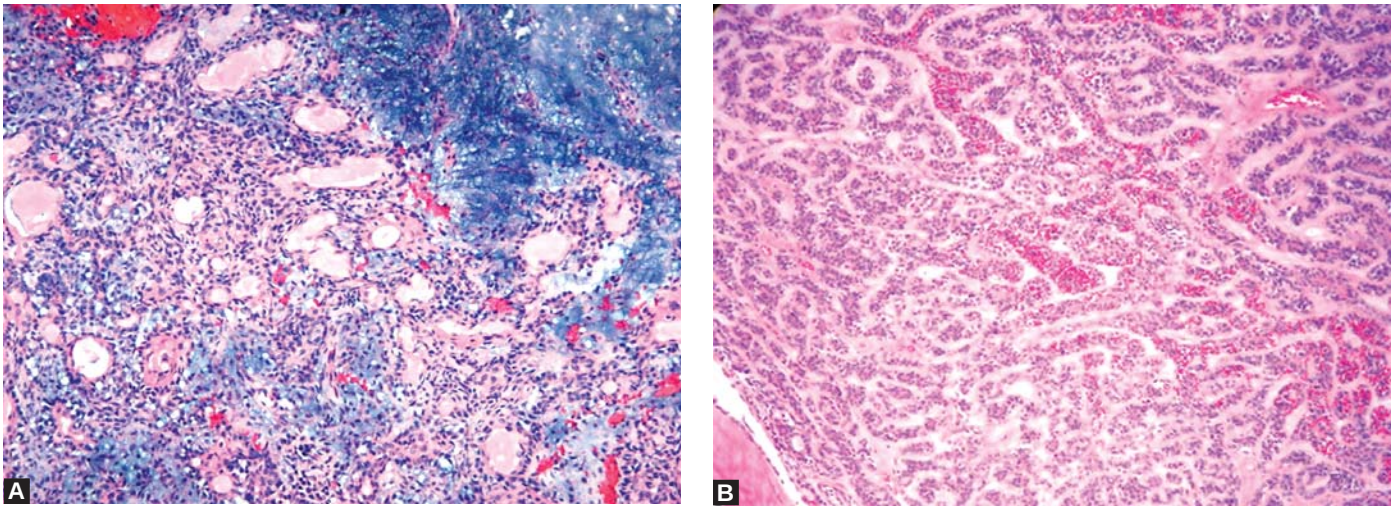
Histopathology

Foote and Frazewell (1954) categorized the tumor histologically in following types:

- Principally myxoid.
- Myxoid and cellular components present in equal proportion.
- Predominantly cellular.
- Extremely cellular.

The mixed tumors will have a well-developed capsule, these are well-demarcated, masses. Unfortunately, this characteristic, coupled with the fact that these tumors are clinically freely moveable, particularly when palpated in such areas as the lip, believes the fact that tumor cells are found within the capsule and as extensions through and beyond it. Thus a "conservative" enucleation would almost ensure residual tumor cells and set the patient up for multifocal recurrences. Grossly, these tumors have a smooth, sometimes bosselated surface. The cut surface is typically white and resembles a cut potato. Bluish areas representing cartilage-like material may be seen, and a gelatinous component may be present. Older tumors often show cyst formation. Tumors in major glands may have incomplete fibrous capsule cut surface is rubbery, fleshy,





Figs 9.5A and B: Histopathology of pleomorphic adenoma

mucoid and glistering. Foci of hyalinization, bone and fat is noted in connective tissue stroma (Figs 9.5A and B).

The microscopic picture is typically diverse .Essentially, there is a proliferation of both ductal epithelium and a myoepithelial component. This gives rise to cellular, epithelial areas as well as mesenchymal-like tissue that usually has a myxochondroid appearance. In general, the minor salivary gland tumors are more cellular than those of the major glands. The cellular portion of the tumor may form a variety of patterns such as islands, sheets, ribbons, or ductal configurations. Squamous cells and keratin pearls may be present. Occasionally, there may be cribriform areas, suggesting the pattern of adenoid cystic carcinoma. However, such areas usually compose only a small portion of the tumor, and the infiltrative nature of the carcinoma is not evident. Aggregates of oncocytic cells may be seen, but this can occur in a variety of salivary gland tumors.

Plasmacytoid (hyaline) cells and spindle cells may also be seen. Both of these have been identified as myoepithelial cells. In some tumors, one or both of these cell types constitute practically the entire lesion. If the ductal and glandular component constitutes less than 5% of the tumor, these would be classified as myoepitheliomas. Basal lamina produced by myoepithelial cells appears to be responsible for the eosinophilic hyalinized material that can form a striking component of many tumors. These were called 'hyaline cell.' The myoepithelium also deposits the basophilic, mucoid material, which then separates the cells so that the tissue appears myxoid. Degeneration of cells with vacuolation produces the chondroid pattern. Crystalline material may sometimes be seen. Glandular epithelium is mainly found. A neoplastic altered cell with the potential for multidirectional differentiation is histogenetically responsible for pleomorphic adenoma. It also shows cytogenetic abnormalities involving chromosome no12q13-15.

Malignant degeneration is possible within pleomorphic adenomas, and the incidence increases with tumor duration and size. Histologic features suggestive of malignant transformation include extensive hyalinization, cellular atypism, necrosis, calcification, and invasion.

Prognosis

Excision with controlled frozen sections and clear intraoral margins and excision via superficial parotidectomy are associated with a cure rate of more than 95%. Incomplete removals uniformly result in tumor recurrence. Clinically, recurrence is first manifested about 4 to 6 years postoperatively and is often unknown to the original surgeon, which has given false credence to enucleation procedures.

Pleomorphic adenomas are benign tumors with a well-documented transformation to malignancy (carcinoma expleomorphic adenoma). It is estimated that up to 25% of untreated pleomorphic adenomas undergo malignant transformation, a process that is size and time related. Therefore, early definitive treatment is strongly recommended. They include ulceration, fluctuance, pain, neural defects, or a change from a single circumscribed mass to a lobulated mass.

Radiotherapy is contraindicated as these tumors are radioresistant. Malignant tumors rarely arise within this tumor, a phenomenon called carcinoma ex pleomorphic adenoma. Metastatizing benign mixed tumors are histologically benign but have many local recurrences. Metastasis occurs to lungs, skin, bone and regional lymph nodes.

BASAL CELL ADENOMA

It is a neoplasm of a uniform population of basaloid epithelial cells arranged in solid, tubular or membranous pattern. It was first reported as distinct entities by Kleinsassar and Klein in 1967. Tumors appear as firm swelling that may be cystic and compressible.

Clinical Presentation

Basal cell adenomas are benign neoplasms of salivary gland origin with a less infiltrative growth behavior than that of a pleomorphic adenoma. They are more common in the parotid gland (70%) than in oral mucosal sites. When they do occur in oral mucosa, they have a predilection for the upper lip and rarely occur in the palatal mucosa, in contrast to the pleomorphic adenoma, which frequently occurs within palatal mucosa and uncommonly in the upper lip (Fig. 9.6). The lesions are painless, well-circumscribed masses that tend to be smaller (1 to 3 cm) than most pleomorphic adenomas. Most occur in men and in older adults (average age, 60 years).

Differential Diagnosis

Basal cell adenoma is similar to a small or recently developed pleomorphic adenoma or Warthin tumor (papillary cystadenoma lymphomatosum). Its superficial location may make it appear to be a sebaceous cyst of skin or an enlarged lymph node, which may be related to lymphoma, HIV-related parotitis, lymphadenopathy, or tuberculosis-related lymphadenitis. In addition, a variety of malignant salivary gland tumors may also be small and appear as a similar mass.

Diagnostic Work-up and Treatment

When the mass is located in the parotid gland, a fine-needle aspiration should be performed to rule out malignancy. If malignancy is ruled out, a superficial parotidectomy should be undertaken. In an oral mucosal site, an excision with 0.5 cm margins is adequate.

Histopathology

These tumors are usually well-circumscribed or encapsulated masses whose cut surface is homogeneous but often interrupted by cystic spaces containing brownish material. They may be multifocal.

The tumors consist of uniform cells with eosinophilic cytoplasm and oval nuclei. The cells may be arranged in several patterns. In the solid pattern, there are large islands with peripheral cells that may be more hyperchromatic and palisading. Occasionally, the central cells are squamous and form keratin pearls. The stroma is usually scanty (Fig. 9.7). The trabecular-tubular pattern forms cords and ductal structures. The membranous pattern has a jigsaw arrangement of epithelial islands in a multilobulated and often unencapsulated tumor. The islands are surrounded by eosinophilic, PAS-positive, hyalinized material representing replicated basal lamina. The islands may also contain small intercellular hyaline masses that may coalesce. This pattern strongly resembles that of dermal cylindroma. Rarely, basal cell adenomas may develop invasive properties; in such cases, they are classified as basal cell adenocarcinomas.

Basal cell adenomas are divided into following types based on morphologic appearances:

- *Solid type:* Most common type. Basaloid cells form island and cords having broad, rounded, lobular pattern. These cells are sharply demarcated from connective tissue by basement membrane. Tubular pattern has multiple, small, round duct like structures tubules lined by the inner cuboidal ductal cells surrounded by outer layer of basaloid cells is the least common variant.

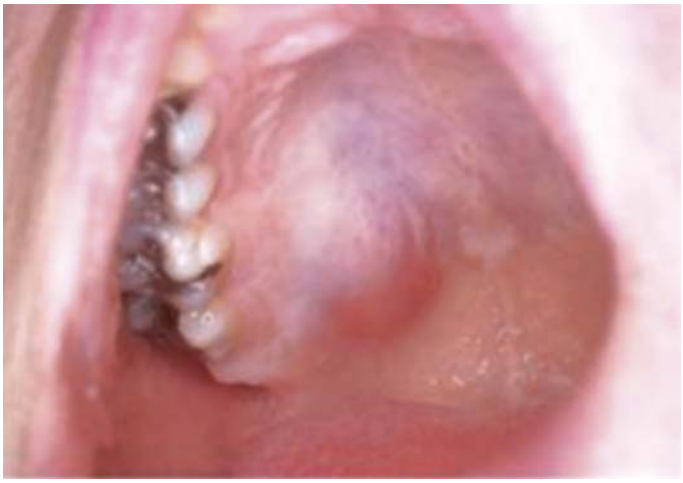


Fig. 9.6: Basal cell adenoma

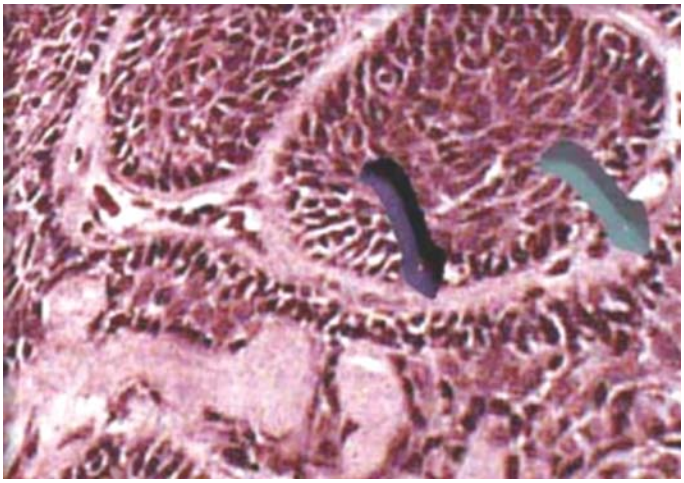
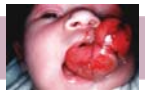


Fig. 9.7: Histopathology of basal cell adenoma



- *Trabecular type:* Some cytologic features as solid type. Epithelial island are narrower and cord like and interconnected (reticular pattern)
- *Membranous type* Abundant, thick, eosinophilic hyaline layer surrounds and separates epithelial island that are arranged in large lobules and resembles jigsaw puzzle pattern.

Prognosis

Excisions are curative, leaving little chance of recurrence. When a rare clinical recurrence develops, it is usually a second tumor rather than a persistence of the original tumor. Some have reported significant recurrence rates with the membranous variant because of its multilobular and multifocal nature. However, these are the result of "conservative" excisions without frozen section- assessed margins. Superficial parotidectomy of parotid lesions reduces such recurrences.

MUCOEPIDERMOID CARCINOMA

It is a malignant epithelial tumor, first studied by Stewart, Foote, Becker in 1945, represents 29-34% of all malignant salivary gland tumor and 5% of all salivary gland tumors (Fig. 9.8).

Clinical Presentation and Pathogenesis

Mucoepidermoid carcinoma is the most common malignant salivary gland tumor. Statistical data indicate that it is the most common parotid malignancy (89%) and that it is the most common malignant salivary gland tumor in children. About 70% of these tumors are found in the parotid gland, 15 to 20% in the oral cavity, and 6 to percent in the submandibular gland. A few are also found centrally within the mandible. In most large series, it has a distinct female predilection of about 3:1.intraorally, strong predilection for palate is seen. Prior exposure to ionizing radiation is a risk factor. Tumors also occur on buccal mucosa, tongue and retromolar areas.

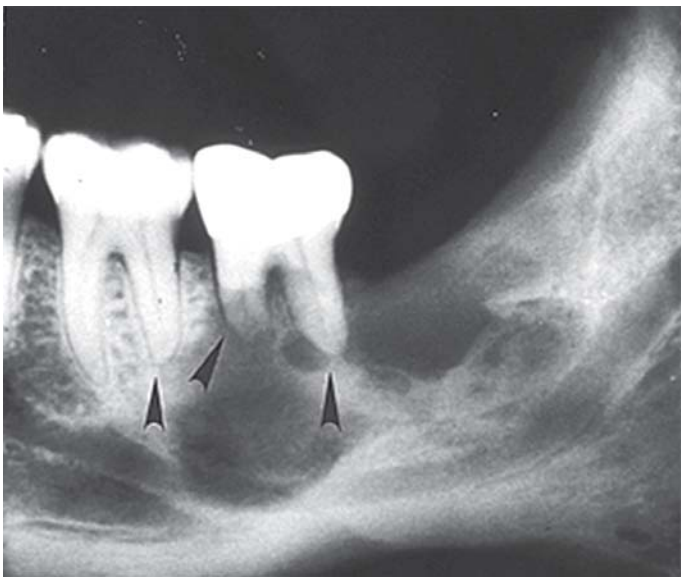


Fig. 9.8: Mucoepidermoid carcinoma intraosseous type

Low grade mucoepidermoid carcinomas will possess an infiltrative growth pattern and a very slow growth rate similar to that of a pleomorphic adenoma. They metastasize infrequently and only late in their course. Conversely, highgrade mucoepidermoid carcinomas behave like poorly differentiated squamous cell carcinomas with rapid infiltrative growth and metastasis.

Determination of the grade (low, intermediate, or high) is not limited to histopathologic criteria alone. The clinical features of each differ and are important in the final determination of grade. Low grade tumors are characteristically less than 3.0 cm and grow very slowly. Patients frequently will have been aware of their presence for 3 to 6 years. Most tumors will not be ulcerated or will have only recently ulcerated after many years, prompting the patient to seek treatment. Many tumors will appear bluish because their well-differentiated character creates mucin-filled spaces that appear blue through the mucosal cover. Most will not invade bone until late in their course. Intermediate-and high-grade mucoepidermoid carcinomas are faster growing, more diffuse, and ulcerate early. Many are obviously destructive to underlying bone, and some are painful. Because they are not sufficiently differentiated to produce mucin, they will not appear blue or vacuolated. They will present as solid masses with a normal color of the overlying epithelium or with an ulcerated surface. In case of high grade malignancy, patient complains of trismus, drainage from ear, dysphagia, numbness of adjacent areasand ulceration. The carcinoma infiltrates surrounding tissue and metastasizes to regional lymph nodes. Distant metastasis is seen in lung, bone, brain and subcutaneous tissues.

A parotid mucoepidermoid carcinoma will present as a parotid mass, which may be freely movable, like the more common benign parotid tumors, but may also be diffuse and less circumscribed. If the facial nerve is infiltrated by tumor, facial muscle paralysis may be evident.

Mucoepidermoid carcinomas arise from reserve cells in the salivary duct system. Therefore, they can partially differentiate into mucin producing cells or duct like epidermoid cells. Both cell types are altered neoplastic cells. Because the reserve cell can become neoplastic at any stage of its maturation, the resultant tumor may emerge with variable biologic behavior and histologic grading as is typical of the mucoepidermoid carcinomas.

Differential Diagnosis

- Adenoid cystic carcinoma
- Polymorphous low grade adenocarcinoma
- Carcinoma expleomorphic adenoma.
- Squamous cell carcinoma
- Sinus or nasal carcinomas
- Pleomorphic adenoma, Warthin's tumor and basal cell adenoma
- Acinic cell carcinoma.

A highgrade mucoepidermoid carcinoma in the parotid gland usually has a presentation suggestive of an aggressive malignancy, including rapid growth, large size, possible facial muscle paralysis, and induration. Its differential diagnosis would include adenoid cystic carcinoma (though this lesion tends to be a small primary), salivary duct carcinoma, carcinoma expleomorphic adenoma, and possibly seeding of a regional metastasis from an oral or a nasopharyngeal squamous cell carcinoma.

Diagnostic Work-Up

If the mass is in a location other than the parotid gland, a representative incisional biopsy is required. It should be in the lesion's center and include overlying mucosa. If the tumor is in the palate, a CT scan or MRI scan with coronal views is needed to assess for sinus, nasal, or palatal bone invasion. If the tumor is in the parotid gland, the same type of scan is required to assess its location and size.

Histopathology

The biologic behavior of these tumors, which ranges from extremely low grade to highly aggressive, depends primarily on the histology. In general, these masses are unencapsulated, although the lowgrade tumors are usually well-circumscribed while the high grade tumors show considerable infiltration (Fig. 9.9).

Several cell types are seen, including:

Mucous-secreting cells, which are usually large cells with pale foamy cytoplasm. They may occur in clusters or single cells, or they may line cystic spaces. They elaborate epithelial mucin, which can be identified by mucicarmine or PAS stain; the latter is resistant to diastase digestion. Particularly when the mucous component is scant, special stains may be necessary for identification (Fig. 9.10A).

Epidermoid cells, which lie in sheets or line cystic spaces. They may show interlacing patterns with intercellular bridges. Occasionally, keratin pearls are seen. They have squamoid features and polygonal shape, arranged in glandular pattern (Fig. 9.10B).

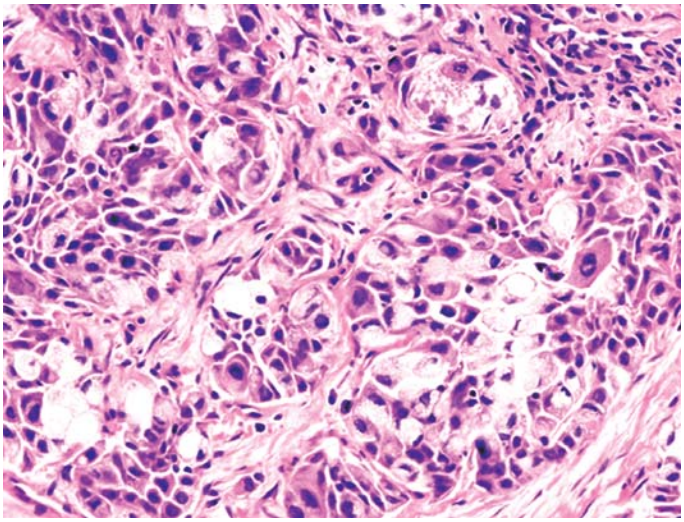


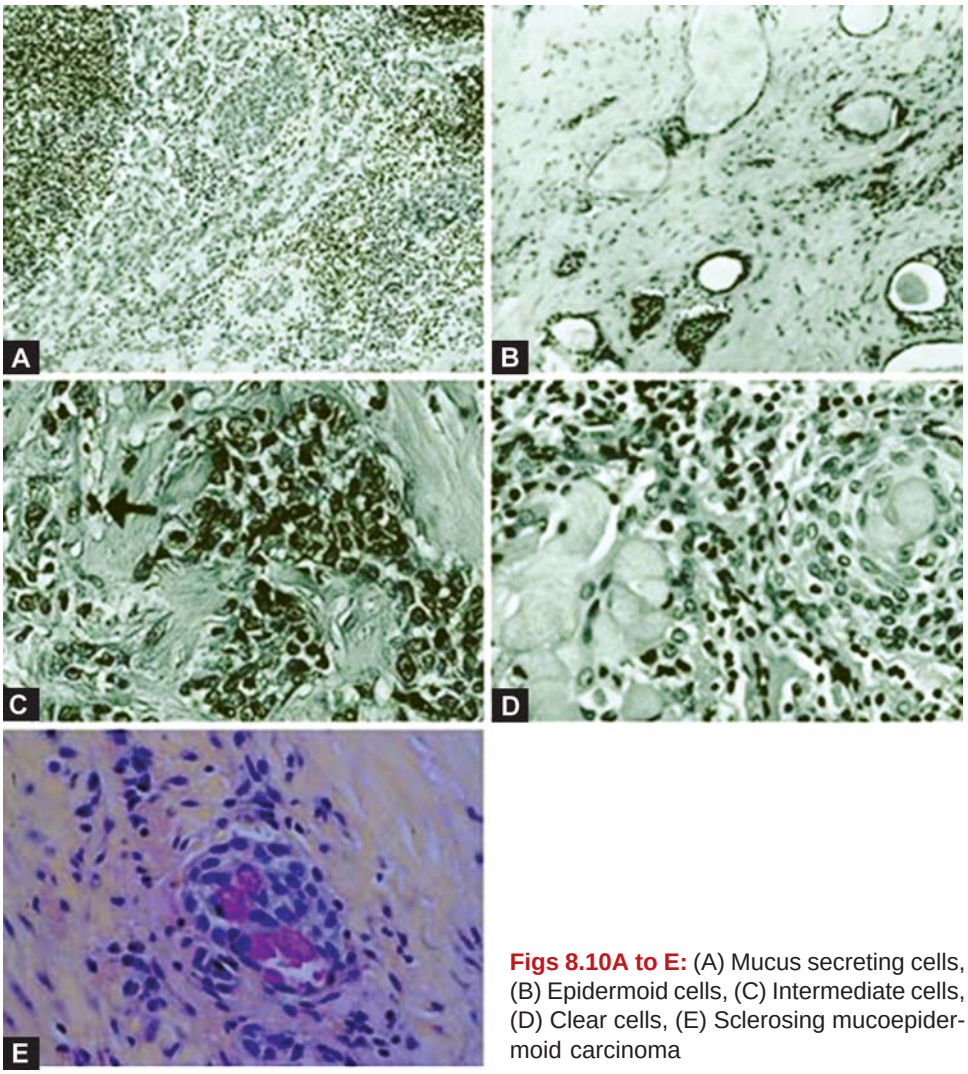
Fig. 9.9: Histopathology of mucoepidermoid carcinoma

Intermediate cells, which are basaloid cells that vary from small, dark-staining cells to larger, more epidermoid-like cells. They may lie in sheets or line cystic spaces. They tend to blend into epidermoid cells. These cells are believed to differentiate into epidermoid, mucous, and clear cells (Fig. 9.10C).

Clear cells that may form broad sheets or occur as single cells or clusters within epidermoid cells. Although these cells are usually negative on mucin staining, some mucin may occasionally be identified. They are glycogen free cells (Fig. 9.10D).

The grading of mucoepidermoid carcinoma depends primarily on the relative mixture of cell types, although growth pattern and cellular atypia also play significant roles.

Low grade mucoepidermoid carcinomas are characterized by well formed cysts that may be quite large. These cysts frequently contain mucin and are lined by a mixture of mucous, intermediate, and epidermoid cells. These cells may also form more solid foci between the cysts. The cells are mature and do not show atypia or mitotic activity. The cysts may rupture, liberating mucin and causing an inflammatory reaction within adjacent tissue. Rupture also facilitates the spread of tumor cells. In relation to other grades, low grade tumors have a more prominent mucous cell component. Clinically, the mucin filled cysts appear similar to mucus retention phenomena. A potential problem with low grade tumors is that large cysts may sometimes develop in the superficial aspect of the tumor. In these cases, an insufficiently deep incisional biopsy may miss the diagnostic portion of the tumor.



Figs 8.10A to E: (A) Mucus secreting cells, (B) Epidermoid cells, (C) Intermediate cells, (D) Clear cells, (E) Sclerosing mucoepidermoid carcinoma

Intermediate grade tumors contain smaller and fewer cysts and have a more solid appearance. The solid areas consist of intermediate cells, epidermoid cells, and some mucous cells. Mitoses are not usually present, but nuclear atypism may be seen. Compared to low grade tumors, intermediate and epidermoid cells are more prominent and mucous cells are sparser.

High grade tumors are solid and consist of intermediate and epidermoid cells, which show considerable atypia. Mitotic activity also is present. Mucous cells may be readily noted, but in many tumors they are so sparse that there is a marked resemblance to squamous cell carcinoma. In these cases, special stains, such as mucicarmine or PAS, are necessary to demonstrate their presence and clarify the diagnosis. These are infiltrative, unencapsulated tumors. Nuclear pleomorphism is seen, cystic component is <20% glandular component is rare. Necrosis and peripheral invasion may be seen.

Clear cells may be seen in all grades of mucoepidermoid carcinoma. Occasionally, they can represent the majority of the tumor. In these instances, they must be differentiated from other clear cell neoplasms, including metastatic renal cell carcinoma. Treatment is based on histologic grading, as it is related to clinical behavior and predicts biological behavior.

Variants

Sclerosing Mucoepidermoid Carcinoma

Extremely rare Characterized by an intense central sclerosis that occupies the typical tumor, frequently with inflammatory infiltrate of plasma cells, eosinophils and lymphocytes at its peripheral regions

It is caused by tumor of infarction and extravasation of mucin resulting in reactive fibrosis (Fig. 9.10E).

Intraosseous Mucoepidermoid Carcinoma

- Also known as central mucous epidermoid carcinoma
- Originates within jaws
- Forms by malignant transformation of epithelial lining of odontogenic cyst
- Tumor presents as asymptomatic radiolucent lesion and has histology of low grade malignancy
- Mandible is effected 3 times more than maxilla.

Treatment and Prognosis

Low grade mucoepidermoid carcinomas of the palate require a soft tissue palatal excision with 1 cm peripheral margins and anatomic barrier margins. The palatal bone does not require excision unless radiographs, scans, or direct observation indicate tumor extension into it. Postoperative radiotherapy or prophylactic neck dissection is not indicated. The same lesion in other oral mucosal sites requires a local excision with 1 cm margins and anatomic barrier margins. The 5-year survival rate for individuals with low grade mucoepidermoid carcinoma of the oral mucosa treated in this fashion is about 95%. Conservative excision with facial nerve preservation is must. Affected sub-mandibular gland should be removed entirely.

Low grade mucoepidermoid carcinomas of the parotid gland are treated with superficial parotidectomy unless they originate from or extend into the deep lobe or involve the facial nerve, in which case a total parotidectomy is required. The 5-year survival rate is about 90 to 95%.

Intermediate and high grade mucoepidermoid carcinomas of the palate require a hemimaxillectomy- type excision with postoperative radiotherapy in the dose range of 5,000 to 7,000 cGy. The bilateral necks should be treated prophylactically with either surgery or radiotherapy. If nodal disease presents in the neck, then surgical neck dissection is accomplished in addition to radiotherapy of the primary tumor site and the neck. The 5-year survival rate for such high grade tumors is about 35%; at 10 years, the survival rate drops to about 25%. Metastasis to regional lymph nodes and uncontrolled tumor at the primary site with cranial invasion are a prime cause of death. Distant metastasis to the lungs is also seen. Chemotherapy is also effective in high grade malignancies. Radical neck desection is performed in cases with clinical evidence of cervical node metastasis and in patient with T3 lesion.

Intermediate and high grade mucoepidermoid carcinomas of the parotid gland require a total parotidectomy and ipsilateral neck dissection followed by postoperative radiotherapy in the dose range of 5,000 to 7,000 cGy. The 5-year survival rate is about 40%; the 10-year rate is approximately 25%.

SJÖGREN'S SYNDROME

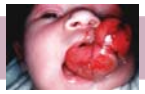
Sjögren's syndrome is a condition originally described by Henrik Sjögren in 1933 as a triad consisting of keratoconjuctivitis sicca, xerostomia and rheumatoid arthritis.

Clinical Presentation and Pathogenesis

A syndrome is defined as a clinical symptom complex. Sjögren's syndrome is an autoimmune destruction of exocrine glands (primarily salivary and lacrimal) that produces the clinical manifestations of dry mouth (xerostomia), dry eyes (xerophthalmia or keratoconjunctivitis sicca), and, in more than 50% of cases, parotid gland enlargement. Primary Sjögren's syndrome is diagnosed when the syndrome is limited to this pattern of involvement. However, this pattern of involvement may be a manifestation of another well-defined autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosis, or primary biliary cirrhosis. In this context, it is referred to as secondary Sjögren syndrome. This is an important distinction because lymphoma development is mostly seen in the primary type of Sjögren's syndrome. F:M ratio 10:1 with painful burning sensation of oral mucosa. Dryness of nose, larynx, pharynx and tracheobranchial tree (buccopharyngitis sicca) is seen.

Newer diagnostic techniques such as parotid biopsies and antibody identifications have shown that many children and teenagers with dry mouth conditions actually have Sjögren's syndrome. Caries at the cervical tooth margins and mucosal candidiasis are frequent. An absence of flow from Stensen's duct or a thick, mucoid secretion is common. The parotid enlargements are usually asymmetric and painless. Those larger than 6 cm, irregular by palpation, or darkened in color should be considered suggestive of lymphoma, particularly if the Sjögren's syndrome is of the primary type. The dry eyes will often become secondarily infected and may have a suppurative collection in the lacrimal lake area and a reddened conjunctiva. Some patients will present with fatigue and mild arthralgia, but most will be active and tolerant of their disease. Many patients will have tooth loss secondary to caries, but they usually tolerate dentures well despite their dryness.

The pathogenesis of Sjögren's syndrome is complex and uncertain, but thought to be similar to that of the benign lymphoepithelial lesion. It is suspected that age or viral changes in exocrine acinar cells result in an antigenicity on the cell surface. This, in turn, creates a stimulation and intense activity of mainly B cells, which infiltrate these glands and destroy the glandular acini. The myoepithelium and ductal elements lack the antigen and are thus spared.



The result is dryness of the affected area and enlargement of the gland if sufficient numbers of lymphocytes have accumulated in it. In the 6 to 10% of cases that undergo transformation to a lymphoma (over a period of 5 to 15 years), the constant polyclonal B cell overactivity selects a single clone (usually of B cells) that overtakes the population, resulting in a lymphoma.

Etiology

Genetic, Hormonal, Infectious and Immunologic

Sjögren's syndrome, like many autoimmune diseases, is associated with certain human lymphocyte-associated (HLA) or histocompatibility antigens, indicative of a genetic vulnerability. HLA-DR4 antigen is found in patients who develop secondary Sjögren's syndrome. HLA-B8 and HLA-DR3 antigens are found in patients with primary Sjögren's syndrome.HLA-DRW52 is associated with both forms of sjögren's syndrome.

Differential Diagnosis

Sarcoidosis, sialosis, mumps, and benign lymphoepithelial lesions. Some medications such as atropine, nifedipine, and antidepressants can produce a subjective dry mouth

Diagnostic Work-Up

Nuclear imaging and injection sialography, CT or MRI scan establish histopathologic confirmation. An incisional parotid biopsy beneath the earlobe for each parotid gland can be done.

A Schirmer tear function's test is recommended to assess the degree of xerophthalmia.

Laboratory tests should include a complete blood count; serum immunoglobulins assessments; autoantibody assessments.

Histopathology

Lymphocytic infiltration of exocrine glands is the hallmark of Sjögren's syndrome. In major salivary glands, the previously described benign lymphoepithelial lesion is considered typical. However, it is not consistently seen in minor salivary glands. The parotid gland will show an early lymphocytic infiltration, acinar atrophy, and epimyoepithelial islands. Proliferation of ductal epithelium and myoepithelium to form 'myoepithelial islands' are seen in some cases.

Within minor salivary glands, the formation of epimyoepithelial islands is uncommon. The usual picture is of a focal lymphocytic sialadenitis., The presence of more than 1 focus per 4 mm square in most of the specimen supports the diagnosis of Sjögren's syndrome Therefore, tissue from an incisional parotid biopsy is preferred. While plasma cells may be seen, they are usually peripheral to the lymphocytic focus. As time passes, the extent of lymphocytic infiltration increases with consequent loss of acini and a resultant clinical xerostomia (atrophy of glands).

Treatment

Like any autoimmune disease, Sjögren's syndrome is incurable. However, its symptoms and complications often require management. The symptom of dry eyes is best managed with a slowly dissolving methylcellulose (Lacrisert, Merck) preparation on a daily basis. The eyes also often require topical antibiotics such as sulfacetamide or ophthalmologic gentamycin. The oral dryness may be managed with oral pilocarpine (Salagen), 5 mg three times daily; atomized water spray (Evian, Evian); or sips of water. Caries controls and topical fluoride carriers, which are used in irradiated patients, also are useful. Frequently, nystatin oral suspensions, 100,000 units/mL used as a 1-teaspoon oral swish and swallow, is needed to control *Candida* colonization.

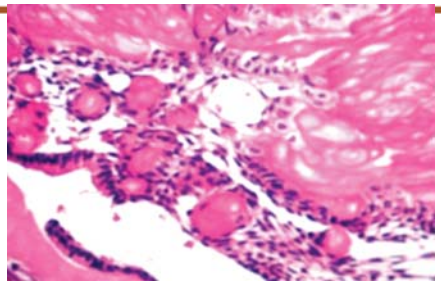
For the 6 to 10% of cases in which Sjögren's syndrome progresses to lymphoma, a complete work-up for lymphoma in other locations and staging are required. Most are B cell lymphomas. The parotid focus of lymphoma is most often treated with radiotherapy of 5,000 to 6,000 cGy, although chemotherapy for stage II or stage IV lymphoma is also used.

Prognosis

Sjögren's syndrome is compatible with long-term survival. A repeat parotid biopsy is indicated if the gland increases in size, darkens, or becomes irregular. In this manner, lymphomatous transformation can be detected early and treated, resulting in a good prognosis.

10

Cysts and Tumors of Odontogenic Origin



ODONTOGENIC CYSTS

INTRODUCTION

Odontogenic cysts are derived from epithelium associated with development of dental apparatus. Several types of odontogenic cysts occur, dependent chiefly upon the stage of odontogenesis during which they originate. Cysts are the most common causes of chronic swellings of the jaws, but few postsignificant diagnostic or management difficulties.

Majority of the jaw cysts are odontogenic and usually radicular cyst. They can be recognized by the history and clinical and radiographic features. In the analysis of the frequency of different types of cysts, radicular cyst is the most commonly occurring followed by dentigerous cyst.

Kramer (1974) described cyst as 'a pathological cavity having fluid, semi-fluid or gaseous contents that are not created by the accumulation of pus; frequently, but not always, is lined by epithelium.

Mervyn Shear (1994) has referred to the new WHO classification.

Epithelial Cysts

Developmental origin	Inflammatory
Odontogenic cyst	Radicular cyst
Gingival cysts of infants	Paradental cyst
Gingival cyst of adults	Residual
Odontogenic keratocyst (Primordial cyst)	
Dentigerous cyst (follicular cyst)	
Eruption cyst	
Lateral periodontal cyst	
Nonodontogenic	
Nasopalatine duct (incisive canal) cyst	
Nasolabial (naso alveolar) cyst	

There are two proposed mechanisms of cyst formation

1. The first suggests that by progressive proliferation of arcades of epithelium, areas of inflammatory tissue progressively become encircled and ultimately liquefy, so forming cyst.
2. The second mechanism postulates that the proliferating strands of avascular epithelium becomes progressively large so that the central cells receive inadequate nutrients and degenerate, so forming a central fluid filled cavity usually the lining epithelium of these cysts arise from cell rests of mallasez but in some instances, the cystic epithelium may originate from gingival crevicular epithelium, sinus mucosa or the lining of fistulous tract.

DENTIGEROUS CYST

A dentigerous cyst is one that encloses the crown of an unerupted tooth by expansion of its follicle, and is attached to its neck.

- It was also known as follicular cyst.
- Browne and smith change the name from follicular cyst to dentigerous cyst.

Reason

- Its derivation from the tooth follicle which is a mesodermal structure.
- Follicular cyst is most commonly used to refer to follicular cysts of the ovary, and also to hair follicle cyst.
- Name dentigerous cyst, because meaning of dentigerous is tooth bearing. This term is most appropriate for the lesion.

Etiopathogenesis

The epithelial lining of this cyst is derived from the reduced enamel epithelium.The cyst arises around the crown of an erupted tooth, lying impacted within in the bone. The odontogenic cysts mechanical disturbance in the eruptive process may lead to fluid accumulation either within the reduced enamel epithelium or between it and the enamel surface resulting in cyst formation. The cyst formation occurs due to fluid accumulation either within the reduced enamel epithelium or between it and the enamel surface. The initiation of this cyst formation can be explained by

the pressure created in the follicle surrounding the crown of the interrupted tooth as consequence of fluid transudation. It has been suggested that thin walled venous channels are constricted by the impacted tooth, so leading to extravasation of fluid. In addition to physical mechanisms, cellular mechanisms are also involved. It has been demonstrated that large numbers of mast cells and IgE staining cells are present in the tissues surrounding the crown of erupting tooth. Interaction of IgE with mast cells results in histamine release and thus vasodilation and exudation.

Clinical Features

Frequency

White women and men are more affected than the black women and men.

Age

- Dentigerous cysts occurred in first decade more commonly than other jaw cyst. But frequency is less comparatively 2nd and 3rd decade.
- This is because of dentigerous cysts most frequently occur in mandibular 3rd molar and maxillary permanent canine.
- The frequency increased sharply in the second decade and reached a peak in the third, after which there was a gradual decline.

Gender

In general, dentigerous cyst was significantly greater in men than women i.e., 1.8:1.

Race

Higher frequency of dentigerous cysts in white than in black patients. This is because of white patients had a higher frequency of impaction, than black patients.

Site

- Majority of cases are involved in the mandibular 3rd molar – maxillary permanent canine → mandibular premolar → maxillary 3rd molars.
- 90% were associated with a maxillary mesiodens.

Clinical Presentation

- Dentigerous cysts may grow to a large size before they are diagnosed.
- Most of them are discovered on radiographs when these are taken because a tooth has failed to erupt or a tooth is missing, or because teeth are tilted or are otherwise out of alignment.
- Many patients first become aware of the cysts because of slowly enlarging swelling, and this is the common form of presentation with edentulous patients in whose jaws unerupted teeth have inadvertently been retained.
- Dentigerous cysts may occasionally be painful particularly if infected.
- Some patients may give a history of a slowly enlarging swelling.

Radiological Features

Radiographs show unilocular radiolucent areas associated with the crowns of unerupted teeth. The cysts have well-defined sclerotic margins unless they become infected. Occasionally, trabeculations may be seen and this may give an erroneous impression of multilocularity. The unerupted teeth may be impacted as a result of inadequate space in the dental arch or as a result malpositioning such as by a horizontally impacted mandibular third molar or an inverted tooth. Supernumerary teeth may develop dentigerous cysts.

Three radiological variations of the dentigerous cyst may be observed.

Central variety: The crown is enveloped symmetrically. In these instances, pressure is applied to the crown of the tooth and may push it away from its direction of eruption. In this way, mandibular third molars may be found at the lower border of the mandible or in the ascending ramus and a maxillary canine may be forced into the maxillary sinus as far as the floor of the orbit. A maxillary incisor may be found below the floor of the nose (Fig. 10.1).

Lateral type of dentigerous cyst is a radiographic appearance which results from dilatation of the follicle on one aspect

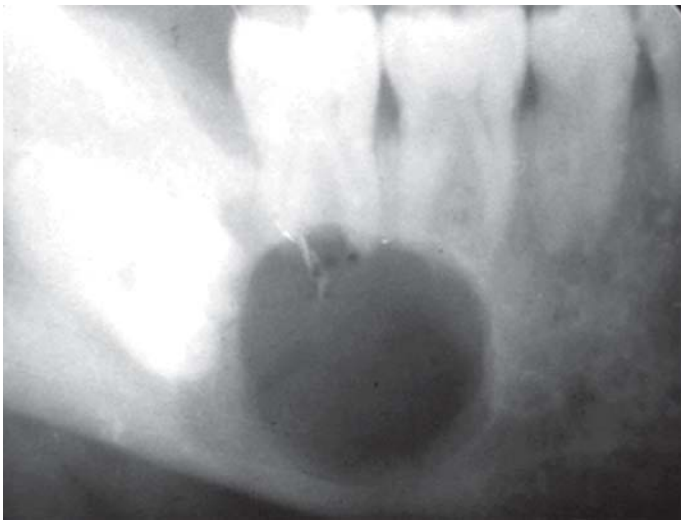


Fig. 10.1: The circular radiolucent lesion seems to be associated with the roots of the erupted first and second molar teeth. Careful examination shows a relationship with the unerupted third molar tooth. "Dentigerous cyst" is a likely candidate

of the crown. This type is commonly seen when an impacted mandibular third molar is partially erupted so that its superior aspect is exposed (Fig. 10.2).

Circumferential dentigerous cyst, the entire tooth appears to be enveloped by cyst along the sides, with the protrusion of the crown through cyst partially or completely and that this variety should be differentiated from the envelopment type of keratocyst. Cysts arising from deciduous teeth may mimic dentigerous cyst radiologically (Fig. 10.3).

Macroscopic Features

Sometimes the cyst is removed intact but more often the thin wall is torn during the surgical procedure. In an inflamed dentigerous cyst the wall may be thickened.

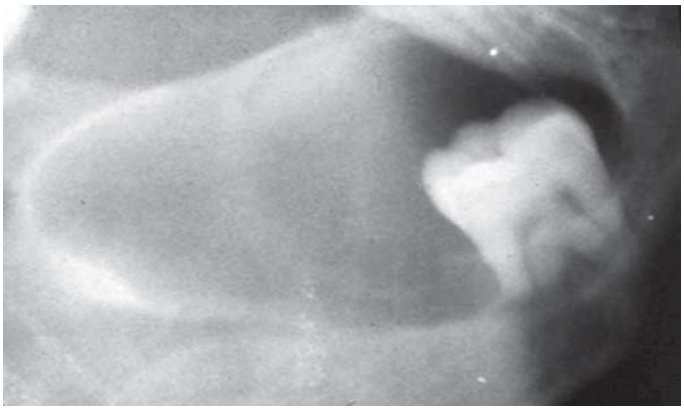


Fig. 10.2: The radiolucency surrounding the impacted molar crown is large. While "dentigerous cyst" is one possibility, more serious lesions should be considered (eg. odontogenic keratocyst and ameloblastoma)

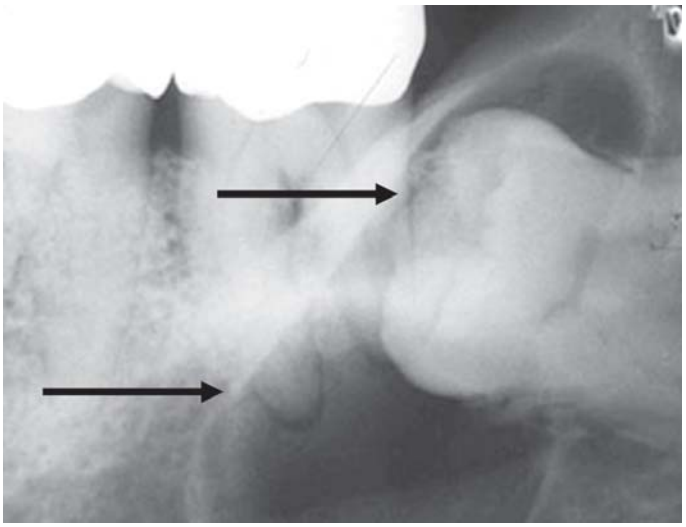


Fig. 10.3: There is radiolucency around the crown of the unerrupted third molar tooth. Dentigerous cyst is a prime candidate in the differential diagnosis of such lesions

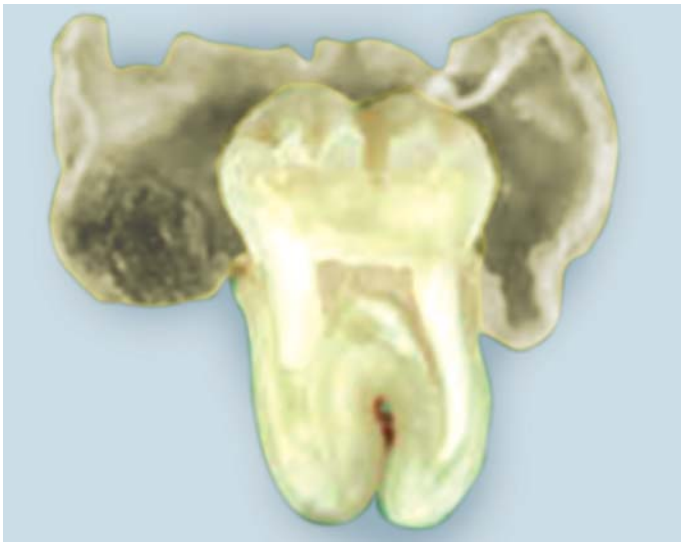


Fig. 10.4: Gross appearance

Histopathology (Fig. 10.4)

The lining typically consists of flattened or cuboidal epithelium, usually about 2 to 5 cells thick arising from a flattened basement membrane. The epithelium ends abruptly at its attachment to the cementoenamel junction of the associated tooth. It is not usually keratinized, but rarely keratin metaplasia can occur. A more common form of metaplasia is the mucous metaplasia of the surface cells, which are present in about 40% of cysts, and sometimes are so numerous as to form a continuous layer in part of the lining. The epithelium exhibits low mitotic activity and mitotic figures are predominantly present in its basal layer.epithelium is flat without rete ridges abuting on noncellular fibrovascular stroma.

Complications of Dentigerous Cyst (Fig. 10.5)

- Development of an ameloblastoma either from the lining epithelium or from rests of odontogenic epithelium in the wall of the cyst.
- The development of epidermal carcinoma from the same two sources of epithelium mentioned above.
- The development of mucoepidermoid carcinoma, basically a malignant salivary gland, from the lining epithelium of dentigerous cyst which contains mucous secreting cells or at least cells with this potential, most commonly seen in dentigerous cyst associated with impacted mandible third molars.

Treatment

The treatment of the dentigerous cyst is usually dictated by the size of the lesion. Smaller lesions can be surgically removed in their entirety with little difficulty. The larger

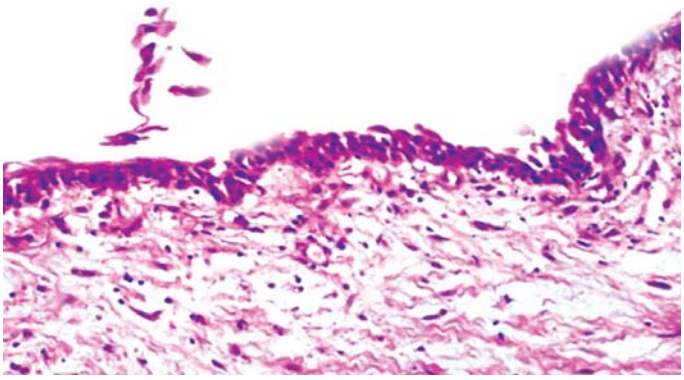


Fig. 10.5: Wall of a dentigerous cyst lined by a thin epithelium of 2–4 layers of undifferentiated cells derived from the reduced enamel epithelium. The fibrous cyst wall is relatively uninflamed and sparsely cellular

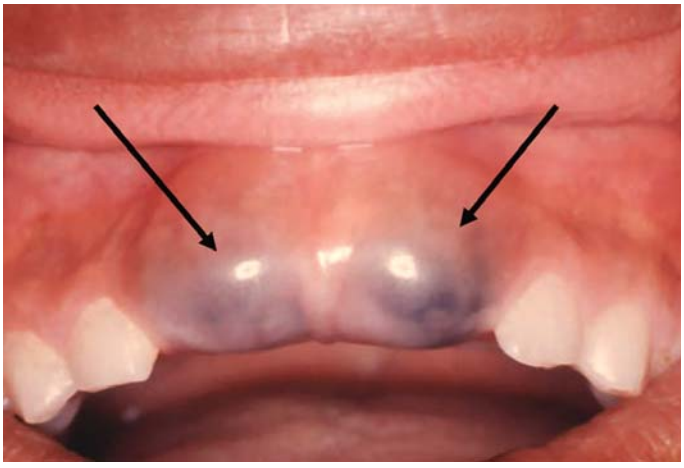


Fig. 10.6: Eruption cysts involving the maxillary permanent incisors

cysts which involve serious loss of bone and thin the bone dangerously are often treated by insertion of a surgical drain or marsupilization. Such a procedure is often necessary because of the potential danger of fracturing the jaw if complete surgical removal were attempted. Recurrence is relatively uncommon.

ERUPTION CYST (Fig. 10.6)

Eruption cyst occurs when a tooth is impeded in its eruption within the soft tissues overlying the bone.

Etiopathogenesis

As the crown of the tooth associated with an eruption cyst usually projects into the cyst lumen, it is widely believed that the epithelial lining is derived from the reduced enamel epithelium, as in the dentigerous cyst. The difference lies in the fact the cystic breakdown occurs as a consequence of the impeded eruption of the tooth during its passage through the mucosa, so that the cyst lies in soft tissue.

- The main difference is, in the case of the eruption cyst is impeded in the soft tissues of the gingival but in case of dentigerous cyst occur in bone.
- Lining epithelium of eruption cyst is derived from the reduced enamel epithelium.
- The factors that actually impede eruption in the soft tissues are not known, but the presence of particularly dense fibrous tissue could be responsible.
- It is believed that the eruption cyst represents a soft tissue form of dentigerous cyst, so similar factors are involved in the initiation of epithelial proliferation.

Clinical Features

Frequency

Eruption cysts are not commonly seen in and they contribute to (0.8 per cent) of jaw cysts. It is likely that they occur more frequently clinically and that as some burst spontaneously. These are not excised and are therefore not submitted for histological examination.

Age

They are usually seen in children during eruption period.

Clinical Presentation

The cysts are found in children of different ages and occasionally in adults if there is delayed eruption. Deciduous and permanent teeth may involved. Most frequently anterior to the first permanent molars.

Eruption cyst generally clinically appear a smooth swelling over the erupting tooth, which may be either the color of normal gingiva or blue. It is usually painless, not infected and is soft and fluctuant. Sometimes more than one cyst may be present. Cyst usually rupture when it is exposed to masticatory mucosa. Transillumination is a useful diagnostic aid in distinguishing an eruption cyst from an eruption hematoma.

Radiological Feature

There is no bone involvement except that the dilated and open crypt may be seen on the radiograph.

Histopathology

The eruption cyst showed histopathologically a keratinized, stratified, squamous epithelium of the overlying gingival. The lining epithelium is separated from the cyst by a strip of dense connective tissue of varying thickness which usually shows a mild chronic inflammatory cell infiltrate. As the cysts are to frequently exposed to masticatory trauma, the inflammatory infiltrate invariably increases in intensity towards the cyst lining (Fig. 10.7).

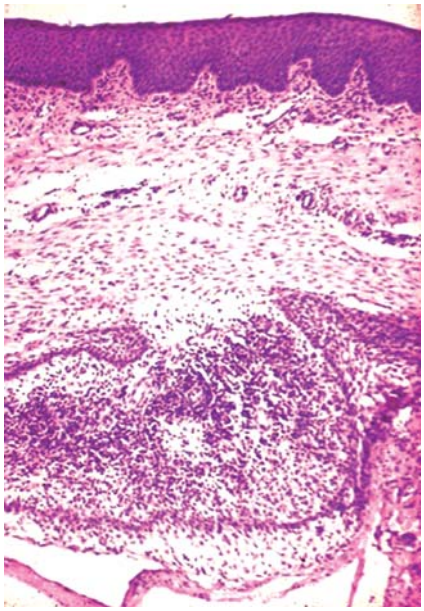


Fig. 10.7: HIstological features of an eruption cyst. The surface epithelium is at the top and the cyst lining at the bottom of the photomicrograph. The intense chronic inflammatory cell infiltrate is a response to masticatory trauma

Treatment

Most frequently treated by mursupialization.

Note: The other odontogenic cyst in classification generally does not found in pediatric patient so their detailed discussion is beyond the scope of this book.

ODONTOGENIC TUMORS

INTRODUCTION

Odontogenic tumors (OT) comprise a group of lesions of the jaw, derived from primordial tooth forming tissues and presenting in a large number of histologic patterns. Some of these lesions, particularly the odontomas, are now interpreted as developmental malformations or hamartomatous lesions rather than true neoplasms. Other lesions, such as ameloblastomas, are accepted as true neoplasms and must be diagnosed and treated as such. Odontogenic tumors share two major characteristics, namely they arise from the tissue with the potential for differentiation into tooth or periodontal structures, and are therefore found exclusively in the mandible and the maxilla and, on rare occasions, the gingiva. Another variable but distinctive feature includes formation of tooth related extracellular substances some of which may calcify and be visible on radiographs; they are a product of epithelial-mesenchymal interactions (Gallagher and Shklar, 2000).

The most common sites of these tumors are the mandibular molar region and the maxillary cuspid region. They are usually slow growing and asymptomatic. Certain odontogenic tumors have a predilection for particular ages, gender, geographic location, and race (Sawyer et al, 1985; Assail, 1992).

So in brief they are the lesions of the mandible and the maxilla and on rare occasions, of the gingiva which should be considered as a differential diagnosis when analyzing jaw lesions. Odontogenic tumors constitute a group of heterogeneous lesions that range from hamartomatous or non-neoplastic tissue proliferations to malignant neoplasms with metastatic capabilities.

CLASSIFICATION OF ODONTOGENIC TUMORS

WHO Classification
(Proposed in 2003 Published in, Lyon in July 2005)

Benign Tumors

Odontogenic epithelium with mature, fibrous stroma; without odontogenic ectomesenchyme

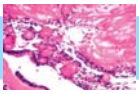
- Ameloblastoms
  - Solid/multicystic ameloblastoma
  - Extraosseous/peripheral ameloblastoma
  - Desmoplastic ameloblastoma
  - Unicystic ameloblastoma
- Squamous odontogenic tumor
- Calcifying epithelial odontogenic tumor
- Adenomatoid odontogenic tumor
- Keratinizing cystic odontogenic tumor

Odontogenic epithelium with odontogenic ectomesenchyme with or without dental hard tissue formation

- Ameloblastic fibroma
- Ameloblastic fibrodentinoma
- Ameloblastic fibro-odontoma
- Complex odontoma
- Compound odontoma
- Odontoameloblastoma
- Calcifying cystic odontogenic tumor
- Dentinogenic ghost cell tumor

Mesenchyme and/or odontogenic ectomesenchyme with or without odontogenic epithelium

- Odontogenic fibroma
  - Epithelium rich type
  - Epithelium poor type
- Odontogenic myxoma or fibromyxoma
- Cementoblastoma



Malignant Tumors

Odontogenic carcinoma

- Metastasizing ameloblastoma
- Ameloblastic carcinoma
  - Primary
  - Secondary (dedifferentiated) intraosseous
  - Secondary (dedifferentiated) extraosseous
- Primary intraosseous squamous cell carcinoma (PIOSCC)
  - PIOSCC solid type
  - PIOSCC derived from odontogenic cyst
  - PIOSCC derived from keratinizing cystic odontogenic tumor
- Clear cell odontogenic carcinoma
- Ghost cell odontogenic carcinoma

Odontogenic sarcomas

- Ameloblastic fibrosarcoma
- Ameloblastic fibrodentinosarcoma
- Ameloblastic fibroodontosarcoma

Benign Neoplasms and Tumors like Lesion Arising From Odontogenic Apparatus Showing Odontogenic Epithelium With Mature Fibrous Stroma Without Ectomesenchyme.

AMELOBLASTOMAS

(Admantinoma, Admantoblastoma, Multilocular cyst)
It is not a single entity so can not call ameloblastoma rather preferred to call it as ameloblastomas.

General Introduction

Based on clinical, radiological feature, histopathology, behavioral and prognostic aspects, four subtypes are there:

- Classic solid/multicystic ameloblastoma (SMA)
- Unicystic ameloblastoma (UA)
- Peripheral ameloblastoma (PA)
- Desmoplastic ameloblastoma (DA)

Desmoplastic ameloblastoma added as new subtype rather then histologic variant due to:

- Atypical morphology of epithelial component.
- Marked stromal desmoplasia
- Unusual radiological appearance.
- Difference in anatomic location compared to other forms of ameloblastomas.

Solid/Multicystic Ameloblastoma (SMA)

Introduction

Classic intraosseous ameloblastoma commences as a solid epithelial tumor.

In some cases, epithelial islands remain relatively small and consequently little tendency towards cystic degeneration—solid tumor.

If neoplastic epithelial island grow, the degenerative process start in center of island due to lack of nutrition and cyst formation occur.

This phenomenon may spread to several islands, where it is first recognized microscopically and later grossly. This led to use term cystic ameloblastoma; confusion with unicystic ameloblastoma which has basically different behavior and a much better prognosis than Solid/multicystic ameloblastoma (SMA).

Robinson defined ameloblastoma as: usually unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent.

Note: Characteristic peripheral cylindrical cells of tumor islands are not true ameloblast in that these cells are not capable of producing enamel, in particular because tumor islands are embedded in a mature fibrous connective tissue.

History

- Earliest evidence of jaw tumor was reported by Guzack in 1826.
- First odontogenic neoplasm was reported by Broca in 1968.
- Adamantinoma was coined by Malassez in 1885. This term was aborted as it implies formation of hard tissue and no such material present in lesion so replaced by ameloblastoma.
- First thorough description of an ameloblastoma was given by Falkson in 1879.
- Term ameloblastoma was coined by Churchill in 1934.
- Second most common odontogenic neoplasm, first being odontoma.

Pathogenesis

Tumor may be derived from any of one following:

- Cell rests of enamel organ, either remnants of dental lamina or remnants of Hertwig's sheath the epithelial rests of malassez.
- Epithelium of odontogenic cysts—dentigerous cysts or odontomas.
- Disturbances of developing enamel organ.
- Basal cells of surface epithelium of jaw-peripheral ameloblastoma.
- Hetrotropic epithelium in other parts of body especially in pituitary gland (rathke's pouch ameloblastoma).

Clinical Features (Fig. 10.8)

- Benign epithelial neoplasm.
- Virtually no tendency to metastasize.
- Slow growing, but locally invasive.
- High rate of recurrence if not removed adequately.
- Local biological behavior is similar to low grade malignant tumor.

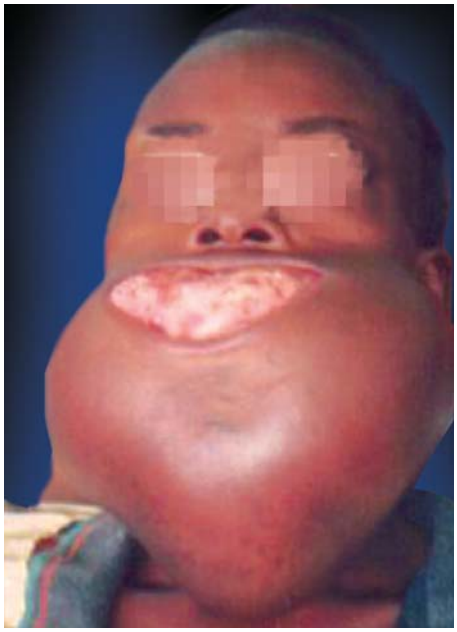


Fig. 10.8: Enlarged facial deformity

- Located centrally/intraosseously in both jaws.
- Few or no signs in early clinical stage.

Later

- Gradual increase in facial deformity.
- Teeth in area may become loose.
- Spontaneous fracture may occur in case where only a rim of normal bone forms the base of mandible.
- Affected part of jaw is bony hard and bulky.
- Pain-varying, quite low and frequent.
- Cause of pain not known so either due to;
  - Pressure from tumor on peripheral nerves.
  - Secondary infection.
- Continued enlargement of tumor may cause surrounding bone to become so thin that crepitation or egg-shell crackling may be elicted.

Late

- Perforation of bone.
- Unusually large ameloblastoma reported by partriella et al.
- Relative frequency among odontogenic tumors; 11-95%
- Race distribution—Mostly affect black population
- Age; (4 to 92) years, mean age = 35.9 year

Among Gender

Gender	Mean age (years)
Male	39.2
Female	35.9

Among Ameloblastoma Subtypes

Subtypes	Mean age (years)
Classic SMA	39
UA	22
PA	51
DA	42

Among Jaws Involvement

Jaw	Mean age (years)
Maxilla	47
Mandible	35.2

Among Radiological Features

SMA with unilocular R/F	26.4 years
SMA with multilocular R/F	37.5 years

Gender

Mostly occur in male affecting 53.5% compared to female with 46.7%.

Location

- Maxilla: mandible = 1:5.8
- Majority lesions occur in molar ramus region of mandible
- In male; premolar region of mandible and maxillary sinus more frequently affected.
- In female; incisor and ramus more affected in mandible.
- Molar region affected equally in both sexes.

Solid/multicystic ameloblastoma associated with unerupted teeth; 38%

Unerupted tooth involved	Relative frequency (%)
Mandibular 3rd molar	82
Mandibular 2nd molar	15
Mandibular premolar	6

Radiological Findings (Fig. 9.9)

Typical; multilocular destruction of bone but unilocular appearance also occurs.

Multilocular Type

- Bone is replaced by a number of small, well-defined radiolucent areas giving honeycomb or larger soap bubble appearance.
- Ranging in size from extensive destruction of half the mandible to a small lesion confined to alveolar process.

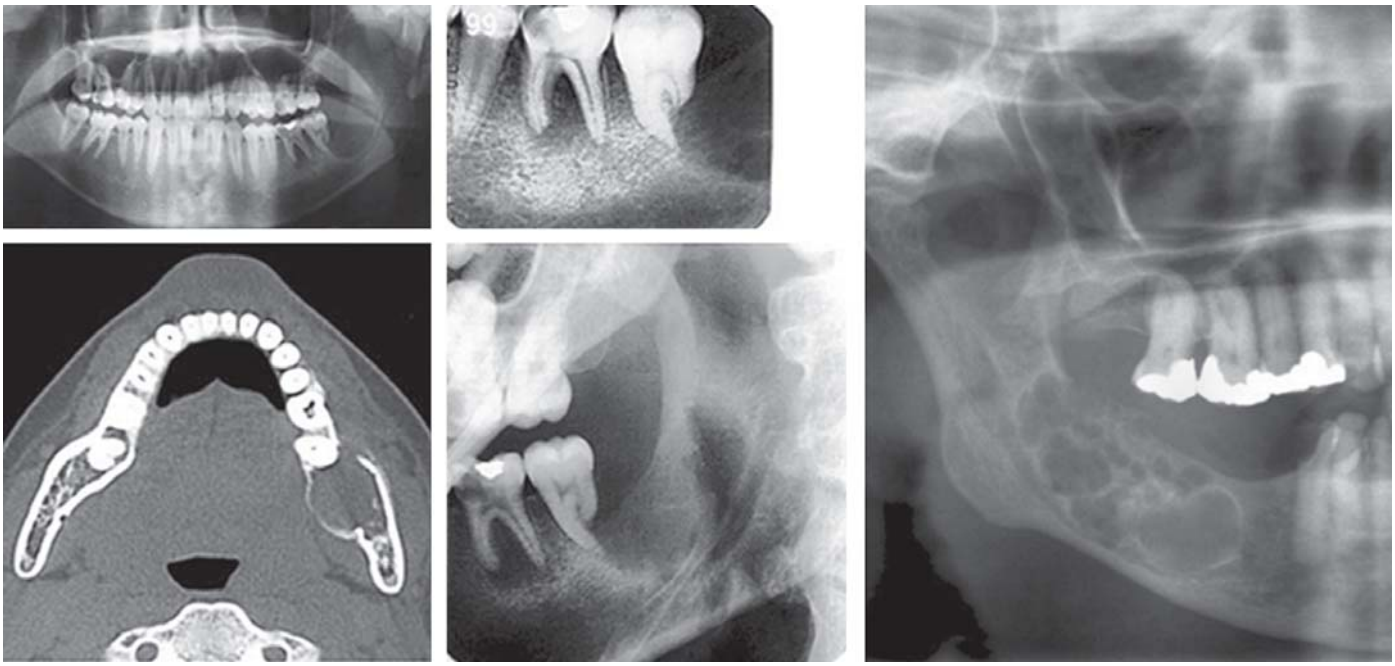


Fig. 10.9: Unilocular to multilocular radiolucency

Unilocular Type

- Well-defined area of radiolucency that forms single compartment.
- If this type associated with unerupted tooth resemble dentigerous or odontogenic keratocyst.
- Can also mimic unicystic ameloblastoma.

Macroscopic Findings

Specimen

- Tumor with surrounding margin of normal bone.
- Color-grayish white or grayish yellow mass replacing bone.
- Tumor tissue cuts readily and contain no calcified mass.
- Some lesions are completely solid.
- But most cases cystic spaces present which are quite small and scattered randomly.
- Less frequently cysts are larger and appear multicystic.

Cyst Content

- Straw-colored fluid to semisolid gelatinous material.
- Sometimes lesion has single cyst in which case there may be close resemblance to unicystic ameloblastoma or an odontogenic cyst. However, if one or more small nodules or growth protrude from unicystic ameloblastoma otherwise smooth lining, a preliminary diagnosis of ua must be considered.
- One or more teeth may be unicystic ameloblastoma involved by the tumor.

Histopathological Features

Definition by WHO 1992 classification

A polymorphic neoplasm consisting of proliferating odontogenic epithelium which usually has follicular or plexiform pattern lying in a fibrous stroma.

Histopathological Variants

Follicular SMA (Fig. 10.10)

- Most common 32% among ameloblastomas.
- Follicular islands consists of central mass of polyhedral cells or loosely connected angular cells resembling stellate reticulum.
- Surrounded by peripherally arranged cuboidal or columnar cells resembling inner enamel epithelium or preameloblasts.
- Cystic degeneration occur within follicular epithelial islands.

Plexiform SMA (Fig. 10.11)

- Second most common—28% among ameloblastomas.
- Tumor epithelium is arranged as a network which is bound by a layer of cuboidal to columnar cells and include cells resembling stellate reticulum.
- Cyst formation occur due to stromal degeneration rather than cystic changes within epithelium.

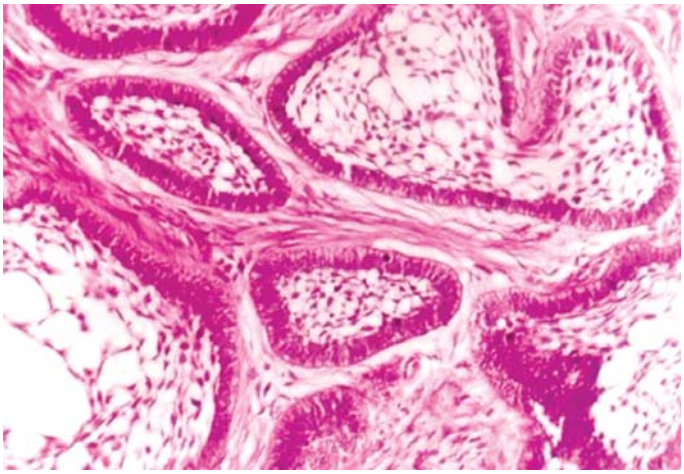


Fig. 10.10: Follicles with ameloblast like cells at periphery and stellate reticulum cells with cyst formation in follicle

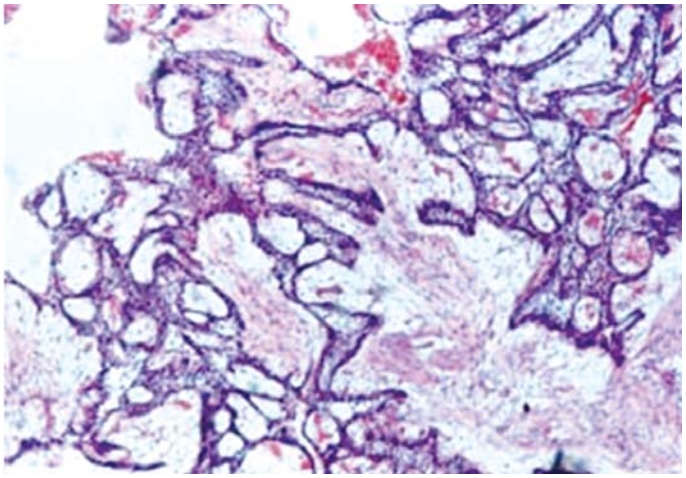


Fig. 10.11: Network of tumor epithelium bound by a layer of cuboidal to columnar cells entrapping stellate reticulum like cells

Acanthomatous SMA (Fig. 10.12)

- Third most common—12% among ameloblastoma.
- Usually in follicular type, there is extensive squamous metaplasia, sometimes with keratin formation within islands of tumor cells.
- Horny pearls may calcify.

Differential Diagnosis

Squamous odontogenic tumor
In squamous odontogenic tumor, peripheral cells of tumor islands are flat rather than columnar.

Granular Cell SMA (Figs 10.13A and B)

- Counts for 5% of SMAs.
- Mostly follicular type shows an extensive granular transformation of central stellate reticulum like cells.
- Some lesion show all cells of tumor or nests are composed of granular cells.
- Granular cells may be cuboidal, columnar or rounded and cytoplasm is filled by acidophilic granules.

Ultrastructurally

Granules are lysosomal aggregates.

Immunohistochemical Analysis

- Granularity might be caused by increased apoptotic cell death and associated phagocytosis by neighboring neoplastic cells.
- Previously this variant was considered to have more aggressive, but now immunhistochemical analysis has shown that these granular cells are nonfunctional so it is not aggressive lesion.

Basal Cell SMA

Counts for 2% of SMAs
- So rare entity.
- Predominantly have basaloid pattern.

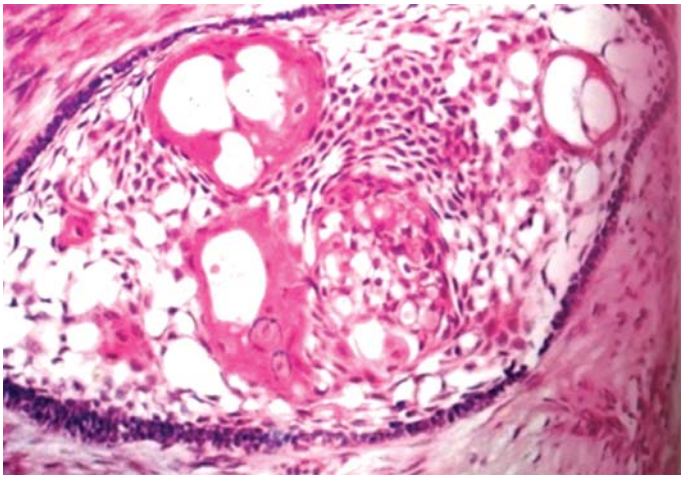
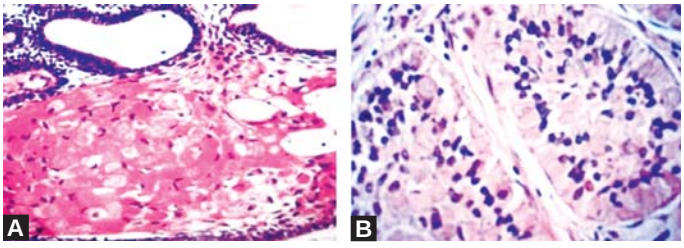
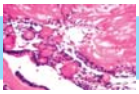


Fig. 10.12: Follicular type showing extensive squamous metaplasia



Figs 10.13A and B: Granular ameloblastoma (central cells showing granularity)



Immunohistochemical Findings

Philipsen et al used monoclonal anti-PCNA (proliferating cell nuclear antigen) antibody and monoclonal anti-ki-67 antibody in this lesion.

Result

Basal cell solid/multicystic ameloblastomas has the highest labeling indices for both PCNA and ki-67.

Conclusion

Basal cell SMAs is most actively proliferating type and so the most immature cells are found in an SMA.

Clear Cell Solid/Multicystic Ameloblastoma

- Clear PAS positive cells most often localized to stellate reticulum like areas of follicular solid/multicystic ameloblastoma type.
- Some clear cell solid/multicystic ameloblastoma proved to be malignant.

Keratoameloblastoma (KA) and Papilliferous KA (PKA)

Pindborg described partly of keratinizing cyst and partly of tumor islands with papilleferous appearance so coined the term PKA. KA, PKA or possible hybrid lesions of the two are extremely rare neoplasms.

Mucous Cell Differentiation in Solid/Multicystic Ameloblastoma

Wilson et al, described intraosseous follicular type solid/multicystic ameloblastoma showing mucous cell differentiation.

Hemangiomatous Ameloblastoma (HA)

Part of solid/multicystic ameloblastoma tumor containing spaces filled with blood or large endothelial lined capillaries described by kuhn in 1932.

Hypothesis for Origin

Excessive stimulation of angiogenesis during tumor development and trauma such as tooth extraction.

- May represent collision tumors.

Lucas Postulated

- Unusual vascularity is not due to a neoplastic process.

According to philipsen et al;

- There was entire absence of vasoformative activity.
- In process of formation of stromal cysts in ordinary type of plexiform ameloblastoma, the blood vessel often persist and dilate instead of disappearing so it is likely to represent a purely secondary change.

Extragnathic (Tibial) Adamantinoma (ETA)

- Rare, primarily intraosseous epithelial neoplasm of low grade malignancy with a marked predilection for tibia.
- 90% case arise in middle third of bone.

Stroma

- Consist of fibroblasts and collagen fibers.
- Tollhouse et al reported occurance of myofibroblast that showed formation of plaque-like structure on extended cell processes which philipsen et al identified as intracellular septate junctions.

Treatment

- Solid/multicystic ameloblastomas —radical surgical intervention
- Follow-up regularly
- Recurrence may occur 5 to 10 years after surgery.

UNICYSTIC AMELOBLASTOMA (UA)

Previously used terms were:

- Cystic (intracystic) ameloblastoma
- Ameloblastoma associated with dentigerous cyst
- Extensive dentigerous cyst with intracystic ameloblastic papilloma
- Mural ameloblastoma
- Dentigerous cyst with ameloblastomatous proliferation
- Ameloblastoma developing in a radicular or globulo-maxillary cyst

Introduction

Philipsen nomenclature

- Term unicystic is derived from macroscopic and microscopic appearance
- Well-defined lesion
- Often large monocystic cavity with a lining, focally but rarely entirely composed of odontogenic epithelium.
- Term unilocular used radiographically of a radiolucent lesion having only one locus or compartment.
- But it is a fact that unicystic ameloblastoma may appear as multilocular bone defect.

Pathogenesis

- Arise from pre-existing odontogenic cyst-dentigerous cyst.
- Arise *de novo.*
- Transition from a non neoplastic cyst to a neoplastic one.

Concept of de novo origin is favored as

Li et al compared PCNA expression in cystic tumor lining of Unicystic ameloblastomas with published data on odontogenic cyst lining.

Result

All areas of unicystic ameloblastoma lining contained significantly more PCNA positive cells than dentigerous cyst linings.

Conclusion

It is favorable to concept that UAs are *de novo* cystic neoplasm.

Clinical Features

- Relative frequency-5% to 22% of all types of ameloblastoma.
- Age—mean 22 years
- Location—maxilla<mandible=1:7
- Local swelling
- Occasionally, pain and signs of lip numbness as well as discharge of drainage in case of secondary infection.

Radiographical Features

Unilocular radiolucency seen.

Macroscopic Findings

- If removed *in toto* then partially or totally collapsed cystic sac seen.
- One or several intraluminal papilloma like tissue proliferations and or intramural focal thickening or nodules seen.
- Definite diagnosis can be made only histopathologically.

Note: Examination of entire lesion through sectioning at many levels is mandatory for securing final diagnosis.

Histopathology

- Minimum criteria for diagnosis is demonstration of a single often macroscopic cystic sac, with an odontogenic epithelium which is usually present only in focal areas.
- Often accompanied by an innocuous epithelium of varying histologic appearance that may mimic the lining of a dentigerous cyst or radicular cyst.

Three Histologic Subtypes (Fig. 10.14)

1	Luminal unicystic ameloblastoma
2a	Luminal and intraluminal
2b	Luminal, intraluminal and intramural unicystic ameloblastoma
3	Luminal and intramural unicystic ameloblastoma.

Luminal Unicystic Ameloblastoma (Fig. 10.15)

According to Vicker and Gorlin proposed three criteria for Epithelial lining of which parts may show transformation;

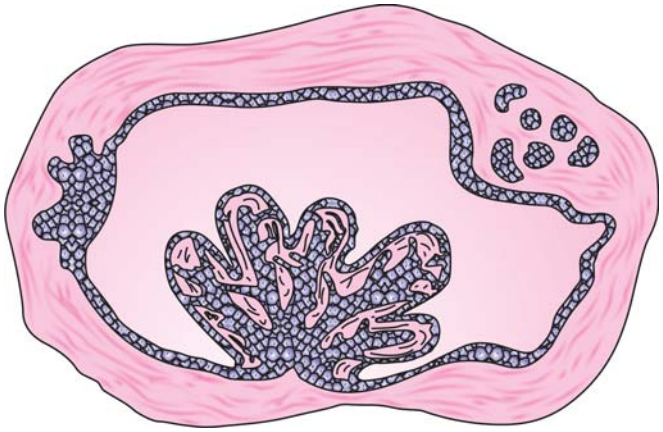


Fig. 10.14: Variants of unicystic ameloblastoma

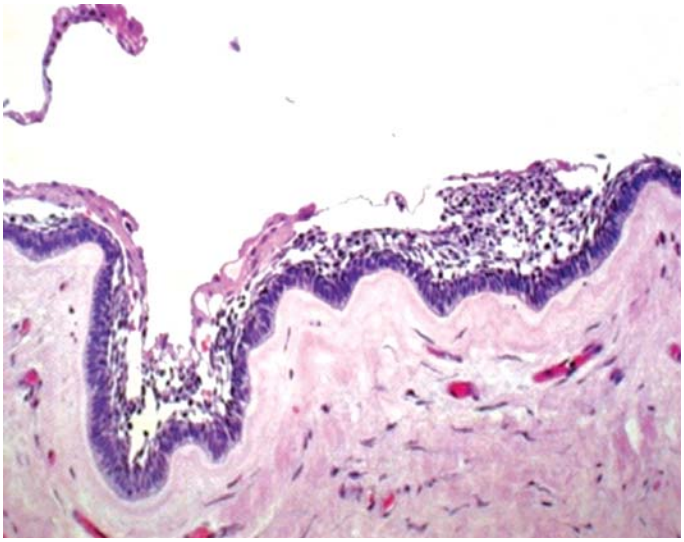


Fig. 10.15: Luminal unicystic ameloblastoma

(V and G criteria as representative of early ameloblastomatous transformation of epithelial lining)

- To cuboidal or columnar basal cells with hyperchromatic nuclei.
- Nuclear palisading with polarization of basal cells.
- Cytoplasmic vacuolization with intercellular spacing and subepithelial hyalinization.

Intraluminal Unicystic Ameloblastoma (Fig. 10.16)

- Mural means wall so neoplastic growth or islands seen in fibrous wall or connective tissue of lesion (Fig. 10.17)
- Type 2 is sometimes refered as plexiform unicystic ameloblastoma.

Treatment

- Conservative surgical enucleation.

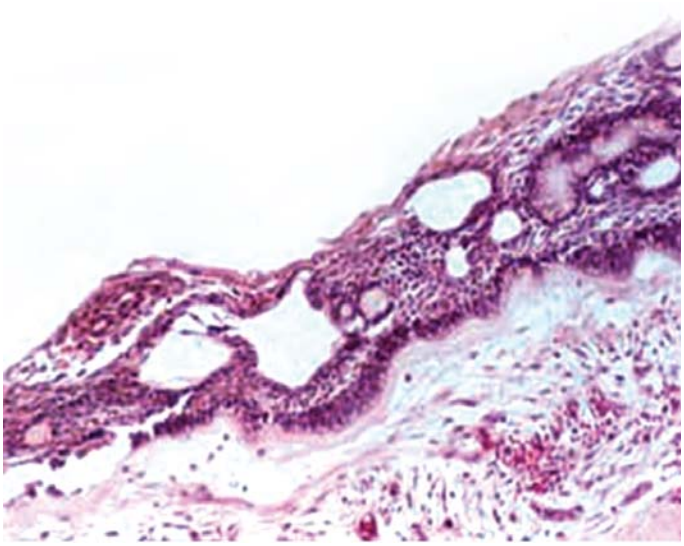


Fig. 10.16: The neoplastic growth extends in cystic lumen

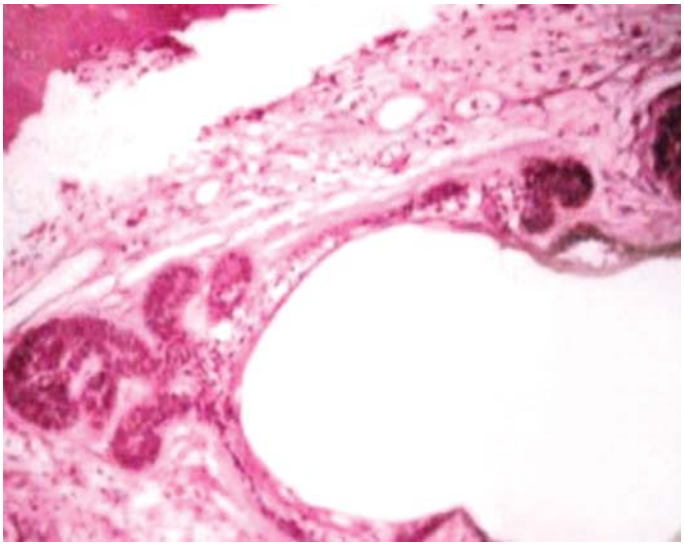


Fig. 10.17: Mural variant exhibiting tumor growth in fibrous wall

- If infiltration from epithelial cyst lining into the cyst wall—treatment should follow that outlined for solid/multicystic ameloblastomas.

PERIPHERAL AMELOBLASTOMA (PA)

- Extrosseous ameloblastoma
- Soft tissue ameloblastoma
- Ameloblastoma of mural origin
- Ameloblastoma of gingiva

Introduction

- Occur in soft tissues overlying tooth bearing areas of maxilla and mandible.
- Do not invade underlying bone.
- Basal cell carcinomas (BCCs) arising in gingiva are same lesions as PA.
- First case of peripheral ameloblastoma was reported by Stanley and Krogh.

Pathogenesis

- Odontogenic epithelial cell remnants.
- Serres pearls.
- Gingival epithelium.

Clinical Features

- Relative frequency—2% to 10% of all ameloblastoma.
- Age: range 9 to 92 years, with mean age of 52 years.
- Mean age for men — 52.9 years.
- Mean age for females — 50.6 years.
- 64% cases occur in 5th, 6th and 7th decade out of it men comprise 45.2% and female 18.5%.
- Men reaches peak in 5th and 6th decade of life.
- Females show two peaks, one in 4th and second in 7th decade.

Note: Most of peripheral odontogenic tumor occur at lower mean age than their corresponding (true) intraosseous counter part.

- *Gender*: male:female = 1.9:1
- *Location*: mandible > maxilla = 72%>28%
- Mandibular premolar region > anterior mandibular region
- If in maxilla then in mostly soft palatal tuberosity area.
- *Majority of mandibular*: Peripheral ameloblastoma are located in lingual aspect of gingiva.
- Lesion occur as painless, sessile, firm and exophytic growth, surface of which is usually relatively smooth but in several cases has been described as 'granular' or 'pebbly'.
- Some cases appear papillary or warty.
- Color: Normal or pink and red or dark red.
- If traumatized often during mastication show ulceration or appear keratotic.
  - Duration: 2 days to 20 years.
  - Size: 0.3 to 4.5 cm in diameter with a mean of 1.3 cm.

Radiographic Features

- Mostly no evidence of radiographic appearance
- At surgery superficial erosion of bone or superficial bony depression, cupping or saucerization can be seen which is caused by pressure resorption.

Macroscopic Examination

- Gross specimen firm to slightly spongy mass of pink to pinkish gray color.

- Cut surface may contain minute cystic spaces filled with clear, pale yellow fluid.
- Occasional areas of dystrophic calcification are very small so cannot be disclose by cutting through specimen or detected on radiographs.

Microscopic Features

Histologic Definition by Philipsen

Benign neoplasm (or hamartomatous lesion) confined to soft tissue overlying the tooth bearing areas of the jaws or alveolar mucosa in edentulous area.

The tumor consist of proliferating odontogenic epithelium that exhibits same histomorphologic cell types and pattern as seen in solid/multicystic ameloblastoma. The stroma is that of mature, fibrous connective tissue. Occurrence of calcification, dentinoid, bone like or cementum like masses are not characteristic histologic feature of Peripheral ameloblastomas.

Histopathology (Fig. 10.18)

- Most of epithelial islands exhibit palisading of columnar basal cells, but stellate reticulum is seldom conspicuous.
- A basaloid lesion without classical follicular component but often exhibiting acanthomatous areas is difficult to distinguish from basal cell carcinoma.
- Some of squamous cells in acanthomatous nests may show ghosting (ghost cell formation and foreign body reaction to this material within connective tissue) features generally associated with calcifying ghost cell odontogenic cyst.
- Number of cases of Peripheral ameloblastomas exhibiting areas composed of clear cells have been reported.
- In some parts of tumor, clear cells occurred as discrete clusters or in direct transition from ameloblastic (often acanthomatous) tumor cells.
- These clear cells are cytomorphologically and histochemically identical to those reported to occur in dental lamina and in several other lesions of odontogenic origin like lateral periodontal cyst, gingival cyst of adult, calcifying ghost cell odontogenic tumor, calcifying epithelial odontogenic tumor and clear cell odontogenic carcinoma.

Biological Behavior

Not aggressive.

Malignant Variants

Total six cases of malignant PAs reported.

Differential Diagnosis

- Epulis > benign tumors > papilloma > pyogenic granuloma Correct diagnosis can be made on histologic evalution.
- Peripheral odontogenic fibroma (POF) (WHO or complex type)

Proliferation of strands and islands of odontogenic epithelium in this tumor may be so extensive as to make the distinction from peripheral ameloblastoma very difficult (Fig. 10.19).

- Peripheral variant of squamous odontogenic tumor
- Odontogenic gingival epithelial hamartoma (OGEH)

Treatment

- Excision
- No recurrence in follow-up

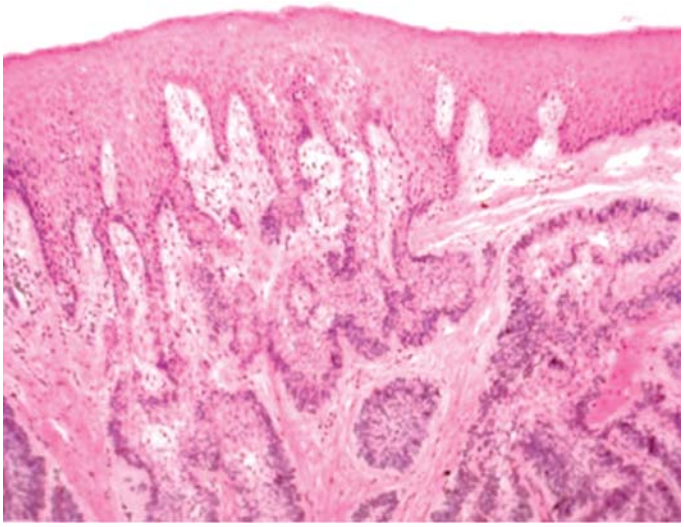


Fig. 10.18: Proliferating odontogenic epithelium as of SMA in mature fibrous connective tissue

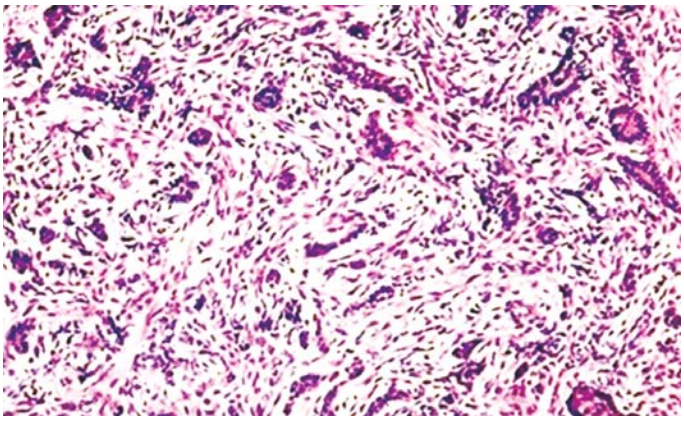


Fig. 10.19: Islands of odontogenic epithelium in fibrous stroma

DESMOPLASTIC AMELOBLASTOMA

Occur in elder age group so not discussed here.

SQUAMOUS ODONTOGENIC TUMOR (SOT)

INTRODUCTION

- Pullon et al in 1975 first described a particular squamous odontogenic tumor in periodontium.
- It is an epithelial odontogenic tumor.
- Also called as squamous odontogenic hamartoid lesion
- Lde et al in 1999 reported sot associated with squamous cell carcinoma.
- Can suspect malignant variant of squamous odontogenic tumor.

Pathogenesis

- Epithelial rests of malassez localized in periodontal ligament.
- Peripheral SOTs in gingival surface epithelium as a "dropping off" phenomenon or from remnants of dental lamina.
- May have hamartomatous nature.
- In case of origin from surface epithelium, tumors appeared histologically as pseudoepithelomatous hyperplasia or peripheral ameloblastomas.

Clinical Feature

- Benign but locally infiltrative odontogenic neoplasm.
- Slow growing with few clinical signs and symptoms.
- Mobility of teeth in area of involvement.
- Swelling of alveolar process.
- Moderate pain.
- Most cases develops in periodontal ligament of permanent teeth, so most common variant is intrabony or central type of squamous odontogenic tumor.
- Rare peripheral variant has also been described.
- Some squamous odontogenic tumors are localized in edentulous area and multicentric occurence been reported.
- Maxillary lesions are aggressive than mandibular.
- Age- range 8 to 74 years with mean of 38 years and peak in 3rd decade.

Gender

Male > female = 1.4:1

Location

Mandibular molar region > anterior mandible = Anterior maxilla > maxillary molar area.

Radiological Features

Central Variant

- Well-defined unilocular and triangular radiolucency between roots of adjacent teeth.
- Radiopacities found in other odontogenic tumors are not found in SOTs.
- Extensive SOTs—multilocular pattern involving mandible or maxillary sinuses.

Peripheral Variants

Saucerization of underlying bone caused by pressure resorption.

Histopathological Findings (Figs 10.20 and 10.21)

- Squamous odontogenic tumor is composed of islands of well differentiated squamous epithelium of varying size and shape.
- Islands are rounded or oval or may be irregular cord-like structure as is characteristic of desmoplastic ameloblastomas.
- Individual tumor reveal a peripheral layer of low cuboidal or even flat epithelial cells.
- Individual epithelial islands may undergo central microcystic degeneration of spinous cells following single cell keratinization.
- Some islands may become large and contain laminar calcified material.
- Mitotic activity of epithelial tumor cells is not increased.
- Tumor islands are surrounded by mature connective tissue with little or no inflammatory reactions.

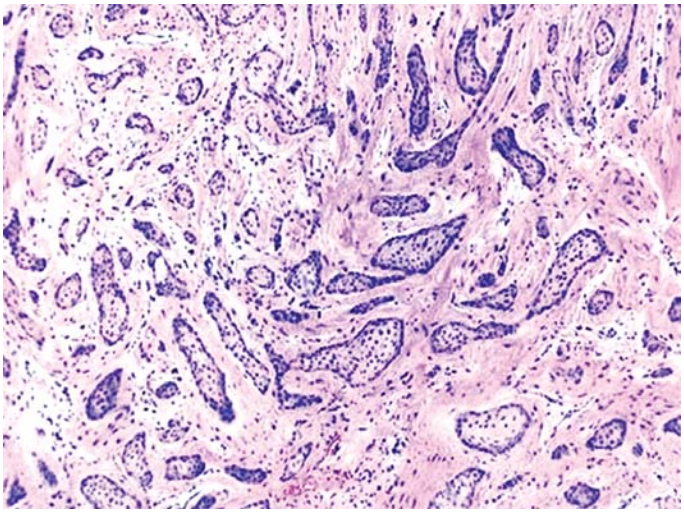


Fig. 10.20: Low power—rounded or oval islands of well-differentiated squamous epithelium in mature connective tissue

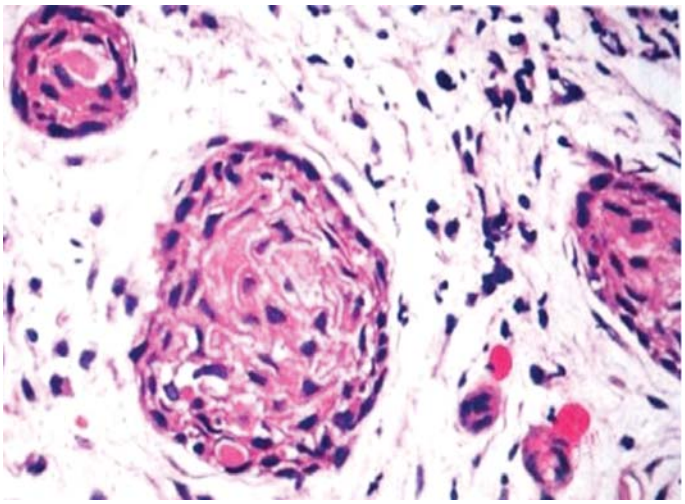


Fig. 10.21: High power—tumor reveal a peripheral layer of low cuboidal epithelial cells

Similar Lesions as Squamous Odontogenic Tumor

- Acanthomatous or desmoplastic ameloblastomas.
- Well differentiated squamous cell carcinoma
- Pseudoepitheliomatous hyperplasia comparable to keratoacanthoma.

Treatment

Enucleation, curettage, or local excision.

CALCIFYING EPITHELIAL ODONTOGENIC TUMOR (PINDBORG TUMOR)

INTRODUCTION

In 1955 Pindborg described this lesion.

Prior to 1955 it was known as:

- Ameloblastoma of unusual type with calcification
- Calcifying ameloblastoma
- Malignant odontoma
- Adenoid admantoblastoma
- Cystic complex odontoma
- Variant of solid/multicystic ameloblastomas.

Pathogenesis

- *Initial opinion*: Reduced enamel epithelium of unerupted tooth as initial case reported were associated with unerupted teeth.
- *Later*: Choudhery and associates stated that tumor cells exhibit morphologic characteristics of squamous epithelium.
- *Peripheral variants*: Rests of dental lamina or from basal cells of oral epithelium.

Clinical Features

- Relative frequency—0.4 to 3%of all odontogenic tumors.
- Peripheral variant—6% of total calcifying epithelial odontogenic tumor.
- Age—range 8 to 92 years with mean of 37years.

Variant	Range (years)	Mean age (years)
Intraosseous	8 - 92	39
Extraosseous	12 - 64	34

Mostly occurred in 3rd, 4th and 5th decade.

Gender

Male: female=1:1

Location

- Maxilla < mandible = 1:2
- Focal lesions but recently one case of multifocal involvement of both jaw been reported.
- Mostly involve premolar and molar region.
- Posterior maxilla > anterior maxilla
- Rare benign neoplasm located intra or extraosseously.
- Intraosseous (more common)- may show local invasiveness.
- Present as painless mass with slow growth.
- If present in maxilla—complains of nasal congestion, epistaxis and headache.
- Expansile lesion of jaw
- Displacement of teeth.
- Pain or parasthesia when tumor grows.

Radiographic Feature

- Irregular uni/multilocular radiolucent areas containing radiopaque masses of varying size and opacity gives 'snow driven appearance'.
- Tumors of short duration— calcified concrements are minute and may be undetectable on radiographs.
- When associated with unerupted tooth— radiopacities tend to be located close to tooth crown.
- At periphery—radiolucent margin may or may not be clearly demarcated from normal bone.

Macroscopic Features

- Intraosseous lesion—easily enucleated
- Size—1 to 4 cm in diameter
- Color-greyish white to yellow to tan pink.
- Bisecting the specimen reveals calcified masses that make crunching sound during cutting.
- Tumor may be solid or contain minute cystic spaces.
- If associated with unerupted tooth, the crown or hard dental structures of an odontoma can be found embedded in tumor mass.

Microscopy

Histologic definition by WHO 1992

Locally invasive epithelial neoplasia characterized by development of intraepithelial structure, probably of an amyloid like nature which may become calcified and which may be liberated as the cells break down.

Histopathological Features (Figs 10.22A and B and 10.23)

- Clusters, sheets and rare isolated pleomorphic cells of squamoid type, blocks of amorphous material encircled by fibroblasts and occasionally calcification.

Epithelial Cells

- Cellular outlines are distinct.
- Intercellular bridges may be noted.
- Pleomorphic nuclei, giant nuclei may be seen but it is not neoplastic.

In between epithelial cells,

- Areas of amyloid like deposition seen.
- Calcification which are distinct feature of tumor develop within amyloid like material and form concentric rings (Liesegang ring calcifications) which tend to fuse together and form large complex masses.

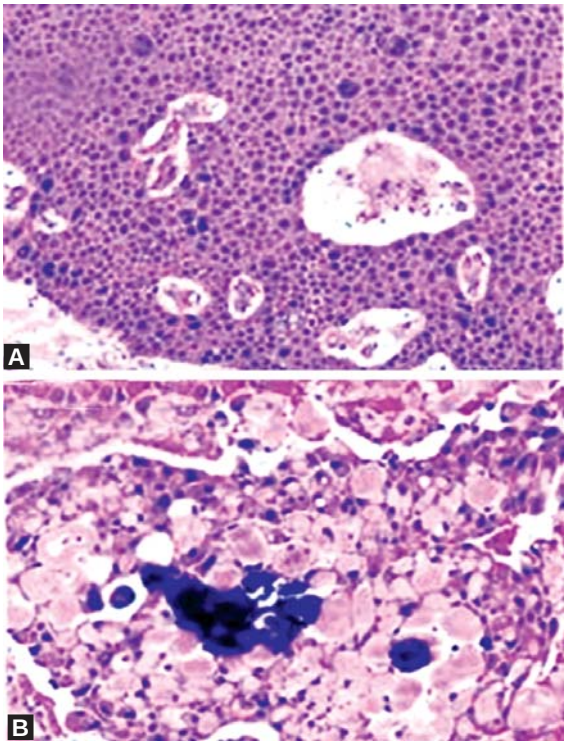


Fig. 10.22: (A) low power—cluster,sheets and isolated pleomorphic epithelial cells with areas of amyloid deposition, (B) medium power showing calcification in amyloid areas

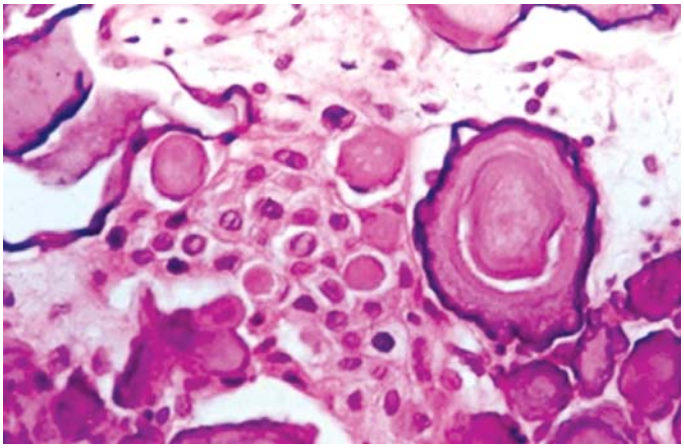


Fig. 10.23: High power—prominent desmosomal attachment of epithelial cells and liese gang ring calcification in amyloid deposition

Microscopic Variants

- Large sheets of epithelial cells with minimal production of amyloid like material and calcification.
- Large diffuse masses of amyloid like material that contain only small nests or islands of epithelial cells.
- A predominant clear cell variant in significant portion of epithelial cells.

Nature of Amyloid

- With Congo-red staining it gave apple green birefringes viewed in polarized light similar to true amyloid.
- Role of APin protein that is present in ameloblasts have been thought to play a role in amyloid production.
- Peripheral variant show minimal or total lack of calcified material.
- Cementum like components of calcifying epithelial odontogenic tumor stroma have been found.
- Mechanism still unclear.
- Majority of homogeneous masses of calcifying epithelial odontogenic tumor stroma is thought to be dystrophic calcifications.
- Slootwey suggested that amyloid-like material is an inductive stimulus for stromal cells to differentiate towards production of collagenous matrix that is destined to mineralize and resemble cementum.

Occurrence of Clear cells

- Sheets of classic polyhedral epithelium with abundant eosinophilic cytoplasm may alternate with zones of epithelium characterized by large cells with clear, foamy cytoplasm and distinct cell border.
- Yamaguchi et al—clear tumor cell represents features of cytodifferentiation rather than simple degenerative phenomenon.

- Age—14 to 68 years with mean of 41.5 years

Clear cell variant of CEOT	Mean age of occurence (years)
Intraosseous clear cell CEOT	41.5
Extraosseous clear cell CEOT	34.3

Gender Involvement

- Intraosseous clear cell calcifying epithelial odontogenic tumor—male: female =1 : 2
- Extraosseous clear cell calcifying epithelial odontogenic tumor —
  male: female = 1 : 1

Note: possibility of aggressiveness can be viewed.

Note: Cystic variant of calcifying epithelial odontogenic tumor also been reported recently.

Treatment

- Calcifying epithelial odontogenic tumor of mandible—enucleation with a margin of macroscopic normal tissue.
- Calcifying epithelial odontogenic tumor of maxilla—need more aggressive treatment as they tend to grow more rapidly then their mandibular counterpart.

ADENOMATOID ODONTOGENIC TUMOR (AOT)

INTRODUCTION

Unal and coworkers stated that steensland's report from 1905 of an epitheloma adamantinum represents earliest adenomatoid odontogenic tumor.

Terms used

- Adenoameloblastoma as was considered a histologic variant of solid/ multicystic ameloblastoma.
- In 1969, Philipsen and Birn proved that it was clearly distinguishable entity from solid/multicystic ameloblastoma and introduced term adenomatoid odontogenic tumor which was adapted by WHO in 1971.

Pathogenesis

Derived from dental lamina or its remnants.

Clinical Features

- Relative frequency = 2.2% to 7.5% of all odontogenic tumors so 4th or 5th among odontogenic tumors after odontomas > SMAs > myxomas.
- Benign, non-neoplastic (hamartomatous) lesion with a slow but progressive gowth.
- Both intra and extraosseous variant exist.

Age

- Range 3 to 82 years with peak in 2nd decade.
- Half of cases occur within teens (13 to 19)years, so unique among other odontogenic tumors.

Gender

Male : female=1:1.9

Location

Three clinicotopographic variants:

- Follicular
- Extrafollicular
- Peripheral
- Follicular and extrafollicular varaiants are intrabony or central tumors and accounts for 95.6% of all adenomatoid odontogenic tumors out of which 71.3% are follicular type.
- More commonly found in maxilla than mandible = 2:1
- Peripheral variant mostly occur in anterior maxilla.

Distribution in unerupted permanent teeth in association with follicular aot:

- All 4 canines—59% out of which maxillary canines involved were 40%.
- Unerupted 1st and 2nd molar are most rarely involved in Adenomatoid odontogenic tumors.
- Association between central adenomatoid odontogenic tumors and unerupted deciduous teeth is rare.

Peripheral variant

- Rare, 4.4% of all adenomatoid odontogenic tumors.
- Mean age—13 years.

Gender

Male < female=1:14 (unique).

Location

Anterior maxillary gingiva is most common site.

Note: Infants also this variant occurred.

Radiographic Features

Variants (Fig. 10.24)

Follicular (F) Intraosseous follicular type—tumor located around the crown and often covers part of the root of an unerupted tooth (envelopmental)

- Extraosseous follicular types
  E_1- no relation to tooth structure either erupted or unerupted.
  E_2- interradicular, adjacent roots diverge apically due to tumor expansion.
  E_3- superimposed on root apex.

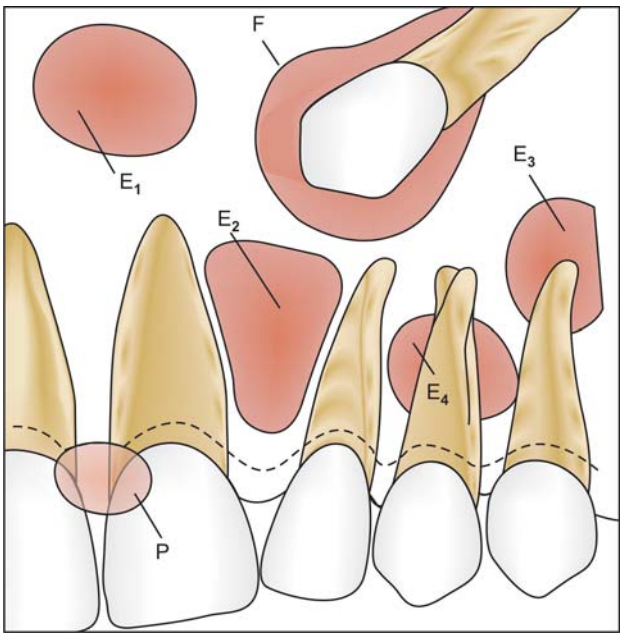


Fig. 10.24: Radiographic variants

E_4- superimposed on mid root level.

- Extraosseous peripheral epulis type: P- exhibit slight erosion of the bone crest.

Note:

- Growth of intrabony variants results in cortical expansion leading to displacement of neighboring teeth due to tumor expansion is much more common than root resorption.
- Peripheral variants appear as gingival fibroma or epulis like growth attached to labial or palatal gingiva.

Macroscopic Features

- Roughly spherical in shape with a well-defined fibrous capsule.
- Cut surface—solid tumor mass or several small cystic spaces containing a yellowish, semisolid material.
- Follicular type—crown and often part of root of an unerupted tooth is found embedded in the tumor mass or projecting into cystic spaces.
- A cystic cavity if present within an adenomatoid odontogenic tumor, is always lined by nonkeratinizing stratified squamous epithelium.

Microscopy

Histologic definition by WHO 1992, A tumor of odontogenic epithelium with duct like structures and with varying degrees of inductive changes in the connective tissue. The tumor may be partly cystic and in some cases the solid lesions may be present only as masses in the wall of a large cyst. It is generally belived that lesion is not a neoplasm.

Histopathological Findings

- Irrespective of tumor variants, histology of adenomatoid odontogenic tumors is identical and exhibit remarkable consistency.
- Low magnification feature—most striking pattern is that of multisized solid nodules of cuboidal or columnar epithelial cells forming nests or rosette like structure with minimal stromal connective tissue (Figs 10.25 and 10.26).
- Between the epithelial cells of nodules and in center of rosette like configuration, eosinophilic amorphous material (tumor droplets) as well as calcified bodies are present.
- Spindle-shaped or polygonal, closely opposed epithelial cells with dense eosinophilic cytoplasm and round hyperchromatic nuclei fill in the spaces between the epithelial nodules.
- Conspicuous within the cellular areas are structures of tubular or duct like appearance.
- Duct-like spaces are lined by a single row of low columnar epithelial cells, the nuclei of which are polarized away from the luminal surface.
- Lumen may be empty or contain a variable amount of eosinophilic material or cellular debris.
- Ducts vary in diameter and not always present.
- However due to the overall distinctive histomorphology of adenomatoid odontogenic tumor; the diagnosis can usually be secured without the presence of duct-like structures.
- In addition to forming ducts, the cuboidal or columnar cells form convoluted cords or bodies in complicated patterns that often exhibit invaginations.

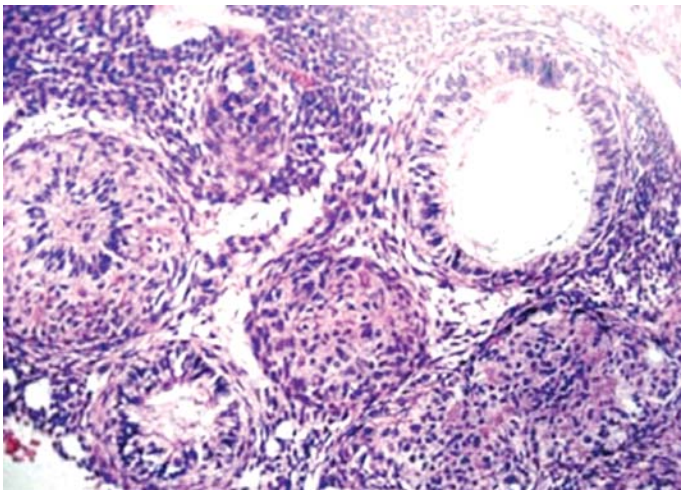


Fig. 10.25: Multisized solid nodules of cuboidal or columnar epithelial cells arranged in rosette pattern (low magnification)

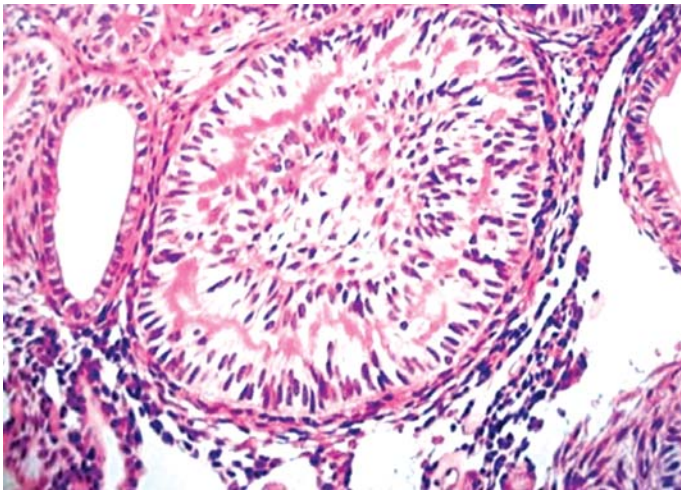


Fig. 10.26: High magnification

- Another characteristic cellular pattern is nodules composed of polyhedral, eosinophilic epithelial cells of squamous appearance exhibiting well-defined cell boundries and prominent intercellular bridges.
- Nuclei may show mild pleomorphism (degeneration).
- These islands may contain pools of amorphous amyloid like material and globular masses of calcified substances.
- So adenomatoid odontogenic tumor combined with calcifying epithelial odontogenic tumor lesion found in many cases termed as combined odontogenic tumors.
- Another epithelial pattern; found between and connecting the cell rich nodules and particularly at the tumor periphery.
- This pattern is composed of structures of epithelium, one to two cells in thickness, forming a trabecular or cribriform configuration.
- Occasional foci of mitotic activity may be found.
- Rarely; melanin pigmentation of both tumor and stroma cells and the presence of melanocytes may be found in AOTs as in several other odontogenic tumors and hamartomas.
- Also found hyaline, dysplastic dentinoid material or calcified osteodentin in adenomatoid odontogenic tumors have been described.
- As the stroma is that of a fibrous, mature connective tissue without ectomesenchymal features, the production of dysplastic dentinoid is likely the result of metaplastic process and not to be interpreted as an epithelioectomesenchymal induction phenomenon.
- Calcified material in varying amounts occur in most lesions.

Connective Tissue Stroma

Loosely structured and contains thin-walled congested vessels characteristically showing marked degenerative (fibrinoid) changes of the endothelial lining, vessel wall and perivascular connective tissue.

Treatment

Conservative surgical enucleation or curettage.

KERATOCYSTIC ODONTOGENIC TUMOR

Note on consideration of odontogenic keratocyst (OKC) as benign cystic neoplasm

Recently a wealth of clinical and molecular (genetic) evidence has indicated that odontogenic keratocyst now has to be regarded as a benign cystic neoplasm.

Earlier mentioned editorial and consensus conference (in July of 2003) in association with the preparation of the forthcoming WHO volume pathology and genetics of Tumors of Head and Neck, there was consensus that odontogenic keratocyst should be included in odontogenic tumor under the term keratinizing cystic odontogenic tumor (KCOT).

There has been a great deal of interest in odontogenic keratocyst since it may grow to a large size before it manifests clinically and that unlike other jaw cyst, it has a particular tendency to reccur following surgical treatment.

A wide discussion on the evidence that has accumulated over the years, that the odontogenic keratocyst may be a benign cystic neoplasm.

So recently a change of terminology shear provocatively used the term 'keratocystoma' in the title.

Other suggestions given are: keratocystic odontogenic tumor by Philipsen in 2005, and keratinzing cystic odontogenic tumor by Reichert and Philipsen in 2004.

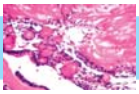
In 2005, the WHO working group considered odontogenic keratocyst (OKC) to be a tumor and recommended the term keratocystic odontogenic tumor (KCOT), separating the lesion from the orthokeratinizing variant, which is now considered an odontogenic cyst termed as orthokeratinized odontogenic cyst (OOC).

Facts for considering odontogenic keratocyst as benign cystic neoplasm:

- Clinical evidence
  - More aggressive than other cysts
  - High recurrence rate
- Molecular (genetic) evidence.

p53

- Ogden et al (1992) investigated to demonstrate increased expression of p53 in odontogenic keratocyst.
- p53- normal p53 gene has short half life in normal cells and cannot be detected by immunohistochemistry (IHC).
- But when it mutates, the p53 protein product is more stable and can be detected using IHC.



- p53 protein has been demonstrated in a wide range of malignant lesions but not in normal cells.

Result

p53 was found positive by presence in nucleus.

Proliferating Cell Nuclear Antigen (PCNA)

- Associated with DNA in S phase.
- To assess rate of cell division, the number of suprabasal mitoses were counted in odontogenic keratocyst.

Result

- Odontogenic keratocyst was only among other types of cyst which was positive for p53 and also positive for PCNA.
- P53 positivity was identified in most of the basal cells of odontogenic keratocyst.
- While PCNA staining was present in all basal cells and most parabasal cells

Remark

PCNA staining indicated that p53 positive cells were actively dividing, because similar regions were positive for both antibodies.

Ki-67

More specific marker of proliferating cells, maximally expressed during S phase.

Result

Increased Ki-67 positive cells in basal and suprabasal layer.

IPO38

- Thosaporn et al (2004) used IPO38 antigen to measure the respective proliferation pattern of odontogenic keratocyst, orthokeratinized odontogenic cyst (OOC), dentigerous cyst (DC) and ameloblastoma.
- IPO38 is an antigen of 14-16 kD, whose expression is constant through most stages of cell cycle except during mitosis where a 400 fold increase in concentration has been observed.
- It is expressed at this high concentration earlier than Ki-67 antigen at the beginning of the cell cycle.

Result

Mean labeling indices of ameloblastomas and odontogenic keratocyst are almost similar and significantly much more higher than other cysts.

CONCLUSION

p53, Ki-67, PCNA and IPO38 antigen have in common that they are all expressed in actively proliferating cells, particularly in neoplasms. The evidence provided by laboratory studies on expression of these substances is that, in general they are expressed more strongly in odontogenic keratocyst than in other odontogenic cysts and more particularly so in the odontogenic keratocysts associated with the nevoid basal cell carcinoma syndrome (NBCCS). Furthermore, evidence of mutation of NBCCS gene patch (PTCH) in odontogenic keratocysts, has made important contribution to the understanding of the cyst, and has provided supportive evidence that the odontogenic keratocyst is a benign cystic neoplasm.

Clinical Features

Parakeratinized and mixed variants (both type keratinization in single lesion) are recognized by:

- Aggressive growth
- Tendency to recur after surgical treatment
- Recurrence rate— 13%
- Time to recur— 1- 23years
- Gender involvement— almost equally seen in both gender
- Age distribution— 6 to 78 years with mean age of 32.8 years
- Peak seen in 3rd decade of life, followed by 2nd decade.
- Mean age for multiple keratocystic odontogenic tumors, with or without nevoid basal cell carcinoma syndrome is lower than focal keratocystic odontogenic tumors.
- Site—mandible>maxilla= 70%:30%, both showing posterior part involvement.
- Multiple keratocystic odontogenic tumor was seen occurring mostly in patients of nevoid basal cell carcinoma syndrome.

Radiographic Appearance

- Range from unilocular to multilocular radiolucency "giving honey coomb" to "soap bubble appearance" .
- May associate with impacted tooth.

Histopathological Features (Fig. 10.27)

- Most of lesions are purely parakeratinized (94%).
- Rest 6% showed mixed parakeratinzation and orthokeratinization.
- Multiple keratocystic odontogenic tumors show parakeratinization.
- Epithelium is corrugated.
- Well-defined basal layer of tall columnar cells showing

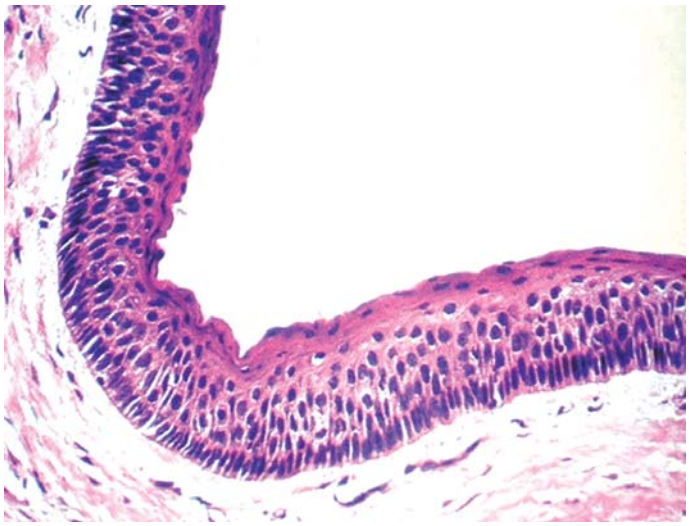


Fig. 10.27: Keratocystic odontogenic tumor (KCOT) showing corrugated, parakeratinized epithelium with palisaded arrangement of basal cells

palisaded appearance due to elongated reverse polarity of nuclei giving "Picket fence appearance".

- Presence of mitotic figures in epithelial layer, as well as epithelial islands, daughter cysts, hyaline bodies, epithelial budding of basal layer and dystrophic calcification been seen.
- Some cases show koilocytosis which is associated with infection with human papilloma virus, a papilloma virus etiology for keratocystic odontogenic tumor can be considered.
- Some keratocystic odontogenic tumor lining may have characteristics of epithelial dysplasia so potential to evolve into ameloblastoma or squamous cell carcinoma.
- Stroma may show daughter cyst, hyaline bodies, dystrophic calcification rarely.

Treatment

Surgical enucleation with long follow-up

BENIGN NEOPLASM AND TUMOR-LIKE LESION SHOWING ODONTOGENIC EPITHELIUM WITH ODONTOGENIC ECTOMESENCHYME WITH OR WITHOUT DENTAL HARD TISSUE FORMATION

Introduction

Also called as mixed tumors as both epithelial and ectomesenchymal component is involved in tumor formation or neoplastic.

As there is epithelial-ectomesenchymal interaction so at any stage these tumors can show dental hard tissue formation.

AMELOBLASTIC FIBROMA

Introduction

- In 1891, kruse described cystic tumors of mandible termed Ameloblastic fibroma.
- True mixed tumor as both epithelial and ectomesenchymal components are neoplastic.
- No hard tissue formation occur in this tumor.

Pathogenesis

According to WHO 1992;

- Ameloblastic fibroma is clearly a neoplasm of odontogenic origin with an epithelial and ectomesenchymal component.
- Morphologically— Ameloblastic fibroma is similar to normal tooth analage before hard tissue formation has started. So due to similarity of Ameloblastic fibroma to dental follicular tissue, latter may be misinterpreted as an odontogenic tumor.

Pathogenetically

- Epithelial component—the ameloblast like-cells are too primitive to induce the cells of ectomesenchyme .
- Little is known about epithelial mesenchymal interation and is unknown why, in contrast to physiologic tooth formation, the step of induction of odontoblastic differentiation is lacking in Ameloblastic fibroma.

According to Philipsen and Reicherts;

They entertain the theory that two variants of ameloblastic fibroma exists:

- Neoplastic type with no induction phenomenon.
- Hamartomatous type showing inductive capabilities.

Clinical Features

- Relative frequency=1.5 to 4.5% of all odontogenic tumors.
- Age = Occur in 1st two decade of life with mean age of 14.8 years.
- Range — 0.5 to 62 years.

Gender

- Male:female=1.4:1

Location

- Mostly involve posterior mandible with mandible to maxilla ratio of 3:1.
- Most of lesions are central variant.
- Recently one case of peripheral variant of ameloblastic fibroma been reported.
- Lesion presents as painless, slow growing, expansile lesion of jaw.

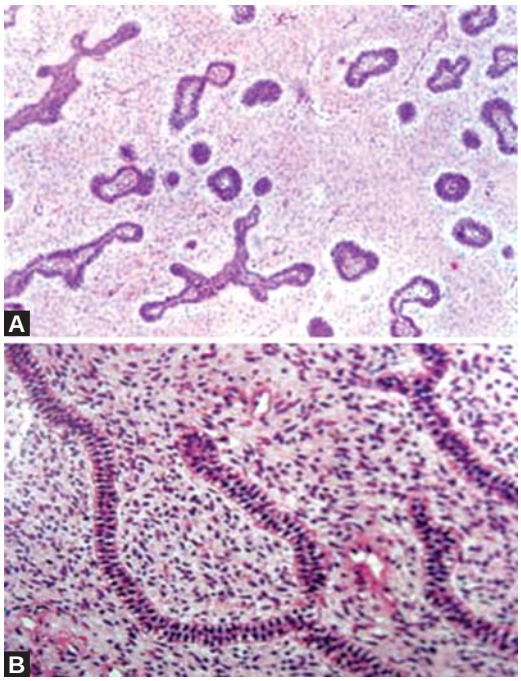
- Clinical symptoms are mild so discovered accidentally on radiographs in about 20% of cases.
- May develop in areas of congenitally missing teeth.
- Size of tumor= 1 to 10 cm in diameter.

Macroscopic Features

- Cut surface—usually round or oval, well circumscribed and of grayish white color.
- Soft mass appears to be surrounded by a thin transparent capsule like border.

Histopathological Findings (Figs 10.28A and B)

- Epithelial tumor component is arranged in strands, cords and islands of proliferating odontogenic epithelium.
- Strands often reveal a double or triple layer of cuboidal cells thus resembling the dental lamina of early tooth development.
- Islands often show peripheral row of high cuboidal or columnar ameloblast like cells.
- Centers of individual tumor islands may enclose a number of cells resembling stellate reticulum.
- Amount and density of epithelial component of ameloblastic fibroma may vary within the same tumor.
- Cyst formation within epithelium is uncommon and if present, remains small.



Figs 10.28A and B: Strands, cords and islands of odontogenic epithelium in immature stroma resembling composed of angular or dental papilla like cells

- Ectomesenchymal cells are rounded or angular and there is little collagen which is represented by a few delicate collagen fibrils.
- Degree of cellularity varies within the same tumor and among tumors.
- Occasionally, some parts of ectomesenchymal components may reveal a loose myxomatous structure with weakly positive metachromatic substance.
- There may be a cell free zone bordering the epithelial islands and strands, rarely juxtaepithelial hyalinization of the type seen in SMA may occur.
- Occasionally hyalinization may be more diffuse.
- Does not reveal a definite capsule histologically.
- Rarely, melanin granules have been found in epithelial tumor component.
- PAP stained specimen reveal branching epithelial structures and a hypercellular stroma.

Variants of Ameloblastic Fibroma

- Granular cell ameloblastic fibroma
  - In 1962 was reported showing characteristically, ectomesenchymal component dominated by granular cells.
  - Proliferative activity of odontogenic epithelium and differentiated towards enamel organ like structure are not present.
  - Foci of dystrophic calcification have been found away from granular cells.

Ultrastructural Findings

- Granular cells found to be similar to those in granular cell myoblastoma and congenital granular cell tumor.
- Granular cells have strong association with the precursors of Langerhan's cells.
- Characteristic mean age is 47 years as opposed to the 1st and 2nd decades for ameloblastic fibroma have led most authors to consider the granular cell ameloblastic fibroma a variant of the odontogenic fibroma.
- Papilleferous ameloblastic fibroma
  - Rare variant
  - Marked proliferation of epithelium with a plexiform arrangement and cyst formation have been described.
- Rare cases ameloblastic fibroma may transform to ameloblastic fibrosarcoma.

Treatment

- Adequate primary surgical removal.
- Recurrence —18-43%, thought to be due to inadequate surgical removal.

AMELOBLASTIC FIBRODENTINOMA (AFD)

INTRODUCTION

- Until now been called dentinoma.
- First described by Straith in 1936.

He defined as 'a very rare neoplasm composed of odontogenic epithelium and immature connective tissue and characterized by the formation of dysplastic dentin.

Pathogenesis

Intermediate stage between ameloblastic fibroma and ameloblastic fibrodontoma (AFO) in terms of histologic differentiation.

Clinical Features

- Slow growing, often asymptomatic tumor which may become quite large.
- May be associated with unerupted teeth in few cases.

Age

First and second decade mostly with a mean of 13.6 years ranging between 4 to 63 years.

Gender

Male : female = 3:1

Location

- Majority in posterior mandible with central variant.
- One case occurring in peripheral ameloblastic fibrodentinoma in gingiva have been described.

Radiological Features

Appears as a fairly well-differentiated radiolucency with varying degree of radiopacity depending upon amount of dentin production either osteodentin or rare tubular dentin.

Pathology

Histologic Definition According to WHO

A neoplasm similar to AF but also showing inductive changes that lead to formation of dentin.

Histopathological Features (Fig. 10.29)

- Ameloblastic fibrodentinoma has same epithelial and ectomesenchymal components as ameloblastic fibroma.
- Composed of strands and islands of odontogenic epithelium in a cell rich primitive ectomesenchyme resembling dental papilla.
- Dentinoid or osteodentin is deposited often preceded by a zone of hyalinization.

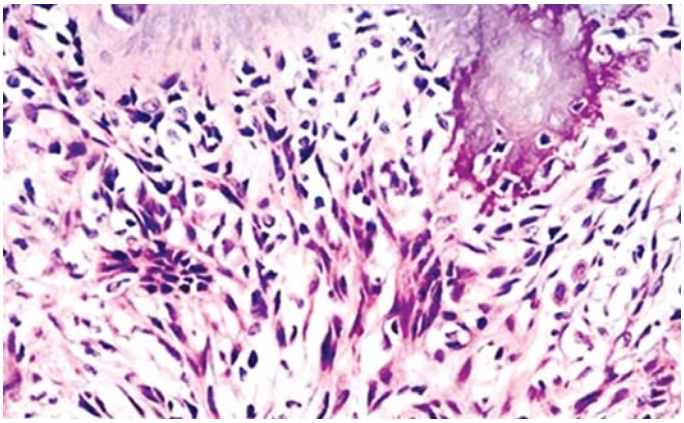


Fig. 10.29: Ameloblastic fibrodentinoma (AFD) showing dentinoid formation

- Abortive or poorly mineralized dentin may contain entrapped odontogenic epithelial and ectomesenchymal cells.
- Active odontoblasts are rare so tubular dentin is rarely seen in ameloblastic fibrodentinomas.
- Enamel matrix is not induced by the presence of osteodentin or dentinoid structures.
- Ameloblastic fibrodentinosarcoma is thought to result from malignant transformation of ectomesenchymal component of ameloblastic fibrodentinoma.

Treatment

Surgical excision.

AMELOBLASTIC FIBRO-ODONTOMA (AFO)

INTRODUCTION

- Immature ameloblastic odontoma.
- Hooker termed it ameloblastic odontoma.
- Rare odontogenic tumor composed of morphological features characteristics of ameloblastic fibroma on one hand and complex odontomas on the other.

Pathogenesis

- Type of mixed odontogenic tumor so odontogenic origin.
- Inductive changes are more advanced and enamel is present in addition to dentin.

Clinical Features

- Well circumscribed, painless, slow growing and expanding tumor with no propensity for bony invasion.
- Tends to produce swelling and has a central location in jaw.

- Majority cases associated with an unerupted tooth which leads to its diagnosis.

Age

- First two decades with mean age of 9 years.
- So tumor of childhood and adolescence.

Gender

Male: female=1.4:1

Location

- Posterior mandible > maxilla
- Exclusive central intraosseous tumor.

Size

Microscopic to large calcified masses of several centimeters diameter.

Variant

- Occurence of multiple ameloblastic fibro-odontomas in family reported by Schmiditseder and Haugmen along with esophageal stenosis, hepatopathy, dyspepsia and increased susceptibility to infection were obsereved.
- A dominant autosomal inherited disorder suspected.

Macroscopic Findings

Appears as circumscribed solid mass of varying size with a smooth surface.

Cut surface of soft part of tumor appears pinkish white and gelatinous.

Calcified masses are of yellowish white color.

Microscopy

Histologic Definition

A lesion similar to ameloblastic fibromas, but also showing inductive changes that lead to formation of dentin and enamel.

Histopathological Features (Fig. 10.30)

- Tissue masses of an ameloblastic fibro-odontomas show structure of an immature complex odontoma consisting of irregularly arranged enamel, dentinoid, cementum and pulp like ectomesenchymal tissue.
- At tumor periphery, next to fibrous capsule, there is a zone of strands and islands of odontogenic epithelium embedded in a typical cell rich ectomesenchyme.
- Dentin production takes place towards the center of lesion.
- Dentin may vary structurally from dentinoid to tubular dentin.

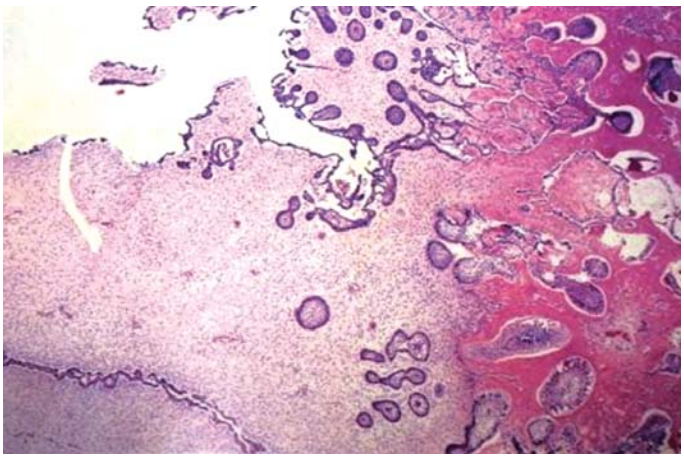


Fig. 10.30: Ameloblastic fibroma like area along with irregularly arranged enamel, dentinoid like hard tissue formation

- Approaching the tumor center, enamel matrix is laid down by the odontogenic epithelium and may appear columnar or pre-ameloblast like.
- Amount of ectomesenchyme gradually decrease as the hard tissue mass dominates the central part of the lesion.
- Cases of excessive melanin deposition was found.

Treatment

Conservative surgical enucleation

ODONTOMA

Mixed tumor as composed of both epithelial and ectomesenchymal component.

Both component, their respective cells may appear normal morphologically, but they seem to have a deficit in structural arrangement.

This defect has led to opinion that odontomas are hamartomatous lesions or malformations rather than true neoplasm.

There are two types of odontomas:

1. Complex odontoma
2. Compound odontoma
   - Distinction between these two entities is based on either;
   - Appearance of well organized tooth like structures (compound)
   - A mass of disorganized odontogenic tissue (complex).
   - Association of odontomas with Gardener's syndrome is also of diagnostic importance.
   - Hirshberg et al reported a case of odontoma with a calcifying odontogenic cyst.

COMPLEX ODONTOMA

Pathogenesis

Considered as a self-limiting developmental anomaly or hamartomatous malformation formed by non descript masses of dental tissues.

Etiology

Unknown but several theories given:

- Local trauma
- Infection
- Family history
- Genetic mutation
- Also suggested inherited from mutant gene or interference possibly post natally with the genetic control of tooth development.

Factors that cause anomalous tissue development in odontomas.

- Unsuccessful or an altered ectomesenchymal interaction in the earliest phase of dental germ development and/or alterations in the subsequent phases of development of these tissues.
- Alteration in the mineralization mechanisms with modifications of the mineral component in the enamel may lead to incomplete maturation.

Clinical Features

- Slow growing, expanding and mostly painless lesions.
- Pain and inflammation associated with odontomas occur only in 4% of cases.
- Often detected on radiograph or diagnosed through failed eruption of a permanent tooth.
- Size— 3 to 4 cm or microscopic (7 to 30) mm.
- Relative frequency— 5 to 30% of odontogenic tumors
- So most common odontogenic lesion superceded in frequency only by compound odontoma.

Age

- 2 to 74 years with mean age of 19.9 years.
- Peak in 2nd of life.

Gender

- Male: female=1.5:1

Location

- Majority of lesions are located in posterior mandible, with the second most common site being anterior maxilla.

Radiographical Features (Fig. 10.31)

Depending on their developmental stage, three stages exists based on degree of mineralization.

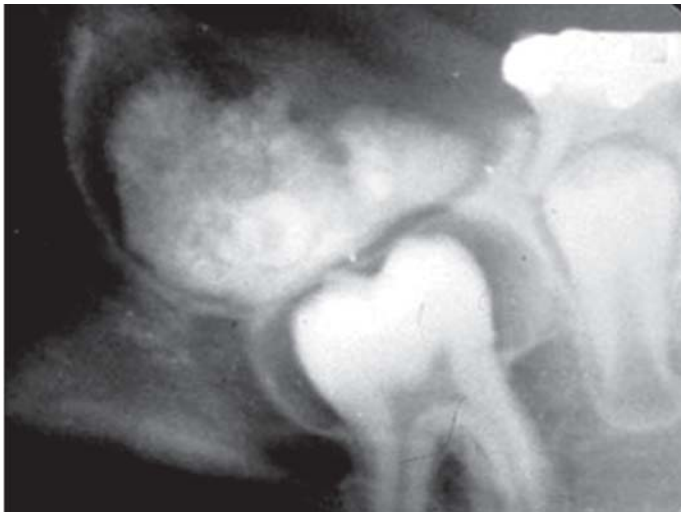


Fig. 10.31: Large radiopaque mass hindering underlying tooth to erupt

First Stage

Radiolucency due to lack of calcification (Weiches odontoma = soft odontoma)

Second Stage

Partial calcification.

Third Stage

Radiopaque with amorphous masses of dental hard tissue surrounded by a thin radiolucent zone.

Note

- Resorption of neighboring tooth is rare.
- Unerupted teeth were associated in 10 to 44% of cases.

Macroscopic Findings

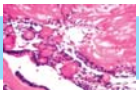
Cut section shows calcified masses as a white to yellowish hard surface surrounded by a capsule of collagenous tissue.

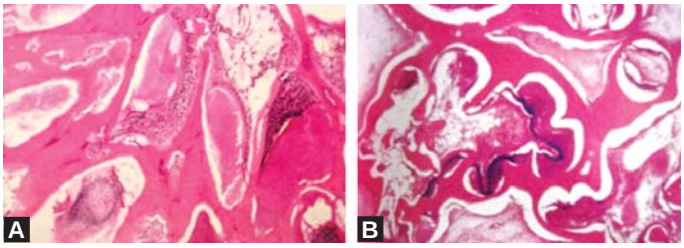
Microscopy

Histologic definition by WHO, "Malformation in which all the dental tissues are represented, individual tissues being mainly well formed but occurring in a more or less disorderly pattern."

Histopathologically Findings (Figs 10.32A and B)

- Consists primarily of a disordered mixture of dental tissues, often of spherical shape.
- Occasionally calcified masses may include tooth-like structures as in compound odontomas, indicating that the degree of morpho differentiation varies greatly.





Figs 10.32A and B: Complex odontoma showing irregularly arranged dental hard tissue

- Cementum or cementum like structures often admixed with the dentinoid substance, small spaces with pulp tissue, enamel matrix and epithelial remnants may be seen in the calcified/mineralized masses of dentin of different qualities.
- Empty spaces and clefts caused by the process of decalcification during which mature enamel is lost, are evident.
- At periphery of lesion, islands of pulp tissue and nests and strands of odontogenic epithelium may be found.
- Enamel never completely matures and show numerous mineralization and structural anomalies.
- Thin, fibrous capsule and occasionally a cyst wall are seen surrounding the lesion.
- 16% of complex odontoma shows areas of ghost cells have been found out of which some may present with melanin pigmentation.
- Histopathological features of complex odontoma largely depend on developmental stage of the lesion, as do its radiological characteristic so, it may be difficult to distinguish odontomas in very early stages of development from ameloblastic fibroma and ameloblastic fibrodontoma.
- Residues of odontogenic epithelium may still be identified even after growth and mineralization completed.

Treatment

Conservative enucleation.

COMPOUND ODONTOMA

Introduction

- Most common lesion of odontogenic origin.
- Term odontoma used for any tumor of odontogenic origin.
- Type of mixed odontogenic tumor.
- Appearance of well organized tooth-like structures.

Pathogenesis

Odontogenic origin.

Clinical Features

- Painless, benign lesion with a more limited growth potential than complex odontomas.
- In fact growth potential ends with the tooth forming period.
- Cause of discovery is failure of a permanent tooth to erupt and/or the persistence of a deciduous tooth.
- Also discovered incidentally on OPG.
- Commonly, compound odontoma is located between the apex of a root of a primary tooth and the crown of a permanent tooth, preventing latter from eruption.
- Size of lesion varies as does the number of denticles.
- Cases of multiple compound odontomas have been described promptly. Many propose odontoma syndrome.
- Occasionally, compound odontomas may be seen in Gardner's syndrome.
- Peripheral compound odontoma are rare, arising extraosseously and having a tendency to exfoliate.
- Relative frequency— 42 to 73.8% so most common odontogenic tumor.

Age

- Mean 17.2 years
- Peak in 2nd decade of life.
- Lesion of childhood and adolescence.

Gender

Male: female = 1.2:1 or nearly equal.

Location

Anterior maxilla— most commonly involved whereas complex odontoma involve posterior mandible.

Radiographic Appearance (Fig. 10.33)

Macroscopical Findings

- Compound odontoma easily distinguished due to the often large number of tooth like structures which are removed during surgery.
- Lesions are usually encapsulated.

Microscopy

Histologic Definition by WHO

A malformation in which all the dental tissues are represented in a more orderly pattern than in the complex odontoma, so that the lesion consists of many tooth-like structures. Most of these structures do not morphologically resemble the teeth of the normal dentition, but in each are enamel, dentin, cementum and pulp are arranged as in normal tooth.

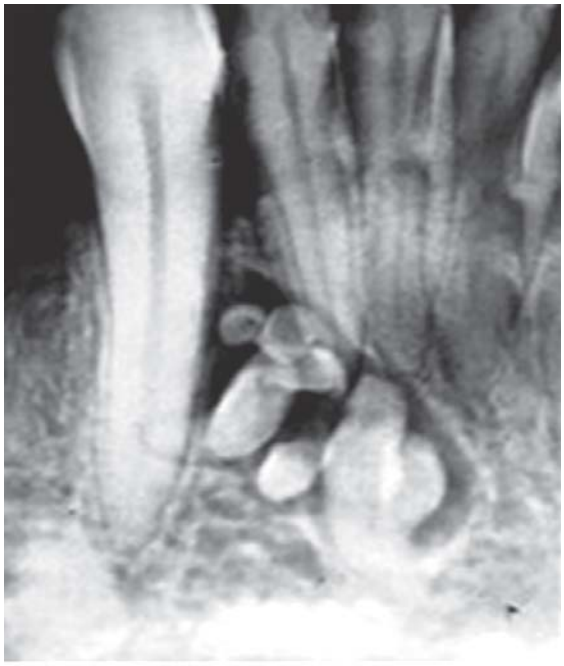


Fig. 10.33: Compound odontoma showing numerous small tooth-like structure

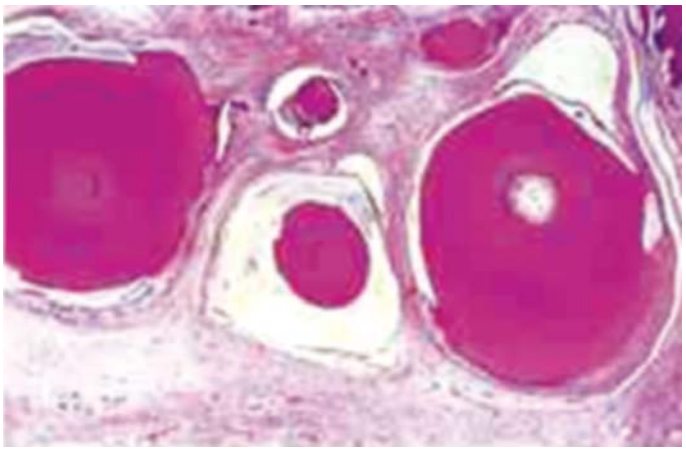


Fig. 10.34: Compound odontoma showing more or less regular arrangement of enamel, dentin, cementum and pulp tissue

Histopathological Features (Fig. 10.34)

- Higher degree of morphodifferentiation than that of complex odontoma, so easily recognizable macroscopically.
- Usually small, but large lesions containing up to hundred denticles have been reported.
- Denticles composed of enamel, dentin, cementum and pulp tissue with a more or less regular arrangement.
- 3% of odontomas may contain ghost cells.

Treatment

Conservative enucleation.

CALCIFYING GHOST CELL ODONTOGENIC CYST/ TUMORS (ODONTOGENIC GHOST CELL LESION)

INTRODUCTION

- Gorlin et al 1st identified calcifying odontogenic cyst.
- Controversy and confusion have existed regarding relationship between non-neoplastic, cystic lesions and solid tumor masses that share the cellular and histomorphologic features.
- In 1971, WHO classified calcifying odontogenic cyst as a 'non-neoplastic cystic' lesion.
- In 1992, *Philipsen* and *Reichert* replaced the phrase with "most lesions appear to be non-neoplastic."
- Presently, these authors believe that lesion has been wrongly classified as mixed benign group that is 1.1.2 group lesion of odontogenic tumor classification, because the stroma is not characterized by ectomesenchyme but rather by mature, collagenous connective tissue.
- Nature of dentinoid material produced in calcifying odontogenic cysts has not been fully clarified, but the production of this material is probably not the result of true induction (though a sequence of reciprocal epithelio-ectomesenchymal interactions) but rather as a result of metaplastic process.
- Lesion shown to be of extreme diversity in its clinical and histopathological features, as well as in its biological behavior.
- Because of this diversity, there has been disagreement concerning the terminology used over past 40 years.

Following terms clearly reveal controversy:

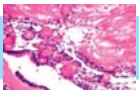
- Calcifying odontogenic cyst
- Keratinizing and calcifying odontogenic cyst
- Atypical ameloblastoma
- Calcifying ghost cell odontogenic tumor
- Dentinogenic ghost cell tumor
- Calcifying odontogenic lesion
- Epithelial odontogenic ghost cell tumor
- Odontogenic ghost cell tumor
- Ghost cell cyst.

Confusion not only plagued with terminology used but a significant source of disagreement stems from the fact that there appear to be two different concepts or schools of thought when looking at the nature of calcifying odontogenic cyst.

a. The monistic
b. The dualistic.

Toida added a new dualistic classification.

Although the 1952 WHO classification cited the terms dentinogenic ghost cell tumor (DGCT) suggested by



praetorious et al and odontogenic ghost cell tumor (OGCT) by Columnar et al, especially for solid lesion whose neoplastic nature is apparent, but still the use of term calcifying odontogenic cyst is in use although this nomenclature may not be appropriate to represent a neoplastic lesion.

However, if all calcifying odontogenic cysts are neoplastic in nature, the term calcifying odontogenic cyst is substituted by Fejerskowv and Krogh – Calcifying ghost cell odontogenic tumor (CGCOT) would be preferable.

- The cystic non-neoplastic and solid (neoplastic) variants may then be called cystic calcifying ghost cell odontogenic tumors and solid calcifying ghost cell odontogenic tumors respectively.
- Recent investigation and current thinking strongly support dualistic concept, and if this proved true, the WHO classification will have to undergo thorough revision when this lesion is reevaluated in a revised classification.

Three classification of calcifying odontogenic cyst previously proposed are all commonly based on the dualistic concept.

- However Toida raised the point that in these classification the authors seem to have used the term cystic as a synonym for non-neoplastic.
- Cystic is basically a morphologic term that does not necessarily cover the term non-neoplastic, which is a biological one.
- In other words; these may well be neoplastic lesions with cystic histoarchitecture.
- To eliminate the confusion arising from previous classification and terminology, Toida proposed a new, simple and basic classification based on dualistic concept.

Divided the group of calcifying odontogenic cyst lesions into three main groups.

- The calcifying ghost cell odontogenic cyst which should be classified with developmental odontogenic cyst.
- The neoplasm which comprise a benign and malignant variant.
- Lesions described under the 1st two groups and associated with odontomas, ameloblastomas and other odontogenic lesions.

So combining all these classification, a new suggested classification is given based upon the proliferative activity and growth pattern of the lining cyst epithelium as suggested by Hong et al.

In this context, Toida et al demonstrated that the proliferative features of cyst lining are the main factor influencing the proliferative activity of calcifying odontogenic cyst.

Classification

1. Non-neoplastic (simple cystic) variants (CGCOC)
   - A. With non proliferative epithelial lining.
   - B. With non proliferative (or proliferative) epithelial lining associated with odontomas.
   - C. With proliferative epithelial lining.
   - D. With unicystic, plexiform ameloblastomatous proliferation of epithelial lining.
2. Neoplastic variants
   - A. Benign type (CGCOT)
     - a. cystic subtype (cystic CGCOT)
       α SMA ex epithelial cyst lining.
     - b. Solid subtype (solid CGCOT)
       α Peripheral ameloblastoma like
       β SMA like
   - B. Malignant type (malignant CGCOT or OGCC)
     - a. Cystic subtype
     - b. Solid subtype

Type 1 A

- The non-neoplastic (simple cystic and nonproliferative variant is lined by a nonkeratinized odontogenic epithelium of 4 to 10 cells in thickness, containing isolated or clustered ghost cells, some of which may be calcified.
- Juxtaepithelia dentinoid and foreign body reaction are not commonly present that occur frequently with cholesterol granulomas and hemorrhage.

Type 1 B

In 1994, Hirshberg et al 1st reviewed calcifying odontogenic cysts associated with odontomas in attempt to clarify the pathogenesis of this variant.

Philipsen and Reichert reviewed 52 cases of calcifying odontogenic cyst associated with odontome (COCaO) and concluded as:

- Mean age of occurence is 16 years, mostly in 2nd decade.
- Relative frequency of this variant among calcifying odontogenic cysts is 22 to 47%.
- Oral examination revealed hard swelling in 52% of cases.
- 1/5th of cases discovered accidentally during routine radiographic examination showed well defined mixed radiolucent-radiopaque lesion.
- The radiopaque foci varied in amount from flecks to well-defined tooth like structures.
- Few cases lesion appeared radiolucent, so demonstrating the early stages of development of odontomas.
- 38% cases were associated with impacted teeth, the canine being most commonly involved.

Histopathological Findings

- Lesion consisted of a single large cyst, the epithelial lining of which showed basal cell layer with hyperchromatic, polarized nuclei.
- Masses of "ghost" epithelial cells were present in the lining or in the fibrous tissue capsule.
- Elements of tooth like structures were found adjacent to the calcifying odontogenic cyst components either in the connective tissue capsule or in direct continuation with the epithelial cystic lining, occasionally protruding into the lumen.
- Components of calcifying odontogenic cyst and odontomas were intermingled and continuous giving the impression of a single lesion.

Hirshberg et al suggested several possibilities regarding pathogenesis of COCaOs.

- Calcifying odontogenic cyst and odontoma may represent co-incidental juxtaposition of a calcifying odontogenic cyst and odontomas as other odontogenic tumors, such as solid/multicystic ameloblastomas, have been reported associated with calcifying odontogenic cysts. But, rarity of co-existence of two separate odontogenic tumors and relative frequent occurence of COCaOs make it an unlikely explanation for pathogenesis of COCaOs.
- Odontoma develops secondarily from the lining epithelium of the calcifying odontogenic cyst (or CGCOC, according to Toida) because the odontogenic epithelium has the potential for induction phenomenon as manifested in odontogenic tumors belongs to group of mixed benign odontogenic tumor lesion that is of 1.1.2 types in WHO classification.
  - However there seems to be no substantial evidence that the epithelial component of the non-odontoma producing calcifying odontogenic cyst (CGCOC) is supported by ectomesenchyme rather than by mature mesenchymal fibrous connective tissue. So it is very unlikely that a CGCOC at some stages develops into a COCaO simply because the reciprocal epithelioectomesenchymal interaction responsible for a possible development of an odontoma are not operational under these conditions.
  - Majority of odontomas associated with a calcifying odontogenic cyst (CGCOC) seems to be of compound type.
  - When the mean age at the time of diagnosis that is 14.7 years with peak in 2nd decade is compared to the corresponding number and a similar comparison is made concerning location of involvement, the following suggestion as to the pathogenesis of COCaOs may be made.

There is remarkable similarity between the two set of data and Philipsen and Reichert interpreted these findings as follow:

- COCaO may be regarded as a compound odontoma (in various stages of development) in which the epithelial component – in addition to initiating the development of a compound (or more rarely a complex) odontoma at a certain stage forms an epithelial cyst lining eventually envelop the odontoma.
- In past it was thought that the epithelial lining of the cyst participates in the formation of odontoma, a concept that Hirshberg et al accept.

Hirshberg et al suggested that COCaO should be regarded as a separate entity and classified as a benign mixed odontogenic tumor called odontocalcifying odontogenic cyst.

- This term is inappropriate as Philipsen and Reichert state that this lesion is not a cyst but a compound odontoma in which an epithelial cyst has formed secondarily.
- Cyst lining may occasionally show some proliferative activity so it should be classified as an odontoma variant that may be called compound complex cystic ghost cell odontoma.

Note: Compound odontoma may contain ghost cells in 11 to 18% of cases.

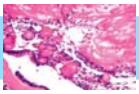
Feature that distinguishes the calcifying odontogenic cyst associated with an odontoma from an odontoma containing ghost cells, is the definite formation of a cyst lined by odontogenic epithelium in the former.

Type 1 C

- In this, cyst lining show proliferative activity with the formation of multiple daughter cysts in the fibrous connective tissue wall.
- Extensive ghost cell formation with a marked tendency for calcification is found in the centers of the cyst.
- Juxtaepithelial dentinoid is rarely seen; whereas foreign body reaction to herniated ghost cell is prominent.

Type 1 D

- Non-neoplastic, cystic subgroup is characterized by uni- or multifocal proliferation activity of the epithelial lining, resembling plexiform unicystic ameloblastoma except for the presence of ghost cells and dystrophic calcification within the proliferating cyst epithelium.
- In contrast to SMAexCOC (group 2Aaα) the ghost cells and calcifications are confined to the cyst lumen.
- Differentiation from lesions in group 2Ab by its obvious cystic histoarchitecture and lack of juxtaepithelial dentinoid.



Type 2Aa α

- Rare neoplastic variant
- Cyst lining shoe uni- or multifocal intramural and intraluminal proliferation of classic solid/multicystic ameloblastoma tissue, often in a plexiform pattern with histopathological features of early ameloblastoma according to Vickers and Gorlin.
- Cyst lining contains a considerable number of ghost cells whereas the transformed ameloblastomatous portion shows little or no ghost cells.
- Juxtaepithelial dentinoid is not present.

Type 2Abα

- Lesions located in the gingival soft tissue or alveolar mucosa and bear striking resemblance to peripheral ameloblastoma, except that clusters of ghost cells are present in central portion of tumor cell nests and dentinoid can be found adjacent to most peripheral cells.
- Multifocal downward proliferation of oral surface epithelium is characteristic findings, but some lesions are entirely within the lamina propria.
- Basal epithelial cells lack palisading of the cell nuclei.
- Clinical appearance of this soft tissue tumor has been described as exophytic and pedunculated, nodular and plaque like with a hard, soft or friable consistency.

Type 2Abβ

Intraosseous subtype

- Composed of nests or clusters of proliferatve odontogenic epithelium resembling solid/multicystic ameloblastoma or occasionally adenomatoid odontogenic tumor.
- Ghost cells are usually encountered centrally in the epithelial islands and juxtaepithelial dentinoid is also present.
- All lacked the ameloblastic histopathological criteria suggested by Vickers and Gorlin.
- Jhonson et al claimed that "the solid variant of calcifying odontogenic cyst seems to represent the ultimate phase of evolution of the COC and not necessarily a separate entity because recurrence is uncommon, there seems to be no clinical justification for subclassifying these lesions".

Pathogenesis

- Odontogenic origin.
- According to Shear, it is widely accepted that those calcifying odontogenic cysts which have other features of odontogenic tumor develop these features secondarily.
- All centrally located calcifying odontogenic cysts are likely to originate from reduced enamel epithelium or remnants of odontogenic epithelium.
- Peripheral neoplastic variants (group 2Abα), there may be two major sources of origin.
- Lesions located entirely within the connective tissue of the gingival and are separated from the surface epithelium by a band of connective tissue—likely arise from remnants of the dental lamina where as other lesions appear to arise from the oral surface epithelium.

Clinical Features

- Relative frequency— 1 to 6.8% for all types of calcifying odontogenic cysts.
- Malignant calcifying odontogenic cyst 0.4% of all odontogenic tumors and 6.5% of all malignant odontogenic tumors.

Age

Group 1a: According to *Hong et al* it has two age peaks with one in the 2nd decade and second in the 8th decade.

Group 1b: Shows sharp peak in 2nd decade with mean age of 14.7 years.

According to Hirshberg et al, Shamaskin et al and Praetorius et al stated that mean age of remaining non-neoplastic (cystic) variants (group 1a, 1c and 1d) is 34.5 years.

- In group 1c lesions show fairly even age distribution.
- In group 1d lesions show two minor peaks in 2nd and 6th decade.

Neoplastic Variants

- Group 2Ab α and 2Abβ— mean ages are 62 years and 45 years respectively.
- Neoplastic peripheral variants showed a mean age of 59 years.
- Shamaskin et al reported mean age of 53.8 years for peripheral variants of calcifying odontogenic cysts without any further subclassification.

Gender

- For non-neoplastic (cystic) calcifying odontogenic cysts (not including odontoma associated lesions
- Male:female = 1.5:1
- Odontoma associated has male:female = 1:1.9.

Location

- 78.5% of calcifying odontogenic cysts arise centrally in bone and 21.5% in gingiva.
- Intraosseous lesions may produce a hard bony swelling of jaws.

- Peripheral lesions appear as local gingival growths.

Note: Majority cases were symptomless irrespective of variants.

Radiological Features

- Intraosseous lesions appear as either uni- or occasionally multilocular radiolucencies.
- Irregular calcified bodies of varying size are seen throughout the radiolucency are typical features.
- Large radiopaque masses may be found in cases associated with odontomas.
- Resorption of tooth roots and root divergence reported.
- One-third of intraosseous lesions were associated with one or more unerupted teeth.
- Extraosseous lesions may show either no radiographic alterations or a superficial erosions (saucerization) of underlying cortical bone.
- MRI accurately differentiate between cystic and solid variants and regarded superior to CT scan in evaluation of mandibular lesions because it can depict both cortical and medullary involvement.

Note: Calcifying odontogenic cyst however lacks pathognomic, clinical, radiological, CT and MRI features.

Definite diagnosis remains dependent on histologic evalution.

Microscopy

Histologic definition by WHO in 1992

"A cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, and overlying layer that is often many cell thick and that may resemble stellate reticulum, and masses of 'ghost, cells that may be present in the epithelial cyst liningor in the fibrous capsule. The ghost cell may calcify, dysplastic dentin may be laid down adjacent to basal layer of the epithelium, and in some instances the cyst is associated with an area of more extensive dental hard tissue formation resembling that of acomplex or compound odontoma.

Definition of COC according to Philipsen et al, and Histopathology

Lesion in which the histopathologic features necessitates a separation into three main variants:

- A non-neoplastic (cystic) variant with three subtypes
- A benign (solid)variant, also with three subtypes
- Malignant or carcinoma variant.

A lesion characterized by a simple cystic structure lined by a non proliferative, odontogenic epithelium with a well defined basal layer composed of 4 to 10 cell layers that may resemble stellate reticulum and contain isolated or clustered ghost cells that may demonstrate dystrophic calcification.

In a proliferative subtype,

- The epithelial lining shows proliferation into the surrounding fibrous capsule with the presence of multiple daughter cysts, the centers of which often shows extensive ghost cell formation.
- Juxtaepithelial dentinoid (osteoid) may be found in both of these calcifying odontogenic cyst types, in particular close to masses of ghost cells.
- Proliferation of cyst lining may also show uni-or multifocal, intraluminal activity producing a net-like pattern resembling a unicystic plexiform ameloblastoma, but containing isolated or clustered ghost cells and calcifications.
- Combined microscopic features of a calcifying odontogenic cyst (non-neoplastic or cystic variant) and a compound or complex odontoma should be classified as a cystic ghost cell odontoma and not as a calcifying odontogenic cyst variant.

A Neoplastic (solid) Lesion

- In which cyst lining shows both intramural and intraluminal proliferations of SMA tissue, often exhibiting a plexiform pattern.
- Epithelium of cyst lining contains a large number of ghost cells in contrast to the transformed ameloblastomas epithelial portion, juxtaepithelial dentinoid material is rarely, if ever present. This neoplastic odontogenic cyst is known as SMA ex COC.

A subtype of neoplastic variant:

- Is a lesion characterized by epithelial proliferations from the surface gingival epithelium into the lamina propria or proliferating epithelial islands or cords entirely located within the lamina propria and separated from the oral epithelium by a band of connective tissue. It thus bears a striking resemblance to the peripheral ameloblastoma except that ghost cells are found centrally in the epithelial tumor components and juxtaepithelial dentinoid is adjacent to the peripheral cells.

A final (rare) subtype of the neoplastic variant has histopathological features that vary from area to area.

- Some portions resemble solid/multicystic ameloblastoma like epithelium, other show adenomatoid odontogenic tumor like features. Both are characterized by the occurrence of ghost cells and dentinoid. Malignant calcifying odontogenic cysts (Discussed later separately).

Histopathologic Features (Fig. 10.35)

Characteristic and distinctive histopathologic feature is occurrence of so called epithelial ghost cells.

Ghost Cells

Pale, eosinophilic, ballon-shaped, elliptic epithelial cells that have lost their nuclei, leaving a faint outline of the original nuclei hence the term ghost cell.

Although the cell outlines are usually well defined, that may sometimes be blurred so that groups of ghost cells appeared fused.

- Dystrophic calcification may occur in some of ghost cells initially as fine basophilic granules and later as small spherical bodies.
- Ghost cell may break through epithelial basement membrane (be extruded) and, when in contact with the connective tissue wall of the cyst, evokes a foreign body reaction with the formation of multinucleate giant cells.

In some variants of COCs:

- A tubular dentinoid material may be found in the cyst wall close to the epithelial lining, adjacent to epithelial proliferations and particularly in contact with masses of ghost cell.
- Whether the dentinoid (or osteoid) material, some of which may become mineralized should be regarded as an inflammatory(metaplastic) response to the presence of ghost cells in the cyst wall or represent a true inductive effect is still to be clarified.

  However former theory is favored.

Note: Ghost cells have been reported in several odontogenic lesions like

- Odontomas
- Ameloblastic fibromas
- Ameloblastic fibrodontoma

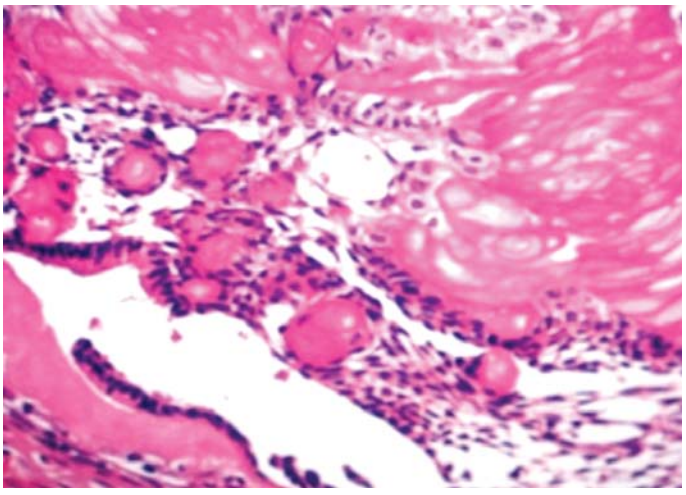


Fig. 10.35: Epithelial ghost cell in COC

- Solid/multicystic ameloblastomas
- Craniopharyngiomas
- Cutaneous calcifying epitheloma of Malherb (Pilomatrixoma)

So mere presence of ghost epithelial cells in a lesion does not, therefore, justify the diagnosis of calcifying odontogenic cyst.

Takata et al found melanin containing cells in epithelial islands ameloblastomatous proliferations in calcifying odontogenic cysts (group 1D). Pigmentation can be seen in:

- Odontogenic keratocyst
- Complex odontoma
- Ameloblastic fibrodontoma
- Odontoameloblastoma
- Adenomatoid odontogenic tumor

Philipsen et al noticed that all pigmented odontogenic lesions except for odontogenic keratocyst, are associated with the formation of dental hard tissue or prominent calcification.

Ng and Siar reported a case of calcifying odontogenic cyst (most likely group 1c) in which nests, cords and islands of typical clear cells were found in connective tissue wall of cyst.

Immunohistochemistry Findings

Philipsen et al concluded that ghost cells in calcifying odontogenic cysts contain enamel related proteins in the cytoplasm, accumulated during the process of pathologic transformations.

Treatment

- Non-neoplastic variant of calcifying odontogenic cyst and neoplastic variant of subtype 2Abα—conservative surgical enucleation
- Remaining neoplastic variants— radical surgical excision.

ODONTOAMELOBLASTOMA(OA)

INTRODUCTION

Also called as

- Adamanto-odontoma
- Calcified mixed odontogenic tumor
- Soft and calcified odontoma
- Ameloblastic odontoma.

Thoma in 1970 termed it as odontoameloblastoma.

- Previously grouped under term ameloblastic odontoma as thought to be another member of odontoma group, together with ameloblastic fibrodontoma.

- Hooker showed that they are two separate tumors with different clinical behavior and differentiated ameloblastic fibrodontoma from odontoameloblastoma and used term odontoameloblastoma for more aggressive tumors composed of an solid/multicystic ameloblastoma and a complex or compound odontoma.
- Extremely rare lesion.
- Majority of reported Odontoameloblastoma cases, appear to be examples of less aggressive ameloblastic fibrodontoma.
- Acceptable cases of Odontoameloblastoma were put in three categories:
  - Unequivocal ameloblastoma
  - Connective tissue with mature, homogenous appearance.
  - Fragments of malformed calcified dental structures.

Pathogenesis

Odontogenic Origin

But relationship between other odontogenic tumor, solid/multicystic ameloblastoma on one hand and odontomas on the other – is not well understood.

Clinical Features

Extremely rare lesion.

Age

Range 3 to 50 years with mean age of about 19 years.

Gender

Male: female = 2:1.

Location

- Mostly involve posterior mandible.
- Slow, progressively growing lesions with growth characteristics similar to those of solid/multicystic ameloblastomas.
- Expansile, centrally destructive lesions.
- Symptoms include progressive swelling of alveolar bone.
- Dull pain
- Change in occlusion.
- Delayed eruption of teeth.

Radiographic Features

- Well-defined uni- or multilocular radiolucency containing varying amounts of radiopaque substances.
- Radiopaque particle may be in the form of small particles (denticles representing a compound odontoma like appearance or of a large centrally located mass of dental hard structures with the features of a complex odontoma which may cause divergence of roots of adjacent teeth).

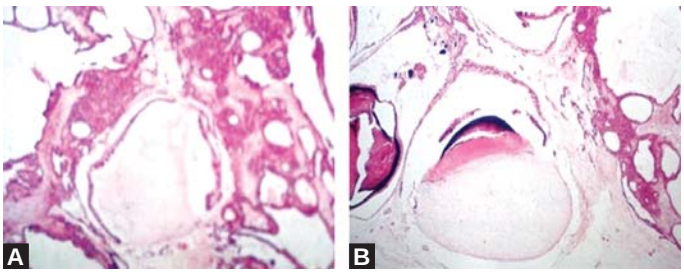
Microscopy

WHO Definition (1992)

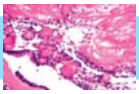
A very rare neoplasm that includes odontogenic ectomesenchyme, in addition to odontogenic epithelium that resembles an ameloblastoma (solid/multicystic ameloblastoma) in both structure and behavior. Because of the presence of the odontogenic ectomesenchyme, inductive changes take place leading to formation of dentin and enamel in parts of tumor.

Histopathological Features (Fig. 10.36)

- Reveals proliferating odontogenic epithelium in a mature connective tissue stroma, characteristic of a solid/multicystic ameloblastoma.
- Epithelium is arranged in islands and rosettes with tall, columnar, peripherally palisaded epithelial cells.
- Reverse nuclear polarization as seen in follicular ameloblastoma may be seen.
- Neoplastic odontogenic epithelium forms islands and cords between dysplastic dentinoid substances and enamel.
- Often large masses of dysplastic dentin and enamel are arranged in a haphazardly pattern as in complex odontoma, although rudimentary teeth (as are found in compound odontomas) also may be present.
- Variable amount of characteristic cellular odontogenic ectomesenchyme is present, which gives rise to induction phenomena resulting in hard tissue formation.
- Comparison between odontoameloblastoma and ameloblastic fibrodontoma found no decisive histologic criteria to separate these two lesions. However, it appeared that solid/multicystic ameloblastoma like structures were more characteristic for odontoameloblastoma, whereas the ectomesenchymal component was more pronounced in the ameloblastic fibrodontoma.
- Ghost cells may be present in odontoameloblastomas.



Figs 10.36A and B: Odontoameloblastoma showing SMA feature alongwith dysplastic dentinoid substance



Treatment

Aggressive lesion so radical treatment.

Benign neoplasms and tumor like lesions showing mesenchyme and/or ectomesenchyme.

INTRODUCTION

Consist of WHO 1992 classification lesions:

- Odontogenic fibroma
- Odontogenic myxoma
- Benign cementoblastoma
- However from histomorphological viewpoint, neither odontogenic fibroma nor odontogenic myxoma contains typical cellular ectomesenchyme with few delicate connective tissue fibers as classically seen in ameloblastic fibroma.
- Connective tissue component in these two entities are of mature, mesenchymal or mesodermal type.
- Likewise benign cementoblastoma does not include a histomorphologically characteristic ectomesenchymal component, a fact the authors of 1992 WHO classification acknowledge where they stated "the soft tissue component consists of vascular loose textured fibrous tissue".

Reichert and Ries stress that from a histologic viewpoint, cementoblasts together with odontoblasts belong to the ectomesenchymally derived cells.

So Philipsen et al modified 1992 WHO classification for the three neoplasm in this section as '*lesions originating from mesenchyme and/or odontogenic ectomesenchyme with or without presence of odontogenic epithelium*'.

In July 2003, new WHO volume tumors of head and neck, following changes in terminology were introduced for tumors of this group.

Two variants of odontogenic fibroma:

- The simple type
- The complex or WHO type,

Were renamed as:

- Epithelium poor
- Epithelium rich respectively.

Term myxoma or myxofibroma are unchanged.

Benign cementoblastoma, the word "benign"has been dropped and it is now called as cementoblastoma.

ODONTOGENIC FIBROMA

INTRODUCTION

It is an elusive because of its rarity and controversial tumor due to uncertainity as to the number of distinct types that exists.

Topographically two variants are known:

- Intraosseous or central type (COF)
- Extraosseous or peripheral type (POF)

In 1971 WHO classification it was stressed that in absence of odontogenic epithelium, the diagnosis of odontogenic fibroma should be made "only if there is good evidence that the tumor originates from odontogenic apparatus."

In 1992 WHO classification added"with caution"to this remark.

Pathogenesis

- Some authors believe that central odontogenic fibroma (COF) to be derived from the ectomesenchymal tissue of periodontal ligament (PDL), dental papilla or dental follicle.
- It is the epithelial component of WHO type of central odontogenic fibroma (COF) and the fact that this tumor does not occur in an extragnathic location that provide the strongest argument for this tumor being of odontogenic origin.

Clinical Features

- Tumor is symptomless when small and may present as painless swelling.
- Few patients complains of sensitivity.
- Growth is slow but progressive, frequently resulting in cortical expansion.
- Mobility of teeth may present in involved area.

Age

Range from 11 to 66 years with mean of 40 years.

Gender

Male: female=1 : 2.8

Location

- Maxilla: mandible=1 : 6.5
- In mandible involves mostly in molar and premolar region.
- In maxilla lesions involve only in anterior region.

Radiological Features

- Not diagnostic
- However seen as unilocular radiolucent area with well-defined borders in approximately half of cases, some of which may show a sclerotic border.
- Larger lesions show scalloping of the margins or multiloculation.
- Few cases may present calcified material may lead to a mixed radiolucent/radiopaque appearance.

- May displace teeth and cause root resorption of adjacent teeth.
- Lesions may be associated with crown of an unerupted molar, premolar or incisor.

Macroscopic Features

- Specimen have gray to brownish color.
- Calcified material may be noticed while cutting specimen.

Microscopy

Histologic definition by 1992 WHO

"A fiboblastic neoplasm containing varying amounts of apparently inactive odontogenic epithelium".

This definition covers various types of lesions.

Simple Type Central Odontogenic Fibroma (COF) (Fig. 10.37)

- An expansile, noninflammatory connective tissue lesions resembling a dental follicle.
- It is relatively acellular, the fibers being quite delicate and there is a considerable amount of ground substance yielding a fibromyxoid quality.
- It may exhibit inactive-looking rests of odontogenic epithelium but they are seldom numerous.
- Occasionally, non-descript calcifications are found.

WHO Type Central Odontogenic Fibroma (COF)

A benign neoplasm composed of cellular connective tissue. It often occurs in fibroblastic strands that are interwoven with less cellular areas in which numerous small blood vessels are present. Foci of calcified collagenous matrix, resembling dysplastic cementum, osteoid (or bone), or atubular dysplastic dentin often occur. Islands or strands of inactive-looking odontogenic epithelium are an integral component of this type; they are usually conspicuous. A clearly defined capsule is not encountered.

Histopathological Features (Fig. 9.38)

WHO type COF showing islands and strands of odontogenic epithelium in fibrous stroma

Central Odontogenic Fibroma (COF) versus Ameloblastic Fibroma (AFs)

- Central odontogenic fibroma (COF) differs considerably from Ameloblastic fibroma (AF) by inactive-looking cell rests found in the central odontogenic fibroma (COFs).
- Ameloblastic fibroma (AF) connective tissue is embryonic looking and considerably more cellular than that seen in Central odontogenic fibroma (COF) and there is little collagen in the form of delicate fibers.

Treatment

- Enucleation by vigorous curettage.
- Recurrence- low

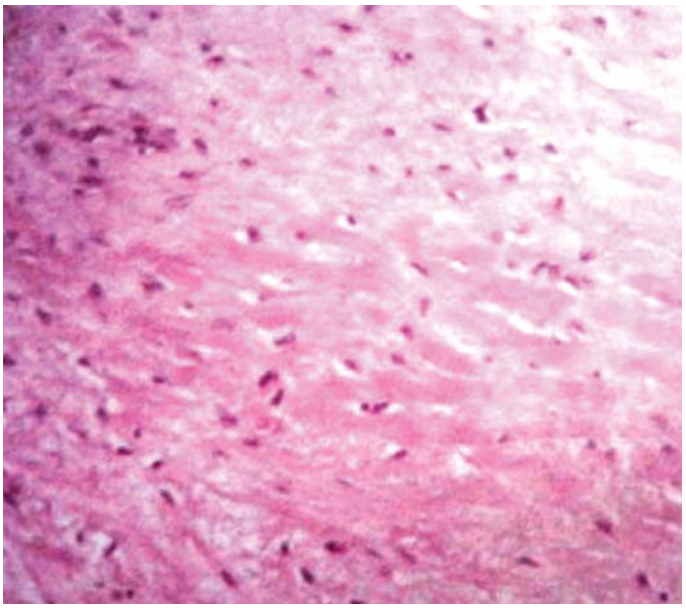


Fig. 10.37: Simple type COF with delicate connective tissue fibers without odontogenic epithelium

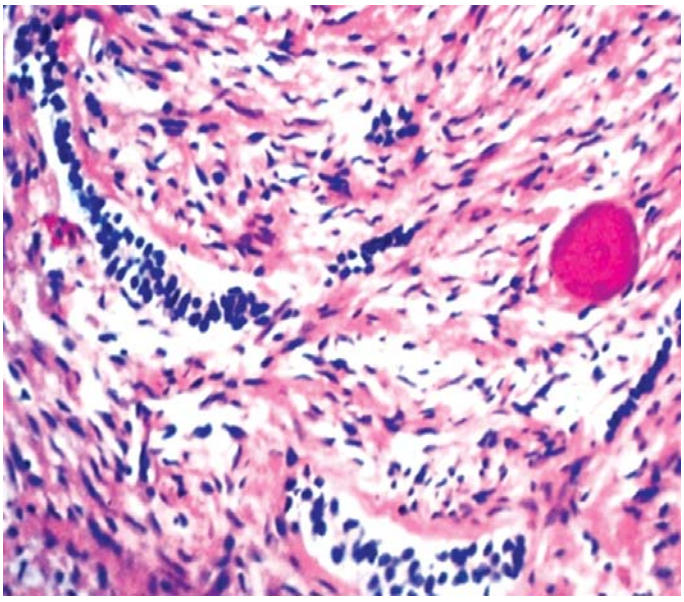
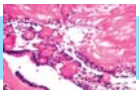


Fig. 10.38: WHO type COF showing islands and strands of odontogenic epithelium in fibrous stroma



ODONTOGENIC MYXOMA (OM) OR MYXOFIBROMA (MF)

INTRODUCTION

- 1863, Rudolph Virchow first described histologic features of myxofibroma (MF).
- 1947, Thoma and Goldman 1st described myxomas of jaw.
- 1992, WHO classification, term myxoma is used along with odontogenic myxoma (OM) and myxofibroma (MF) as alternative terms.

Pathogenesis

- Designation of odontogenic myxoma (OM) as an odontogenic tumor (OT) is uncertain.
- According to Lucas, the classification of the odontogenic myxoma (OM) as an odontogenic tumor (OT) has been justified by its frequent occurence in adolescence, its association with missing or unerupted teeth and the sporadic presence of odontogenic epithelium (OE) within the neoplastic, myxomatous tissue.
- Philipsen et al supposed that the rarity of odontogenic myxomas (OMs) in any extragnathic bone could be the only firm reason for suggesting the odontogenic origin.
- Recently, ultrastructural studies found no resemblance between the matrix in odontogenic myxomas (OMs) and that found in normal tooth development.
- Also Lombardi et al found no similar staining pattern for vimentin and S-100 protein in odontogenic myxomas (OMs) compared to dental follicles, dental papilla and periodontal ligament cells, suggesting a non-odontogenic origin for the tumor.
- Other studies suggested that cells in odontogenic myxomas (OMs) are of dual fibroblastic-histocytic origin.

Clinical Features

Rare neoplasm

Age

- Range 1-77 years with mean of 30 years.
- Mostly in between 2nd and 4th decade.

Gender

Male: female =1 : 1.6

Location

- Mandible > maxilla= 66.4% > 37.6% mostly in posterior region.
- 1st noticed as a result of a slowly increasing swelling or asymmetry of the affected jaw.
- Lesions are generally painless.
- Ulceration of lesion in case of interference with occlusion
- Growth may be rapid.
- Infiltration of neighboring soft tissue structures may occur.
- Mostly intraosseous lesions but peripheral variants been reported.
- Buccal and lingual cortical plates of mandible may occasionally expand.
- Maxillary lesions often fills entire antrum.
- Severe cases show nasal obstruction or exopthalmous may be leading symptoms.
- Displacement of tooth roots and resorption of roots may occur.
- Only 5% cases shown to be associated with unerupted teeth.

Radiological Features

- Variable features
- Majority are characterized by multilocular radiolucency with a "soap bubble" or "honeycomb" appearance.
- Few cases are non loculated.

Size

- Unilocular lesions were smaller than 4 cm
- Multilocular lesions were larger than 4 cm.

MRI revealed a well defined, well enhanced lesion with homogeneous signal intensity on every pulse sequence.

Macroscopic Features

Cut section of odontogenic myxoma (OM) specimen reveals a white gray color in the mucoid substance, which will stick to an instrument when touched.

Microscopy

Histologic Definition by WHO, 1992

A locally invasive neoplasm consisting of rounded and angular cells lying in an abundant mucoid stroma.

Histopathological Features (Figs 10.39 and 10.40)

- Locally aggressive, non-encapsulated, non-metastasizing neoplasm that infiltrate bone marrow space.
- H/P characterized by loose, abundant mucoid stroma that contains rounded, spindle shaped, or angular cells.
- Cellular and nuclear polymorphism is rare, as is mitotic activity.
- Usually tumor cells are evenly spaced with in a fine fibrillar mucinous matrix.
- Stroma may be relatively avascular or may exhibit delicate capillaries.

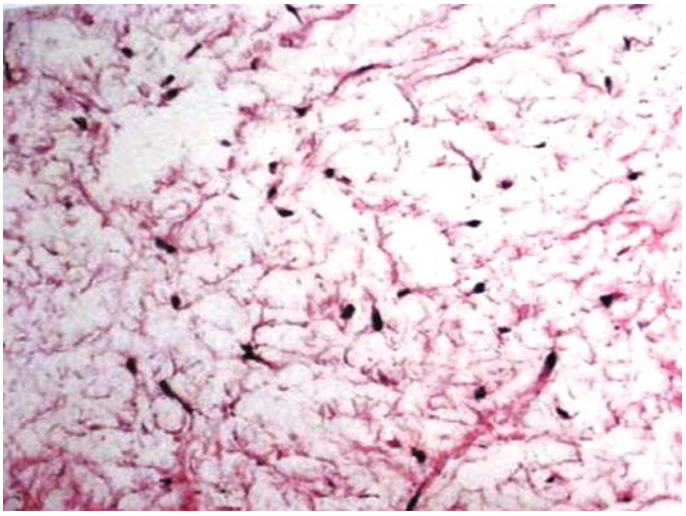


Fig. 10.39: Odontogenic myxoma showing mucoid stroma with sparse cellularity

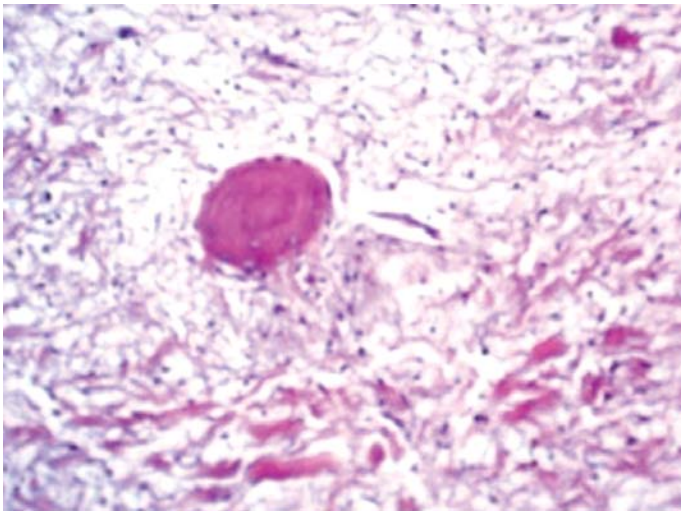


Fig. 10.40: Fibromyxoma showing prominent collagen along with dental hard tissue seen

- In case of myxofibroma, the amount of collagen in the mucoid stroma is more prominent.
- Fibrils have been shown by silver impregnation to be reticulins.
- Inflammatory infiltrates rarely seen.
- Remnants of odontogenic epithelium occasionally noted; sometimes they are rare surrounded by a narrow zone of hyalinization.
- Myxomatous components of odontogenic myxoma (OMs) has been compared to primitive mesenchyme which is found throughout the body and also with the dental papilla and dental follicle.

Differential Diagnosis

- It should not be confused with that of the thickened follicle of a tooth with delayed eruption.
- Histopathologically, thickened follicle is characterized by a non-neoplastic, myxoid, basophilic ground substance and commonly by islands of odontogenic epithelium.

Other Lesions

Myxomatous degeneration as seen in fast growing neoplasm or particularly in fibrosarcomas, chondrosarcomas and liposarcomas.

Treatment

- Local excision
- Curettage for smaller lesions
- Enucleation
- Radical resection for maxillary OMs
- Recurrence= 10 to 33% and related to type of therapy.

CEMENTOBLASTOMA

INTRODUCTION

Previously termed as benign cementoblastoma.

- True cementoma
- First described by Norberg in 1930.
- Rare benign odontogenic tumor of ectomesenchymal origin.
- Only true neoplasm of cemental origin and characterized by the proliferation of cellular cementum.

Pathogenesis

Odontogenic tumor derived from ectomesenchymal cells of periodontium, including cementoblasts.
Evolve in three stages:
1st stage: Characterized by peripheral osteolysis
2nd stage: Followed by a cementoblastic stage
3rd stage: Then an inactive stage of maturation and calcification.

- Cementoblastoma is considered a neoplasm with unlimted growth potential.
- Etiology is unknown.

Clinical Features (Fig. 10.41)

Relative frequency— 0.2 to 6.2% of all odontogenic tumor, so rare.

Age

First to seventh decade, mostly diagnosed before 3rd decade.

Gender

Male: female = 1 : 1.2

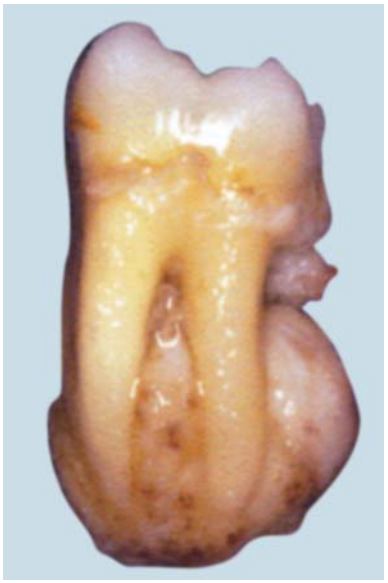


Fig. 10.41: Cementoblastoma as globular mass attached to root surface

Location

- Mandibular permanent molar and premolar > maxillary molars and premolars.
- Deciduous teeth rarely affected.
- Several teeth may involve.
- Bilateral lesion have been reported.
- Lesion is associated with a tooth root.
- Presents as a slow growing, unilateral swelling with expansion of the affected bone.
- Uncommon to other benign odontogenic tumor, cementoblastomas are associated with pain and occasionally paresthesia.
- Type of pain is usually characterized as a toothache arising in the pulp.
- Vitality test of involved teeth in process is generally positive.
- A cementoblastoma may resorb roots and even invades root canals.
- Rarely may involve unerupted tooth.

Radiological Features (Fig. 10.42)

- Radiopaque, often round mass, fused with one or several roots of associated roots, thus obliterating the radiopaque details of root(s).
- Opacity is surrounded by a thin, well-defined radiolucent border.
- Size = 0.5 cm to 5 cm

Philipsen et al stressed that radiographic features depends on its degree of mineralization, thus early stage cementoblastomas generally appear more radiolucent.

Differential Diagnosis

- Periapical inflammatory lesions
- Focal (periapical) cementosseous dysplasia
- Central giant cell lesions
- Odontogenic myxoma
- Solid/multicystic ameloblastoma
- Mature, more calcified cementoblastoma lesions may mimic cemento-ossifying fibromas, osteoblastomas, odontomas, calcifying epithelial odontogenic tumor (CEOT).

Macroscopic Features

Lesion appears as mineralized mass which is fused to the roots of a tooth, in most cases involving the apical 3rd.

Microscopy

WHO Histologic Definition (1992)

A neoplasm characterized by the formation of sheets of cementum like tissuewhich contains a large number of reversal lines and is unmineralized at the periphery of the mass or in the more active growth areas.

Histopathological Features

- Numerous basophilic reversal lines are similar to those observed in Paget's disease (Figs 10.43A and B).
- Cemental trabecule are rimmed with plump, active cementoblasts.
- Fibrous tissue with dilated blood vessels and multinucleated classic giant cell may be observed between the calcified bands.
- At periphery of mineralized mass, proliferation of cementoblasts and cementoclasts is evident.

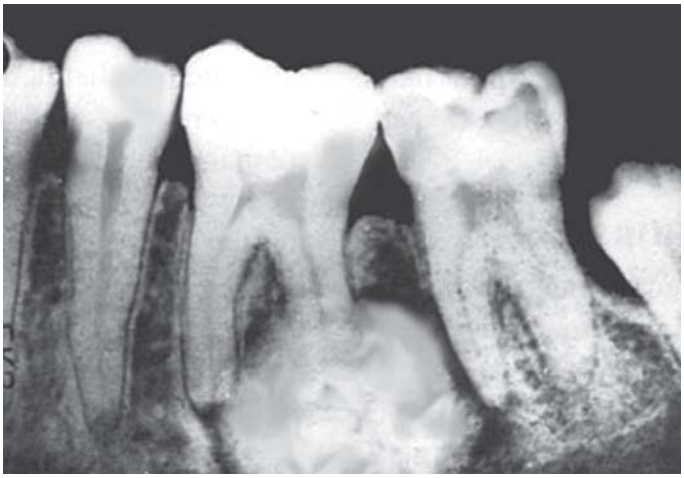
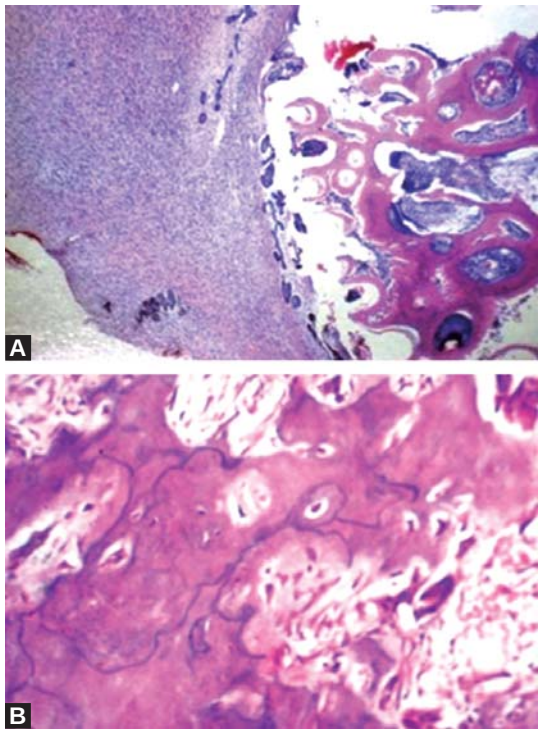


Fig. 10.42: Cementoblastoma featuring round radiopaque mass fused to root of tooth



Figs 10.43A and B: Cementoblastoma showing numerous basophilic reversal lines along with rimming of trabecule by cementoblasts nearing root surface of tooth

- According to Slootweg; histologically cementoblastomas and osteoblastomas cannot be distinguished.
- Diagnosis of cementoblastoma is made easier when the lesion is fused to tooth root.

Differential Diagnosis

- Cementifying/ossifying fibroma
- Benign osteoblastoma
- Osteoid osteoma
- Fibrous dysplasia
- Osteosarcomas
- Chronic focal sclerosing osteitis

In many instances, cementoblast and cementclasts are difficult to differentiate these cells from osteoblasts and they may exhibit pleomorphism.

Peripheral unmineralized border of cementoblastoma, corresponds to radiolucent zone seen in radiographs.

Note: Correct diagnosis can be made by correlating histopathology, clinical features and radiological features.

Treatment

- Surgical removal due to BCs capacity of persistent growth, expansion and involvement of adjacent structures.
- Growth rate—0.5 cm/year
- Recurrence—rare and if occur its due to incomplete removal.

Malignant Epithelial Odontogenic Neoplasm

Eversole's classification is most appropriate of malignant epithelial odontogenic tumor and agreed in WHO in july 2003.

METASTASIZING AMELOBLASTOMA

INTRODUCTION

Newer WHO 2005 classification removed term malignant and termed it metastasizing ameloblastoma as it does not show any malignant atypia

- Ameloblastomas share a number of features with the basal cell carcinoma of skin, both in biologic behavior and histopathologic feature.
- Rare cases an ameloblastoma may undergo malignant transformation (becoming an ameloblastic carcinoma).
- Like Basal cell carcinoma (BCC) of skin, Solid/multicystic ameloblastomas may metastasize rarely.
- Emura 1st to describe metastasis to local lymph nodes.
- Vorzimer and Perla mentioned metastasis of ameloblastoma to the lung for the first time in 1932.

Pathogenesis

- Origin same as non-metastasizing ameloblastoma.
- It was thought that metastasis of ameloblastoma is preceded by local recurrence, the spread of tumor could result from either:
  - Increasingly malignant behavior stimulated by multiple recurrences of the tumor itself.
  - Implantation of the tumor into lymphatic or blood vessels by repeated surgical interventions.
- Eisenberg concluded that surgical transplantation of tumor cell is unlikely as the vast majority of these cells are destroyed by natural defence mechanisms, and remaining cells would fail to thrive and attain sufficient size or biochemical capability to survive and attain deleterious effects.

Note: Most cases recurred after delay of more than 10 years after initial treatment, somewhat disqualifying the theory of metastasis due to surgical transplantation.

- Generally cases of metastasizing ameloblastomas with pulmonary metastasis are thought to spread through hematogenous route due to the fact that metastasis is bilateral and with multiple nodules.
- Eisenberg proposed that in some cases the lymph node tumor may represent neoplasia occurring in conjunction with the phenomenon of heterotropia.

- Malignant behavior is present in about 2% of solid/multicystic ameloblastom.

Clinical Features

Do not have any specific features.
Reichert et al found,
Swelling, pain, delayed tooth eruption, ulceration, and tooth mobility to be the most common symptoms.

Factors that appear to contribute to a potential metastatic spread.

- Duration of neoplasm
- Extent and size of the initial tumor.
- Initial type of surgery (conservative versuses radical therapy).
- Multiple recurrences and respective surgery interventions.
- Use of radiation or chemotherapy.

Most Common Site to Metastasis

Lung than hilar lymph node, bones, skull, vertebrae and femur, cervical lymph nodes, liver, brain, other nodes, spleen and kidney. Pulmonary metastasis most commonly found bilaterally and with multiple nodules.

Rare cases, metastasizing ameloblastoma (MA) may be associated with hypercalcemia.

Age

5-74 years with mean of 35 years.

Gender

Male: female=1.2 : 1

Location

Mandible : maxilla=7.6 : 1

Pathology (Fig. 10.44)

Histologic Definition

A neoplasm in which both the primary and metastatic growths are characterized histologically by benign innocuous-appearing solid/multicystic ameloblastoma (SMA) tissue components that lack any features of malignancy.

Histopathologic Features

Reveals plexiform SMA type mostly.

Treatment

- Radical resection with primary reconstruction of mandibular ameloblastomas
- Chemotherapy and radiation therapy for palliative therapy.

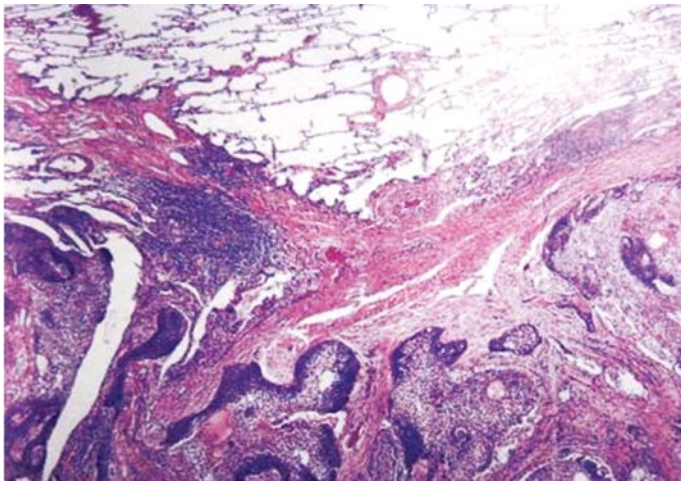


Fig. 10.44: Metastasizing ameloblastoma to lung

AMELOBLASTIC CARCINOMA

- Primary, secondary (dedifferentiated) intraosseous
- Secondary (dedifferentiated) extraosseous

INTRODUCTION

Malignant epithelial odontogenic tumor that histologically retained the features of ameloblastic differentiation, yet also exhibits cytologic features of malignancy.

Pathogenesis

- Not clear
- May originate exameloblastoma or exodontogenic cyst.
- Both central (intraosseous) and peripheral (extraosseous) variants have been described.
- Peripheral ameloblastic carcinomas (ACs) may arise de novo and as dedifferentiated ameloblastic carcinomas (ACs) from pre-existing benign peripheral ameloblastomas.

Histomorphogenetically, two different ameloblastic carcinoma (AC) entities may be recognized;

- Characterized by lesion that initially demonstrate the morphology of a solid/multicystic ameloblastoma (SMA) but dedifferentiated overtime.
- Ameloblastic carcinomas (ACs) that have malignant cytologic features de novo.

Clinical Features

- Rare lesion
- Ameloblastic carcinoma (AC) more common than metastasizing ameloblastoma (MA).
- Age: Mainly involve elder patient, range is 15 to 84 years.

Gender

Male: female=1.4 : 1

Location

Majority of lesion occur in mandible.

- Swelling, pain, trismus and dysphonia are evident.
- Rapid growth of the tumor is important clinical feature.
- Mental nerve paresthesia may occur.
- Maxillary ACs—complains of mass in the cheek also pain, anesthesia of infraorbital nerve and a fistula in the palate have been noted.
- Rarely AC may occur with malignancy—associated with hypercalcemia.
- Metastasized to lungs and distant sites.

Radiological Features

- Resembles Solid/multicystic ameloblastoma (SMAs), but most cases they present as ill-defined radiolucencies.
- Foci of radiopacities, probably due to dystrophic calcification have also been observed.
- Often perforation of cortical bones and may extend to neighboring soft tissues.
- Pathologic fractures may occur.
- Axial and coronal CT scan may reveal cortical thining, perforation and soft tissue invasion.

Histopathological Definition

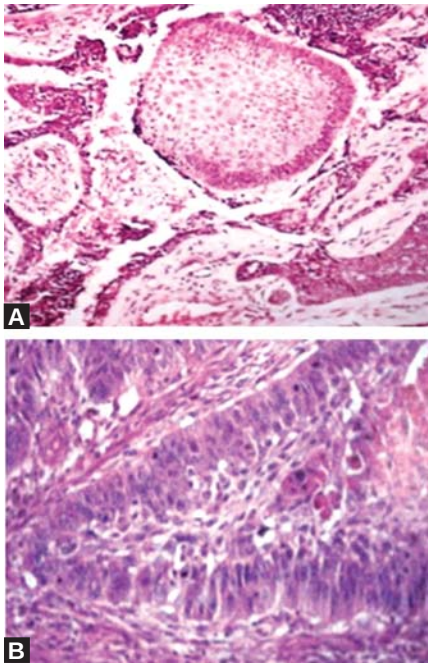
A neoplasm in which the histologic pattern of a solid/multicystic ameloblastoma (SMA) has been retained in the primary growth in the jaws and/or in any metastatic growth, yet also exhibits cytologic features of malignancy.

Histopathology (Figs 10.45A and B)

- Composed of islands and cords of ameloblastomatous odontogenic epithelium in an infiltrating pattern with in the stroma of mature fibrous tissue.
- Epithelium may reveal a single outer layer of ameloblastic cells of columnar to cuboidal shape which exhibit a tendency for palisading and reverse nuclear polarization, but not always evident.
- Stellate reticulum within epithelial islands is often condensed and hypercellular, presenting a less orderly pattern.

Characteristic differentiating fetures are:

- Nuclear enlargement with granular-stippled nucleoplasm
- Nuclear hyperchromatism
- Mild pleomorphism
- Increased nucleo/cytoplasmic ratio.
- Increased mitotic activity with abnormal forms of mitoses.
- Some cases individual cell keratinization and keratin pearl formation may occur.



Figs 10.45A and B: Low and high power: Ameloblastic carcinoma showing neoplastic infiltration of ameloblastic component

- Necrosis and dystrophic calcification may be seen.
- Different histologic patterns may be noted within the malignant components—highly differentiated squamous cell or a more basaloid, poorly differentiated variety.
- Connective tissue component is composed of mature collagen fibers with occasional inflammatory cells, hemorrhage and/or hemosiderin pigment.
- Rare cases—Clear cell differentiation can be seen.

Treatment

Radical surgery with neck dissection.

PRIMARY INTRAOSSEOUS SQUAMOUS CELL CARCINOMA

PRIMARY INTRAOSSEOUS SQUAMOUS CELL CARCINOMA (SOLID)

Introduction

- Central squamous cell carcinoma was 1st described by Loos in 1913.
- Wills suggested term intra-alveolar epidermoid carcinoma.
- Pindborg suggested primary introsseous carcinoma which was accepted by the WHO classification of 1992.
- PIOSCC must be differentiated from other odontogenic carcinomas.

- Such as malignant ameloblastomas and carcinomas arising from odontogenic cysts.

Pathogenesis

- Unknown
- Cells of origin—odontogenic epithelial cells consisting of reduced enamel epithelium, the rests of malassez in periodontal ligament (PDL) and in the alveolar bone subsequent to tooth loss, and remnants of dental lamina in gingiva.

Clinical Features

Extremely rare lesion.

Age

Involve elder age group ranging from 4 to 81 years with mean 53 years.

Gender

Male: female= 2 : 1

Location

- Mostly in posterior mandible.
- Persistent symptoms like postextraction pain, toothache, periodontal disease or pericoronitis were presenting complaints.
- Diagnosis was delayed due to dental problems were given top priority and the underlying disease were missed.
- Swelling, pain and sensory disturbances were other symptoms.
- Persistent pain and swelling of jaw seem to be important presenting symptoms of primary intraosseous squamous cell carcinoma (PIOSCCs), the diagnosis has to be considered in all cases where initial dental treatment has failed.
- Diagnosis of PISC is difficult and an infectious etiology may often (wrongly) be considered.
- Once histologic diagnosis has been made, metastatic disease has to be ruled out.
- Principally, the investigation of the primary tumor should include a chest radiograph to exclude lung metastasis.

Radiological Features

- Osteolytic bone changes seen.
- Margins of primary intraosseous squamous cell carcinoma lesions are poorly defined, diffuse and irregular in most cases.

Microscopy

WHO Definition (1992)

A squamous cell carcinoma arising within the jaw, having no initial connection with the oral mucosa and presumably developing from residues of odontogenic epithelium.

Histopathological Features (Fig. 10.46)

- Some cases revealed histologic features of squamous cell carcinoma which were indistinguishable from SCC of oral mucosa, a definite diagnosis may be impossible without reliable clinical radiographic data.
- PISCC may reveal a distinct odontogenic pattern with basal type cells forming alveoli or arranged in a plexiform pattern with palisading of the peripheral cells.
- Nuclei of these cells are often oriented away from the basement membrane.
- Squamous metaplasia may be seen.
- Few cases show foci of degeneration within epithelial islands.
- Since histopathology of primary intraosseous squamous cell carcinoma are not pathognomic, a diagnosis can be made only if there is no evidence of the tumor arising from either the oral mucosa or from an odontogenic cysts.
- Serial section recommended to exclude other origins of squamous cell carcinomas.

Differential Diagnosis

- Metastatic tumors
- Primary intraosseous mucoepidermoid carcinoma.

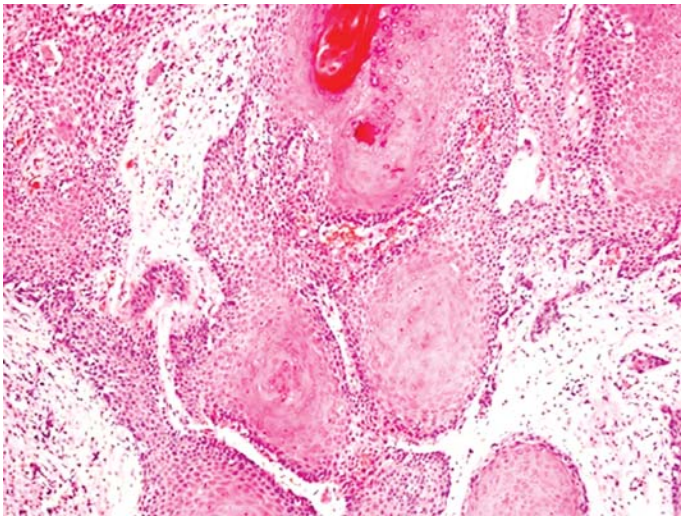


Fig. 10.46: Squamous cell carcinoma (SCC) showing distinct basal type cells arranged in alveoli and plexiform pattern with palisaded nuclei SCC

Treatment

- Radical surgery
- Lymph node involvement requires block resection combined with the excision of the primary tumor.

PRIMARY INTRAOSSEOUS SQUAMOUS CELL CARCINOMA DERIVED FROM ODONTOGENIC CYSTS

Introduction

- Rare cases
- PIOSCC may arise from the epithelial lining of odontogenic cysts either non-keratinizing or odontogenic keratocyst (OKC) now termed keratinizing tumor (KCOT).

Pathogenesis

- Unknown
- Long standing chronic inflammatory changes have been proposed as possible predisposing factors of malignant transformation of epithelial lining of the cyst, but this cannot be substantiated .
- Some reports say that keratinization of cyst epithelium may be associated with a higher risk of transformation.

Clinical Features

- Symptoms are nonspecific and include pain and swelling.
- Mandibular lesions cause cortical expansion.
- Cervical lymphadenopathy been reported.
- Paresthesia or anesthesia is uncommon but may occur, often local invasion of inferior alveolar nerve.
- Lesions are rare
- Age—range from 4 to 90 years with mean of 57 years.

Location

Maxilla: Mandible = 1:3

Gender

Male: female = 1.8 : 1

Radiological Features

Nonspecific and characterized by a radiolucency surrounded by a relatively well-defined radiopaque border.

Macrosopic Feature

Lesion is cystic in nature.

Microscopy

Histopathologic Definition

Basic criteria for the diagnosis of this type of lesion is that the transition between normal cyst epithelium and squamous cell carcinoma has to be demonstrated histologically.

So squamous cell carcinoma (SCC) arising from the epithelial lining of an odontogenic cyst.

Histopathologic Features (Fig. 10.47)

- Majority of cyst arise from 37.5% inflammatory residual type>19.7% follicular cyst >17.8% keratinized residual cyst= 17.8% lateral or apical radicular cyst > remaining 7.2% of cyst were not classified.
- Eversole doubted that lateral periodontal cyst (LPC) was place of origin for PIOSCCs.
- Dysplastic changes of stratified squamous epithelium are common and include pleomorphism, increased mitotic activity, dropping off of bulbous rete ridges, hyperchromatism and cellular crowding.
- Secondary epithelial changes such as pseudoepithelmatous hyperplasia, acanthosis and hyperkeratosis also may be observed.
- Foci of invasion of cyst epithelium may be evident in early cases of PISCs.
- *Advance cases*: Solid tumor islands may invade the fibrous cyst wall and alveolar bone.
- Most carcinomas arising from cyst epithelium are well or moderately differentiated.
- Fibrous capsule of cyst may be thickened as a result of chronic inflammation.

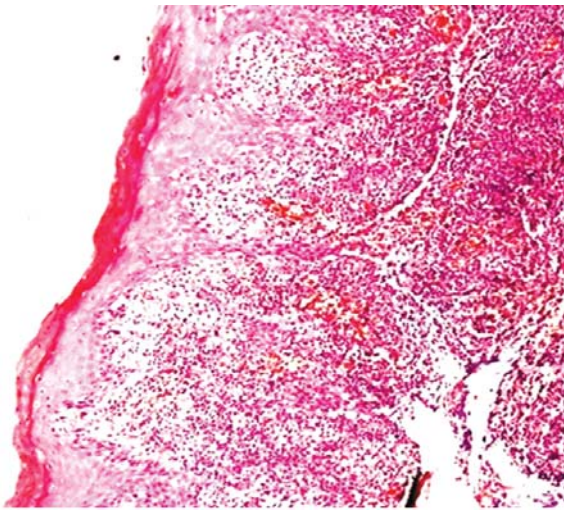
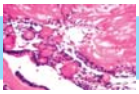


Fig. 10.47: Squamous cell carcinoma (SCC) arising from cystic epithelial lining



Note: Careful examination should be done to exclude invasion to cyst lining from adjacent primary or metastatic carcinoma.

Treatment

- Radical surgery
- Larger lesions—Mandibulectomy or maxillectomy or partial resection of affected jaw with lymph node dissection to radical neck dissection.

PRIMARY INTRAOSSEOUS SQUAMOUS CELL CARCINOMA (PIOSCC) DERIVED FROM KERATINIZING CYSTIC ODONTOGENIC TUMOR (KCOT)

Introduction

Very rare when compared to PIOSCCs arising from other odontogenic non keratinizing cysts.

Pathogenesis

Some factors (unknown) that lead to transformation of cyst epithelium in nonkeatinizing cysts may also be relevant for keratinizing cystic odontogenic tumor (KCOTs).

Clinical Features

- May be similar to PIOSCC derived from odontogenic cysts.
- Rare entity.

Age

Involve elder age group patients.

Gender

Male: female= 1.3 : 1

Location

Mostly involve posterior mandible.

Pathology

Histologic Definition by Philipsen et al

A squamous cell carcinoma arising from the epithelial lining of a keratinizing cystic odontogenic tumor.

Histopathologic Features

- Transition of the normal cyst epithelium of keratinizing cystic odontogenic tumor (KCOT) to squamous cell carcinoma (SCC).
- May develop from parakeratinized or orthokeratinized cyst epithelium.
- Epithelial dysplasia of varying degrees are found.
- Metastasis to cervical and submandibular lymph nodes occur.

Treatment

Radical surgery with neck dissection of lymph nodes.

CLEAR CELL ODONTOGENIC CARCINOMA

- Odontogenic tumor containing a significant number of clear cells are rare.
- They are represented by the clear cell variant of calcifying epithelial odontogenic cyst (CEOT), clear cell ameloblastoma/malignant clear cell ameloblastoma (CCA/MCCA), clear cell odontogenic carcinoma (CCOC).
- Clear cell odontogenic carcinoma (CCOC) and clear cell ameloblastoma/malignant clear cell ameloblastomas (CCAs/MCCAs) have still few data available to allow definitive conclusions as to whether the lesions are separate entities.

Pathogenesis

- Eversole concluded that the clear cell odontogenic carcinoma (CCOC) is a primary, non-glandular epithelial neoplasm of odontogenic origin.
- According to WHO classification (1992), it arises from residues or derivatives of the dental lamina or from rests of malassez.

Clinical Features

Rare lesion.

Age

- Range 17 to 89 years with mean of 56.7 years.
- Mean age of clear cell ameloblastoma/malignant clear cell ameloblastoma (CCAs/MCCAs) are 44.6 years so approaching the mean age for SMA (37.4 years).

Gender

Male: Female for clear cell odontogenic carcinoma (CCOCs) is 1: 1.6 and for clear cell ameloblastoma/malignant clear cell ameloblastoma (CCA/MCCAs) is 1:2.

Location

- Maxilla: mandible for clear cell odontogenic carcinoma (CCOCs)=1 : 7.7 and for clear cell ameloblastoma/malignant clear cell ameloblastoma (CCAs/MCCAs)=1 : 3.5
- Posterior region of mandible is mostly affected.
- Most common presenting sign of both clear cell odontogenic carcinoma (CCOCs) and clear cell

ameloblastoma/malignant clear cell ameloblastoma (CCAs/MCCAs) is jaw enlargement.
- Sensory deficit which is often encountered in metastatic carcinomas of the mandible (as with the hypernephroma), is a rare feature.
- Some patients may complain of mild pain or dull ache in the affected area.
- Mobility of teeth is often present.
- Edentulous patient complains of ill fitting dentures (may be an early sign of tumor presence)
- Clear cell odontogenic carcinoma (CCOC) occurs as a central tumor in either jaw, whereas the Clear cell ameloblastoma/malignant clear cell ameloblastoma (CCA/MCCA) may in extremely rare cases be located in the gingival soft tissues.

Radiological Features

- Clear cell odontogenic carcinoma (CCOC) appears as a poorly delineated uni-or multilocular radiolucent lesion that occurs with prominent bone destruction.
- Divergence of root with or without root resorption is common.
- Nair et al. found that in its initial stage the clear cell odontogenic carcinoma (CCOC) may resemble early periodontitis that fails to resolve in spite of periodontal therapy.
- Clear cell ameloblastoma/malignant clear cell ameloblastoma (CCA/MCCA) has same radiographic appearance as that of its benign counterpart, the solid/multicystic ameloblastoma (SMA).

Macroscopy

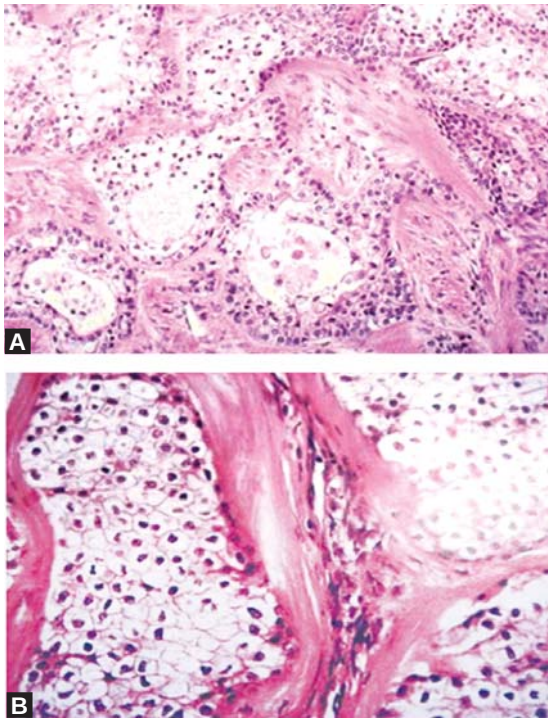
Homogeneous, pinkish gray or white, solid often glistening tumor with no necrotic areas.

According to Philipsen (Figs 10.48A and B)

Clear Cell Odontogenic Carcinoma (CCOC)

A malignant neoplasm capable of locally destructive growth an both nodal and distant metastasis.

Two histologic variant are identifiable:
The islands of cells are biphasic; contains both
– Clear cells,
– More hyperchromatic appearing polygonal cells;
- Exhibit cytoplasmic eosinophilia that fails to show any squamous, glandular or ameloblastic features.
- Occasionally, these two cell populations co-exist in a tumor nest, creating a "glomeruloid" appearance.
- The islands are separated by zones of a mature, fibrous and partly hyalinized connective tissue stroma.



Figs 10.48A and B: Low and high power: clear cell odontogenic carcinoma (CCOC) showing clear cells in center and hyperchromatic polygonal cells in periphery seperated by fibrous septae

- No encapsulation and tumor cell invade medullary bone.
- Cellular pleomorphism and mitotic activity are rare but generally within the population of polygonal cells when present.

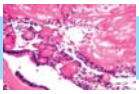
2. Clear cell odontogenic carcinoma (CCOC) has islands that are almost exclusively of the clear cell phenotype.

Clear Cell Ameloblastoma/Malignant Clear Cell Ameloblastoma (CCA/MCCA)

- Malignant neoplasm showing areas consistent with a diagnosis of follicular ameloblastoma in which varying number of tumor island show peripheral palisading of cuboidal and cylindrical cells with reversed nuclear polarity.
- A prominent clear cell component is present within follicular nests replacing the stellate reticulum.
- Stroma is composed of dense, fibrous connective tissue with hyalinized areas.

Treatment

- Radical resection
- Early aggressive therapy should be done.
- Close follow-up required for several years.



GHOST CELL ODONTOGENIC CARCINOMA

INTRODUCTION

First case, malignancy arising in a calcifying odontogenic cyst (COC) was reported by Lkemura et al in 1985.

Pathogenesis

- Not fully known
- Lu et al stated that the immunophenotype of malignant cells supports an epithelial origin.

Three patterns of development:

- *Most common*: Tumor histological presents as de novo but with a benign Calcifying odontogenic cyst (COC) and malignant epithelial component present in the same lesion.
- *Less common*: Ghost cell odontogenic carcinoma (GCOC) occurs after the recurrence of a benign calcifying odontogenic cyst (COC).
- *Third pattern*: Ghost cell odontogenic carcinoma (GCOC) arising from another odontogenic tumor such as an solid/multicystic ameloblastoma.

Clinical Features

Rare lesion.

Age

Range 13 to 72 years with age of 37 years with half of cases occurred in 4th and 5th decade.

Gender

- Male: female = 2.6:1

Location

- Maxilla: mandible = 2:1
- Swelling with or without pain can occur.
- Osseous destruction with paresthesia.

Radiological Features

Poorly demarcated radiolucency mixed with radiopaque material.

Histopathological Features

Malignant neoplasm generally characterized by two types of epithelial cells.

- Malignant components of some tumors is found in nests, strands and islands of varying size dominated by small round, undifferentiated basaloid cells with hyperchromatic nuclei, frequent mitoses and cytologic atypia.
- Masses of ghost cells, some of which may show dystrophic calcification, often intermingle with the small basaloid cells.
- Small droplets of dentinoid in association with ghost cell may or may not present.
- Areas of necrosis with an acute and chronic inflammatory cell infiltrate are frequent findings.
- Simple unicystic type of calcifying odontogenic cyst (COC) is lined by stratified epithelium with distinct columnar basal cells overlaid by a loose stellate reticulum-like epithelium of variable thickness.
- Foci of ghost cells are scattered with in epithelial lining.
- Nests of tumor cells invade and destroy surrounding bone, skeletal muscle and connective tissue.
- Stroma is of mature fibrous connective tissue which may occasionally show desmoplasia.

Treatment

- Radical surgery combined with radiation therapy.
- Long-term follow-up mandatory.

MALIGNANT ECTOMESENCHYMAL ODONTOGENIC NEOPLASM (ODONTOGENIC SARCOMA)

Introduction

Rare malignancies of jaw include:

- Ameloblastic fibrosarcoma (AFS)
- Ameloblastic fibrodentino sarcoma (AFDS)
- Ameloblastic odonto sarcoma (AOS)
- Odontogenic carcino sarcoma (OCS)

In ameloblastic fibrosarcoma (AFS), ameloblastic fibrodentino sarcoma (AFDS), ameloblastic odontosarcoma (AOS) only ectomesenchymal component has undergone malignant transformation while in odontogenic carcinosarcoma (OCS) both ectomesenchymal and epithelial component reveal malignant changes.

Generally, prognosis of this group lesions are poor.

AMELOBLASTIC FIBROSARCOMA (AFS)

INTRODUCTION

- Also known as ameloblastic sarcomas.
- Rare malignant neoplasm composed of a benign odontogenic ameloblastomatous epithelium and malignant ectomesenchyme which resembles a fibrosarcoma.
- Generally, considered malignant form of ameloblastic fibroma in which the ectomesenchymal cells have

retained their embryonic appearance and develop malignant characteristics.
- First report of ameloblastic fibrosarcoma was published by Heath in 1887.

Pathogenesis

- Gradual transformation of an Ameloblastic fibroma (AF) to an ameloblastic fibrosarcoma (AFS).
- The difference in mean age at time of diagnosis for Ameloblastic fibroma (15 to 22 years) and ameloblastic fibrosarcoma cases (25 years) which supports a stepwise progression of a benign to a malignant neoplasm as opposed to a *de novo* malignancy.

Clinical Features

Exceedingly rare lesion.

Age

Range 3 to 78 years with mean age of 25 years.

Gender

Male : female=2:1

Location

- Mandible: Maxilla=2.3 :1 (posterior region of both jaw were more frequently involved.
- Pain and swelling most constant findings.
- Ulceration and bleeding as well as paresthesia of the lower lip also occurred.
- Mobility of teeth in some cases found.
- History of Ameloblastic fibrosarcoma must be taken with great care in order to know its origin whether de novo or transformation type.

Size

- Smallest— 4 × 4 × 3 cm
- Biggest— 7 × 6 × 4 cm
- Metastasis is rare.

Radiologic Features

- Radiolucencies with irregular and distinct margins are characteristics.
- Large radiolucencies with a multilocular appearance and gross expansion and thinning of cortical bone can be seen.
- CT scan show well-defined heterogeneous mass of soft tissue density and a thin enhancing capsule in the submandibular area.

Macroscopic Appearance

- Tender but solid and whitish at cut surfaces.
- Buccal and lingual cortices of the mandible were extremely thin.

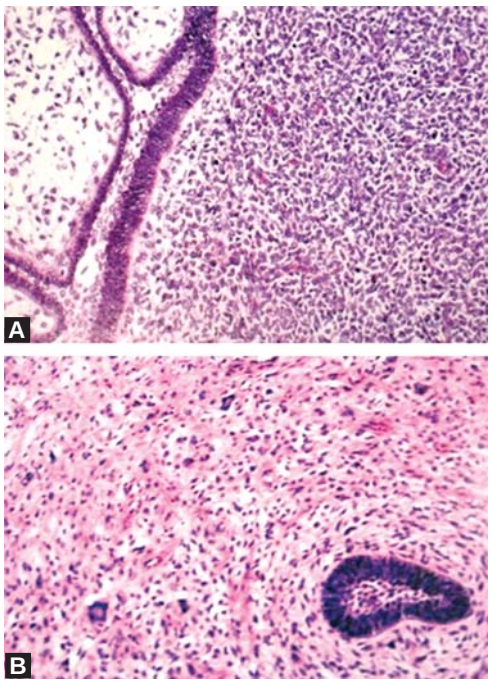
Microscopy

Histologic Definition by WHO (1992)

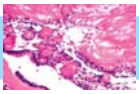
A neoplasm with a similar structures to Ameloblastic fibroma, but in which the ectomesenchymal component shows the features of a sarcomas.

Histopathological Features (Figs 10.49A and B)

- Characterized by consistent appearance in which a malignant ectomesenchymal component is mixed with a benign epithelial odontogenic component.
- Malignant ectomesenchymal component consistently takes up more than 70% of tumor area compared to 30% of odontogenic epithelium.
- Benign epithelial component shows budding and slender cords, usually only two layers thick, composed of small polygonal epithelial cells.
- In addition, epithelial islands and nests with the same histopathologic appearance as ameloblastic fibroma are evident.
- Columnar or cuboidal epithelial tumor cells resembling preameloblasts are arranged at periphery in a palisading pattern.



Figs 10.49A and B: Ameloblastic fibrosarcoma showing minor ameloblastic fibroma component with majority of malignant counterpart



- Nuclei are hyperchromatic and are polarized away from the basement membrane; the cytoplasm is clear and vacuolated.
- Polyhedral cells resembling stellate reticulum-like epithelial cells are seen in center of epithelial islands.
- No mitoses or malignant cytologic features are detected in the epithelial component.
- Ectomesenchymal component of neoplasms shows a marked increase in cellularity.
- Fibroblast like cells are pleomorphic, rounded or fusiform and display increased, sometimes atypical mitotic activity.
- Cytologically these cells shows hyperchromatic nuclei and scant cytoplasm.
- Collagen is usually present in small amount.
- Some case, osteoid matrix have been found.
- Vascular component may reveal different grades of malignancy from low to high.
- Epithelial component of the ameloblastic fibromas eventually becomes less prominent and may disappear altogether after local recurrences.

Ultrastructural Features

Yamamato et al observed two cell type:

Columnar and polyhedral in epithelial component

1. Columnar cells— Had slightly enlarged oval nuclei located apically within the cells.
2. Polyhedral cells— displayed large amount of tonofilaments and glycogen granules.

Mesenchymal spindle shaped fibroblast-like cells showed irregular nuclei which are two nucleoli and a variable amount of heterochromatin.

Treatment

- Ameloblastic fibromas should be treated more radically to prevent recurrences and possible transformation to ameloblastic fibrosarcomas.
- Radical extensive surgery for ameloblastic fibrosarcomas, usually necessitating partial or total mandibulectomy or maxilloectomy.

AMELOBLASTIC FIBRODENTINO SARCOMA (AFDS) AND AMELOBLASTIC FIBROODONTO SARCOMA (AFOS)

INTRODUCTION

Exceedingly rare malignant odontogenic sarcomas.

Pathogenesis

- Unknown
- As in ameloblastic fibrosarcomas, however the lesion may theoretically occur as a synchronus or metachronus process at the site of an ameloblastic fibroma or ameloblastic fibrodontoma.

Common Clinical Features

- Swelling
- Frequent pain
- Oral mucosal ulceration and/or tissue proliferation through extraction sockets were noted.
- Usually moderate growth rate but rarely rapid also.

Age

Occurs mostly in second decade.

Gender

Clearly not known, may be equal in both sexes.

Location

Mostly affect posterior mandible.

Radiological Feature

Radiopaque foci in otherwise radiolucent lesion.

Microscopy

Histological Definition by WHO (1992)

Neoplasms similar to Ameloblastic fibrosarcomas in which limited amounts of dysplastic dentin (dentinoid) have formed and, in ameloblastic fibro-odontosarcoma, enamel as well.

Histopathological Features

Ameloblastic Fibrodentinosarcoma (AFDS)

- Consist of an epithelial and ectomesenchymal component, both including dentinoid, some of which may be dysplastic.
- Epithelial component is composed of follicles and strands of odontogenic epithelium as observed in Ameloblastic fibroma.
- Intraepithelial and stromal microcyst may form.
- Some epithelial islands may show ghost cells representative of a form of intracellular keratinization.
- Some areas, odontogenic epithelium may induce the deposition of dentinoid adjacent to ameloblastomatous islands which rarely show dentinal tubules.
- Malignant ectomesenchymal component is characterized by increased cellularity, pleomorphism, hyperchromatism and increased abnormal mitotic activity, as in ameloblastic fibrosarcomas.

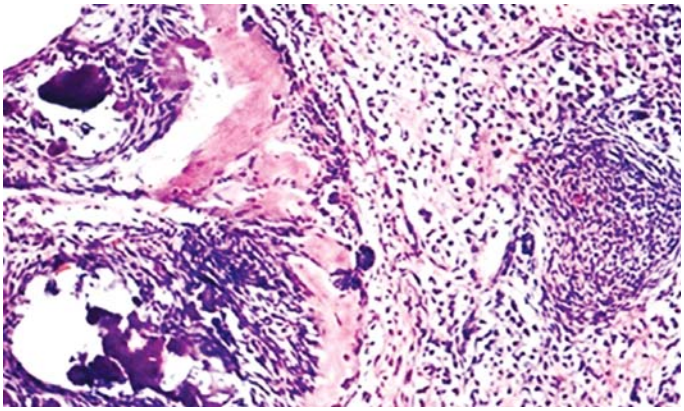


Fig. 10.50: AFOS showing dysplastic enamel formation

- Areas of apparently benign ectomesenchymal tissue were also present.

Ameloblastic Fibroodonto Sarcoma (AFOS) (Fig. 10.50)

- Identical to those of ameloblastic fibrodentinosarcoma except that enameloid is found in the former in addition to dentinoid.
- Histologic presence of prismatic or dysplastic enamel has been considered sufficient to justify the prefix odonto, although no grossly discernible tooth formation takes place in the AFOS.
- Benign odontogenic epithelium in AFOS may reveal mitotic activity or cytologic atypia.

Treatment

- Radical surgery
- Recurrence in case of ameloblastic fibroodontosarcoma and also metastasis been reported.

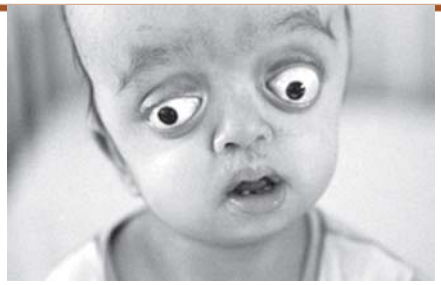
ODONTOGENIC CARCINOSARCOMA (OCS)

Very rare neoplasm similar in pattern to ameloblastic fibrosarcoma, but in which both the epithelial and ectomesenchymal components show cytologic features of malignancy.

Due to very few cases, still no clear available data exist to give some definitve conclusion about this entity.

11

Diseases of Bones and Joints



CHERUBISM (FAMILIAL FIBROUS DYSPLASIA OF THE JAW)

Cherubism, a non-neoplastic hereditary bone lesion that is histologically similar to central giant cell granuloma, affects the jaws of children bilaterally and symmetrically, usually producing the so called cherubic look.

Clinical Presentation and Pathogenesis

Cherubism is an autosomal dominant genetic defect that affects bone remodeling in the specific anatomically confined limits of the embryologic mandible and sometimes of the mandible and maxilla. Cherubism does not occur in any other bone and will not cross a bony suture to an adjacent bone.

Cherubism first begins to manifest itself by the age of 2.5 years and is fully expressed by the age of 5 years. It affects males slightly more than females because of a 100% genetic penetrance in males and only a 50 to 70% genetic penetrance in females. Its relatively rapid progression between the ages of 2.5 and 5 years is often associated with regional lymphadenopathy and, if the maxilla is involved, nasal obstruction with resultant mouthbreathing. Nasal obstruction is caused by enlargement of the middle concha. Because the genetic defect is expressed on the embryologic maxilla or mandible only, the other conchae—the inferior concha, which is an independent bone, and the superior concha, which is part of the ethmoid bone—are not involved. The rapid evolution of the disease often creates significant concern in the parents, particularly if the defect is a mutation and no direct family members or ancestors are known to possess the condition. Spontaneous mutations, called "sporadic occurrences," are more common in cherubism than in most other inherited diseases and account for up to 40% of cases.

Cherubism has three levels of expression. Type I forms only in the bilateral ramus of the mandible, sparing the condyle and extending only to the third molar region. This form may be so subtle that it escapes clinical detection until radiographs are taken years later. It is probable that most of the reported cases of so, called bilateral giant cell lesions of the mandible actually represent this type of cherubism, often called a forme fruste or incomplete expression of the disease. Type II forms only in the mandible and also spares the condyle, but it extends to at least the mental foramen bilaterally and may extend to involve the entire mandible. Type III is the form that prompted the name "cherubism". This form involves the mandible to an advanced degree as compared to type II and also includes the maxilla. The involvement of the maxilla's contribution to the orbital floor and orbital rim displaces the globes upward, causing a scleral show. This feature, combined with the expansion of the maxilla, gives a child with cherubism the chubby-faced appearance and the "upward to heaven" looking eyes of a cherub. The maxillary involvement includes the alveolar bone and palate but does not extend beyond the maxillary sutures. Therefore, the adjacent palatine bones, vomer, zygomas, and nasal bones are completely normal.

The child will, therefore, present with some degree of expanded facies and the possibility of nasal obstruction, lymphadenopathy, dry mouth, drooling, and rarely pain. Clinically, there may be missing teeth, multiple diastemas, and misplaced teeth.

Radiographically, the involved bones show a dramatic multilocular radiolucency with thin and expanded cortices, including the inferior border. The condyle and condylar neck appear normal. Unerupted and displaced teeth are common. Radiographically and clinically, cases show symmetric involvement (Fig. 11.1).

Differential Diagnosis

Cherubism, like most fibro-osseous diseases, requires a clinical and radiographic diagnosis rather than a histopathologic diagnosis. It must, therefore, be distinguished from other bilateral multilocular radiolucent lesions of the jaws in young children. Other entities that may mimic this presentation are primary hyperparathyroidism, Langerhans cell histiocytosis, and multiple odontogenic keratocysts, perhaps as part of the basal cell nevus syndrome. In addition, Noonan syndrome and Jaffe Campanacci syndrome may be considered,

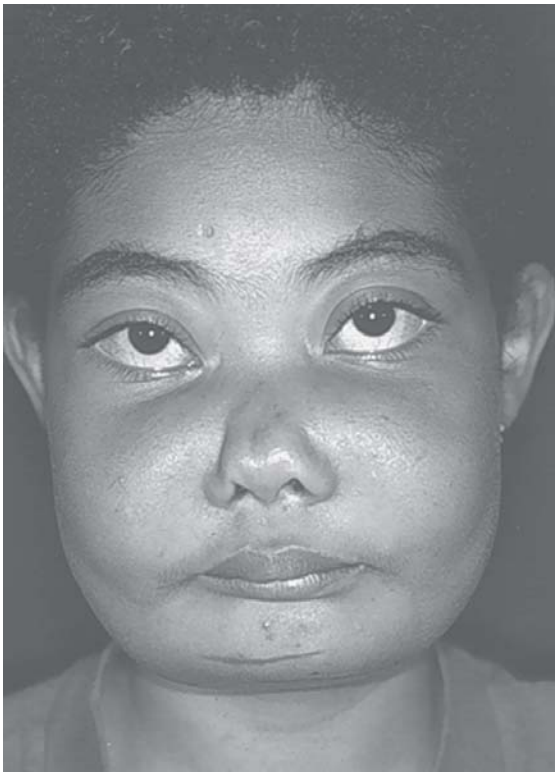


Fig. 11.1: Cherubism

particularly if a fibrovascular giant cell lesion is confirmed by a biopsy.

The specific clinical and radiographic features that permit a diagnosis of cherubism are symmetric presentation, radiographic evidence of multilocular contiguous lesions, sparing of the condyle, lack of involvement of adjacent bones, middle concha enlargement (variable) in the maxilla, and emergence and expression of the disease between the ages of 2 and 5 years.

Histopathology

The lesions of cherubism consist of a vascular fibrous stroma, extravasated erythrocytes, and scattered multinucleated giant cell. An increase in the amount of fibrous tissue and a corresponding decrease in the number of giant cells is probably associated with regressing lesions. An eosinophilic perivascular cuffing of collagen is considered characteristic of cherubism; however, this feature is frequently absent. Clinical and radiographic correlation is necessary, as the histologic features strongly resemble those seen in central giant cell tumors and the lesions of hyperparathyroidism.

Treatment and Prognosis

As with any genetic disease, cherubism currently is not curable. However, the natural course of cherubism is one of gradual enlargement that continues until the onset of puberty. After puberty, a gradual involution begins and is often complete by age 18 to 20 years, and almost never lasting beyond age 30 years. The result is a nearly complete reversal of the facial expansion, which is usually very well accepted by the individual . Radiographs show only partial bony regeneration as residual radiolucent areas persist. There also may be unerupted and displaced teeth. This eruption disturbance, which occurs throughout the childhood years, may cause the patient to be partially edentulous.

The general clinical approach is to avoid surgery altogether and allow natural involution to take place or defer surgeries until after puberty. If reduction of the expanded bone (osseous contouring) is required because of pain or psychologic needs, it is done with the knowledge that the operated bone will reexpand at the same or a higher rate of expansion as before surgery. There is some concern that osseous contouring may accelerate the rate of expansion, but the limited experience with surgery on these patients does not support this concern. There is also no evidence that surgical intervention will stimulate malignant transformation. If osseous contouring is required, especially on a young patient, the surgeon must be aware of the vascular nature of the bone and proceed with the same intraoperative hemorrhage control procedures as would be used in treating a central giant cell tumor (i.e., an elevated head position, hypotensive anesthesia, an accessible supply of hemostatic packs, and a preparation of autologous blood or "designated donor" blood available for transfusion). On occasion, the nasal obstruction can become severe, leading to airway concerns or to significant mouth breathing and an openbite deformity. In such cases, removal of the middle concha and turbinates, mandible as well as a small portion of the maxillary tuberosities is a reasonable and beneficial procedure.

FIBROUS DYSPLASIA

Clinical Presentation and Pathogenesis

Fibrous dysplasia is a disease of bone maturation and remodeling in which the normal medullary bone and cortices are replaced by a disorganized fibrous woven bone. The resultant fibroosseous bone is more elastic and structurally weaker than the original bone. It is caused by the deletion of a bone maturation protein during embryogenesis. There is no evidence to suggest a hereditary influence.

Fibrous dysplasia is conceptualized into three types. Each type usually presents as an asymptomatic, slowly expanding portion of one or more bones. The condition develops in children and teenagers primarily, with few if

cases beginning after the age of 25 years. Monostotic fibrous dysplasia, which involves a single focus in one bone, accounts for about 75% of fibrous dysplasia cases. In the jaws, this may be seen most frequently in the body of the mandible or in the premolar molar regions of the maxilla.

Today it is understood that all types of fibrous dysplasia result from a defect in bone maturation that begins in the embryo. At certain times in the histodifferentiation phase of the embryo, a genetic mutation or deletion occurs in the gene that encodes for an intracytoplasmic transducer protein required for bone maturation. When altered cells migrate into several skeletal sites, they produce polyostotic fibrous dysplasia. If the genetic defect occurs in an even earlier phase of embryonic development, the original cell may produce daughter cells of divergent differentiation that is, some that will migrate into bone primordia, some into skin primordia, and some into endocrine gland primordia—and thus produce either the McCune -Albright syndrome or the Jaffe Lichtenstein type of polyostotic fibrous dysplasia. The time at which these genetic alterations occur is thought to be before the sixth week of fetal life.

When the embryo is in its sixth week of development, most histodifferentiation and cell migration have already occurred. If the same genetic defect occurs around this time, the daughter cells will be localized to one region and thus may produce the craniofacial type of fibrous dysplasia, which involves several contiguous bones in a broad area. If the genetic defect occurs slightly later, the daughter cells will be even more localized and will thus produce monostotic fibrous dysplasia .

Polyostotic fibrous dysplasia involves two or more noncontiguous bones. This form is less common than monostotic fibrous dysplasia and may involve the skull, jaws, or a facial bone together with ribs, long bones, or the pelvis. Two syndromes involving polyostotic fibrous dysplasia have been isolated. McCune-Albright syndrome encompasses polyostotic fibrous dysplasia with cutaneous melanotic pigmentations called Café-au-lait macules and endocrine abnormalities. The most common of the endocrine abnormalities is precocious puberty. Other endocrinopathies that may be part of this syndrome are hyperthyroidism, acromegaly, and hyperprolactinemia. Jaffe-Lichtenstein syndrome, less well known than McCune-Albright syndrome, describes polyostotic fibrous dysplasia with cutaneous melanotic pigmentations in the absence of endocrine abnormalities. Craniofacial fibrous dysplasia involves two or more bones of the jaw midface skull complex in continuity. This type of fibrous dysplasia is seen relatively often in dental and oral and maxillofacial practices. It is frequently underestimated and thought to be a monostotic fibrous dysplasia of the maxilla, yet it often includes the zygoma, sphenoid, temporal bone, nasal concha, and clivus.

Radiographic Presentation

Nearly all cases of fibrous dysplasia will show a diffuse, hazy trabecular pattern that has been called the ground glass appearance. However, some reports have described this pattern as radiolucent while others have described it as mottled pagetoid.

Today, most radiographic and CT scan pictures of fibrous dysplasia show a homogeneous, finely trabecular bone pattern replacing the medullary bone and both cortices and often the lamina dura as well. Its shape is fusiform and its margins are indistinct, showing a gradual blend into normal bone. It shows greater buccal than lingual expansion and does not displace the inferior alveolar canal (Fig. 11.2).

Differential Diagnosis

The single most important differential diagnosis for fibrous dysplasia is to distinguish it from an ossifying fibroma. Other entities that may resemble fibrous dysplasia include chronic sclerosing osteomyelitis, Paget's disease, and sometimes osteosarcoma. Fibrous dysplasia arises and is established by the age of 20 years. Although some ossifying fibromas also develop in youth, most begin at an older age.

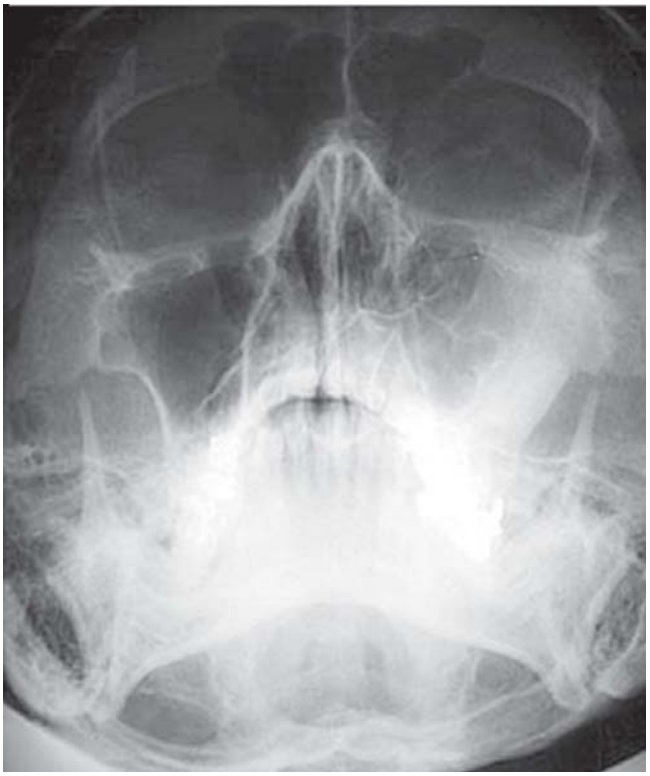


Fig. 11.2: Fibrous dysplasia of jaw

Radiographs and/or CT scans of axial views show an ossifying fibroma to be spherical to egg shaped, heterogeneous, and well demarcated from normal bone. Also shown are an expanded or a thinned residual uninvolved cortex and displacement of the inferior alveolar canal. The radiographs and scans support the concept advanced by Worth that an ossifying fibroma is a disease within bone while fibrous dysplasia is a disease of bone.

Chronic diffuse sclerosing osteomyelitis resembles fibrous dysplasia in its diffuse and poorly demarcated radiographic appearance. It too may occur in teenagers and preteens, but it is more common in adults. However, unlike fibrous dysplasia, chronic diffuse sclerosing osteomyelitis is usually severely and constantly painful; there is frequently a history of endodontic therapy, an abscessed tooth, or some other infection; and appropriate cultures may yield Actinomyces species and Eikenella corrodens. Paget's disease can be distinguished from fibrous dysplasia by its onset in individuals older than 40 years and its increased alkaline phosphatase levels. Osteosarcoma may be difficult to distinguish from fibrous dysplasia radiographically and certainly must be ruled out by histopathologic studies if the diagnosis is not clear. In general, osteosarcomas do not remodel but rather resorb a cortex and expand outward from a destroyed cortex.

Histopathology

In fibrous dysplasia, normal bone is replaced by a generally loose, cellular fibrous tissue composed of haphazardly arranged, variably shaped trabeculae of woven bone, which typically lack osteoblastic rimming but often contain numerous osteocytes. The osseous component thus may appear to arise directly from the fibrous stroma . The lesion has no definable borders, and the osseous trabeculae blend into the normal surrounding bone. Aggregates of multinucleated giant cells may be present. Overtime, fibrous dysplasia of the jaws may show maturation, which is characterized by formation of lamellar bone and parallel arrangement of the trabeculae. Histologic features alone, however, are unreliable for diagnosis; therefore, clinical and radiographic correlation is imperative.

Treatment and Prognosis

The preferred approach to maxillofacial monostotic fibrous dysplasia and craniofacial fibrous dysplasia is no treatment. Most children adapt well to the facial expansion and do not desire osseous contouring surgery. If osseous contouring surgery is desired, it is ideal to defer it until adulthood (ages 18 to 21 years). Like cherubism, fibrous dysplasia shows less growth and its activity is reduced as adulthood approaches, although occasional late expansions and regrowth have occurred in adulthood. Regrowth is most commonly seen when surgeries are performed on patients younger than 21 years. If, because of symptoms or psychologic needs, surgery is required during this time period, it is important to remember that fibrous dysplasia undergoes episodic growth, unlike cherubism, which undergoes a slow and steady growth. Although the surgery itself does not stimulate regrowth, the earlier in life a surgery is performed, the more likely it is that a natural episode of growth will occur postsurgically. Therefore, surgery should be avoided during a period of active expansion

Resection is not usually indicated, even for severe craniofacial fibrous dysplasia, unless neural compression threatens vision or hearing. In such cases, local resection only around the area of the nerve compression or around the involved foramen is often necessary. Monostotic fibrous dysplasia or a focus of polyostotic fibrous dysplasia of the skull does lend itself to a local enbloc resection. The defect is usually reconstructed with a split calvarial graft from an adjacent area. However, resection is not indicated in monostotic fibrous dysplasia of the jaws. The structural weakness of fibrous dysplasia does not functionally impair the jaws to a great extent. Therefore, jaw resection with subsequent bony reconstruction is not justified unless it is an unusual situation in which the patient's function and appearance are significantly altered and osseous contouring is not an option.

Radiotherapy is contraindicated in the treatment of fibrous dysplasias. Numerous cases of radiation sarcomas arising from radiotherapy have been documented. The time from radiation to sarcoma ranges from 10 to 35 years, with a mean at about 20 years.

OSTEOPETROSIS (MARBLE BONE DISEASE)

Osteopetrosis is a rare hereditary bone disease of hetrogeneous pathophysiology in which failure of osteoclastic bone resorption leads to increased bone mass.

Clinical Presentation and Pathogenesis

Osteopetrosis is caused by an inherited defect in osteoclasts. Defective osteoclasts fail to resorb bone in the normal (0.7% per day) resorption remodeling cycle of the skeleton. Therefore, all bones progressively become more dense, less cellular, and less vascular. Because the resorption remodeling cycle of bone eliminates microstress lines and microfractures and maintains foramen and the marrow cavity spaces, these areas become compromised and compressed in osteopetrosis. Therefore, fractures, anemia, thrombocytopenia, and nerve dysfunction ranging from hearing loss to visual disturbance to facial palsy are possible, depending on the genetic type and level of expression of this condition.

Three inheritance patterns of osteopetrosis have been found: Severe autosomal recessive osteopetrosis, which is also known as Albers-Schonberg disease; mild autosomal recessive osteopetrosis; and benign autosomal dominant osteopetrosis. Each of these inheritance patterns may produce a similar presentation clinically and will have overlapping signs because of the heterogenicity of the gene defect. Distinguishing the conditions requires genetic testing and long-term clinical observation.

Individuals with osteopetrosis often have exposed bone with granulation tissue and a low grade osteomyelitis in the head and neck region.

Exposed dense and discolored bone is common and almost always follows tooth extraction. Erupted teeth may be ankylosed. Cutaneous fistulae also are frequently seen. Some cases progress to a facial cellulitis.

Defective vision and nystagmus are common. However, any of the cranial nerves may be compressed at several foramina and, therefore, can present with a varied group of paresthesias and pareses.

Anemia and thrombocytopenia may be seen but are uncommon because significant bone formation within the marrow cavity of long bones and a reduced compensatory extramedullary hematopoiesis would be required for their development. Because osteopetrosis begins in the cortex of long bones and progresses inward, significant marrow cavity obliteration is a later finding.

Radiographic Appearance

Skull and jaw radiographs can be astonishing. The skull in particular will show an extreme density. The mandible should be assessed for fractures, unerupted teeth, and areas of past debridement. The maxillary sinuses may be smaller than usual and the frontal sinus obliterated altogether. Radiographs of the cervical spine in early stages will show the "sandwich" appearance. In later stages, a generalized opacification is apparent. However, the most clinically important assessment of the cervical spine is for subluxations and a fracture of the odontoid process. Either may produce a serious spinal cord compression or laceration.

Differential Diagnosis

A fully expressed case of osteopetrosis is radiographically pathognomonic by its involvement of all bones. However, if the presentation is one of only clinically exposed dense bone and no radiographs have been taken, the clinician should be concerned about florid cemento osseous dysplasia, osteoradionecrosis if there is a history of radiotherapy, a later stage of Paget's disease, and osteomyelitis. If only a panoramic radiograph of the jaws has been taken, osteopetrosis may resemble an advanced case of Paget disease, secondary hyperparathyroidism, fibrous dysplasia, or a chronic diffuse sclerosing osteomyelitis. Early cases may also produce a radiographic picture resembling the bony changes seen in severe anemias, such as severe sickle cell anemia and beta thalassemia.

Diagnostic Work-Up

Osteopetrosis is most commonly confirmed by history because the patient is usually well aware of his or her condition. Skull radiographs are useful to confirm a suspected case. Cervical spine radiographs are needed to assess for the serious complication potential of odontoid fracture or subluxations. A panoramic radiograph also is needed to rule out fractures and to identify unerupted and/or ankylosed teeth. In addition, a complete blood count is recommended either to document anemia/pancytopenia or to establish a reference point for future comparisons.

Histopathology

Because the underlying defect concerns osteoclastic function and bone remodeling, the pattern of endochondral bone formation is disrupted. The trabeculae have cores of heavily calcified cartilage surrounded by irregular woven bone. While the trabeculae may show little thickening in mild disease, in the severe form they may become confluent, ultimately obliterating the marrow and merging with the thickened cortex. The numbers of osteoclasts and osteoblasts vary from few to many. Ultrastructurally, the osteoclasts lack ruffled borders, which normally release lysosomal enzymes at the bone osteoclast interface. Therefore, these defective osteoclasts fail to resorb bone in the normal resorption remodeling cycle.

Teeth in osteopetrosis may show enamel hypoplasia, defects in mineralization of dentin, and abnormal pulp chambers. Unerupted teeth show areas of ankylosis between cementum and bone with absence of periodontal membrane. The periodontal membrane has also been noted to contain fibrous tissue that runs parallel to the root surface, suggesting an abnormality. Areas of osteomyelitis involving the mandible show fibrosis with chronic inflammatory cells.

Biologic Behavior and Treatment

Osteopetrosis is frustrating for the clinician and the individual. Unlike in other diseases involving exposed nonviable bone, debridement is not the focus of therapy in osteopetrosis. In fact, the strategy is to avoid bony surgery and to limit the degree of surgery as much as possible. The involvement of the entire skeleton does not allow the surgeon to debride to "healthy bone", and bone grafts are

not available from any site. Therefore, almost all surgeries in which bone is debrided and a soft tissue closure is obtained result in re-exposure of a greater amount of bone and further risk of fracture.

In a similar sense, tooth removal should be avoided if possible. Therefore, frequent dental visits with prophylaxis and prompt restorative and endodontic care are recommended. A removed tooth often initiates the development of persistently exposed bone and low grade infection.

The clinician is relegated to mostly nonsurgical management even when fractures occur. The exposed bone is cultured and then best treated with the limited intervention of smoothing rough or sharp bony edges, chlorhexidine gluconate oral rinses, and frequent irrigations to reduce numbers of the microorganisms. During periods of secondary infection, culture directed antibiotics are recommended. Hyperbaric oxygen, which produces angiogenesis in osteoradionecrosis, has been suggested for the treatment of osteopetrosis. However, its use is of limited value because osteopetrosis, unlike osteoradionecrosis, does not produce the necessary oxygen gradient loss in soft tissues. It therefore should be reserved for use as an adjunct to antibiotics and wound irrigations in episodes of secondary infection.

Should a patient with osteopetrosis require surgery under general anesthesia, the intubation should be either a fiberoptic assisted or an awake nasal intubation. Use of a laryngoscope, which extends the neck, risks paralysis from spinal cord compression because of the high-risk of cervical spine subluxation and fracture.

CENTRAL GIANT CELL TUMOR

Clinical Presentation and Pathogenesis

Central giant cell tumors of the jaws are benign but aggressively destructive osteolytic lesions. This tumor, and biologic behavior in the jaws, is identical to that in the long bones, and the terminology related to both of them has become extremely confused. Today, these tumors seem to represent benign tumors of osteoclastic origin. They are not unique to the jaws and are not odontogenic. The giant cells have osteoclast receptors and thus represent osteoclast precursors or are themselves osteoclasts. The tumor is not a true granuloma and is not at all reparative. Even the generic term "giant cell lesion" is incorrect and misleading. In addition, there is no difference in histopathologic features or biologic behavior between a central giant cell "lesion" and an aneurysmal bone cyst (which is not a true cyst either). This tumor is histopathologically and behaviorally identical to the benign giant cell tumor of long bones, the most common neoplasm found in long bones; it is not to be confused with what some authors have described as malignant giant cell tumors, which may represent an osteosarcoma with prominent osteoclasts or a true malignant variant of osteoclasts.

In the jaws, a central giant cell tumor presents as a painless clinical expansion that may have a short (2-week to 2-month) ascendancy. The expanded lesion may appear blue because of its cortical and mucosal thinning and internal vascularity. Occasionally, the rapid expansion will stretch periosteum, producing pain. The peak range of occurrence is between 5 and 15 years of age, although some cases develop in the 20s and 30s as well. Women are affected twice as frequently as men. The mandible is involved three times as frequently as the maxilla. Although this lesion is one that is known to cross the midline and to occur in the anterior jaw regions, the posterior regions are affected as well.

Radiographic Findings

The central giant cell tumor will classically present as a multilocular radiolucent lesion that severely thins the cortices, including the inferior border. It is also known to scallop the inferior border, displace teeth, and resorb interradicular bone. It may also resorb tooth roots to some degree.

Differential Diagnosis

A multilocular, expansile, radiolucent lesion in a child or teenager is suggestive of several lesions, most notably an odontogenic keratocyst, an odontogenic myxoma, an ameloblastic fibroma, or Langerhans cell histiocytosis. If the patient is older than 14 or 15 years, an ameloblastoma becomes a statistically more likely consideration as well. In addition, because of the bleeding potential and generally young age of presentation, as well as a multilocular "soap bubble" radiolucency, a central arteriovenous hemangioma must be considered.

Diagnostic Work-Up

A clinical presentation such as that of a central giant cell tumor is approached first with the goal of ruling out a high pressure vascular lesion. Central giant cell tumors are not high pressure vascular lesions and will either fail to return blood or will return only a small amount. In most cases, an incisional biopsy is then performed, although it is not unreasonable to thoroughly curet the entire lesion if it is small, the access is good, and it seems consistent with the red brown friable tissue of a central giant cell tumor. If the lesion is determined to be any type of a giant cell tumor, it is prudent to obtain a serum calcium determination to rule out both primary and secondary hyperparathyroidism. A parathyroid hormone assay is not required because primary

hyperparathyroidism of sufficient severity to produce a so-called brown tumor will evidence hypercalcemia, and secondary hyperparathyroidism of sufficient severity to produce a brown tumor will evidence hypocalcemia. An alkaline phosphatase determination also is not required because this age group frequently has growth-related elevations of this enzyme.

Histopathology

Grossly, these tumors are red to brown in color. The mass consists of a spindle cell stroma that may be quite cellular. There is a variable amount of collagen, and mitoses are sometimes seen. Extravasated erythrocytes are present, and hemosiderin may be noted. The hemosiderin may be contained within macrophages. Multinucleated giant cells are conspicuous and tend to be irregularly distributed throughout the mass, often concentrating in areas of hemorrhage. There may be considerable variation in the size of the giant cells and the number of nuclei present.

Osteoid may be deposited, particularly at the periphery of the lesion. Giant cell tumors are unencapsulated but usually delimited and frequently develop locules. They often abut tooth roots and may resorb them.

The giant cells have been shown to excavate bone, respond to calcitonin, and bind osteoclast specific monoclonal antibody, indicating that they are indeed osteoclasts.

Central giant cell tumors cannot be distinguished histologically from lesions of hyperparathyroidism, and therefore this latter possibility must be ruled out. Cherubism also has the same histologic features. Occasionally, fibrous dysplasia contains a sufficient number of giant cells so that it may also enter the histologic differential.

The so, called aneurysmal bone cyst is a condition that frequently develops secondarily within another lesion of bone. Most frequently, it is associated with central giant cell tumors. Large, blood-filled spaces develop that lack an endothelial lining. Solid areas of the lesion consist of central giant cell tumor with cellular fibrous tissue, extravasated blood, and multinucleated giant cells. However, if these dilated, blood-filled spaces have developed within another lesion, the solid areas will consist of that entity.

Treatment

The most common treatment is a thorough curettage of the lesion and its bony cavity. Multiple recurrent lesions or lesions with significant destructive bone resorption to the point of near pathologic fracture may require resection. The lesion itself is confined to and requires bone for its existence. It cannot exist outside of bone.

The central giant cell lesion does have a recurrence potential with curettage that reaches as high as 50% by some reports. Recurrences are seen more frequently with larger lesions and those that involve significant numbers of teeth. These recurrences are related to incomplete removal of a friable, bleeding lesion, which is more difficult to remove from between teeth and furcations, or to a greater possibility of incomplete excision in a larger sized lesion . The weak points in curettage are thus the areas between teeth, the areas around unerupted teeth, and the neurovascular bundle area; additionally, the vascular nature of this lesion, which produces an oozing type of blood loss, obscures the clinician's view.

Because of the known recurrence potential and the unencapsulated vascular nature of this lesion, two other treatment concepts have been advanced. One is the use of Carnoy's solution as a cellular fixative to sterilize remaining tumor cells. However, statistics do not support a reduction in recurrences when Carnoy's solution is used. Another is to perform endodontic therapy of erupted teeth within the lesion. This also does not reduce recurrences because it is the presence of the roots, rather than their vitality, that limits curettage in this area.

More recently, intralesional corticosteroid use has shown some value, inducing complete involution in many cases and partial involution in others. The suggested treatment is triamcinolone, 10 mg/mL, of which 1 mL is injected for each 1 cm of jaw involvement throughout the lesion, once a week for 6 weeks. Each injection sequence is performed with local anesthesia (bupivacaine) added to the injection solution. Today, most cases of central giant cell tumor are initially treated with the series of intralesional corticosteroid injections. The potential value of resolving these tumors without invasive surgery is compeling. Because the treatment sequence is associated with minimal morbidity and does not preclude further therapy should it be unsuccessful, it is a reasonable first choice. If the tumor fails to respond or accelerated growth results, a population of altered osteoclasts that do not have cell membrane receptors for corticosteroids is implied. Such tumors are then treated with either curettage or a resection with 0.5 to 1.0 cm margins if they are sufficiently large.

Prognosis

Lesions approached with wide access, thorough curettage rarely recur. Recurrent lesions may be recuretted before resection is considered. If a recurrence develops, it is usually within the first 12 to 18 months, much sooner than recurrent odontogenic tumors. Patient age does not affect recurrence; however, the size of the lesion does seem to be related to recurrence, which is often the result of limited access caused by the tumor's infiltration between and around teeth. The

biologic behavior of the giant cells varies greatly but is unrelated to patient age and the size of the lesion.

OSTEOSARCOMA

Clinical Presentation and Pathogenesis

Osteosarcomas represent malignant neoplasms arising from mesenchymal stem cells and/or their early progeny. Their partial differentiation leading to the production of tumor bone from a malignant cellular stroma is what defines them as osteosarcomas rather than any other malignant mesenchymal tumor that can arise from a mesenchymal stem cell. Recent genetic findings have indicated that osteosarcoma development is related to loss of the P53 tumor suppressor gene, loss of the retinoblastoma tumor suppressor gene, and development of independence from regulation by platelet derived growth factor (PDGF). No doubt other tumor suppressor gene losses and oncogene expressions may be involved. However, these three are known to be part of the stem cell or its early progeny's escape from its normal differentiation pathway and loss of controlled proliferation, leading to a sarcoma.

Osteosarcomas occur in the jaws at an average age of 37 years, whereas osteosarcomas occur in long bones at an average age of 25 years. However, numerous jaw osteosarcomas occur in the teen years and early 20s as well.

Osteosarcomas may present with an expansion of bone, an incidental radiographic finding of a radiopacity, a widened periodontal ligament space (Garrington sign), a mobile tooth, a "numb lip" or other paresthesia, and/or pain. Because some of these signs and symptoms can be produced by a number of different developmental, infectious, benign neoplastic diseases, or malignancies, an osteosarcoma often goes undiagnosed for a significant period of time. No doubt its presentation, similar to that of osteomyelitis with proliferative periostitis, suppurative osteomyelitis, ossifying fibroma, osteoblastoma, and even fibrous dysplasia, has too often caused an osteosarcoma to be delayed in its diagnosis or approached with less concern than its biology would warrant.

Osteosarcomas occur evenly among males and females. Mandibular osteosarcomas are more frequent than those in the maxilla (60 vs 40%). All but a rare few arise from within the bone. Parosteal (also called juxtacortical) osteosarcomas arise from periosteum and occur outside the bone cortex.

Radiographic Findings

Osteosarcomas may indeed produce the often described "sunray" appearance. A widening of the periodontal ligament space, also called Garrington sign, is seen in several mesenchymal malignancies as an early finding but is most commonly seen in osteosarcoma.

Most radiographs and computed tomographic (CT) scans show a mottled radiopaque or mixed radiolucent radiopaque appearance in the medullary space. Extracortical bone formation is common and may or may not produce the sunray appearance. However, cortical bone destruction is characteristic and should be evident.

Maxillary osteosarcomas produce a sunray appearance and extracortical bone formation less frequently. Because they also grow into the airspace of the maxillary sinus as a bulbous radiopaque mass, they may suggest a benign tumor of bone or a fibro-osseous disease rather than an infiltrating malignant bone tumor (Fig. 11.3).

Differential Diagnosis

The radiographic and clinical picture of an osteosarcoma can be similar to that of infections such as osteomyelitis with proliferative periostitis, chronic sclerosing osteomyelitis, and suppurative osteomyelitis; to benign bone tumors or benign tumors within bone such as osteoblastomas, ossifying fibromas, and cavernous hemangiomas within bone; to odontogenic tumors such as calcifying epithelial odontogenic tumors and ameloblastic fibro odontomas; and to fibro-osseous diseases or systemic diseases of bone such as fibrous dysplasia and Paget's disease.

An important clinical differential feature is neurosensory loss. Other than a rare osteomyelitis or neural loss from a previous biopsy or surgery, only malignancies can produce objective paresthesias. In addition, radiographs or CT scans at right angles to the cortex should show extracortical bone and a destroyed cortex. Fibrous dysplasia and ossifying fibroma will not have extracortical bone. The extracortical bone seen in osteomyelitis with proliferative periostitis will

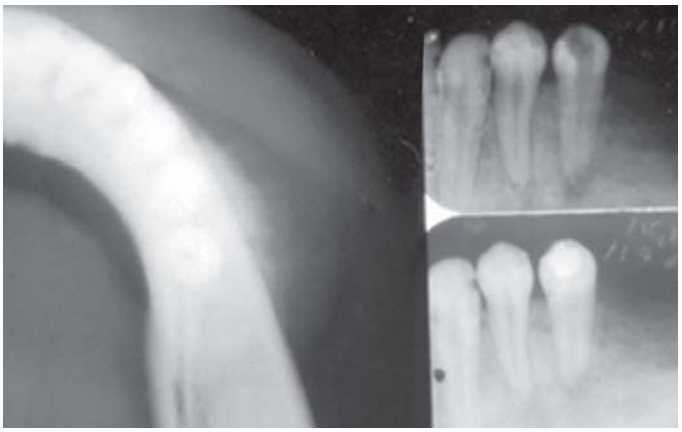


Fig. 11.3: Occlusal radiograph view showing the external cortical portion with radiopacity similar to 'sunrays' and increased periapical space of the premolar tooth seen in osteosarcoma

be associated with an intact cortex. Even when other osteomyelitis produce extracortical bone, it is parallel to the cortex rather than at right angles as is seen in osteosarcoma.

Diagnostic Work-Up

A presentation suggestive of osteosarcoma requires a biopsy as soon as possible. A tissue biopsy is the only means of making a definitive diagnosis. The biopsy should be taken from the lesion's center to avoid missing the diagnostic portion of the tumor or including benign reactive periosteal bone in the specimen, which could lead to a misdiagnosis. The remainder of the work-up requires at least a chest radiograph and perhaps a chest CT scan. Because early and small lung metastatic deposits are a concern, either will establish absence of disease or early metastasis. In addition, a CT scan of the primary site and adjacent structures is suggested for surgical planning.

Histopathology

The histologic appearance of osteosarcomas is highly variable. What all osteosarcomas have in common is the direct formation of osteoid from a sarcomatous stroma . The quantity of osteoid and bone that is formed varies considerably, ranging from a sclerotic osseous tumor to one in which multiple sections may be necessary to identify some semblance of osteoid. The stromal cells may be osteoblastic, chondroblastic, and/or fibroblastic . However, distinguishing osteoblastic, chondroblastic, and fibroblastic osteosarcomas based on the most prominent pattern does not seem to have any prognostic significance. In general, osteoblastic tumors are most common, but in the jaws the chondroblastic pattern prevails. A myxoid stroma is also frequently seen, and an atypical myxoid proliferation should alert one to the possibility of osteosarcoma. The majority of tumors are not homogeneous, reflecting the pluripotentiality of the proliferating mesenchymal cell.

Some osteosarcomas are very heavily ossified, and in these cases, there may be entrapment of tumor cells within the sclerotic osteoid, such that the cells appear to represent osteocytes.

Mitoses may be present, but they are not usually numerous. Multinucleated giant cells may also be present, sometimes in large numbers, although they are unusual in the jaws. Stromal cells may be predominantly rounded, spindled, angulated, or pleomorphic with marked atypia.

Other histologic variants include a telangiectatic type in which there are numerous widely dilated vascular channels and prominent multinucleated giant cells. This type is uncommon in the jaws. The small cell osteosarcoma may resemble Ewing's sarcoma histologically, but unlike Ewing's sarcoma, it forms osteoid. Particularly in tumors

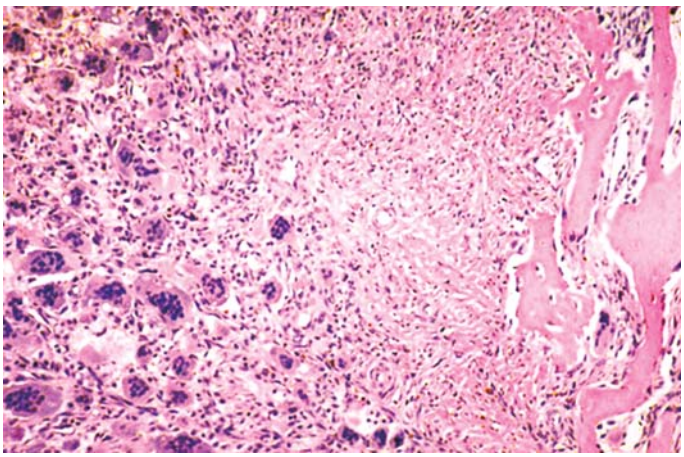


Fig. 11.4: Histopathology of osteosarcoma

with prominent chondroblastic or fibroblastic features, or those in which identification of osteoid is difficult, the recognition of bone specific alkaline phosphatase in fresh tissue may be helpful diagnostically.

It is important to emphasize that biopsy specimens from the superficial or peripheral aspects of the tumor—that is, from the advancing edge—are least likely to be representative of the tumor and frequently fail to demonstrate osteoid formation.

Periosteal osteosarcomas are essentially chondroblastic osteosarcomas that expand into the soft tissue from an intact cortex (Fig. 11.4).

FIBROSARCOMA

Fibrosarcoma is tumor of mesenchymal cell origin that is composed of malignant fibroblasts in a collagenous background.

Clinical Presentation

Since the 1990s, when true fibrosarcomas were first distinguished from malignant fibrous histiocytomas, they have been found to be very rare. Fibrosarcomas are distinct from malignant fibrous histiocytomas by virtue of a uniform spindle cell fibroblastic cell population arranged in parallel bands or a herringbone pattern. The malignant fibrous histiocytoma has round mononuclear cells with significant pleomorphism mixed with the fibroblastic cells and a whorled arrangement called a storiform pattern.

The fibrosarcoma also differs from the malignant fibrous histiocytoma by virtue of its various grades. Not all are high grade malignancies like malignant fibrous histiocytoma. In fact, some are very low grade in behavior and in histopathology. Some of these may have an onset of more than a year's duration, indicative of slow but infiltrative growth. They occur in an even age distribution between 10 and 70 years with no sex predilection.

In the jaws, a fibrosarcoma will present as a fleshy to firm mass destructive of bone and often growing out of bone. Bone resorption in an ill-defined, irregular pattern is common. Pain is usually not the chief complaint; instead, it is usually jaw expansion and tooth mobility. Paresthesia and overt anesthesia are often seen if the tumor is near a nerve trunk.

Radiographic Appearance

Radiographs and CT scans will show an ill-defined and irregular bone resorption. Early or low-grade tumors may show a widening of the periodontal membrane space (Garrington sign) or a "floating tooth" appearance due to extensive resorption of alveolar bone. There should be no extracortical bone formation. On a CT scan, the soft tissue mass will appear to gradually blend into the surrounding tissues, indicative of its infiltrative growth.

Differential Diagnosis

The destructive radiographic pattern and the fleshy to firm mass will be suggestive of both malignant fibrous histiocytoma and an osteosarcoma, which has little if any tumor bone formation. In young individuals, the presentation may resemble that of a Ewing's sarcoma or a rhabdomyosarcoma. In older adults, the presentation is consistent with carcinomas metastatic to bone such as from the lung, prostate, breast, or kidney. If the mass is more fleshy than firm, it may clinically resemble a non-Hodgkin lymphoma.

Although some believe that the desmoplastic fibroma and aggressive fibromatosis represent a very low-grade fibrosarcoma (grade 1/2), these may be part of the differential diagnosis as separate entities with an improved prognosis.

Diagnostic Work-up

The mass should undergo biopsy without delay. As with all other mass lesions in the jaws, the biopsy should be taken from the lesion's center to avoid the possibility of confusion created by overlying scar tissue or inflammation caused by exposure to the oral environment.

A CT scan is recommended to assess the degree of bony involvement and the tumor extension into surrounding soft tissues. A chest radiograph is required to rule out metastasis to the lung, which is the most common organ to which fibrosarcoma metastasizes.

Histopathology

Fibrosarcomas are spindle cell, fibroblastic tumors that produce varying amounts of collagen but no osteoid or cartilage. Those occurring in bone are histologically identical to those occurring in soft tissue. Well-differentiated tumors demonstrate a Herringbone pattern with rare mitoses. More poorly differentiated tumors will show more mitoses, which are often abnormal, and less collagen production with a loss of the Herringbone pattern. The less collagen that is produced, the more densely packed are the nuclei. Tumors that are less differentiated are more likely to resemble malignant fibrohistiocytomas. Immunohistochemically, alpha-l-antitrypsin, alpha-1-antichymotrypsin, and lysozyme are negative for fibrosarcomas but positive for malignant fibrous histiocytomas. Fibrosarcomas must also be distinguished from desmoplastic fibromas and fibroblastic osteosarcomas. The latter show alkaline phosphatase activity, while fibrosarcomas do not. Reactive bone formation should not be misconstrued as tumor bone deposition.

Treatment and Biologic Behavior

The general consensus is that true fibrosarcomas are of only lowgrade to intermediate-grade nature at most (grades I and II). Most highgrade fibrosarcomas actually represent malignant fibrous histiocytomas. Therefore, the clinician should be sure that he or she and the pathologist understand each other's definitions of the diagnosis and of the tumor grading.

If the tumor is indeed a true fibrosarcoma, chemotherapy may not be required. Rather than combined therapy, resective surgery becomes the sole treatment modality.

Fibrosarcomas in the mandible require a continuity resection with 1.5 to 2.0 cm margins in both bone and soft tissue. The bony defect can undergo immediate stabilization with a rigid plate followed by delayed bony reconstruction after the mucosa has healed. If the tumor was sufficiently large to create a significant soft tissue defect, a myocutaneous flap or free vascular flap may be used for reconstruction.

In the maxilla, a type of partial maxillectomy is required.

A neck dissection is not required unless an obvious palpable node suggestive of tumor is present. Chemotherapy or radiation also is not required unless the tumor is high grade (i.e. grade III).

Prognosis

The usual true fibrosarcomas, which represent a low grade malignancy, have an 80% 10- year survival rate. Recurrences at the surgical site do occur. However, because of the tumor's low grade, slow growth, and minimal metastatic potential, salvage surgery often effects a cure. Metastasis to the lungs does occur but much less frequently than with other sarcomas such as osteosarcoma, Ewing's sarcoma, or malignant fibrous histiocytoma. Most high-

grade fibrosarcomas are today diagnosed as malignant fibrous histiocytomas and have only a 30 to 40% 5-year survival rate.

Follow-up

Low to intermediate grade fibrosarcomas (grades I and II) may occur any time over several decades. Therefore, follow-up is life-long and can be limited to an oral and head and neck examination and local radiographic studies. Semi-annual chest radiographs also are recommended.

High grade fibrosarcomas (grade III) usually recur within the first 2 years. Therefore, follow-up consisting of an oral and head and neck examination, local radiographs, and a chest radiograph are recommended every 4 months for the first 2 years. For the next 3 years, these examinations are conducted every 6 months, and then annually thereafter

LANGERHANS CELL HISTIOCYTOSIS

Clinical Presentation and Pathogenesis

Langerhans cell histiocytosis (LCH) is a true neoplastic proliferation of cells of the immune system owing to its histogenesis from the ubiquitous dendritic antigen-processing and -presenting cells, termed Langerhans cells. Langerhans cells themselves are a type of macrophage (histiocyte). They arise from marrow precursor cells and are part of the monocytic series. Langerhans cell histiocytosis was formerly referred to as histiocytosis X based on the appearance of these cells under light microscopy Langerhans cells are found in every organ, but they are somewhat more numerous in bone marrow, the lungs, mucosa, and skin. Therefore, LCH may have unifocal or multifocal presentations in any bone, most commonly the skull, facial bones, proximal femur, and ribs, but also the lungs and either skin or mucosa, usually around the oral cavity and genitals.

Pertinent to the oral and maxillofacial specialist are cases presenting in the jaws, facial bones, or head and neck soft tissues. In the jaws, where about 7% of bony lesions occur, oral and maxillofacial specialists mostly see LCH in children, teenagers, or young adults. However, it is important to remember that bony lesions occur in this young age group in any part of the skeleton, but soft tissue and particularly lung lesions occur between the ages of 20 and 40 years.

Jaw lesions may present with the classic picture of alveolar bone loss and mobile teeth, producing the "floating tooth" picture . However, others may present in the rami at the inferior border of the mandible or in other facial bones, mimicking an osteomyelitis, a sarcoma, or an odontogenic neoplasm. Some may even present with a multilocular radiographic appearance. Jaw lesions do not usually produce significant symptoms other than mild bone pain, tooth mobility, and at times expansion. Of course, sphenoid lesions often produce diabetes insipidus, exophthalmos, and diplopia, while pulmonary lesions produce dyspnea, chronic cough, and fatigue.

Differential Diagnosis

The presentation of alveolar bone loss with loose teeth in a child represents a classic differential in oral and maxillofacial surgery. Other entities that may produce this same picture are juvenile periodontitis, acute lymphocytic leukemia, the juvenile periodontitis associated with Papillon-Lefevre syndrome, nonspecific periodontitis associated with juvenile-onset diabetes mellitus, osteomyelitis, and a variety of sarcoma or sarcoma-like diseases such as osteosarcoma, fibrosarcoma, and aggressive fibromatosis.

Diagnostic Work-up

A presentation suspicious for LCH requires a biopsy that should include the removal of involved teeth to gain an adequate tissue specimen. The involved teeth are not salvageable since the alveolar bone will not regenerate.

If a biopsy is taken, it is advisable to alert the pathologist that LCH is one of the considerations and to recommend immunostaining for the CD1a glycoprotein cell membrane antigen, which is specific for LCH, and for S-100 protein, which is nonspecific but usually positive. This is important since oral LCH biopsies may appear to be very similar to nonspecific periodontal inflammation and accepted as such without a closer review and/or pursuit of these specific tests. In difficult cases, electron microscopy of even formalin fixed paraffin-embedded specimens (glutaraldehyde or Karnofsky fixative is preferred) that identify Birbeck granules will be pathognomonic.

Histopathology

The low power view often suggests an inflammatory process. It is characterized, however, by the proliferation of Langerhans cells, which have abundant ill-defined cytoplasm and oval or indented nuclei that often have a central groove, giving it a coffee bean appearance. Inflammatory cells are also present and may include lymphocytes and neutrophils, but eosinophils predominate. There may be infiltration of overlying epithelium. Giant cells and necrosis may be present, but mitoses are very uncommon. The histologic appearance does not seem to correlate with behavior. The recognition of Birbeck granules in the lesional cell by electron microscopy is also pathognomonic. Birbeck granules are cytoplasmic structures that are rod-shaped and have periodic striations that resemble a zipper. One end may be

dilated. The impracticality of these latter techniques has been overcome by the use of the CDIa mouse monoclonal antibody 010, which can be employed on routinely processed paraffin-embedded tissue and has made this the diagnostic test of choice. Therefore, definitive diagnosis is achieved by light microscopy and positivity for the CD1a antigen by immunostaining.

Treatment and Prognosis

Langerhans cell histiocytosis is generally responsive to a variety of treatments, each of which provides a cure or long-term palliation; only rare cases are unresponsive and progress to death. Therefore, many treatment modalities have been suggested, including surgical curettage, resection, radiotherapy, chemotherapy, intralesional steroids, and systemic steroids. However, surgical curettage or a peripheral resection with 3 to 5 mm margins is the most curative and predictable and is recommended for all accessible jaw and facial bone lesions, including those in the skull. For lesions that are not accessible or have recurred in spite of surgery, radiotherapy of 1200 to 1,800 cGy is the next line of therapy.For widespread lesions involving the jaws/facial bone areas and particularly the lung or lymph nodes, systemic chemotherapy becomes a necessary part of the treatment protocol. In such cases, vinblastine or 6-mercaptopurine (Purinethol, GlaxoSmithKline) as single agents have been shown to be the most effective with the least side effects. Of course, in LCH that produces a diabetes insipidus, long-term hormone replacement with desmopressin acetate (DDAVP, Aventis), 10 to 40 mg nasally at bedtime, is required.

The prognosis of LCH is generally very good because of its slow natural progression and its responsiveness to therapy. Both unifocal and multifocal lesions respond well to therapies selected for their particular presentation so that an overall 80% cure rate is achieved. However, about 20% of patients seem to develop a more aggressive multi organ involvement requiring repeated therapies, leading to an overall LCH death rate of 9%. The majority of the refractory cases and the life-threatening involvements are those involving the lungs. By contrast, LCH with isolated bone involvements has a 97% cure rate.

TRAUMATIC EOSINOPHILIC GRANULOMA

The traumatic eosinophilic granuloma is a rare ulcerated condition of uncertain pathogenesis.

Clinical Presentation and Pathogenesis

It is mostly seen in adults older than 30 years and is almost exclusively seen in the tongue or, more rarely, in the lip. It is presumed to be a condition initiated by a traumatic injury to the skeletal muscle in one of these two sites. The muscle injury itself stimulates a chemotaxis of eosinophils, which infiltrate and efface the local muscle fibers. The traumatic incident is a single injury rather than a chronic repetitive trauma and is usually of a puncture type.

Lesions on the lip will be ulcerated and crusted. Such ulcerated lesions will have an indurated base and periphery, giving the strong impression of a squamous cell carcinoma. This impression may be reinforced by a history of excision with local recurrence. The ulcer is usually small (less than 2 cm) and may have an exophytic protrusion similar to that of a pyogenic granuloma. The lesion itself is only mildly painful or asymptomatic. Most patients seek care because of its long duration without healing or recurrence after an initial excision.

Differential Diagnosis

The indurated ulcer presentation of the traumatic eosinophilic granuloma of the tongue or lip may indeed be identical to that of a squamous cell carcinoma. In those that have an exophytic bulge of muscle or red mass of friable granulation tissue, a pyogenic granuloma or a fungal ulceration such as histoplasmosis or coccidioidomycosis are considerations. If the trauma is constant and repetitive, such as that from a sharp dental restoration or a habit, a nonspecific traumatic ulcer should be suspected. In addition, other mild to severe, painful, single ulcerative conditions, such as a syphilitic chancre or a tuberculosis ulcer, must also be considered.

Diagnostic Work-up

Unless an obvious source of chronic trauma is evident, these tumors should be biopsied without hesitation. Even if a source of chronic trauma is found and removed, no more than 14 days should be allowed for the area to show unequivocal signs of healing before a biopsy is accomplished. There are no specific radiographic or blood studies that will confirm a diagnosis of traumatic eosinophilic granuloma, and no peripheral blood eosinophilia is seen with this diagnosis.

Histopathology

This reactive lesion is usually ulcerated. The most striking feature is the presence of numerous histiocytes and eosinophils, which infiltrate deeply into skeletal muscle. Varying numbers of neutrophils and plasma cells will also be seen, with the heaviest concentrations in the area of the ulcer. Degeneration of skeletal muscle fibers is often noted.

Treatment and Prognosis

Once an incisional biopsy has ruled out the other ulcerative lesions on the differential diagnosis and hopefully

established the diagnosis of a traumatic eosinophilic granuloma, the lesion should be excised with 0.5 cm peripheral margins. Although common, recurrences are usually the result of an inadequate depth of excision rather than positive margins at the surface. Therefore, excision with frozen section guidance and close follow-up are recommended. Recurrent lesions should be re-excised with particular attention to the deep margins and controlled with frozen sections, and the histopathology should be carefully reviewed to be certain that one of the other lesions on the differential list is not present.

CLEIDOCRANIAL DYSPLASIA (MARIE-SAINTON'S DISEASE)

It is a congenital disorder of bone formation manifested with clavicular hypoplasia or agenesis with a narrow thorax, which allows approximation of the shoulders in front of the chest.

Clinical Presentation and Pathogenesis

Cleidocranial dysplasia produces a pathognomonic facial and general physical appearance. Individuals will be short of stature (males, 5 feet average height; females, 4 feet 9 inches average height). They will appear to have a long neck with narrow, drooping shoulders due to absence of or hypoplastic clavicles. Their head will appear brachycephalic with obvious frontal and parietal bossing.

The cranium will be enlarged in the anteroposterior dimension and shortened in the superoinferior dimension, and the nasal bridge will appear flat and broad. There may be a groove in the midline of the forehead, and there may be palpable soft areas in the scalp due to open sutures. The supraorbital and infraorbital ridges are often prominent, and exorbitism may be seen because of a deficient orbital volume due to frontal bone thickening.

The absent clavicles have always been the focus of attention in cleidocranial dysplasia patients. The added motion of the shoulder girdle allows patients to touch their shoulders together in the midline. Many patients have residual hypoplastic clavicles rather than complete agenesis, with the residual portion articulating to the sternum. Some have only unilateral clavicular absence (more common on the right side).

An oral examination will be striking for a malocclusion with over retained primary teeth and missing permanent teeth. The maxilla will be hypoplastic with a deep, narrow palate that may harbor a submucosal cleft. The anteroposterior deficiency of the maxilla will create a pseudoprognathism. The nasolabial angle is usually excessively obtuse. Other skeletal abnormalities may also be variably present. These may include spina bifida, delayed closure of the pubic symphysis, and malformation of the metacarpals and phalanges, among others.

Cleidocranial dysplasia is an autosomal-dominant syndrome. The multiple unerupted teeth are believed to be due to absence of cellular cementum, and the delayed exfoliation of the primary dentition due to delayed root resorption. The multiple supernumerary teeth seem to be related to a delayed involution of the dental lamina, which becomes reactivated when the expected permanent tooth develops. Because the dental lamina arises from and forms the teeth from a lingual position, the supernumerary teeth lie lingual and occlusal to the permanent teeth (Fig. 11.5).

Radiographic Findings

Skull radiographs will show areas of radiolucency corresponding to delayed cranial bone formation. They will also show radiopaque centers of secondary calcification and wormian bones in the sutures. The frontal and sphenoid sinuses will be small or absent, and the mastoid air cells will be missing. The maxillary and ethmoid sinuses will be absent or small. The orbital ridges will appear dense.

Panoramic radiographs will show, for those in the primary dentition stage (ages 2.5 to 6 years), normal eruption and formation of all 20 primary teeth. Those in

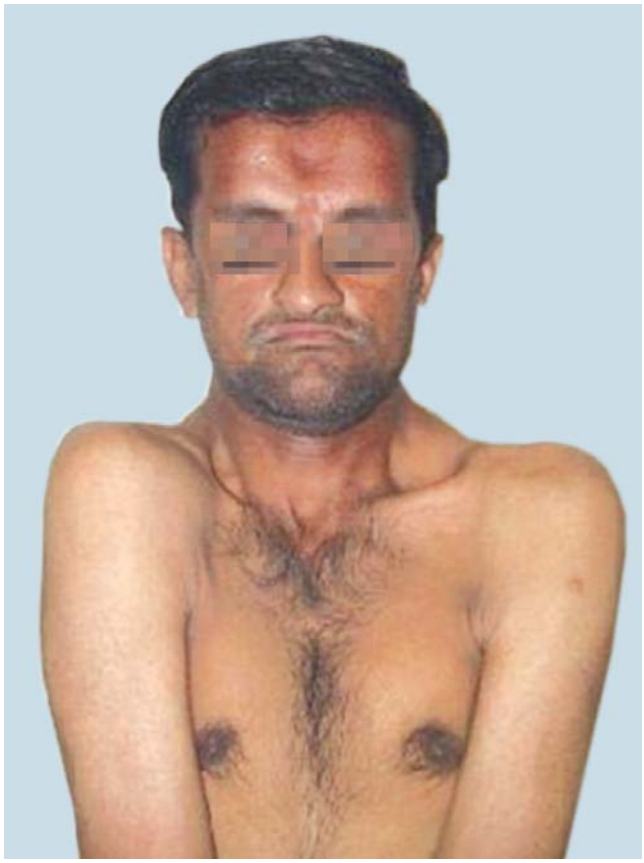


Fig. 11.5: Cleidocranial dysplasia

the mixed dentition stage and into adulthood will show numerous unerupted and supernumerary teeth. The primary dentition will show delayed root resorption and physiologic exfoliation. As a general rule, there is one supernumerary tooth for every expected permanent tooth. This "double dentition" characteristically forms lingual and occlusal to the expected normal but unerupted permanent premolar teeth and prevents their eruption. The supernumerary teeth are premolar teeth morphologically even if they form in association with molars. In rare cases, there may be a radiolucent line in the mandibular symphysis indicating failure to unite in the midline. Chest radiographs may reveal absent or incomplete clavicles. Hypoplastic clavicles often show a remnant at the sternoclavicular joint or medial and lateral segments with a central gap.

Differential Diagnosis

The clinical and radiographic appearance is distinctive and pathognomonic. The diagnosis is made by recognition of the components of this syndrome.

Histopathology

The few studies of teeth of these patients have shown almost complete lack of cellular cementum of both primary and secondary dentition.

Treatment

Treatment is focused on reducing the dentofacial deformity and correcting the malocclusion. A coordinated treatment plan is required and generally involves removing some (but not necessarily all) supernumerary teeth. Those that seem to be forming dentigerous cysts or other pathologic entities or those that might interfere with orthodontic therapy and arch coordination are the ones indicated for removal. If a submucosal cleft exists, it can be corrected separately or at the time of orthognathic surgery, which is frequently required in these individuals. Follow-up orthodontic refinement and stabilization is necessary as is restorative and prosthetic dentistry for areas of carious or missing teeth. Uncovering of unerupted teeth with planned attempts to guide eruption by orthodontic means cannot be expected to be successful because of the lack of cellular cementum.

OSTEOGENESIS IMPERFECTA (BRITTLE BONE DISEASE)

It is serious disease resulting from abnormality in the type I collagen, which most commonly manifests as fragility of bones.

Clinical Presentation and Pathogenesis

The osteogenesis imperfectas are an extremely varied and overlapping group with multiorgan and therefore heterogeneous clinical involvements that have the commonality of defective Type I collagen. Therefore, it would perhaps be better to collectively term these diseases connective tissue imperfectas. In the past, students have been taught to remember these diseases as a single entity through the phrase "brittle bones and blue scleras." While this is mostly true, some cases will be sufficiently subclinical as to lack brittle bones or fractures but have blue sclerae and several other features, and others will lack blue sclerae but will have multiple fractures that are more common at certain ages. The "brittle bones" result from normal mineralization of a defective Type I collagen, which does not have the elasticity of normal bone and is therefore prone to fracture following mild trauma. The blue sclerae are not due to an abnormal thinness of the sclera but rather to a decreased collagen fiber thickness and fiber diameter, allowing the retinal and uveal vessels and pigments to show through as blue.

Since the osteogenesis imperfectas involve all collagen synthesis in the individual in addition to fractures, they may also variably have aortic dilations, joint hypermobility, bowing of the long bones, easy bruising, and various dentinogenesis imperfecta manifestations, among other organ involvements. Although various dentin abnormalities are associated with osteogenesis imperfectas, dentinogenesis imperfecta may occur as a single entity unassociated with osteogenesis imperfecta, and conversely, osteogenesis imperfecta may or may not have concomitant dentinogenesis imperfecta. In fact, this association has led to the classification of two subtypes of type I osteogenesis imperfecta (Fig. 11.6).

Major Types

In an attempt to develop a general categorization, the many clinical expressions of osteogenesis imperfecta have been divided into four major types as follows:

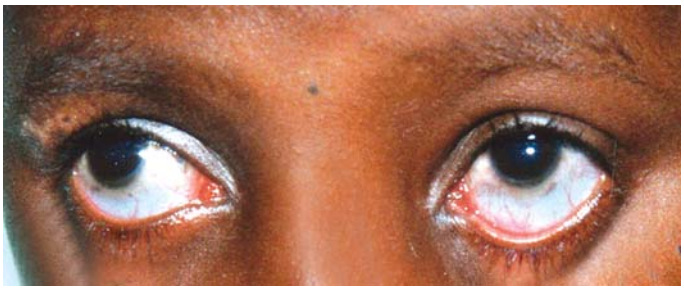


Fig. 11.6: Blue sclera seen in osteogenesis imperfecta

Type IA

Individuals with type IA will tend to have multiple bone fractures, although 10% will have no fractures. The number of fractures will range from 2 to more than 70 throughout the individual's lifetime. Such fractures will be more frequent in children and older individuals, and less frequent at puberty and for some years afterward. Fracture frequency thus increases with age and is particularly high among postmenopausal women. These individuals may also have varying degrees of kyphosis, scoliosis, bowing of long bones, and increased cranial size (macrocephaly).

Individuals with type IA will not have dentinogenesis imperfecta; the teeth are clinically and radiographically normal. However, 95% of those in this group over the age of 30 will develop some conductive hearing loss due to immobility of the middle ear ossicles at the stapes footplate. This group may also have aortic dilations; however, only 24% of men and 4% of women have this involvement, and it is usually asymptomatic. Joint hypermobility may also be seen, but to a lesser degree than that seen in Ehlers-Danlos syndrome or Marfan syndrome, two other diseases of defective collagen synthesis or structure.

Type IB

Individuals with type IB may have any or all of the involvements of osteogenesis imperfecta in type IA, as well as various degrees of dentinogenesis imperfecta. Usually both the primary and secondary teeth erupt with opalescent dentin, which is the gray or blue-gray appearance of the teeth. Like the blue sclerae, the malformed collagen component of the dentin allows the pulp vascular network to reflect light through the teeth as blue. A widened pulp chamber, resulting from incomplete and shortened dentinal tubules, may also contribute to this effect. The enamel is normal, but the dentinoenamel junction is usually flat. Therefore, the enamel rods wear off rapidly to expose the dentin, producing a brown discoloration soon after eruption that may resemble a restorative crown preparation. Significant secondary dentin is deposited so that the teeth will lose their blue-gray opalescence, and a radiograph will show obliterated pulp chambers. Therefore, depending on the timing, the teeth may appear gray-blue, normal, or brown clinically and show enlarged, normal, or obliterated pulp chambers radiographically.

Types IIA, IIB, and IIC

The three subgroups of type II osteogenesis imperfecta are distinguished by the mode of inheritance. Type IIA is thought to be the result of new mutations, which are autosomal dominant. Type IIB is thought to be inherited from parents who are carriers and is an autosomal-dominant inheritance. Type IIC is very rare but is thought to represent autosomal-recessive inheritance.

In each of the subtypes, type II osteogenesis imperfecta is a severe expression characterized by extreme bone fragility and multiple early fractures, including fractures in utero and stillbirths or early infant deaths (14 hours to 4 weeks). In fact, much of the data available in this group have been derived from autopsies. Similar to type IB, type II has enlarged dental pulps with shortened and incomplete dentinal tubules, but no information is available concerning secondary dentin and eventual pulpal obliteration because of the short lifespans. In this general type, radiographs show dramatically incomplete skeletal development with malformed ribs, wormian bones in the calvarium (island of bone), and absent ossifications of the distal segments in the extremities.

Type III

Type III osteogenesis imperfecta is also a more severe form than type I although not as severe as type II. This type progressively worsens so that about 38% survive long-term, as do most type I individuals, but none dies in early infancy as do those with type II. Most deaths result from complications of fractures or inadequate skeletal support of internal organs, leading to scoliosis, pulmonary hypertension, and cardiopulmonary failure.

This type will not have blue sclerae. The sclerae will appear normal clinically in adults, although children may have blue sclerae throughout their first year. The dentitions in this group have not been adequately reported; however, it seems that 50% will have some form of dentinogenesis imperfecta.

Type IV

Type IV osteogenesis imperfecta will have normal sclerae as does type III individuals. However, this type has more fractures at birth than type III and, also in contrast to type III, does not worsen overtime but actually has fewer fractures after puberty. This type has a high incidence of concomitant dentinogenesis imperfecta similar to that of type IB. The specific degree of dentinogenesis imperfecta and its course are consistent within a family. They generally include a slight variation of opalescent teeth on eruption, enamel loss once in function, and obliterations of the pulp due to secondary dentin deposition.

Differential Diagnosis

There are several rare syndromes that may produce bone radiolucency and fractures. These include Cole-Carpenter syndrome, Campomelic syndrome, and Bruck syndrome. If wormian bone in the calvarium is the prominent feature, cleidocranial dysplasia, progeria, mandibuloacral dysplasia, and acroosteolysis may be considered as well. If blue sclerae is the prominent feature, Marfan syndrome

and Ehlers-Danlos syndrome may be included. If dentinogenesis imperfecta features predominate, it is well to remember that dentinogenesis imperfecta can exist independently and that dentin dysplasia type I and type II will produce dentin abnormalities similar to dentinogenesis imperfecta.

In a practical sense, a young child who presents with multiple fractures should be considered a potential "battered child." This may be particularly difficult to distinguish from some of the osteogenesis imperfectas because of the easy bruising that may be a part of the collagen abnormality and the obvious bruising seen in a battered child. In such cases, the dental examination, the color of the sclerae, and the pattern of bony fractures become the important differential points.

Diagnostic Work-up

A detailed complete body physical examination, oral examination, jaw radiographs, and full skeletal radiographs are the baseline studies recommended. If these studies suggest a diagnosis of osteogenesis imperfecta, genetic testing of parents and patient may be accomplished as well as collagen mapping and DNA probe studies, which usually require biopsy material.

Histopathology

The ossification centers develop normally in cartilaginous bone, but no ossification occurs. Cortices are thin, and medullary trabeculae are few, fragile, and subject to microfractures. In the severely affected infant, the skull may be fibrous and in adults it may be composed of small wormian bones with irregular sutures.

Treatment

There is no specific treatment for the disease itself. It will progress to its full expression as dictated by the degree of genetic mutation of the particular type, which in turn has dictated the degree and amount of "imperfect" collagen.

The oral and maxillofacial surgeon may be required to treat facial bone or jaw fractures in these individuals. In such cases, the rate and degree of bone regeneration is the same as for normal individuals. However, the bony callus and bony union will be of osteogenesis imperfecta-type bone. Therefore, standard fracture treatment approaches may be used with little modification. There is no compelling recommendation to use more rigid internal fixation plates in these individuals because the gain of rigidity is offset by the stress rizors that are more prominent in "brittle bones" when screw holes are drilled and the potential for new fractures adjacent to plates where the stress differential between plate and bone may be significant.

The dentinogenesis component is usually treated with onlay or full-crown coverage. In the anterior teeth, cosmetic full crowns or veneers may be used. Selective orthodontic therapy to correct the frequent malocclusions is feasible as these teeth will move through this type of bone, but the treatment risks are higher because of the increased mechanics required and the already shortened roots.

Prognosis

Prognosis is dependent on the type of osteogenesis imperfecta and the degree of genetic expression. As has been stated, this can vary greatly from intrauterine death to a full lifespan. In those with one of the milder expressions, cautious lifestyles and prompt medical and surgical management of disease related complications can extend longevity.

MANDIBULOFACIAL DYSOSTOSIS (TREACHER COLLINS SYNDROME)

Mandibulofacial dysostosis syndrome encompasses a group of closely related defects of the head and face, often hereditary or familial in pattern, following an irregular form of dominant transmission.

Clinical Presentation and Pathogenesis

Mandibulofacial dysostosis (MFD), also termed Treacher-Collins syndrome after the individual who described its important components in 1900, is a distinct syndrome of known autosomal-dominant inheritance. Surviving individuals with MFD have a distinctive facial appearance. It is characterized as "bird-like" or "fish-like" because of the convexity of the midface and underdevelopment of the mandible. The lower eyelid characteristically droops in the outer third, creating a downward sloping lateral canthus. The cheek prominences are flattened as a result of hypoplasia of the zygomas, and the pinnas of the ears are deformed.

The mandible is hypoplastic and creates an anteroposterior deficiency with an anterior open bite. The mandibular plane angle is very obtuse with prominent antegonial notching. The ramus and condyle are present but hypoplastic in all aspects. The maxilla is also hypoplastic but may show a posterior vertical maxillary excess, widely spaced teeth, and a highly arched palatal vault. The occlusion is usually a "scissors bite" type of malocclusion with rotated and lingually tipped teeth .

Vision is normal, but the coloboma of the outer one-third of the lower eyelid gives rise to a prominent "antimongoloid"slant, which is the prime recognition feature of this syndrome in 75% of individuals. In those with this feature, eyelashes medial to the coloboma are absent.

Hearing is abnormal. Conductive hearing loss is found to some degree in nearly all cases. This is most often due to sclerosis of the middle ear ossicles with fusion preventing transmission of vibratory energy. In some cases, one or more of the middle ossicles is absent or the oval window is absent. The external ear is deformed in about 80% of cases. The pinna may be hypoplastic, incomplete, crumpled, or displaced. The external ear canal is completely absent in about 30% of cases. In others, ear tags and skin pits occur in the cheek along the alatragal line .

This syndrome does not seem to be directly associated with mental deficiencies, but learning disabilities exist and cognitive functions are secondarily impaired related to the hearing loss.

An associated cleft palate component is present in 30% of patients, and 15% have a lateral facial cleft created by elongation of one or both commissures. As part of the hypoplasia, the maxillary sinuses and the mastoid sinus usually are not pneumatized.

Mandibulofacial dysostosis is said to occur in half of cases as an autosomal-dominant trait and in the other half as a spontaneous mutation. This may be somewhat overstated because seemingly non inherited cases may emerge from an existing inheritance that has a minimal or subclinical phenotypic expression. It is well-known that succeeding generations phenotypically express the defect as a more severe deformity.

The clinical disease is thought to be related to the absence or abnormality of the anterior portion of the fetal stapedial artery, which supplies the middle ear, maxilla, and the mandibular components of the first branchial arch; hence the location of the facial defects. Because the posterior branch of the stapedial artery is normal, the skull, scalp, and the area posterior to the ear are normal (Fig. 11.7).

Differential Diagnosis

Fully expressed MFD is distinctive. However, like most inherited deformities, a wide range of phenotypic expressions may be seen. Some cases will show only minimal signs and will, therefore, be difficult to recognize or seem to represent other syndromes.

One separate entity correctly belonging on a differential list with MFD of the Treacher Collins type is called acrofacial dysostosis as described by Nager and de Reynier. This syndrome is an autosomal-recessive trait that also manifests a "bird-like" facies due to mandibular hypoplasia, lower eyelid colobomas with a downward slope, and atresia of the external ear canal if lower eyelid colobomas are not present. This syndrome can be separated from MFD of the Treacher Collins type because of its additional components of hypoplastic or absent thumbs.

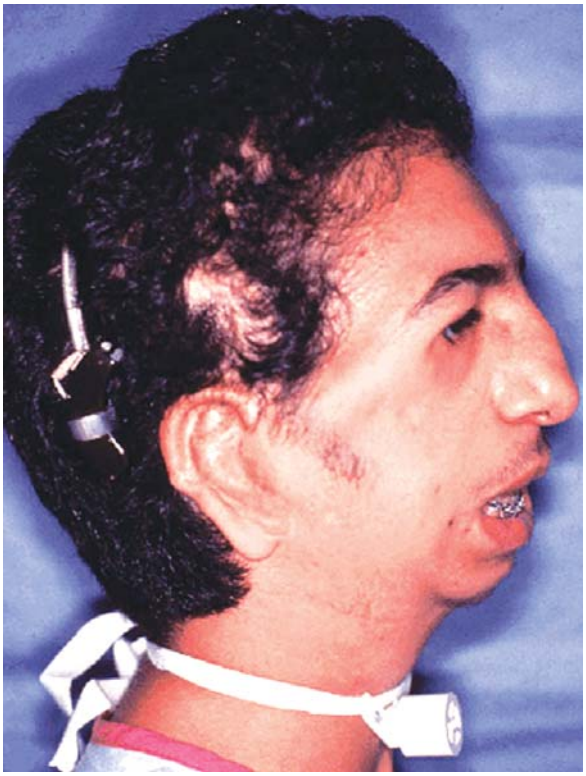


Fig. 11.7: Mandibulofacial dysostosis

There may also be fusion of the radius to the ulna or absence of either of these bones or of a metacarpal.

Diagnostic Work-up

Mandibulofacial dysostosis of the Treacher Collins type is a diagnosis of clinical recognition. However, reconstructive surgical planning requires cephalometric tracings and CT scans in most cases. A complete audiologic examination is required.

Treatment

The first priority in reconstructive surgery should be middle ear reconstruction to restore as much conductive hearing as possible. Hearing aids may also be required.

Orbital reconstruction and the zygoma deficiency are often approached with cranial bone grafts. Zygomatic osteotomies and Le Fort II-type osteotomies are other approaches that have been used to correct the midface and zygomatic maxillary complex. The lower eyelid can be improved with a cross eyelid flap and a lateral canthus repositioning.

The mandibular and maxillary hypoplasia usually requires extensive presurgical orthodontic arch coordination followed by a Le Fort I osteotomy and mandibular ramus osteotomies. Each case is different, but

the general goal of orthognathic surgery is to impact and widen the posterior maxilla and autorotate and advance the mandible.

Prognosis

Reconstructive surgery can greatly improve the self-esteem and quality of life for these individuals. However, multiple staged surgeries followed by revisions are the rule, and the involvement of multiple specialists is required.

CEMENTOBLASTOMA

The cementoblastoma is a hamartomatous proliferation of cementoblasts forming disorganized cementum around the apical one half of a tooth root.

Clinical Presentation and Pathogenesis

It will usually present as a hard expansion in the premolar or molar region of either jaw. There is frequently a deep, dull pain associated with the expansion. The overlying mucosa is intact, and the associated teeth are not mobile. More lesions occur in the mandible than in the maxilla. Most occur in teenagers or adults younger than 30 years.

Radiographically, the lesion characteristically shows a spherical, radiopaque mass encompassing and essentially replacing the apical half of the root. There is a characteristic radiolucent margin around the mass, giving the impression of a periodontal membrane space. The tooth is vital unless it is nonvital for other reasons. This lesion arises from the cellular cementum. It produces a disorganized and vascular cementum that seems to recapitulate a periodontal membrane like encapsulation (Fig. 11.8).

Differential Diagnosis

The distinguishing features of a cementoblastoma are its peripheral radiolucent margin to adjacent bone and its obliteration of one half of the root. These features distinguish it from other radiopaque lesions that may become superimposed over tooth roots, such as an osteoblastoma, an ossifying fibroma, and an odontoma. These features also distinguish a small cementoblastoma from hypercementosis and focal bone sclerosis, so-called condensing osteitis.

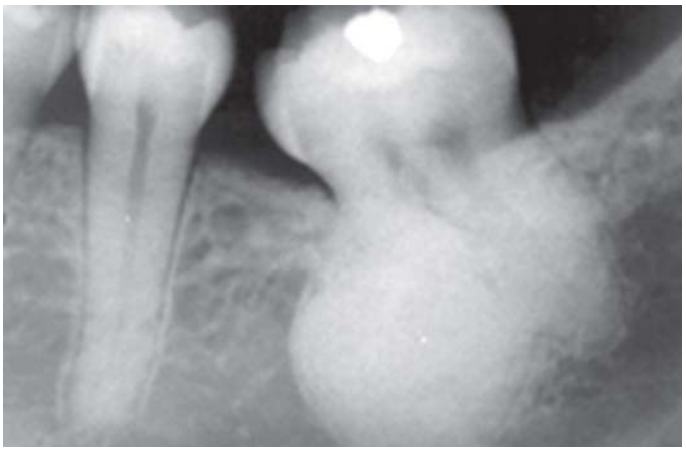


Fig. 11.8: Cementoblastoma

Diagnostic Work-up

A cementoblastoma is diagnosed and treated by removal of the associated tooth with the lesion attached. Because of its capsule, the apparently bulbous mass is readily separated from the surrounding bone. The buccal cortex around this tumor may be absent or severely thinned. The tumor can then be removed in one unit with the tooth attached. The lesion and tooth is removed toward the buccal aspect. If the lesion has gained sufficient size as to abut adjacent teeth, its cementum may fuse to the adjacent tooth, making the removal of that tooth necessary as well.

The resultant bone cavity is closed at the mucosal level without the need for a drain or packing. A long-term resorbable membrane or a permanent membrane requiring later removal placed over the buccal cortical opening may be used to inhibit fibrous tissue ingrowth and to ensure a more complete bone regeneration.

Histopathology

The cementoblastoma has a thin fibrous capsule that is usually continuous with the periodontal membrane. The tumor consists of sheets of cementum-like material continuous with the tooth root. Frequently, there is root resorption with replacement by cementum. Invasion of the root canal is common. The proliferating cementum is lined by numerous plump cells. Cementoclasts may also be present, and reversal lines are prominent. Some of the cemental material may be uncalcified, particularly at the periphery of the mass. The tumor cementum is often arranged in struts perpendicular to the capsule. The fibrous stroma is highly vascular.

Prognosis

Tooth removal with the lesion attached is curative without risk of recurrence. Theoretically, one could also effect a cure with a root resection, removing the lesion attached to the resected apical one half of the root. However, this is impractical as the resulting crown-root ratio would be insufficient for retention of the remainder of the tooth.

HYPERPLASIA OF CORONOID

Hyperplasia of the coronoid processes of the mandible is an uncommon condition that is often associated with limitation of mandibular motion.

Etiology and Pathogenesis

The cause of this process remains unknown. A history of trauma is present in many instances; however, the precise relationship between the traumatic episode and the onset of coronoid enlargement has been difficult to establish. The coronoid enlargement appears to represent a hyperplastic process, although it has been suggested that the lesion may be neoplastic. Unilateral coronoid hyperplasia may be the result of a solitary osteochondroma; bilateral coronoid hyperplasia is apparently the result of a different process. The majority of cases have been reported in males, leading some investigators to suggest an X-linked inherited etiology. However, some cases have been reported in females, a finding that seems to preclude this possibility. Increased activity of the temporalis muscle with unbalanced condylar support has also been postulated as an etiologic factor. Hyperplasia of the coronoid processes is often bilateral, although unilateral enlargement has been noted. Bilateral coronoid hyperplasia typically results in limitation of mandibular movement, which is progressive overtime. The disorder is usually painless and, with a few exceptions, is not associated with facial swelling or asymmetry. Coronoid hyperplasia has been reported most often in young male patients. The age of onset is typically around puberty, although presentation for evaluation may be delayed for many years. Some cases have been noted, especially in females, before puberty and during adult life. Enlarged and elongated coronoid processes are evident radiographically, although the general shape of the processes is usually normal. Unilateral coronoid hyperplasia often results in mis-shapen or mushroom-shaped coronoid processes on radiographs. Temporomandibular joint radiographs are unremarkable.

Histopathology

The enlarged coronoid processes consist of mature, hyperplastic bone. The bone may be partially covered by cartilaginous and fibrous connective tissue.

Differential Diagnosis

Bilateral coronoid hyperplasia rarely presents diagnostic difficulties. However, cases of unilateral coronoid hyperplasia must be differentiated from osseous and chondroid neoplasms.

Treatment and Prognosis

Treatment consists of surgical excision of the hyperplastic coronoid processes. Postoperative physiotherapy is also advocated. Long-term functional improvement has been variably successful as measured by an increase in mouth opening after surgical intervention. Recurrence has been rarely reported.

INFANTILE CORTICAL HYPEROSTOSIS (CAFFEY'S DISEASE)

Infantile cortical hyperostosis, or Caffey's disease, is a self-limited, short-lived proliferative bone disease of undetermined etiology. It is characterized by cortical thickening of various bones, most commonly the mandible (80% of cases) and less commonly the clavicles, long bones, maxilla, ribs, and scapulae. Pain, fever, and hyperirritability may precede or develop concurrently with the swelling. From 75 to 90% of cases demonstrate mandibular involvement, typically over the angle and ascending ramus symmetrically. In addition to the osseous changes, swelling of the overlying soft tissues usually occurs. There are no gender, racial, or geographic predilections. The characteristic age of onset is usually by the seventh month of life, with the average age of onset being 9 weeks. Radiographically, an expansile hyperostotic process is visible over the cortical surface, with rounding or blunting of the mandibular coronoid process. Initially, the hyperostotic element is separated from the underlying bone by a thin radiolucent line. Diagnosis may be facilitated by the use of technetium (99mTc) scans, which are often positive before routine radiographic detection is made. Laboratory findings that are also helpful in establishing the diagnosis include an elevated erythrocyte sedimentation rate, increased phosphatase levels, anemia, leukocytosis, and occasionally thrombocytopenia or thrombocytosis. Infantile cortical hyperostosis is usually a self-limiting process, with treatment generally directed at supportive care. Systemic corticosteroids and nonsteroidal antiinflammatory drugs have been used with some success. This disease has a tendency to follow an uneven though predictable course, with relapses and remissions possible. During such recurrences or relapses, the use of nonsteroidal anti-inflammatory drugs has been recommended to control symptoms and halt progression **of** the disease, suggesting that prostaglandins may have a role in the etiology. The resolution phase ranges from 6 weeks to 23 months, with an average duration of 9 months. Radiographic and histologic resolution may take up to several years, with a generally excellent prognosis despite the possibility of recurrences and occasional residual effects, such as severe malocclusion and mandibular asymmetry.

CROUZON'S SYNDROME (CRANIOFACIAL DYSOSTOSIS)

Crouzon's syndrome is characterized by variable cranial deformity, maxillary hypoplasia, and shallow orbits with exophthalmos and divergent strabismus. The character of the cranial deformity depends on the sutures affected, the degree of involvement, and the sequence of sutural fusion.

Increased interpupillary distance and exophthalmos are constant features of Crouzon's syndrome and develop in early childhood as a result of premature synostosis of the coronal suture. Systemic complications include mental retardation, hearing loss, speech and visual impairment, and convulsions.

Etiology and Pathogenesis

Craniofacial dysostosis is inherited in an autosomal-dominant mode, with complete penetrance and variable expressivity. About one-third of the cases reported arise spontaneously. The genetic abnormality is thought to be a mis-sense mutation in the fibroblast growth factor receptor 2 (EGFR2) gene. The severity of expression of the disease increases in successive siblings, with the youngest child most severely affected. Craniosynostosis results when premature fusion of the cranial sutures occurs. The cause is not known, but premature closure of these sutures can initiate changes in the brain secondary to increased intracranial pressure. The deformities of the cranial bones and orbital cavities are the result of the fusion of sutures and increased intracranial pressure. Underdevelopment of the supraorbital ridges and overgrowth of the sphenoid wing result in small and shallow orbits. Exophthalmos and reduced orbital volume arc the result. Hypertelorism is accentuated by a downward and forward displacement of the ethmoid plate. Abnormalities of the bony orbit account for several functional ocular abnormalities. Severe distortion of the cranial base leads to reduced maxillary growth and nasopharyngeal hypoplasia with potential upper airway restriction.

Clinical Features

Patients with Crouzon's syndrome have a characteristic facies that is often described as frog-like Midface hypoplasia and exophthalmos are striking. Patients have relative mandibular prognathism, with the nose resembling a parrot's beak. The upper lip and philtrum are usually short, and the lower lip often droops. The cranial deformity is dependent on which sutures are involved. Proptosis with strabismus and orbital hypertelorism is common. Optic nerve damage occurs in 80% of cases. Oral findings include severe maxillary hypoplasia, resulting in a narrowing of the maxillary arch and a compressed, high-arched palate. Bilateral posterior lingual crossbites are common. Premature posterior occlusion as a result of the inferiorly positioned maxilla results in an anterior open bite. Radiographs of the skull reveal obliterated suture lines with obvious bony continuity. A hammered-silver appearance is often seen in regions of the skull where compensatory deformity cannot occur. Lordosis of the cranial base is apparent on lateral skull projections, and angular deformities with vertical sloping of the anterior cranial fossa can be visualized. A large calvarium with hypoplasia of the maxilla, shallow orbits, and a relatively large mandible is common (Fig. 11.9).

Treatment and Prognosis

The age of onset and the degree of craniosynostosis influence the severity of the complications, which range from craniofacial dystrophy to hearing loss, speech and visual impairment, and mental retardation. With a high degree of suspicion, the condition is often identifiable at birth. Ultrasonic prenatal diagnosis of exophthalmos has been reported. Early recognition is essential to guide growth and development of the face and cranium. Surgical intervention may be necessary if exophthalmos is progressive, optic nerve damage or visual acuity is impaired, evidence of developing mental deficiency is noted, or intracranial pressure continues to rise. Treatment includes the surgical placement of artificial sutures to allow growth of the brain while minimizing intracranial pressure and secondary calvarial deformities. Orthodontic treatment with subsequent orthognathic surgical intervention has been successful in managing the concomitant dentofacial deformity.

MARFAN'S SYNDROME

Marfan's syndrome is a heritable disorder of connective tissue, characterized by abnormalities of the skeletal, cardiovascular, and ocular systems. It is currently estimated that 23,000 Americans have Marfan's syndrome. Diagnosis is problematic because of the extreme variability of clinical expression. The disorder is notable for a number of sudden catastrophic deaths that have occurred in affected (undiagnosed) athletes.

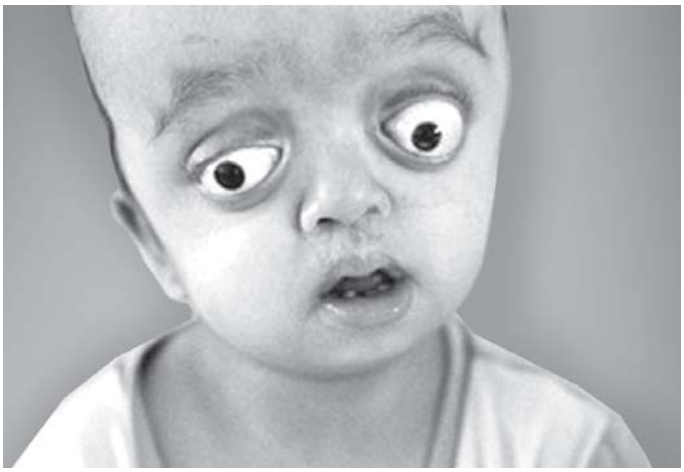


Fig. 11.9: Craniofacial dysostosis

Etiology and Pathogenesis

Marfan's syndrome is an inherited autosomal-dominant disorder that affects 1 in 10,000 individuals. There are no ethnic, racial, or gender predilections. The condition exhibits complete but extremely variable penetrance, with the offspring of an affected individual having a 50% chance of acquiring the disorder. Diagnosis is currently based on characteristic abnormalities of the musculoskeletal, ocular, and cardiovascular systems and a positive family history. Because most features progress with age, the diagnosis is often more obvious in older persons. The gene for Marfan's syndrome has been located on chromosome 15 and will provide for diagnostic testing in pairs at risk. Recent studies involving factors responsible for assisting in microfibril formation have identified the gene for fibrillin (FBN1) as the disease-causing gene in this disorder. The Marfan's gene is believed to produce a change in one of the proteins that provides strength to a component of connective tissue, probably collagen.

Clinical Features

Patients characteristically possess a tall, slender stature with relatively long legs and arms, large hands with long fingers, and loose joints. The arms, legs, and digits are disproportionately long compared with the patient's trunk. Chest deformities include a protrusion or indentation of the breast bone (pectus carinatum or pectus excavatum, respectively). The normal thoracic kyphosis is often absent, leading to a straight back. Various degrees of scoliosis are present. Oral findings include a narrow, high-arched palate and dental crowding. The face appears long and narrow. The cardiovascular system is affected in nearly all persons. Mitral valve prolapse, as a result of myxomatous change, occurs in 75 to 85% of affected patients, and a small percentage develop mitral regurgitation. There is cystic medionecrosis of the aorta, resulting in ascending aortic dilation, aortic regurgitation, and heart failure. A significant consequence of this change to the media layer of the aorta is progressive dissection, which may lead to aneurysms and placing patients at great risk for death. Ocular findings include dislocation of the lens (ectopia lentis), which occurs in half of these patients. The most common eye anomaly, however, is myopia (nearsightedness). Retinal detachment occurs infrequently,but it is more prevalent after lens removal.

Treatment and Prognosis

Morbidity and mortality are directly related to the degree of connective tissue abnormality in the involved organ systems. The cardiovascular abnormalities of ascending aorta dilation and mitral valve prolapse, subluxation of the lens of the eye, chest cavity deformities and scoliosis, and the potential for pneumothorax are serious prognostic indicators. Treatment of patients with Marfan's syndrome consists of annual medical examinations with a cardiovascular emphasis, frequent ophthalmologic examination, scoliosis screening, and echocardiography. Physical activity often is restricted and redirected in an attempt to protect the aorta. Antibiotic prophylaxis has been recommended for infective endocarditis, regardless of the clinical evidence of valvular disease. Beta-blockers such as propranolol are often used to reduce aortic stress and have been shown to significantly reduce both the rate of aortic dilation and the risk of serious complications. Mortality has been drastically reduced with the use of composite grafts to replace the aortic valve and the region containing the aortic aneurysm. The prognosis for untreated aneurysms of the ascending aorta is extremely poor.

DOWN'S SYNDROME

Down's syndrome is a common and easily recognizable chromosome aberration. The incidence is reported to be 1 in 600 to 1 in 700 livebirths; however, more than half of the affected fetuses spontaneously abort during early pregnancy. Approximately 10 to 15% of all institutionalized patients have Down's syndrome. Most cases of trisomy 21 (94%) are caused by nondysjunction, resulting in an extrachromosome. The remaining patients with Down's syndrome have various chromosome abnormalities. The incidence of this condition rises with increasing maternal age.

Etiology and Pathogenesis

Possible etiologies for Down's syndrome include undetected mosaicism in a parent, repeated exposure to the same environmental insult, genetic predisposition to non disjunction, an ovum with an extra chromosome 21, or a preferential survival in utero of trisomy 21 embryos and fetuses with increasing maternal age. Parents of any age who have had one child with trisomy 21 have a significant risk (about 1 %) of having a similarly affected child—a risk of recurrence equivalent to that affecting births to a mother older than age 45 years. No racial, social, economic, or gender predilections have been identified.

Clinical Features

Patients with Down syndrome present with numerous characteristic clinical findings and various common systemic manifestations. A number of common phenotypic findings in children with Down's syndrome have been identified; these can assist in establishing a diagnosis.

Various degrees of mental retardation exist in all patients with Down's syndrome. Most mildly affected individuals are highly functioning and are able to perform well in a workshop environment. Dementia affects about 30% of patients with Down's syndrome, and early aging is common. After age 35, nearly all individuals develop the neuropathologic changes analogous to those found in Alzheimer's disease, although 70% exhibit no clinically detectable behavioral changes. These two disorders have many neuropathologic and neurochemical similarities, and an increased risk for Down syndrome has been found in families with a predilection for Alzheimer's disease. In Down's syndrome the skull is brachycephalic, with a flat occiput and prominent forehead. A third or fourth fontanel is present, and all the fontanels are large and have extended patency. Sagittal suture separation greater than 5 mm is present in 98% of affected individuals. Frontal and sphenoid sinuses are absent, and the maxillary sinus is hypoplastic in more than 90% of patients. Midface skeletal deficiency is quite marked, with ocular hypotelorism, a flattened nasal bridge, and relative mandibular prognathism. The eyes are almond-shaped, with upward-slanting palpebral fissures, epicanthic folds, and Brushfield's spots of the iris often noted. Other ocular anomalies include convergent, strabismus, nystagmus, refractive errors, keratoconus, and congenital cataracts. Congenital heart disease is present in 30 to 45% of all patients with Down's syndrome. Anomalies include atrioventricular communication, partial endocardial cushion abnormalities, and ventricular septal defects. A study revealed a 50% prevalence of mitral valve prolapse; one-third of these patients had negative auscultatory findings. Tetralogy of Fallot, patent ductus arteriosus, and secundum atrial septal defects are seen less often. It appears that T-cell and probably B-cell function is aberrant, with some affected children being more susceptible to infectious diseases. Respiratory tract infections arc extremely common. Thyroid dysfunction occurs in about 50% of all patients. There is also an increased incidence of acute lymphocytic leukemia and hepatitis B antigen carrier status. Skeletal problems include hypoplasia of the maxilla and sphenoid bones, rib and pelvic abnormalities, hip dislocation, and patella subluxation. Of particular concern is the presence of atlantoaxial instability in 12 to 20% of persons with Down's syndrome, as a result of the increased laxity of the transverse ligaments between the atlas and the odontoid process. Delay in recognizing this condition may result in irreversible spinal cord damage, which might occur during manipulation of the neck in patients undergoing dental therapy or general anesthesia. Oral manifestations of Down syndrome are common. The tongue is often fissured, and macroglossia is usually relative to the small oral cavity, although true macroglossia is possible. An open-mouth posture is common because a narrow nasopharynx and hypertrophied tonsils and adenoids cause upper airway compromise.

A protruding tongue and habitual mouth breathing result in drying and cracking of the lips. Palatal width and length are significantly decreased, and a bifid uvula and cleft lip and palate are occasionally observed. Elevated concentrations of sodium, calcium, and bicarbonate ion have been demonstrated in parotid saliva. The dentition exhibits a number of characteristic anomalies, and periodontal disease is prevalent. The incidence of dental caries, however, appears to be no greater than in normal individuals. Considering the existence of poor oral hygiene, this may reflect the greater buffering capacity of the saliva or the ability to control dietary intake in institutional and home settings. The defective immune system and neutrophil motility defect directly contribute to rampant and precocious periodontal disease. Eruption of both the primary and the permanent dentitions is delayed in 75% of cases. Abnormalities in eruption sequence occur often. Hypodontia occurs in both dentitions, and microdontia is often seen. Developmental tooth anomalies, including crown and root malformations, are often present. Almost 50% of patients with Down syndrome exhibit three or more dental anomalies. Enamel hypocalcification occurs in about 20% of patients. Occlusal disharmonies consisting of malocclusion due to a relative prognathisin, posterior crossbites, apertognathia, and severe crowding of the anterior teeth are common. Posterior crossbites are of maxillary basal bone origin, whereas an tenor open bites are due to dentoalveolar discrepancies (Fig. 11.10).

Treatment and Prognosis

Infants with Down's syndrome that includes significant congenital heart disease have a poor prognosis. Causes of death commonly include cardiopulmonary complications, gastrointestinal malformations, and acute lymphoblastic

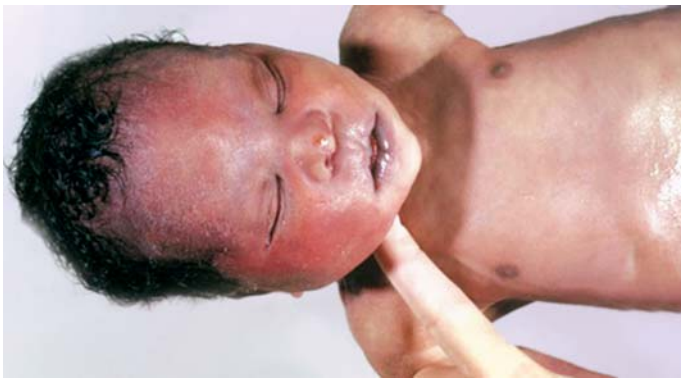


Fig. 11.10: Down syndrome newborn

leukemia. Recent technologic advances in cardiovascular diagnosis have brought about a marked improvement in the prognosis. Newborns require chest X-ray studies, electrocardiograms, echocardiograms, and subsequent pediatric cardiac consultation if cardiovascular anomalies are detected. Regular ophthalmologic and audiologic follow-ups are extremely important. They can intercept **early visual** and hearing problems that may affect **learning** and development. Detection of atlantoaxial instability may prevent **a** catastrophic spinal injury. Dental therapy is directed at prevention of dental caries and periodontal disease. Frequent follow-up and institution of stringent home care regimens are critical. Highly functioning children may be candidates for orthodontic intervention and subsequent maxillofacial surgery, if required. Guidelines established by the American Heart Association for antibiotic prophylaxis should be **followed** for those patients with congenital heart disease.

ACHONDROGENESIS

Marco Fraccaro *first* described achondrogenesis in 1952. By the 1970s, researchers concluded that achondrogenesis was a heterogeneous group of chondrodysplasias lethal to neonates; achondro genesis type I (Fraccaro-Houston-Harris type) and type II (Langer-Saldino type) were disting-uished on the basis of radiological and his-tological criteria. In 1983, a new radiological classification of achondrogenesis (types I-IV) by Witley and Gorlin was adopted in the McKusick catalog.

Etiology

Type IA is an autosomal recessive disorder with an unknown chromosomal locus. Type IB is an autosonial recessive disorder resulting from mutations of the diastrophic dysplasia sul-fate transporter (DDST) gene. which is located at **5q32-5q33.** Type II is an autosomal dominant type collageno-pathy resulting *from* mutations in the COL2AI (collagen 2 alfa1 chain) gene, which is located at **12q13.1-q13.3.**

Clinical Features

Achondrogenesis type I results in stillbirth more frequently than type II. Males and females are affected equally. Achondrogenesis is detected prenatally or at birth because of typical clinical, radiological, histological, and molecular findings.

In achondrogenesis type I, the craniofacial features include a disproportionately large head, soft skull, sloping forehead, convex facial plane, flat nasal bridge, occasionally associated with a deep horizontal groove, small nose, often with inteverted nostrils, long philtrum, retrognathia, increased distance between Iower lip and lower edge of chin and double chin appearance. In achondrogenesis type II, the features seen are a disproportionately large head, large and prominent forehead, flat facial plane, flat nasal bridge, small nose with severely anteverted nos-trils, normal philtrum (often), micrognathia. The differential diagnoses include achondroplasia, hvpophosphatasia, osteogenesis imperfecta and thanatophoric dysplasia.

Roentgenographic Features

The radiological features may vary, and no single feature is consistently noticed. Distinction between type IA and type IB on radiographs is not always possible. Degree of ossification is age dependent and caution is needed when comparing radiographs at different gestational ages.

Histologic Findings

Achondrogenesis type IA has a normal cartilage matrix. No collagen rings are present around the chondrocytes. Vacuolated chondrocytes, intrachondrocytic inclusion bodies (periodic acid-Schiff stain [PAS] positive, diastase resistant), extraskeletal cartilage involvement, enlarged lacunas, and woven bone are all present.

Achondrogenesis type IB has a cartilage matrix that shows coarsened collagen fibers that are particularly dense around the chondrocytes, forming collegen rings.

Achondrogenesis type II has slightly larger than normal and grossly distorted (lobulated and mushroomed) epiphyseal cartilage. There is severe disturbance in endochondral ossification and hypercellular reserve cartilage with large, primitive mesenchymal (ballooned) chondrocytes with abundant clear cytoplasm. The cartilaginous matrix is markedly deficient.

Treatment and Prognosis

Medical care is supportive. No treatment is available for the underlying disorder. The condition is universally lethal.

HYPOPHOSPHATASIA

Hypophosphatasia is **a rare** inherited metabolic disease of decreased tissue nonspecific alkaline phosphatase and *defective bone* mineralization. It was initially rccognized by Rathbun in 1948. It has been subdivided into five categories known as **perinatal, infantile, childhood, adult, and odontohypophosphatasia**. The different clinical forms have different modes of presentation, history, and inheritance.

Etiology

Patients with hypophosphatasia have defects in mineralization of bone due to tissue nonspecific alkaline phosphatase(TNSALP) deficiency. A mutation in the gene(ALPL)coding for tissue non-specific alkaline phosphatase is believed to be the cause of hypophosphatasia.

Clinical Features

Hypophosphatasia affects all age groups: however, severity of the disease differs with age, Males and females are affected equally. Hypophosphatasia occurs in all races. The perinatal form is considered lethal, while the infantile form has a mortality rate of 50 percent. Individuals with the other forms can reach adulthood, although often with increased morbidity. Patients with the childhood form often have rachitic deformities, and those with the adult type have increased morbidity from poorly healing stress fractures. All patients are affected by premature loss of dentition.

The **perinatal form** has the most severe manifestations. It is usually diagnosed at birth and the infant rarely survives for more than a few hours. Death is due to respiratory failure. Marked hypocalcification of the skeletal structures is observed.

Patients with the **infantile form** may appear normal at birth; however the clinical signs of hvpophosphatasia appear during the first six months. This form also has respiratory complications due to rachitic deformities of the chest. Despite the presence of an open fontanelle, premature craniosynostosis is a common finding that may result in increased intracranial pressure.

Hypercalcemia is also present and increased excre¯tion of calcium may lead to renal damage.

Skeletal deformities, such as dolichocephalic skull and enlarged joints, a delay—in walking. short stature, and a waddling gait accompany the **child-hood form**. A history of fractures and bone pain usually exists as well. Premature loss of dentition is common with the incisor teeth often being the first affected.

The adult form presents during middle age. The first complaint may be foot pain, which is due to stress fractures of the metatarsals. Thigh pain, due to pseudofractures of the femur, may also be a presenting symptom. Upon obtaining an in-depth history, many of these patients will reveal that they had premature loss of deciduous teeth.

The only physical finding in the odontohypophosphatasic form is the premature loss of teeth.

Oral Manifestations

The earliest manifestation of the disease may be loosening and premature loss of deciduous teeth chiefly the incisors. There are varying reports of gingivitis, however it does not seem to be a consistent feature of the disease The differential diagnoses include achondrogenesis, osteogenesis imperfecta, rickets and thanatophoric dysplasia.

Roentgenographic Features

The childhood form is characterized by rachitic deformities. Upon radiologic examination of the metaphysis, evidence of radiolucent projections from the epiphyseal plate into the metaphysis is present. This is not found in other types of rickets. Radiograph findings are normal for patients with odontohypophosphatasia. Dental roentgenograms generally reveal hypocalcification of teeth and the presence of large pulp chambers, as well as alveolar bone loss.

Histologic Findings

Histologic examination of the skeleton will reveal rachitic abnormalities of the growth plates such as failure of cartilage calcification. Both osteoclasts and osteoblasts appear morphologically normal, but the latter lack membrane associated alkaline phosphatase (ALP) activity on histochemical testing. This disrupts incorporation of calcium into the matrix. The long bones characteristically exhibit an increased width of proliferating cartilage with widening of the hypertrophic cell zone, irregularity of cell columns, irregular penetration of the cartilage by marrow with persistence of numerous cartilage islands in the marrow. and formation of large amounts of osteoid which is inadequately calcified. These findings are indistinguishable from those in true rickets. Histological examination of the teeth reveals a decrease in cementum, which varies with the severity of the disease. This is presumably as a result of failure of cementogenesis, so that there is no sound functional attachment of the tooth to bone by periodonnt.il ligament. This lack of attachment is thought to account for the early spontaneous exfoliation of the deciduous teeth. The pulp chamber also appears to be enlarged. The incisors tend to be the most affected. Bone biopsy findings are normal for patients with odontohypophosphatasia.

Treatment and Prognosis

Currently. no medical therapy is available. Various treatments have been attempted including zinc, magnesium, cortisone, plasma. and enzyme replacement therapy. The results have been inconsistent. Orthopedic surgical involvement may be necessary in patients with hypophosphatasia. The perinatal form is considered lethal. The infantile form is thought to be fatal in approximately 50 percent of patients. Individuals with the adult and odontohypophosphatasia forms are believed to have normal lifespans.

CHONDRODYSPLASIA PUNCTATA

This is a rare congenital syndrome caused by a peroxisomal dysfunction and was first described in I 1914. It is one of the Four syndromes of the **'peroxisome biogenesis disorders'** resulting from anomalous enzymatic function of the metabolism of the fatty acid. It has been defined as *erratic cartilage calcification during growth which produces the heterogenous group of disoders that result in small ossification centers in the epiphyseal cartilage of the long bones and spine, skin lesion, cataracts,* ***craniofacial dysmorphism,*** *joint contractures, and cardiac malformations.* In surviving children, abnormal growth leads to dysmorphism, kyphoscoliosis, limb shortness, and luxation of the hip.

Classification

- Autosomal dominant type (nonrhizomelic)
- Autosomal recessive type (rhizomelic)
- X- linked dominant type
- X- linked recessive type
- Sheffield, mild type
- Other varient

Autosomal Dominant Type

(Nonrhizomelic, nonlethal type, dysplasia epiphysealis congenital, stippled epiphyses, chondrodysplasia punctata dominant type, chondrodysplasia epiphysealis punctata, chondrodystrophia calcificans congenital, Conradi-Hunermann syndrome)

It is the most common of all chondrodysplasia punctata; most are new mutations. An autosomal dominant inheritance is observed with a male : female ratio of 3 : 1.

Major Diagnostic Criteria

Craniofacial dysmorphism Asymmetric head, frontal bossing; flat nasal bridge; dysplastic, auricles; mongoloid palpebral fissures; hypertelorism, high arched palate.

Ocular abnormalities Cataract; corneal opacity; nystagmus; microcornea; glaucoma; and dislocated lens.

Cutaneus abnormalities Ichthyosis and hyperkeratosis; alopecia; layered and split nails.

Skeletal abnormalities Asymmetric mild shortening of all long bones; bowing; stippled epiphysis; vertebral scoliosis, clefting; or wedging; flexion contracture of the joints; clubfoot or vagus deformity.

Roentgenographic Features

Mild shortening of all long bones with multiple epiphyseal punctate calcific deposits in the infantile cartilaginous skeleton, which may or may not be seen by ultrasound after 14 weeks. Vertebral body deformities and scoliosis can also be seen. Stippling of the proximal humerus may also help to identity the condition.

Prognosis

The prognosis is excellent. Affected individuals usually have a normal life span and intelligence.

PYKNODYSOSTOSIS

The disorder was first described and named by Maroteaux and Lamy in 1962. The features are deformity of the skull (including *wide sutures).* maxilla *and phalanges (acro-osteolysis),* osteasclerosis, *and fragil*ity of bone. Pyknodysostosis is inherited as an autosomal recessive trait. The locus for the dysplasia has been mapped to chromosome Iq2l. Mutations in this region lead to cathepsin K deficiency. Cathepsin K is a cysteine protease that is highly expressed in osteoclasts.

Clinical Features

This dysplasia is characterized by a short-limbed stature. There is hypoplasia or absence of the lateral portion of the clavicles, and hypoplasia of the terminal phalanges of the digits (teamed acro-osteolysis), leading to short, stubby hands with large finger nails. The skull has widened sutures and persistent open fontanels even into adulthood. The mandible is small, and the angle of the mandible is obtuse, leading to very small chin. The nose is protuberant. The teeth are delayed in appearance and disordered.

Roentgenographic Features

Radiograph shows generalized osteosclerosis. The medullary canal is always present, but it is small and irregular. The sclerotic bone has a propensity to fracture, with fractures generally occurring in the lower extremities. Bone formation and resorption are simultaneously diminished. MRI studies have shown the cortex to be of normal thickness, whereas the space within the medullary canal was limited as a result of the increase in trabecular bone. Bone scan reveals increased uptake.

Histologic Features

Microscopic examination of bone biopsy specimens are similar to those in osteopetrosis. Meredith and associates (1978) proposed that normal osteoblasts and osteoclasts fail to respond as they should to the demands of stress on the bone. Although osteoclasts are present, they do not appear to function properly in resorbing bone. At fracture sites, all cellular elements of fracture repair are present.

The differential diagnosis includes osteopetrosis. Unlike osteopetrosis, pycnodysostosis does not lead to aplastic

anemia because the medullary canal is partially preserved. Cleidocranial dysostosis may be considered because of the hvpoplasia of the clavicles; however, osteosclerosis is not seen in cleidocranial dysostosis.

Treatment and Prognosis

Orthopedic treatment consists of fracture care. Life expectancy is normal. Chronic osteomyelitis of the jaw occurs frequently and is resistant to standard forms of treatment.

MUCOPOLYSACCHARIDOSES TYPE I-VII (LYSOSOMAL STORAGE DISEASE)

Mucopolysaccharidoses (MPS) are a group of lysosomal storage diseases, each of which is produced by an inherited deficiency of an enzyme involved in the degradation of acid mucopolysaccharides (now called glycosaminoglycans [GAG]). These diseases are autosomal recessive except for MPS type II which is X-linked.

Etiology

Glycosaminoglycans (GAG) are long, linear polysaccharide molecules composed of repeating dimers each of which contains a hexuronic acid and an amino acid. The turnover of these molecules depends on their subsequent internalization by endocytosis, their delivery to the lysosymes, and their digestion by lysosomal enzymes. The enzyme deficiencies lead to the accumulation of mucopolysaccharides in the lysosomes of the cells in the connective tissue and to an increase in their excretion in the urine.

Clinical Features

Onset usually occurs in early childhood. Skeletal findings include dwarfism with rather characteristic radiologic changes of the hands and the lumbar vertebral column; stiff articulations: and coarse facies. Patients with Hurler syndrome usually die by the time they are aged 5-10 years. The life expectancy of patients with Scheie syndrome may be nearly normal. They can live until the fifth or sixth decade of life, and they can have healthy offspring. As for patients with Hunter and Sanfilippo syndrome, death usually occurs by the time of puberty. In the classic form of Morquio syndrome, long-term survival is rare, with death occurring in persons aged 20-40 years. In patients with the severe form of Maroteaux-Lamy syndrome, death usually occurs by early adulthood.

Differential diagnosis includes Gaucher disease, Niemann-Pick disease, syphilis, osteogenesis imperfecta, vitamin D-resistant rickets, nephrogenic osteopathy, spondyloepiphysial dysplasia, metaphysial dysplasia.

Treatment

No cure for MPS exists, treatment is symptomatic and supportive. However, possible treatments are being investigated in several clinical trials.

RICKETS

Rickets is an entity that commonly affects children leading to decreased mineralization at the level of the growth plates with resultant growth retardation and delayed skeletal development. Osteomalacia is found in adults which affects trabecular bone, and results in undermineralization of osteoid. By definition, rickets is found only in children prior to the closure of the growth plates, while osteomalacia occurs in persons of any age.

Etiology

Rickets results either from a deficiency or abnormal metabolism of vitamin D or from abnormal metabolism or excretion of inorganic phosphate. Histologic changes are seen at the level of the growth plates, or more specifically, at the level of the hypertrophic zone, where an increased number of disorganized cells is found. The increased number of cells results in increased width and thickness of the hypertrophic zone (Rachetic metaphysis).

An exception occurs in groups of women who are rarely allowed to leave the house (largely for religions reasons) or who must wear veils when they do. Since these women may have low vitamin D levels, their babies are at a higher risk of developing rickets. When patients receive adequate treatment, no mortality is associated with this disease. Boys and girls are affected equally with rickets. There is a form of genetic rickets, called X-linked hypophosphatemic rickets, in which some children, often girls, may be only moderately affected. By definition, rickets occurs only in children whose growth plates have not closed. The growth plates close at the end of puberty, at approximately age 17 years in females and age 19 years in males. Premature neonates are especially at risk because their requirements for vitamin D, calcium, and phosphate are higher than the requirements in full-term neonates (Fig. 11.11).

A useful mnemonic for remembering the findings of rickets is as follows:

- Reaction of the periosteum (may occur)
- Indistinct cortex
- Coarse trabeculation
- Knees, wrists, and ankles affected predominantly

HYPERPARATHYROIDISM

Hyperparathyroidism is a syndrome of hypercalcemia resulting from excessive release of parathyroid hormone.

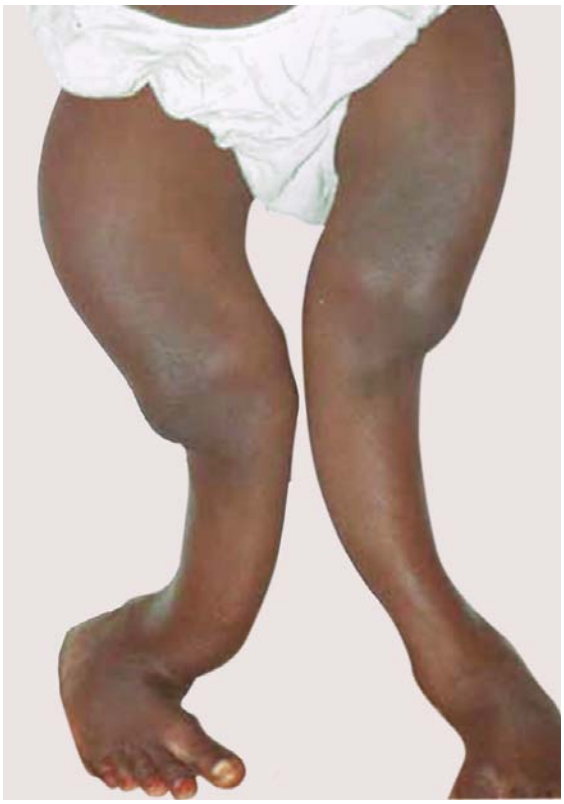


Fig 11.11: Rickets

Most cases of hyperparathyroidism are discovered accidentally when hypercalcemia is noted during a routine serum chemistry examination.

Etiology

Hyperparathyroidism is common in patients with type 1 and type II multiple endocrine neoplasia (MEN) and in patients who received radiation therapy to the head and neck during childhood for benign diseases. In 85 percent of affected persons, primary hyperparathyroidism results from an adenoma in a single parathyroid gland. Hypertrophy of the parathyroid glands causes hyperparathyroidism in 15 percent of patients. **Secondary hyperparathyroidism** occurs when the parathyroid glands become hyperplastic after long-term stimulation to release PTH in response to chronically low serum calcium. Chronic renal failure, rickets and malabsorption syndromes are the most frequent causes. In secondary hyperparathyroidism, high levels of PTH do not cause hypercaIcemia because the primary problem makes calcium unavailable. With long-term hyperstimulation, the glands eventually function autonomously and continue to produce high levels of parathyroid hormone even after the chronic hypocalcemia has been corrected. HypercaIcemia caused by autonomous parathyroid function after long-term hyperstimulation is referred to as **tertiary hyperparathyroidism**.

Clinical Features

Hereditary hyperparathyroidism occurs most frequently as part of a syndrome of multiple endocrine neoplasia (MEN). MEN I consists of hyperparathyroidism with tumors of the pituitary and pancreas. MEN 2A consists of hyperparathyroidism, of the thyroid. Although hyperparathyroidism can occur at any age, it is most common in the fifth and sixth decades of life. Prevalence is higher in females than in males, with a male-to-female ratio of approximately 1:2. At least one half of patients with hyperparathyroidism are asymptomatic. Manifestations of hyperparathyroidism may be subtle and the disease may run a benign course for many years. Less commonly, hyperparathyroidism may worsen abrupty and cause severe hypercalcemic complications. This is referred to as **hypercalcemic parathyroid crisis.** The skeletal and neuromuscular changes manifest is bone pain and tenderness, muscle fatigue, weakness and spontaneous fractures; non-specific myalgias, osteoporosis, osteopenia, cystic bone lesions, vertebral collapse, chondrocalcinosis and pseudogout can develop. Patients have a tendency to develop pancreatitis and/or pancreatic calcification and peptic ulcer disease which call result in abdominal distress, constipation, vomiting. anorexia and weight loss. Neuropsychiatric illness and altered mental status such as anxiety. depression, psychosis and apathy have been reported.

Roentgenographic Features

The bones of affected persons show a general radiolucency as compared with those of normal people. Sharply defined round or oval radiolucent areas develop, which may be lobulated. If such a lobulated lesions develops in mandible, it must be carefully differentiated from ameloblastoma, which frequently has the same appearance. Small cystic areas may be seen in the calvarium, and /or small sharply defined radiolucencies may be present in the maxilla and/or mandible. In the jaws, the bone roentgenogram shows "ground-glass" appearance. The lamina dura around the teeth may be particularly lost.

Laboratory Findings

The diagnosis of hyperparathyroidism is made by demonstrating elevated parathyroid hormone levels in the setting of high serum calcium. Almost all other causes of hypercalcemia suppress the release of parathyroid hormone, which is measured by radioimmunoassay Other findings include elevated serum chloride levels, decreased serum phosphate level (less than 2.5 mg/dl (0.81 mmol/L), decreased serum carbon dioxide, hyperchloremic metabolic acidosis, increase in urine cyclic adenosine monophosphate (cAMP).

Histologic Features

Histologic findings in the bone lesions of hyperparathyroidism are not pathognomonic of the disease, but are of considerable assistance in making the diagnosis. The most characteristic change in the bone is an osteoclastic resorption of the trabeculae of the spongiosa and along the blood vessels in the Haversian system of the cortex. In the area of resorption, many plump osteoblasts lining islands of osteoid are seen. Fibrosis, especially of the marrow spaces is marked. The fibroblasts replace resorbed trabeculae, and in the fibrotic islands there is recent and old hemorrhage, and much hemosiderin is evident. As the disease progresses, 'osteoclastoma' develop, characterized by masses of fibroblasts growing in a loose syncytium, among which are numerous capillaries and endothelium-lined blood spaces, red blood cells, many areas of yellow or brown hemosiderin, and innumerable multinucleated giant cells. Therefore, any patient who has a giant cell lesion should be evaluated medically to rule out the possibility of hyper-parathyroidism.

Treatment and Prognosis

The emergency management of hyperparathyroidism is focused on the treatment of the hypercalcemia. Specifically, the goal of treatment is to reduce the calcium level to below 11.5 mg/dl, less than the level in which most patients have resolution of hypercalcemia-induced symptoms.

HYPOPARATHYROIDISM

Primary hypoparathyroidism is caused by a group of heterogeneous conditions in which hypocalcemia and hyperphosphatemia occur as a result of deficient parathyroid hormone (PTH) secretion. This most commonly results from surgical excision of, or damage to the parathyroid glands. However, genetic forms of hypoparathyroidism due to decreased secretion of PTH are known.

Clinical Features

The signs and symptoms of hypoparathyroidism include latent or overt neuromuscular hyperexcitability due to hypocalcemia. The effect may be aggravated by hyperkalemia or hypomagnesemia. Patients may complain of circumoral numbness, paresthesia of the distal extremities or muscle cramping which can progress to carpopedal spasm or tetany. Laryngospasm or bronchospasm and seizures may also occur. Other less specific manifestations include fatigue, irritability, and personality disturbance. Patients with chronic hypocalcemia may have calcification of the basal ganglia or more widespread intracranial calcification, detected by skull X-ray or CT scan.

In hypoparathyroidism, serum calcium concenrations are decreased and serum phosphate levels are increased. Serum PTH is low or undetectable.

Autoimmune Parathyroid Gland Ablation or Destruction

Antibodies directed against parathyroid tissue have been detected in over 30 percent of patients with isolated hypoparathyroid disease and over 40 percent of patients having hypoparathyroidism combined with other endocrine deficiencies. It remains to be seen whether the autoantibodies are of primary or secondary importance in these cases.

Pseudohypoparathyroidism

Several clinical disorders characterized by end-organ resistance to PTH have been described collectively by the term pseudohypoparathyroidism (PTH). They are associated with hypocalcemia hyperphosphatemia and increased circulating PTH, but target tissue unresponsiveness to the hormone manifests as a lack of increased cAMP excretion in response to PTH administration.

Treatment

The goal of treatment in hypoparathyroid state is to raise the serum calcium sufficiently to elevate acute symptoms and prevent the complications of chronic hypocalcemia. The calcium concentration required for this purpose is generally the low-normal range. Acute or severe symptomatic hypocalcemia is best treated with intravenous calcium infusion. Initial doses of 2-5 millimoles of elemental calcium as the gluconate salt can be given over a 10-20 minute period followed by 2 milimoles elemental calcium per hour as a maintenance dose, to be adjusted according to svmptoms and biochemical response.

VITAMIN D-RESISTANT RICKETS (FAMILIAL HYPOPHOSPHATEMIC RICKETS, REFRACTORY RICKETS, PHOSPHATE DIABETES)

Since the early 20th century, ultraviolet radiation or vitamin D ingestion has been recognized as a cure for nutritional rickets, although certain forms of rachitic diseases have remained refractory to this therapy. Study of these refractory cases has revealed low serum phosphate concentration as a common factor. Familial occurrence of this conditioned led to the diagnosis of familial hypophosphatemic rickets. Treatment with vitamin D produced no change in the rachitic state of these patients,

even at rather high doses, leading to the term vitamin D-resistant rickets.

Etiology

Several of the most vexing questions about the underlying mechanism causing the clinical phenotype of X-linked hypophosphatemia remain unanswered. Great strides have been made in recent years, particularly with the cloning of the mutant gene known as PEX. This gene, found on the X-chromosome, is thought to produce a currently unknown hormone involved in phosphate regulation. The gene for hypophosphatemic rickets has been localized, The X-linked dominant form of the disease is attributed to mutations in the PEX gene, located at Xp 22.1. The gene locus for autosomal dominant hypophosphatemic rickets has been located on chromosome 12p13. The pathogenesis of this disorder is clear; phosphate wasting at the proximal tubule level is the basis of the affected individual's inability to establish normal ossification. This phenomenon is secondary to defective regulation of the sodium-phosphate cotransporter in the epithelial cell brush border. Normal phosphate reabsorption in response to 1,25-dihydroxycholecalciferol (calcitriol) provides clear evidence that the sodium-phosphate cotransporter is capable of proper function and is not intrinsically defective.

Clinical Features

As in all genetic disorders, the disease is present from conception. Affected newborns are of normal weight, but infants may show growth retardation. Intellectual development is unaffected. Although serum phosphate levels are depressed similarly in affected males and females, the degree of bone involvement is substantially less severe in heterozygous females. All hemizygous males are clinically affected. Widened joint spaces and flaring at the knees may become apparent in children by their first birthday, particularly in boys. When a child begins to stand and walk, bowing of the weight-bearing long bones quickly becomes clinically evident. Dentition may be absent or delayed in very young children due to abnormal tooth formation; older children may experience multiple dental abscesses.

Laboratory Findings

Laboratory evaluation of rickets begins with assessment of serum calcium, phosphate, and alkaline phosphatase levels. In hypophosphatemic rickets, calcium levels may be within or slightly below reference ranges; alkaline phosphatase levels are significantly above reference ranges. Serum phosphate levels must be carefully evaluated in the first year because the concentration reference range for infants (5.0 – 7.5 mg/dL) is high compared to adults (2.7-4.5 mg/dL). Hypophosphatemia can be missed easily in a baby. Serum parathyroid hormone level is within reference ranges to slightly elevated, while calcitriol level is low or in the lower reference range. Most importantly, urinary loss of phosphate is above reference ranges.

Roentgenographic Features

In all cases of rickets, the study of choice is radiography of the wrists, knees, ankles, and long bones. No pathognomonic sign on X-ray distinguishes hypophosphatemic rickets from other variants of rickets.

Treatment and Prognosis

Treatment can be administered safely on an outpatient basis, although serum calcium concentrations must be monitored periodically and carefully. Conscientious follow-up is essential. The usual vitamin D preparations are not useful for treatment in this disorder because they lack significant 1-alpha-hydroxylase activity. Original treatment protocols advocated vitamin D at levels of 25,000-50,000 U/d (at the lower limit of toxic dosage), which placed the patient in jeopardy of frequent hypercalcemic episodes. Now more widely available, calcitriol substantially diminishes but does not eliminate this risk. Amiloride and hydrochlorothiazide are administrered to enhance calcium reabsorption and to reduce the risk of nephrocalcinosis. Surgical care involves osteotomy to realign extremely distorted leg curvatures in children whose diagnosis was delayed or whose initial treatment was inadequate. Skull deformity may require treatment for synostosis. Spontaneous abscesses often require periodic dental procedures. Apart from the short stature of most affected adults, the prognosis for a normal lifespan and normal health is good.

CRANIOSYNOSTOSIS SYNDROMES

Craniosynostosis consists of premature fusion of one or more cranial sutures, often resulting in an abnormal head shape. It may result from a primary defect of ossification (primary craniosynostosis), or more commonly, from a failure of brain growth (secondary craniosynostosis). Simple craniosynostosis is a term used when only one suture fuses prematurely. Compolex or compound craniosynostosis is used to describe premature fusion of multiple sutures. When children with craniosynostosis, usually compolex, also display other body deformities, this is termed syndromic craniosynostosis.

Etiology

Multiple theories have been proposed for the etiology of primary craniosynostosis, but the most widely accepted is a primary defect in the mesenchymal layer ossification in the cranial bones. Secondary craniosynostosis typically results from systemic disorders such as endocrine disorders, hypothyroidism, hypophosphatemia, vitamin D deficiency, renal osteodystrophy, hypercalcemia, and rickets; hematologic disorders that cause bone marrow hyperplasia (e.g. sickle cell disease, thalassemia) and inadequate brain growth, including microcephaly and its causes.

The syndromic causes appear to result from genetic mutations responsible for fibroblast growth factor receptors 2 and 3. A gene locus for single suture craniosynostosis has not been identified. Primary craniosynostosis results when one or more sutures fuse prematurely, skull growth can be restricted perpendicular to the suture. If multiple sutures fuse while the brain is still increasing in size, intracranial pressure can increase. Secondary craniosynostosis is more frequent than the primary type, and results from early fusion of sutures due to primary failure of brain growth. Since brain growth drives the bony plates apart at the sutures, a primary lack of brain growth allows premature fusion of all the sutures. Intracranial pressure usually is normal, and surgery seldom is needed. Typically, failure of brain growth results in microcephaly. Intrauterine space constraints may play a role in the premature fusion of sutures in the fetal skull. This has been demonstrated in coronal craniosynostosis.

Clinical Features

Craniosynostosis may be evident at birth or in infancy from craniofacial abnormalities. It is equally distributed in both genders. It may become evident later when the child exhibits neurodevelopmental delays. Typically, careful examination alone can make the diagnosis. Craniosynostosis sometimes is associated with sporadic craniofacial syndromes such as Crouzon. Apert, Chotzen, Pfeiffer, or Carpenter syndromes. In this context, facial features, typically craniofacial abnormalities, suture ridging, and early closure of fontanelles, suggest the diagnosis. Raised intracranial pressure is rare with fusion of a single suture. Intracranial pressure may be elevated in primary multiple suture craniosynostosis, such as cloverleaf skull and the syndromic synostoses. Signs include sun-setting eyes, papilledema, vomiting, and lethargy. Differential diagnoses include benign skull tumors, hydrocephalus, mental retardation, neural tube defects, syringomyelia, thyroid disease and torticollis.

Roentgenographic Features

Skull X-ray with anterior-posterior, lateral, and Water's views show prematurely fused sutures which are easily identified by the absence of sutures and associated ridging of the suture line. Sutures either are not visible or have evidence of sclerosis.

Treatment and Prognosis

In the past 30 years, a better understanding of the pathophysiology and management of craniosynostosis has developed. Currently, surgery is usually cosmetic for infants with fusion of one or two sutures that result in a misshapen head. For infants with microcephaly (i.e. secondary craniosynostosis), surgery usually is not required. Surgery typically is indicated for increased intracranial pressure or for cosmetic reasons. Patients with primary craniosynostosis must be monitored after surgery. In secondary craniosynostosis, prognosis is dependent upon underlying etiology.

PIERRE ROBIN MALFORMATION (PIERRE ROBIN SYNDROME, ROBIN SEQUENCE, PIERRE ROBIN ANOMALAD, ROBIN COMPLEXES, PIERRE ROBIN MALFORMATION COMPLEX)

Robin sequence, previously known as Pierre Robin syndrome and Pierre Robin anomalad, consists of three essential components which include:

- Micrognathia or retrognathia.
- Cleft palate, and
- Glossoptosis, often accompanied by airway obstruction. (The tongue is not actually larger than normal, but because of the small mandible, the tongue is large for the airway and therefore causes obstruction. Rarely, the tongue is smaller than normal).

Robin sequence occurs as an isolated defect, as part of a recognized syndrome, or as part of a complex of multiple congenital anomalies. The condition is named after the French dental surgeon Pierre Robin (1867-1950).

Etiology

Three pathophysiological theories exist to explain the occurrence of Pierre Robin sequence:

1. **The mechanical theory:** This is the most accepted theory. Initially, mandibular hypoplasia occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves. This theory explains the classic inverted U-shaped cleft and the absence of an associated cleft lip. Oligohydramnios could play a role in the etiology since the lack of amniotic fluid

could cause deformation of the chin and subsequent impaction of the tongue between the palatal shelves.

2. **The neurological maturation theory:** A delay in neurological maturation has been noted on electromyography of the tongue musculature, the pharyngeal pillars, and the palate, as has a delay in hypoglossal nerve conduction. The spontaneous correction of the majority of cases with age supports this theory.
3. **The rhombencephalic dysneurulation theory:** In this theory, the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis.

Clinical Features

This heterogeneous birth defect has a prevalence of approximately 1 per 8,500 live births. The male-to-female ratio is 1 : 1. Micrognathia is reported in the majority of cases (91.7%). The mandible has a small body, obtuse gonial angle, and a posteriorly located condyle. The mandibular hypoplasia however, resolves and the child attains a normal profile by the age of five to six years. Glossoptosis is noted in 70-85 percent of reported cases. Macroglossia and ankyloglossia are relatively rare findings, noted in 10-15 percent of reported cases. The combination of micrognathia and glossoptosis may cause severe respiratory and feeding difficulty in the newborn. Obstructive sleep apnea may also occur. The prevalence of cleft palate varies from 14-91 percent. It can affect the soft and hard palate and is usually U-shaped (80%) or V –s haped. Occasionally, it may present as a bifid or double uvula or as an occult submucous cleft. Velopharyngeal insufficiency is usually more pronounced in these patients than in those with isolated cleft palate.

Other associated anomalies are also seen which include; otitis media, hearing loss, nasal deformities, dental and philtral malformations. Anomalies involving the musculoskeletal system are the most frequent systemic anomalies (noted in 70-80% of cases). They include syndactyly dysplastic phalanges, polydactyly, clinodactyly, hyperextensible joints, and oligodactyly in the upper limbs. Central nervous system (CNS) defects such as language delay, epilepsy, neuroe-developmental delay, hypotonia, and hydrocephalus may occur (Fig. 11.12).

Treatment and Prognosis

A multidisciplinary approach is required to manage the complex features involved in the case of these children. Treatment is prioritized according to the severity of airway compromise followed by the extent of feeding difficulties. Infants with pronounced micrognathia may experience severe respiratory histress or failure to thrive. Surgical intervention is necessary in these cases.

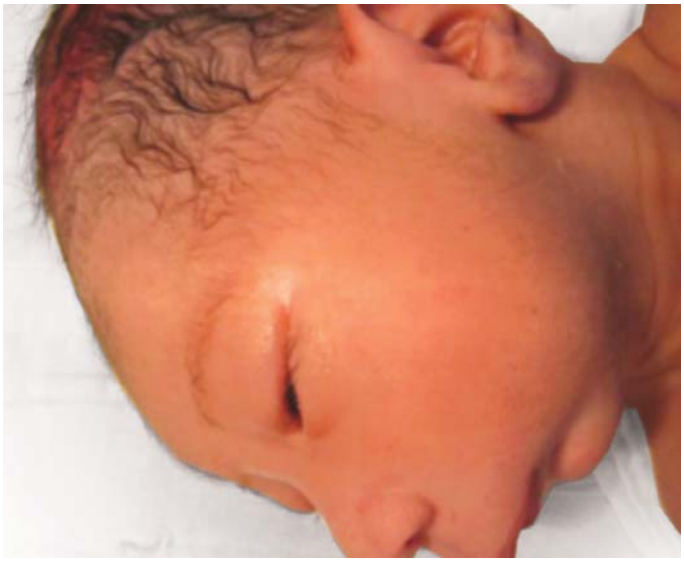


Fig 11.12: Pierre Robin syndrome

APERT SYNDROME (ACROCEPHALOSYNDACTYLY)

Apert syndrome is named after the French physician who described the syndrome acrocephalosyndactylia in 1906. It is a rare autosomal dominant disorder characterized by craniosynostosis, craniofacial anomalies, and severe symmetrical syndactyly (cutaneous and bony fusion) of the hands and feet. It is probably the most familiar and best described type of acrocephalosyndactyly.

Etiology

More than 98 percent of cases of Apert syndrome are caused by specific missense substitution mutations involving fibroblast growth factor preceptor 2, which maps to chromosome bands 10q25-q26. The remaining cases are due to mutations in or near exon 9 of FGFR2. Fibroblast growth factor receptor 2 (GFFR2) mutations lead to an increase in the number of precursor cells that enter the osteogenic pathway. Ultimately, this leads to increased subperiosteal bone matrix formation and premature calvaria ossification during fetal development.The order and rate of suture fusion determine the degree of deformity and disability. The evidence that syndactyly of Apert syndrome could be a keratinocyte growth factor receptor (KGFR)-mediated effect has also been reported.

Clinical Features

Apert syndrome is detected in the neonatal period due to cranisynostosis and associated findings of syndactyly in the hands and feet. Asians have the highest reported prevalence (22.3 per million live births). No gender predilection is seen. Craniostenosis is present and most

commonly involves the coronal sutures, resulting in acrocephaly, brachycephaly, flat occiput, and high prominent forehead. Large late-closing fontanels and a gaping midline defect are seen. Patients have apparent low-set ears with occasional conductive hearing loss. Eyes exhibit down-slanting palpebral fissures, hypertelorism, shallow orbits, proptosis and exophthalmos. The nose has a markedly depressed nasal bridge. It is short and wide with a bulbous tip, parrot-beaked appearance, and choanal stenosis or atresia.

The jaw shows a prominent mandible, maxillary hypoplasia, dropping angles of the mouth, high arched palate, bifid uvula, cleft palate, crowded upper teeth, malocclusion, delayed and ectopic eruption, shovel-shaped incisors, supernumerary teeth, V-shaped maxillary dental arch, and bulging alveolar ridges.

Syndactyly involves the hands and feet with partial-to-complete fusion of the digits, often involving second, third, and fourth digits. These often are termed mitten hands and sock feet. In severe cases, all digits are fused, with the palm deeply concave and cup-shaped and the sole supinated. Intelligence varies from normal to subnormal mentality. Malformations of the CNS may be responsible for most cases. Papilledema and optic atrophy with loss of vision may be present in cases of subtle increased intracranial pressure. Hyperhidrosis is commonly seen. Cardiovascular manifestations like atrial septal defect, patent ductus arteriosus, ventricular septal defect and pulmonary stenosis are present. Gastrointestinal, genitourinary and respiratory symptoms may be present in a small percentage of cases (Fig. 11.13).

Treatment

Surgical care involves early release of the coronal suture and front-orbital advancement and reshaping. Prognosis largely depends on the age at operation. Craniosynostosis can result in brain compression and mental retardation unless relieved by early craniotomy.

THANATOPHORIC DYSPLASIA

Thanatophoric dysplasia (TD) is the most common form of skeletal dysplasia that is lethal in the neonatal period. It is an autosomal dominant disorder resulting from sporadic *de novo* mutations in the FGFR3 gene. Characteristics of TD include severe shortening of the limbs, a narrow thorax, macrocephaly, and a normal trunk length. It is divided into two clinically defined subtypes. TD type 1, the most common subtype, features a normally shaped skull and curved long bones (shaped like a telephone receiver) with the femurs affected most. TD type 2 features a cloverleaf-shaped skull and straight femurs.

Fig 11.13: Apert syndrome

Clinical Features

A macrocephalic head with a frontal bossing, a flattened nasal bridge, and proptotic eyes has been observed. In TD2, a cloverleaf shaped skull resulting from premature closure of the cranial sutures. Narrow thorax with small ribs, micromelic limbs with brachydactyly, protuberant adomen, hydrocephalus and other cerebral parenchymal abnormalities are seen. Characteristic orodental abnormalities are not described associated with this syndrome.

Prognosis

TD is usually lethal in the first few days of life. Death is caused by respiratory insufficiency.

ACHONDROPLASIA (CHONDRODYSTROPHIA FETALIS)

Achondroplasia is a common nonlethal form of chondrodysplasia. It is transmitted as an autosomal dominant trait with complete penetrance. De novo mutations cause 75-80 percent of cases.

Etiology

Achondroplasia is caused by mutations in the gene for fibroblast growth factor receptor – 3 (FGFR3). The gene

has been mapped to band 4p16.3. The common mutations cause a gain of function of the FGFR3 gene, resulting in decreased endochondral ossification, inhibited proliferation of chondrocytes in growth plate cartilage, decreased cellular hypertrophy, and decreased cartilage matrix production.

Clinical Features

Frequency is believed to be 1 case per 15,000 – 40,000 births worldwide. Cardinal features include short stature, rhizomelic shortening of the arms and legs, a disproportionately long trunk, trident hands, midfacial hypoplasia, prominent forehead (frontal bossing), thoracolumbar protruberence, true megalencephaly, and characteristic limitation of joint motion. The incongruous appearance of the achondroplastic dwarf is in contrast to that of the pituitary dwarf, and the incongruity becomes more pronounced as he approaches adulthood and later life, chiefly because of the disproportionate size of the head in relation to the remainder of the body. Despite their misshapen appearance, achondroplastic dwarfs are of normal intelligence. Often they are also endowed with unusual strength and agility, characteristics which have led some to adopt the occupation of professional wrestler.

Oral Manifestations

The maxilla is often retruded because of restriction of growth of the base of the skull, and the retrusion may produce a relative mandibular prognathism. The resultant disparity in size of the two jaws produces an obvious malocclusion. The dentition itself is usually normal, although congenitally missing teeth with disturbance in the shape of those present have been reported.

Roentgenographic Features

Radiographs of the skull, spine, and extremities reveal the characteristic features. A lateral skull radiograph demonstrates midface hypoplasia, enlarged calvaria, frontal prominence, and shortening of the base of the skull. The size of the foramen magnum is diminished. The long bones are shorter than normal, and there is thickening or mild clubbing of the ends. The epiphyses generally appear normal, but may close either early or late. The bones at the base of the skull fuse prematurely. Except for the retrusion of the maxilla and the malocclusion between the two jaws, there are no changes in the jawbones.

Histologic Features

The abnormality seen in the bone of patients with achondroplasia is failure of endochondral ossification. Intramembranous and periosteal ossification are undisturbed. Histologic studies have shown disarrary of the chondrocytes, with loss of columnation and loss of normal chondrocyte proliferation. Fibrous tissue is present in the zone of provisional calcification, but bone trabeculae present are irregular. Because endochondral growth is affected, the orderly longitudinal growth of bone is disrupted, resulting in stunting of the bone. Intramembranous ossification is normal, leading to normal clavicles and skull. Because the width of the long bones is a product of intramembranous periosteal ossification, these bones are of normal diameter.

Treatment and Prognosis

There is no treatment for achondroplasia. There may be delay in motor milestones but speech is normal. The firequent middle ear infections and dental crowding require attention. If the patient survives the first few years of life, the chances are excellent that he will have the life expectancy of a normal person.

ROBINOW SYNDROME

Around 1969, Dr. Meinhard Robinow identified a new syndrome, which was unreported before. He named it 'fetal face' syndrome, based upon his views of the facial features of an eight-month old fetus. Later the name was changed to 'Robinow' syndrome.

Two types of this syndrome have been described, dominant and recessive. The dominant type is the most common and the parents are usually not carriers of the dominant gene that pronounces the syndrome. In the recessive type, which is the rarer of the two, both parents carry the recessive gene (but are not affected) and have a 25 percent chance of producing an affected offspring. The recessive form is caused by mutation in ROR2 gene. This gene is located in chromosome 9q22 and works in cartilage and bone formation. The gene responsible for the dominant form has not been established yet, but genes related to ROR2 are being studied as candidates.

Clinical Features

The features described refers to both types of this syndrome. The patients usually have most of these signs in varied proportions.

Skeletal System

Mild to moderate short stature (dwarfism), short lower arms (mesomelic brachymelia), small hands with clinodactyly usually of the fifth finger (abnormal lateral or medial bending of one or more fingers or toes) and brachydactyly (abnormally short fingers or toes) and small feet.

Craniofacial

Hypertelorism, short upturned nose, broad nasal bridge, anteverted nares, triangular mouth, frontal bossing, long or short philtrum, micrognathia, wide and downslanting palpebral fissures, ear abnormality, facial nevus and normal intelligence.

Oral

Dental abnormalities including malaligned teeth, gingival hyperplasia, abnormal uvula, cleft lip and/or palate (nonmidline), shortened tongue sometimes with midline indentation.

Complications

These include frequent ear infections and hearing loss, hypotonia, risk for developmental delays, breathing or respiratory problems, feeding difficulties, photophobia (light sensitivity) and esophageal reflux.

HYPEROSTOSIS CORTICALIS GENERALISATA (VAN BUCHEM'S DISEASE, HYPERPHOSPHATASEMIA TARDA, ENDOSTEAL HYPEROSTOSIS, AUTOSOMAL RECESSIVE)

This disease of bone, described by van Buchem and his associates in 1955, appears to represent an excessive deposition of endosteal bone throughout the skeleton in a pattern suggestive of a hereditary condition with an autosomal recessive characteristic. The disease gene has been mapped to chromosome 17q11.2.

Clinical Features

The disease is usually not discovered until adult life, and in nearly all reported cases, has been a chance finding. The facial appearance of these patients may be altered and this may be the reason that they seek professional advice. Such a case has been reported by Dyson. The face may appear swollen, particularly with widening at the angles of the mandible and at the bridge of the nose. Some patients also have loss of visual acuity, loss of facial sensation, some degree of facial paralysis and deafness, all due to cranial nerve involvement through closure of foramina. Intraorally, there is sometimes overgrowth of the alveolar process. Most patients, except for the facial appearance, appear normal and are free of symptoms, including bone tenderness.

Roentgenographic Features

A skeletal survey will reveal increased density of many bones of the body, although some bones, such as those of the hands and feet, may be unaffected. The skull also exhibits diffuse sclerosis, as may the jaws.

Histologic Features

The bone is normal dense bone but without evidence of remodeling.

Differential Diagnosis

Three other diseases must also be considered in the diagnosis in as-much-as they may also present widespread sclerosis: osteopetrosis, osteitis deformans and progressive diaphyseal dysplasia.

Treatment and Prognosis

There is no treatment for the disease, although the patients usually lead a normal life.

CHONDROECTODERMAL DYSPLASIA (ELLIS-VAN CREVELD)

Ellis-van Creveld is an extremely rare form of dysplasia first described by Ellis and van Creveld in 1940. It is characterized by four components; chondrodysplasia; polydactyly; ectodermal dysplasia affecting the hair, teeth, and nails; and congenital heart failure. The dysplasia is one of the short-rib polydactyly syndromes. As its name implies, this syndrome affects both mesodermal and ectodermal tissues. The prevalence of Ellis-van Creveld dysplasia is 0.1 per million.

Ellis-van Creveld syndrome is inherited as an autosomal recessive disorder. The locus gene has been mapped to chromosome 4p16.1.

CLINICAL FEATURES AND ORAL MANIFESTATIONS

Clinical Features

Chondroectodermal dysplasia is characterized by a number of ectodermal disturbances, including involvement of the nails and teeth.

The nails are generally hypoplastic with marked koilonychias. The sweat mechanism is normal. Bilateral polydactyly is seen affecting the hands and occasionally the feet.

Oral Manifestations

The most constant oral finding is a fusion of the middle portion of the upper lip to the maxillary gingival margin eliminating the normal mucolateral sulcus.

Natal teeth, prematurely erupted deciduous teeth, frequently occur as well as congenital absence of teeth, particularly in the anterior mandibular segment. Tooth eruption is often delayed and those erupted are commonly defective, being small, cone-shaped and demonstrating enamel hypoplasia. Supernumerary teeth are also reported.

Treatment

During infancy, cardiac surgery is often required to treat congenital malformations.

TRICHO-DENTO-OSSEOUS SYNDROME

The tricho-dento-osseous syndrome is a hereditary condition which chiefly involves the hair, teeth, and bones. Individuals with this syndrome are born with a full head of kinky hair, which sometimes tends to straighten with age. Nails are thin and likely to peel or fracture. The sweat glands are developed normally. The chief bony abnormality in patients with the condition are bones which are found to be more dense than normal. In some families, the skull bones are excessively thick. These abnormalities are of no clinical significance and should not cause individuals with this syndrome any problem. They are, however, helpful in making the diagnosis. There is no evidence that people who have this condition are shorter or taller than normal.

Teeth may become infected and dental abscesses are common during the first few years of life. They have thin, pitted and yellow-brown enamel. On dental x-ray, large pulp chambers (taurodontia) are found. In addition, teeth may remain unerupted for long giving the condition of partial anodontia. Intelligence is normal, as is life span. The condition is inherited as an autosomal dominant disorder. Prenatal diagnosis for this syndrome is not yet possible. The disorder has been mapped to locus 17q21.3 – q22.

There may be three distinct types of TDO syndrome that have similar but not identical characteristics. Some researchers suggest that these variants may be differentiated mainly by whether the calvaria and/or long bones exhibit abnormal hardening (sclerosis), thickening, and/or density. Other symptoms also vary among the three types.

MASSIVE OSTEOLYSIS

Massive osteolysis is unusual and uncommon disease characterized by spontaneous, progressive resorption of bone with ultimate total disappearance of the bone. Disappearing, or 'Phantom' bone disease also called Gorham's disease, may be form of hemangioma of bone. This relatively rare condition, usually occurring in children or young adults, is characterized by the dissolution in whole or inpart of one or several adjacent bones. A cavernous, angioma-like permeation may be a prominent pathologic feature of the affected bones. The process is self limited, but the extent of progression is unpredictable. It is not genetically transmitted.

Clinical Features

Massive osteolysis is most common in older children and young and middle aged adults, affecting both genders equally. About 50 percent of all patients report an episode of trauma before the diagnosis, but this is often trivial in nature. Usually only one bone is affected in a given patient, although polyostotic cases have been reported. The most commonly affected bones are the clavicle, scapula, humerus, ribs, ilium, ischium, and sacrum.

The disease, which may or may not be painful, begins suddenly and advanced rapidly until the involved bone is replaced by a thin layer of fibrous tissue surrounding a cavity. All laboratory values are usually normal.

Oral Manifestations

A number of cases have been reported involving the mandible and other facial bones, and these have been reviewed by Ellis and Adams and by Murphy and his coworkers. In only two of these cases was there destruction of the entire mandible. In at least three cases, there was concomitant involvement of the maxilla. The patient may present with pain or facial asymmetry or both. One of the consistent findings in the disease has been pathologic fracture following minor trauma.

Histologic Features

The typical histologic findings is replacement of bone by connective tissue containing many thin-walled blood vessels or anastomosing vascular spaces lined by endothelial cells. It does not represent a hemangioma of bone, which remains a localized lesion, although the term hemangiomatosis' has been applied. Most authorities do not believe that the disease is due to increased osteoclastic activity although osteoclasts may often be found in the tissues. On the other hand, their absence in areas of active resorption is often quite striking.

Treatment and Prognosis

There is no specific treatment. Radiation therapy has been of benefit in some cases, while surgical resection has stopped the progess of the disease in others. Left untreated, the disease commonly progresses to total destruction of the involved bone.

DISEASES OF THE TEMPOROMANDIBULAR JOINT

The temporomandibular joint is one of the most important yet most poorly understood of the main joints in the body. Because of its unique anatomic position and association

with other structures, the dentist in previous years often considered it outside his realm of responsibility. For this reason, the otolaryngologist contributed greatly to our knowledge for the anatomy and physiology of this joint and probably did much to stimulate the interest of the dental profession in this articulation. It is unfortunate that a great deal of misinformation about the temporomandibular joint has appeared in the medical and dental literature, arising chiefly through misinterpretation of anatomic and pathologic findings, and this has caused considerable confusion among investigators in their early phases of study.

It has been only within recent years that painstaking work dealing with the temporomandibular joint has been reported in any quantity and the determined efforts of a number of workers have clarified much of the aural of mystery which surrounded this structure. As Schwartz pointed out, there have been more changes in concepts and methods of treatment in the past 25 years than in the previous 2500 years. Even today a great deal remains to be answered about the many osteopathoses that occur here. Desite many advances that have been made, most men experienced in the problems of the temporomandibular joint will agree that we are only at the threshold in our development of knowledge of its disturbances.

The diagnosis of these diseases has often been a perplexing problem because the clinician has been almost wholly dependent upon the description of the symptoms by the patient; seldom are definite clinical signs of temporomandibular joint disease manifested. Recent development of techniques for obtaining useful roentgenograms of this joint and the application of cinefluoroscopy and computerized axial tomography offer great promise of helping to solve the many unanswered questions pertaining to the temporomandbular joint in health and disease.

DEVELOPMENT DISTURBANCES OF THE TEMPOROMADIBULAR JOINT

Aplasia of the Mandibular Condyle

Condylar aplasia, or failure of development of the mandibular condyle, may occur unilaterally or bilaterally, but in either event is a rare condition. Five cases have been reported by Kazanjian and isolated cases by other authors.

Clinical Features

This abnormality is frequently associated with other anatomically related defects such as a defective or absent eternal ear, an underdeveloped mandibular ramus or macrostomia. If the condylar aplasia is unilateral, there is obvious facial asymmetry, and both occlusion and mastication may be altered. A shift of the mandible toward the affected side occurs during opening. In bilateral cases this shift is not present.

Treatment

Treatment of condylar aplasia consists in osteoplasty, if the derangement is severe, and correction of the malocclusion by orthodontic appliances. If the patient exhibits little difficulty, surgical intervention is not warranted, although cosmetic surgery may aid in correcting facial deformity.

HYPOPLASIA OF THE MANDIBULAR CONDYLE

Underdevelopment or defective formation of the mandibular condyle may be congenital or acquired. Congenital hypoplasia, which is of idiopathic origin, is characterized by unilateral or bilateral underdevelopment of the condyle beginning early in life.

The acquired form of hypoplasia may be due to any agent which interferes with the normal development of the condyle. It has been suggested that this may occur in forceps deliveries that cause traumatic birth injury. External trauma to the condylar area in infants or younger children may also result in hypoplasia. Other cases have been observed in children following X- ray radiation over the temporomandibular joint area for local treatment of skin lesions such as the hemangioma, or 'birth mark'.

Infection spreading locally from the dental area or by the hematogenous route from a distant site may involve the joint, interfere with condylar growth and result in a hypoplastic condyle. Discussing arthritis inchildren, Kuhns and Swaim emphasized the fact that inflammation or a circulatory disorder in proximity to an epiphysis may result in a severe disturbance in growth.

A variety of endocrine and vitamin derangements in the experimental animal have been reported to cause disturbances in growth and development of the mandibular condyles. The possibility that such factors play any significant role in the development of human temporomandibular arthropathy has not been completely evaluated, but they are probably of minor clinical importance.

Clinical Features

The clinical deformity occasioned by condylar hypoplasia depends upon whether the disturbance has affected one or both condyles and upon the degree of the malformation. This in turn is directly related to the age of the patient at the time the involvement occurred, the duration of the injury and its severity. Unilateral involvement is the most common clinical type.

Severe unilateral arrest of growth will produce facial asymmetry, often accompanied by limitation of lateral excursion on one side and exaggeration of the antegonial notch of the mandible on the involved side. A mild disturbance presents only lesser degrees of these features, perhaps accompanied by a mandibular midline shift during opening and closing. The distortion of the mandible in this pathognomonic pattern results from lack of downward and forward growth of the body of the mandible due to the arrest of the chief growth center of the mandible, the condyle. Some growth continues at the outer posterior border of the angle of the mandible, resulting in thickening of the bone in this area. The older the patient at the time of the growth disturbance, the less severe will be the facial deformation. It should be remembered, however, that growth frequently persists in this condyle until the age of 20 years, and even more important, that a growth potential is maintained indefinitely, unlike most other joints in the body.

Treatment and Prognosis

Treatment of condylar hypoplasia is a difficult problem since there are no available means of stimulating its growth locally or compensating for its failure. Although the condition itself is not necessarily a progressive one, the resulting disturbance may become more severe as the patient approaches puberty. Cartilage or bone transplants have been used to build up the underdeveloped parts, preceded in some cases by unilateral or bilateral sliding osteotomy, to improve the appearanceof the patient with asymmetry and retrusion.

HYPERPLASIA OF THE MANDIBULAR CONDYLE

Condylar hyperplasia is a rare unilateral enlargement of the condyle which should not be confused with a neoplasm of this structure, although it may superficially resemble an osteoma or chondroma.

The cause of this condition is obscure, but it has been suggested that mild chronic inflammation, resulting in a condition analogous to a proliferative osteomyelitis, stimulates the growth of the condyle or adjacent tissues. The unilateral occurrence strongly suggests a local phenomenon.

Clinical Features

The patients usually exhibit a unilateral, slowly progressive elongation of the face with deviation of the chin away from the affected side. The enlarged condyle may be clinically evident or at least palpated and presents a striking roentgenographic appearance in both anteroposterior and lateral views as well as in specific condylar films. The affected joint may or may not be painful. A severe malocclusion is a usual sequela of the condition.

Treatment and Prognosis

The treatment of condylar hyperplasia usully involves resection of the condyle. This is generally sufficient to restore normal occlusion, although complete correction of the facial asymmetry may not be accomplished by this procedure.

TRAUMATIC DISTURBANCES OF THE TEMPOROMANDIBULAR JOINT

Luxation and Subluxation

Dislocation of the temporomandibular joint occurs when the head of the condyle move anteriorly over the articular eminence into such a position that it cannot be returned voluntarily to its normal position. Many workers believe that this inability to retrude that mandible is caused by spasm of the temporal muscle initiated by myotatic reflex. Thus, in movements of the mandible involving forward translation of the condyle, tension may be placed on the temporalis and lead to formation of the muscle spasm.

A great deal of confusion persists as to the use of the terms 'luxation' and 'sublaxation'. Luxation of the joint refers to complete dislocation, while subluxation is a partial or incomplete dislocation, actually a form of hypermobility. Despite wide acceptance of the term 'subluxation', many investigators discourage its use, arguing that when the condyle is obviously outside the limits of normal in its position, the joint is actually dislocated. It can be demonstrated that in cases of joint disturbances classified as subluxation, there is no abnormal joint relation visible on the temporomandibular roentgenogram. In such instances, though the condyle may lie well anterior to the articular eminence, such a position is normal for many persons.

Luxation may be acute, owing to a sudden traumatic injury resulting in fracture of the condyle, or more frequently, only in stretching of the capsule, usually at the point of attachment for the external pterygoid muscle into the capsule. There is often some tearing of the tendon at this insertion point. Most commonly, however, luxation is a result of yawning or having the mouth opened too widely, as by a dentist extracting teeth or by a physician removing tonsils or through injudicious use of a mouth prop.

Clinical Features

The typical form of luxation is characterized by sudden locking and immobilization of the jaws when the mouth is

open, accompanied by prolonged spasmodic contraction of the temporal, internal ptergoid and masseter muscles, with protrusion of the jaw. All activities requiring motion of the mandible, such as eating or taking, are impossible; the mouth cannot be closed, and the patient frequently becomes panicky, especially it is his first experience. In some instances, the patient may be able to reduce the dislocation himself. This is particularly true in cases of chronic dislocation when the ligaments become stretched.

Superior and posterior dislocation of the condyle may occur in rare instances as the result of an acute traumatic impaction injury, and the head of the condyle may be forced through the glenoid fossa or tympanic plate into the middle cranial fossa.

Treatment

Reduction of a dislocated condyle is accomplished by including relaxation of the muscles and the guiding the head of the condyle under the articular eminence into its normal position by an inferior and posterior pressure of the thumbs in the mandibular molar area. The necessary relaxation can sometimes be brought about only by means of general anesthesia or by tiring the masticatory muscles by cupping the chin in the palm of the hand and applying a posterior and superior pressure for five to ten minutes.

Ankylosis

Ankylosis of the temporomandibular joint is one of the most incapacitating of all diseases involving this structure.

Etiology

The most frequent causes of ankylosis of the temporomandibular joint are traumatic injuries and infections in and about the joint. Straith and Lewis elaborated on the etiologic factors and enumerated them as follows:

- Abnormal intrauterine development
- Birth injury (by forceps particularly)
- Trauma to the chin forcing the condyle against the glenoid fossa particularly with bleeding into the joint space
- Malunion of condylar fracturers
- Injuries associated with fractures of the malar – zygomatic compound
- Loss of tissues with scarring
- Congenital syphilis
- Primary inflammation of the joint (rheumatoid arthritis, infectious arthritis, Marie – Strumpell disease)
- Inflammation of the joint secondary to a local inflammatory process (e.g. otitis media, mastoiditis, osteomyelitis of the temporal bone or condyle)
- Inflammation of the joint secondary to a bloodstream infection (e.g. septicemia, scarlet fever)
- Metastatic malignancies, and
- Inflammation secondary to radiation therapy.

Topazian has reviewed 229 cases of temporomandibular joint ankylosis and found that 49 percent were a result of joint inflammation of the one type or another, 31 percent were related to trauma, and the remainder were idiopathic.

Clinical Features

This condition occurs at any age, but most cases occur before the age of 10 years. Distribution is approximately equal between the genders. The patient may or may not be able to open his mouth to any appreciable extent, depending on the type ankylosis. In complete ankylosis, there is abony fusion with absolute limitation of motion. There is usually somewhat greater motion in fibrous ankylosis than in bony ankylosis.

If the jnjury which brough about the ankylosis was sustained in infancy or childhood, at least before the age of 15 years, there is nearly always an associated facial deformity. The type of deformity is partially dependent upon whether the ankylosis is unilateral or bilateral. In unilateral ankylosis occurring at an early age, the chin is displaced laterally and backward on the affected side because of a failure of development of the mandible. When an attempt is made to open the mouth, the chin deviates toward the ankylosed side, if any motion is present. Bilateral ankylosed occurring in childhood results in underdevelopment of the lower portion of the face, a receding chin and micrognathia. The maxillary incisors often manifest overjet due to failure of this mandibular growth.

Temporomandibular joint ankylosis has been divided into two types, depending upon the anatomic site of the ankylosis with respect to the joint itself: intra-articular ankylosis and extra-articular ankylosis. It is important that the distinction between the two types be made, but this is not usually difficult. In intra-articular ankylosis, the joint undergoes progressive destruction of the meniscus with flattening of the mandibular fossa thickening of the head of the condyle and narrowing of the joint space. The ankylosis is basically fibrous, although ossification in the scar may result in a bony union.

Treatment

Treatment of temporomandibular bony ankylosis is surgical, usually complicated by the concomitant underdevelopment of the jaw. Basically, the operation consists of osteotomy or removal of a section of bone below the condyle. Fibrous ankylosis may be treated by functional methods.

TEMPOROMANDIBULAR JOINT SYNDROME

Temporomandibular joint syndrome or temporomandibular disorder (TMD) is the most common cause of facial pain after toothache. No unequivocal definition of the disease exists; discrepancies concerning the terminology, definitions, and practical treatment methodologies exist. TMD can be classified broadly as TMD secondary to myofacial pain and dysfunction (MPD), and TMD secondary to true articular disease. The two types can be present at the same time, making diagnosis and treatment more challenging. The MPD type forms the majority of the cases of TMD and is associated with pain without apparent destructive changes of the TMJ on X-ray. It is frequently associated with bruxism and daytime jaw clenching in a stressed and anxious person. True intra-articular disease can be grouped under disk displacement disorder, chronic recurrent dislocations, degenerative joint disorders, systemic arthritic conditions, ankylosis, infections and neoplasia.

Etiology

The etiology of MPD is multifactorial and includes malocclusion, jaw clenching, bruxism, personality disorders, increased pain sensitivity, and stress and anxiety. The principal factors responsible for the clinical manifestations in MPD (i.e. pain, tenderness, and spasm of the masticatory muscles) is muscular hyperactivity and dysfunction due to malocclusion of variable degree and duration. The significance of psychological factors has been recognized during the past few years. Of the causes of TMD of articular origin, disk displacement is the most common. Other diseases such as degenerative joint disorders, rheumatoid arthritis, ankylosis, dislocation, infection, neoplasia, and congenital anomalies may contribute to pain. In TMD of articular origin, the spasm of the masticatory muscles is secondary in nature. One study found that in patients with chronic inflammatory connective tissue disease, the pain on mandibular movement and tenderness to palpation of TMJ is related to the level of tumor necrosis factor alpha (TNF – α) in the synovial fluid.

Clinical Features

TMD primarily affects young women aged 20-40 years. The male to female ratio is 1:4. A comprehensive, chronological history and physical examination of the patient, including dental history and examination, is essential to diagnose the specific condition to decide further investigations, if any, and to provide specific treatment. There are four cardinal signs and symptoms of the syndrome (1) pain (2) muscle tenderness (3) a clicking or popping noise in the temporomandibular joint, and (4) limitation of jaw motion, unilaterally or bilaterally in approximately an equal ratio, sometimes with deviation on opening. The pain is usually periauricular, associated with chewing, and may radiate to the head but is not like the common headache. It may be unilateral or bilateral in MPD, and usually is unilateral in TMD of articular origin, except in rheumatoid arthritis. In MPD, the pain may be associated with history of bruxism, jaw clenching, stress, and anxiety; the pain may be more severe during periods of increased stress clicking popping and snapping sounds usually are associated with pain in TMD. An isolated click is very common in the general population and is not a risk factor for development of TMD. Limited jaw opening due to pain or disk displacement may be seen. TMD may act as a trigger in patients prone to headaches, and when present in association with TMD, they tend to be severe in nature. Other symptoms associated with TMD are otalgia, neck pain and/or stiffness, shoulder pain, and dizziness. About one-third of these patients have a history of psychiatric problems. History of facial trauma, systemic arthritic disease, and recurrent dislocation also should be elicited.

Differential diagnosis includes cluster headache, migraine headache, postherpetic neuralgia, temporal/giant cell arteritis, trigeminal neuralgia and middle car infections.

Laboratory Findings

Blood examination is required if systemic illness is suspected to be the cause of TMD. A complete blood count is done if infection is suspected. Rheumatoid factor (RF), ESR, antinuclear antibody (ANA), and other specific antibodies are checked if rheumatoid arthritis, temporal arteritis, or a connective tissue disorder is suspected. Uric acid should be checked for gout.

Roentgenographic Features

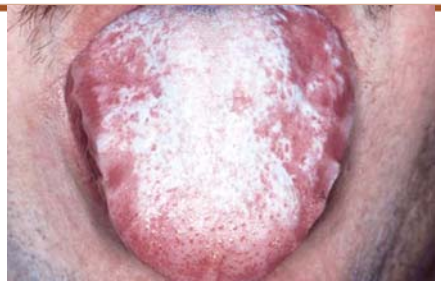
Radiographic findings in TMJ correlate to the etiology of TMD in cases of rheumatoid arthritis and seronegative spondyloarthropathies, conventional radiographs show erosions, osteophytes, subchondral bony sclerosis, and condylar–glenoid fossa remodeling. A variety of new imaging techniques are being used and perfected to study TMJ. CT scan can explore both bony structures and muscular soft tissues. It is relatively less expensive and can be done with contrast material injected into the joint cavity. MRI, though costly, should be used as the study of choice if an articular or meniscal pathology is suspected and an endoscopic or surgical procedure is contemplated, and in a case of traumatic TMD.

Treatment and Prognosis

Most TMDs are self-limiting. Conservation treatment involving self-care practices, rehabilitation aimed at eliminating muscle spasms, andrestoring correct coordination, is all that is required. Nonsterodial anti inflammatory analgesics (NSAIDs) should be used on a short-term, regular basis. On the other hand, treatment of chronic TMD can be difficult and the condition is best managed by a team approach, consisting of a primary care physician, a dentist, a physiotherapist, a psychologist, a pharmacologist, and in small number of cases, a nitrogen. The different modalities include patient education and self-care practices, medication, physical therapy, splints, psychological counseling, relaxation techniques, biofeedback, hypnotherapy, acupuncture, and arthrocentesis. Most cases of TMD respond to simple treatment and the prognosis is good. Symptoms usually remit with simple care. In cases of secondary involvement of TMJ the prognosis depends on the primary disease.

12

Diseases of the Skin



LICHEN PLANUS

Lichen planus is one of the most common dermatologic disease to manifest itself in the oral cavity and therefore, should be completely familiar to the dentist.

Clinical Presentation and Pathogenesis

Lichen planus is a T-cell-mediated autoimmune interface disease in which the basal cell layer of mucosa and/or skin is attacked.

Lichen planus presents in one of three different clinical forms that rarely transform from one to another. All forms are seen mostly in patients older than 40 years and in men and women equally; in addition, all have a predilection for the buccal mucosa, the tongue, and the attached gingiva. The three forms, in order of advancing severity and symptomatology, are reticular, plaque, and erosive.

Reticular Form (Fig. 12.1)

The reticular form is characterized by so-called Wickham's striae of white interlacing lines found mostly on the characteristic sites of the buccal mucosa, attached gingiva, and tongue. These striae are usually asymptomatic, reach a certain area of involvement, and then cease to extend. This form requires no specific diagnostic measure or treatment.

Plaque Form (Fig. 12.2)

The plaque form is characterized by a white patch or leukoplakia appearance. In this form, slightly elevated, irregular hyperkeratotic plaques develop at the characteristic sites. These patches are usually asymptomatic but may be associated with some discomfort. Biopsy is required to differentiate this form from premalignant or malignant mucosal changes.

Erosive Form (Fig. 12.3)

The erosive form is characterized by intense pain and erythematous mucosal inflammation. When it involves the buccal mucosa or the tongue, it will produce fibrinous-based ulcers against a background of erythema and sometimes white hyperkeratotic foci. When it involves the attached gingiva, it will produce a boggy, red, friable tissue that bleeds easily. Because the inflammatory destruction is focused on the basal cells, some presentations will demonstrate vesicle formation, and a Nikolsky's sign may even be elicited. Some label this finding a separate form, bullous lichen planus, but it merely represents a part of

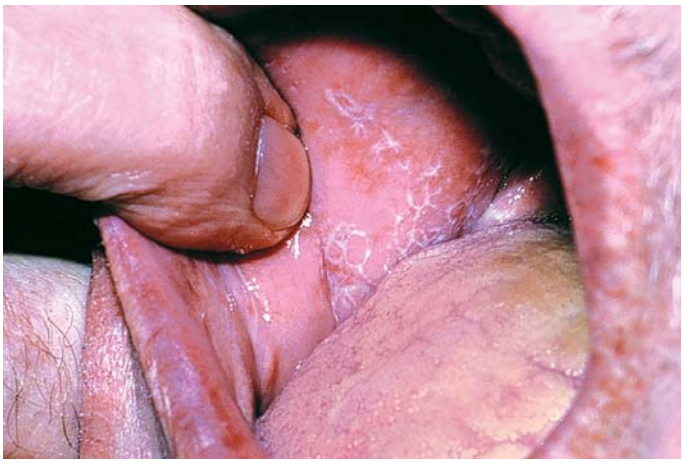


Fig. 12.1: Buccal lichen planus showing the typical fine lace-like pattern (Wicham's stria)

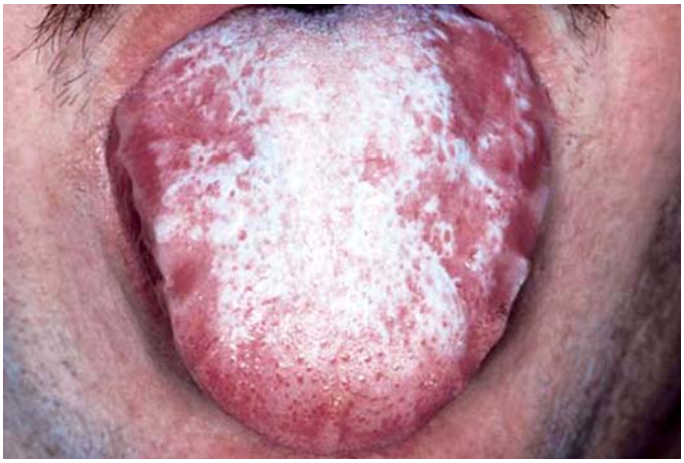


Fig. 12.2: Plaque form of lichen planus

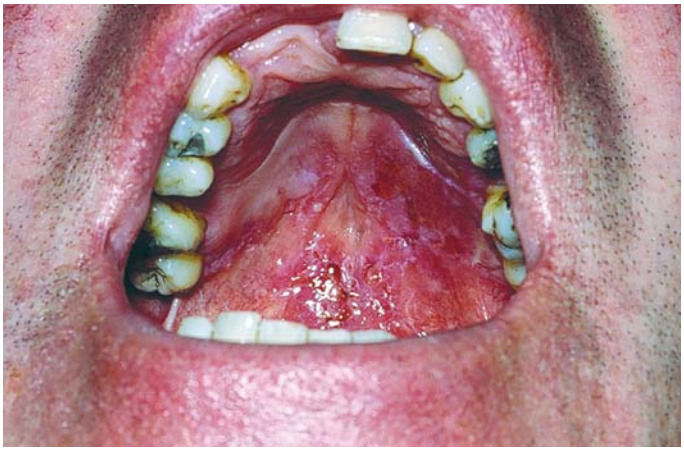


Fig. 12.3: Erosive lichen planus of palate

the erosive lichen planus spectrum. Similarly, the attached gingiva presentation of erosive lichen planus closely resembles what many in the past referred to as desquamative gingivitis, and what some today refer to as an atrophic form, but this represents an unnecessary splitting of terminology as this is again merely part of the erosive lichen planus spectrum.

The postulated pathogenic mechanism for lichen planus is that native proteins are falsely identified as foreign antigens. This may result from basal cells expressing surface proteins that bear a close structural resemblance to a foreign protein, thus stimulating a delayed cell-mediated hyperimmune response. It may also result from the exposure of basal cell proteins, which are normally hidden from lymphocytes, to lymphocytes or macrophages, which can then process them as antigens. Basal cells that do not normally express class II histocompatibility antigens are induced to do so by injury, drugs, nonspecific activated lymphocytes secreting gamma-interferon, or other factors. They then express human lymphocyte antigen HLA-DR, which is also expressed by lymphocytes and antigen-processing macrophages called Langerhans cells. If both basal cells and lymphocytes carry HLA-DR surface antigens, they can come into contact and transfer antigenic information, as is common to Langerhans cell-lymphocyte interactions, which confer normal cell-mediated immunity. In this sense, basal cell antigen may become transferred to these lymphocytes and initiate the cell-mediated autoimmunity that is known to be the mechanism of lichen planus.

Differential Diagnosis

The reticular form of lichen planus is clinically distinct. The plaque form of lichen planus could be described as "clinical leukoplakia." Such "clinical leukoplakia" carries with it a subset of different lesions that, like lichen planus, can produce a white leukoplakic patch. These include the nonspecific benign hyperkeratoses, a spectrum of epithelial dysplasias, verrucous hyperplasia, verrucous carcinoma, and invasive squamous cell carcinoma. In addition, hypertrophic candidiasis is also known to produce a white patch that will not rub off as do other forms of candidiasis.

The erosive form of lichen planus can be particularly treacherous because its clinical presentation may be identical to that of dysplasia. The similarity of clinical and even histopathologic appearance has stirred a controversy in which lichen planus is considered a premalignant disease by some. The term lichenoid dysplasia correctly describes the histopathologic similarities of the two entities but is confusing because atypical cells are part of dysplasia from its onset but are not part of uncomplicated lichen planus. Therefore, a field dysplasia exists separate from lichen planus and should be included in the differential diagnosis. However, recent documentation of lichen planus transforming into squamous cell carcinoma has identified erosive lichen planus to indeed have this premalignant potential. Although its transformation incidence is about 1% to 3%, erosive lichen planus transitioning into an invasive squamous cell carcinoma is a realistic inclusion in the differential diagnosis.

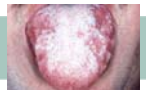
The presentation of painful, red attached gingiva in particular will closely resemble pemphigoid, and the generally painful oral lesions, usually without skin lesions, will strongly suggest pemphigus vulgaris at times. Chronic ulcerative stomatitis may present with ulceration and desquamation of the gingiva.

Diagnostic Work-Up

The diagnosis is made from a mucosal biopsy; skin biopsies are also diagnostic if skin lesions are present. The critical guideline to obtaining a diagnostic tissue specimen is to avoid biopsy of an ulcerated area. Ulcerated areas will be distorted by epithelial loss and secondary nonspecific inflammation. It is best to biopsy a red or white area and include some surrounding normal appearing tissue. The use of direct immunofluorescence is not specifically required to diagnose lichen planus because it is a T-cell-mediated disease in which there are no autoantibodies or other specific markers to identify. However, biopsies also submitted in Michel's medium for direct immunofluorescence may be required to rule out other immune-based diseases such as pemphigus vulgaris and pemphigoid, which have a definitive direct immunofluorescence marker.

Histopathology

Lichen planus involves a cell-mediated immune reaction that damages epithelial basal cells. Langerhans cells are increased in number in lichen planus. These are the antigen-



presenting cells to which T cells respond and are consequently drawn into the area, forming a banded infiltrate subjacent to the epithelium. The infiltrate is typically well demarcated inferiorly, but it invades the epithelium, effacing the epithelial-connective tissue junction. The T cells are cytotoxic to the basal cells, which undergo vacuolation and destruction (liquefaction degeneration). Secondary to the loss of basal cells, melanin may be released into the connective tissue, where it is picked up by macrophages which then are termed melanophages. Known as melanin incontinence, this process is responsible for the frequent violaceous color that may be associated with lichen planus. The rete ridges lose their well-defined architecture and often appear to "melt" into the fibrous tissue. The epithelium also reacts to the assault, possibly through lymphocyte mediation, so that hyperkeratosis and/or hyperparakeratosis is seen with varying degrees of acanthosis and/or atrophy. Round to oval eosinophilic cells are frequently found in the lower epithelium or lamina propria. These represent necrotic epithelial cells and have been called Civatte bodies, colloid bodies, or apoptotic cells (Fig. 12.4).

The histologic features of lichen planus vary according to the age of the lesion. Following regeneration of the basal layer, a discrete eosinophilic band that separates the epithelium from the underlying lymphocytic infiltrate is often seen. Secondary to the destruction of basal cells, desquamation of the epithelium may occur (as in desquamative gingivitis) or a bulla may develop (as in bullous lichen planus). In erosive lichen planus, the inflammatory infiltrate is extremely dense and, because of the ulceration, more pleomorphic.

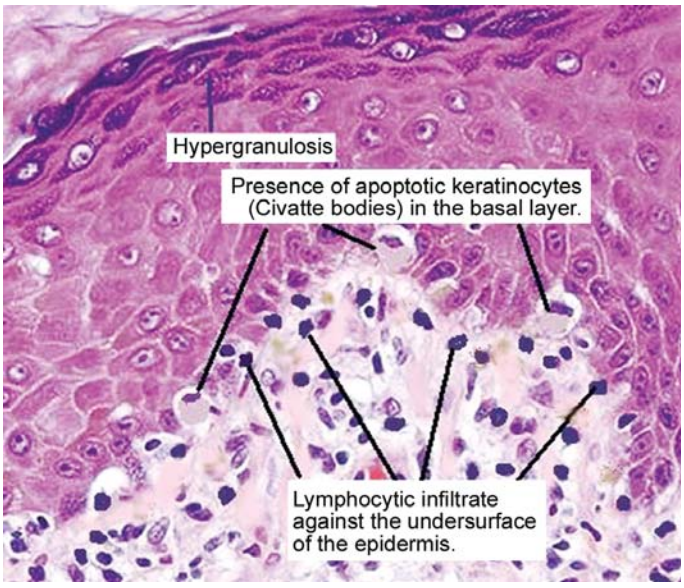


Fig. 12.4: Histology of lichen planus

Lichen planus does not produce a single definitive histologic picture and, depending on the stage, the changes may be nonspecific. Dysplastic disease can also be associated with banded lymphocytic infiltrates, which should not be construed as representing lichen planus. By means of direct immunofluorescence, fibrinogen may be demonstrated in the basement membrane zone, extending in little tags into the connective tissue. This is nonspecific and may be seen in other inflammatory conditions. The colloid apoptotic cells can also be demonstrated by direct immunofluorescence. They typically stain for IgM, but IgG, IgA, C3, and fibrin may also be seen. Although not unique to lichen planus, when seen in large numbers they are strongly suggestive of this disease.

Chronic ulcerative stomatitis is a condition that mimics lichen planus histologically. However, the immunopathologic picture is different. It is characterized by anti-nuclear antibodies directed against the stratified squamous epithelium. This can be demonstrated by both direct and indirect immunofluorescence. Significantly, this disease is not as responsive as lichen planus to corticosteroids but will respond to hydroxychlorquine (Plaquenil, Sanofi Winthrop).

Treatment

Reticular and plaque forms usually do not require treatment other than reassurance and follow-up. The milder cases of erosive lichen planus and some symptomatic cases of the other forms often can be managed with topical corticosteroids, usually 0.05% fluocinonide gel (Lidex gel, Medicis Dermatologics), four times daily, or combined with the antifungal agent griseofulvin (Fulvicin, Schering), 250 mg of the micronized form twice daily. The efficacy of this agent seems to be related to its side effect of promoting epithelial cell differentiation and maturity. Intralesional triamcinolone (Kenalog 0.5%), injected in 1-mL increments, may also be used for focal symptomatic areas.

Most erosive lichen planus requires systemic corticosteroid regimen I or II and only rarely IIIA or IIIB. Griseofulvin or topical fluocinonide can be added to either regimen to reduce the prednisone requirements or help maintain a remission.

Recently, some authors have suggested topical retinoids (isotretinoin), a vitamin A analog, for reticular lichen planus. However, almost all reticular lichen planus is asymptomatic and nonprogressive. In addition, the striae return if the drug is discontinued. Systemic retinoids have also been attempted, but their value is questionable owing to their minimal effect on the disease and significant side effects, such as increase of liver enzyme levels, hypercholesterolemia, hypertriglyceridemia, mucositis, mood changes, and possible teratogenicity.

Dapsone (diaminodiphenylsulfone) has been effective for mild cases of lichen planus involving skin. If used, the patient's serum should be tested for the presence of glucose-6-phosphate dehydrogenase (G6PD) because dapsone may precipitate a G6PD-deficiency hemolytic episode. Dapsone is given in a dose of 50 mg per day and may be continued for several weeks.

Prognosis

Erosive lichen planus responds well to systemic corticosteroids but not as completely as does pemphigus vulgaris or the various pemphigoids. A milder, residual clinical disease often persists and consequently a drug-free remission is less common than a maintenance-control remission. Often the disease can be suppressed with prednisone to a point at which topical fluocinonide and/or griseofulvin can maintain the remission without continued prednisone or with only a low, every other day prednisone schedule.

The premalignant potential of erosive lichen planus is now proven. Certainly there is a higher incidence of oral mucosal squamous cell carcinoma in patients with a history or a diagnosis of erosive lichen planus than in the general population. The transformation is uncommon (1% to 3%) and usually takes 15 years or more. Therefore, any erosive lichen planus that does not respond to therapy, especially prednisone, should be viewed with suspicion. These patients should undergo another biopsy. The original histopathology slides should be reviewed for subtle evidence of cellular atypia and the features of true lichen planus and then compared to the new slides.

PEMPHIGUS VULGARIS

Pemphigus vulgaris is a B cell-mediated autoimmune disease in which autoantibodies develop to antigens within the desmosome-tonofilament junction of the intercellular bridges. Such autoantibodies fix complement and initiate inflammation, which causes a suprabasilar split (intraepithelial blister) as the primary pathogenesis.

Clinical Presentation and Pathogenesis

Pemphigus vulgaris usually presents with painful skin and/or oral ulcers (Fig. 12.5). The lesions actually begin as short lived vesicles that rapidly rupture because of their suprabasilar position. Skin lesions will more likely show vesicles or even bullae because of the increased thickness of skin epithelium and a greater keratin layer as compared with mucosa. Many physician believe that pemphigus vulgaris is primarily a skin disease in which oral lesions precede skin lesions in 60% of cases. While this is correct, many patients will develop oral pemphigus lesions and no skin lesions. Such "oral pemphigus" represents a distinctive clinical form of pemphigus vulgaris. In this form, blacks are affected more frequently than are other races.

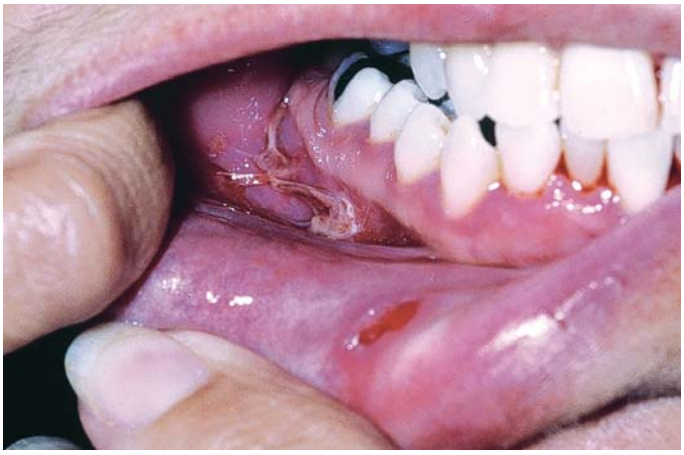


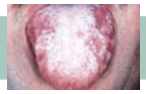
Fig. 12.5: Oral lesions in a patient with pemphigus vulgaris

With either clinical presentation, the oral lesions are particularly painful. They form on all oral mucosal sites and may exhibit a Nikolsky sign, which is not pathognomonic of pemphigus as it can be elicited in other mucocutaneous diseases such as erythema multiforme and bullous lichen planus. Nikolsky sign identifies a loss of mucosal cohesiveness.

The individual will often present with irritability from the pain, fever from secondary infection and dehydration, and cervical lymphadenitis from secondary infections of numerous oral ulcers. The individual may not be eating because of the pain and may appear listless from dehydration, hypoglycemia, and analgesic use.

Pemphigus vulgaris is the type associated with oral mucosal lesions. Pemphigus foliaceus and its variant pemphigus erythematosus occur only on skin and have no oral mucosal involvement. The specific antigen in pemphigus vulgaris is a glycoprotein found in the desmosomes of intercellular bridges. The specific antigen in pemphigus foliaceus is a complex of several desmosomal proteins called desmoglein I, which is more common in skin epithelium, hence the limitation of this form of pemphigus to skin.

The autoantibodies (IgG type) in pemphigus vulgaris (desmoglein III) degrade the desmosome by initiating the release of intracellular lysosomes and proteolytic enzymes, causing the squamous cells to separate from each other (acantholysis). As individual squamous cells lose their intercellular bridge connections to adjacent cells, they retract into rounded cells called acantholytic cells. This occurs mostly at the level just superficial to the basal cells. Once the vesicle forms, its superficial nature lends itself to rapid rupture, exposing the basal cell layer where the close proximity of free nerve endings and the fixation of complement initiate inflammation and pain.



Differential Diagnosis

The oral pemphigus presentation will include a subset of diseases that can produce painful oral lesions without concomitant skin lesions. The most common similar presentation is erosive lichen planus, which may be further confused with pemphigus vulgaris by its own tendency to form mucosal vesicles. However, lichen planus targets the dorsum of the tongue, buccal mucosa, and attached gingiva. Mild forms of pemphigus vulgaris may closely resemble pemphigoid. However, pemphigus does not usually produce a conjunctivitis, which is frequently present in pemphigoid cases, and pemphigus is much more painful than pemphigoid. A set of painful oral lesions with some vesicles is also consistent with the general picture of primary herpetic gingivostomatitis.

The presentation of pemphigus vulgaris that expresses vesicular skin lesions in addition to painful oral lesions includes a subset of diseases that present in both areas, including erythema multiforme. If the skin lesions show larger vesicles suggesting bullae (greater than 2 cm in diameter), a diagnosis of bullous pemphigoid should be considered. If the oral lesions are not especially painful and more prominent than the skin lesions, and if the individual is older than 50 years, pemphigoid becomes a realistic consideration. Bullous erosive lichen planus is another possibility, but lichen planus lesions of skin associated with bullous erosive lichen planus are rare and more pruritic than painful. They are also violet red, not the pale gray vesicles seen in pemphigus vulgaris.

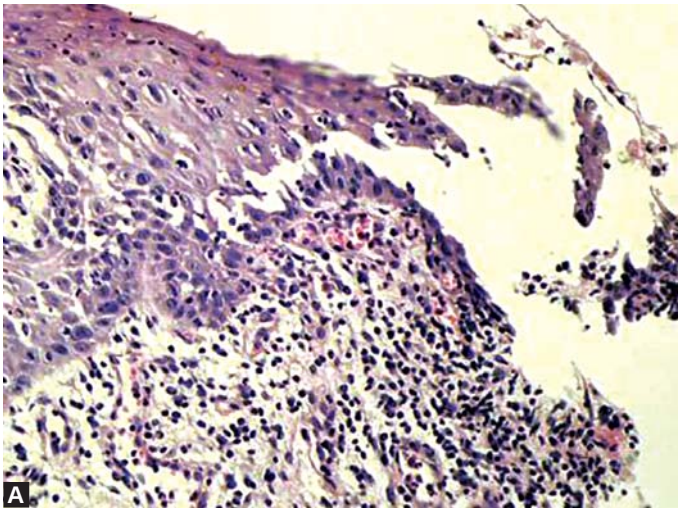
Diagnostic Work-up

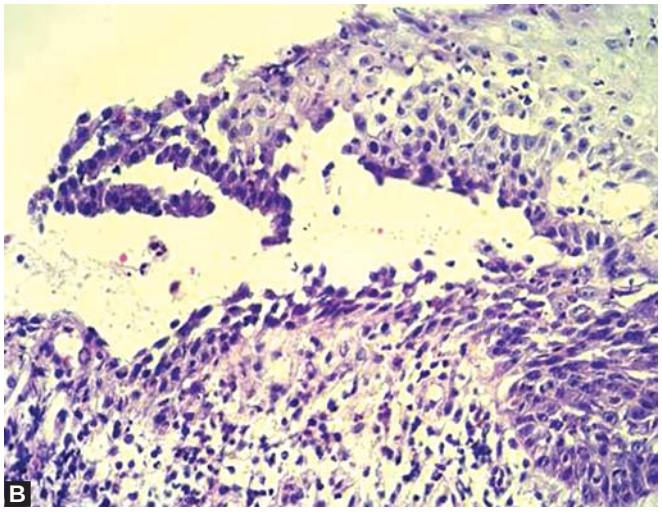
The diagnosis of pemphigus vulgaris is made from a mucosal or skin biopsy that includes tissue that appears clinically normal. The oral mucosa is the preferred biopsy site. The identifiable suprabasilar separation and acantholysis is seen best in such tissues. Biopsy in an ulcerated area may be misleading because it may not show the roof of a vesicle or it may be obscured by secondary inflammation and necrosis. Obtaining two biopsy specimens or one specimen separated into two equally representative pieces is ideal. One is placed into 10% neutral-buffered formalin for hematoxylin and eosin (H&E) staining, and the other in Michel's medium for possible direct immunofluorescence studies. Direct immunofluorescence is not required in unequivocal cases but will confirm or rule out the diagnosis when there is doubt. Alternatives to Michel's medium are freezing of the specimen with liquid nitrogen or direct immunofluorescence of the fresh specimen within 4 hours. Once a tissue specimen has been placed into formalin, direct immunofluorescence studies cannot be performed on that specimen.

Indirect immunofluorescence may be performed to assess the titer of circulating autoantibodies and is thought to be an index of disease severity against which to adjust treatment dosage.

Histopathology

The histopathologic features of pemphigus vulgaris reflect the action of the circulating antibody on the cell surface of the prickle cells and the consequent destruction of the desmosomes, which are responsible for maintaining the adhesion of these cells. Basal cells are attached to each other by desmosomes and can thus separate from each other. However, because they are attached to the basement membrane by hemidesmosomes, they are not affected in this area, and the basal cells do not separate from the basement membrane. With loss of epithelial adhesion, a bulla is formed. This is seen in a predominantly suprabasilar location because this is the area of greatest cellular activity (Figs 12.6A and B). Within the bulla,





Figs 12.6A and B: Pemphigus vulgaris. Suprabasal dyshesion reveals crispy delineated basal epithelial cells slightly separated from each other and totally separated from stratum spinosum. Hematoxilin-eosin, (A) × 180; (B) × 560

acantholytic cells are seen. These are the detached prickle cells that have lost their polyhedral shape and become rounded. The nucleus is typically larger and hyperchromatic. Acantholytic cells are crucial to the diagnosis. They can also be demonstrated by taking a cytologic smear of the contents of an unroofed bulla, a procedure for which Giemsa stain is usually used.

A feature that is often helpful diagnostically is the villous projections that may develop at the base of a bulla. When the surface epithelium ultimately separates, the mucosa will appear to have a surface of papillary projections lined by basal cells with some acantholytic cells. Once the bulla has ruptured, the underlying connective tissue becomes densely inflamed. The eosinophilic infiltrate often seen in the skin occurs infrequently in oral mucosa. Study of perilesional tissue by direct immunofluorescence demonstrates the presence of IgG antibodies intercellularly in almost all cases. Direct immunofluorescence may remain positive even when the patient is in prolonged remission. Indirect immunofluorescence can also be useful. Most patients will demonstrate circulating autoantibodies, and in this disease the antibody titer loosely correlates with disease severity.

Treatment

Oral pemphigus vulgaris responds well to systemic corticosteroid regimen I. Approximately 70% of pemphigus vulgaris with both oral and skin lesions also respond to systemic corticosteroid regimen I. The remaining 30% of cases of this type of pemphigus vulgaris respond incompletely to prednisone and require the addition of either cyclophosphamide (Cytoxan, Mead Johnson), 50 to 100 mg by mouth twice daily, or azathioprine (Imuran, Glaxo Wellcome), 50 to 100 mg by mouth twice daily, as in systemic corticosteroid regimen IIIB. In cases that remain refractory to this regimen, methotrexate, 25 mg per week, may be substituted for azathioprine, or plasmapheresis combined with azathioprine may be used as a method for reducing the corticosteroid dosage. In resistant or progressive cases or in cases in which the effects of long-term corticosteroids accumulate, dapsone, 100 mg per day, combined with either gold sodium thiomalate as used for rheumatoid arthritis or azathioprine or plasmapheresis, has also been used as a corticosteroid-sparing regimen.

Because patients will present with a recent history of a decreased oral intake and frequently secondary infection, it is often necessary first to provide hydration with intravenous fluids and to begin antibiotic therapy and pain control measures while the biopsy specimen is being processed. The clinician must resist the temptation to begin prednisone therapy before the diagnosis is confirmed. If corticosteroid therapy is initiated and the biopsy specimen is nondiagnostic, a second biopsy will have an altered tissue response, obscuring diagnosis and complicating treatment.

Prognosis

Untreated pemphigus vulgaris is usually fatal in 2 to 5 years. Treatment results in a residual 10% to 15% mortality rate at 15 years because of complications of long-term prednisone therapy and other immunosuppressive drugs. The most common cause of death is *Staphylococcus aureus* septicemia, which is often difficult to detect because of the immune suppression caused by concomitant corticosteroid therapy.

Oral pemphigus vulgaris is more responsive to therapy and has a much greater remission rate in patients either on maintenance therapy or in a drug free state. It also has a reduced mortality rate due to a more complete response to corticosteroid therapy and hence fewer complications.

PARANEOPLASTIC PEMPHIGUS

Clinical Presentation and Pathogenesis

The clinician should be aware that a severe clinical picture of pemphigus vulgaris can occasionally represent a complication of a malignancy. When this happens, the malignancy is usually a Hodgkin's lymphoma, a non Hodgkin's lymphoma, or a leukemia, but it can be associated with literally any malignancy and rarely a benign neoplasm. In such cases, numerous painful lesions develop on both the oral mucosa and the skin and are often evidence of an uncontrolled malignancy (Fig. 12.7). The course is usually rapid and fatal despite steroid and/or immunosuppressive therapy.

The mechanism of paraneoplastic pemphigus is thought to be a result of the neoplasm's ability to structurally alter normal epidermal proteins into antigenicity or to systemically secrete an antigenically similar protein to which autoantibodies develop and cross react with epidermal proteins. In either case, autoantibodies against epidermal desmoplakin I and II proteins are detected on skin biopsies by direct immunofluorescence and circulating in the serum by indirect immunofluorescence.

Histopathology

The histologic findings of paraneoplastic pemphigus are frequently a combination of pemphigus vulgaris and lichen planus. Suprabasilar separation of the epithelium with acantholysis can be seen in conjunction with vacuolization of basal cells, individual cell necrosis within the prickle cell layer, and a lymphoid infiltrate at the epithelial

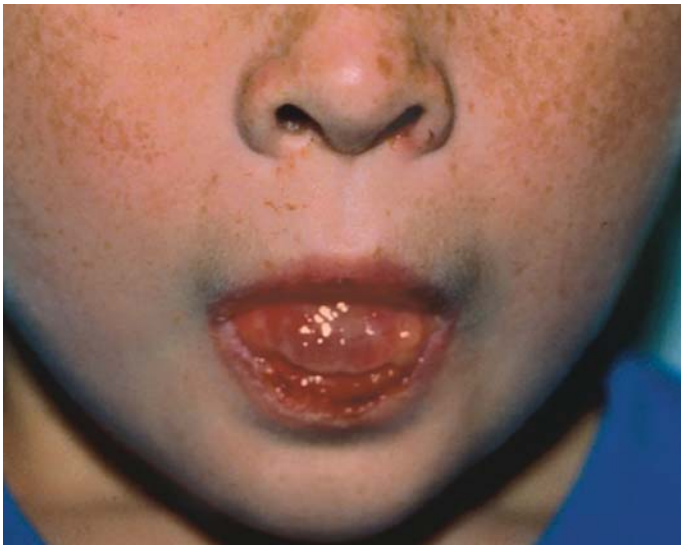


Fig. 12.7: Paraneoplastic pemphigus

connective tissue interface. In some cases, only one of these patterns will occur.

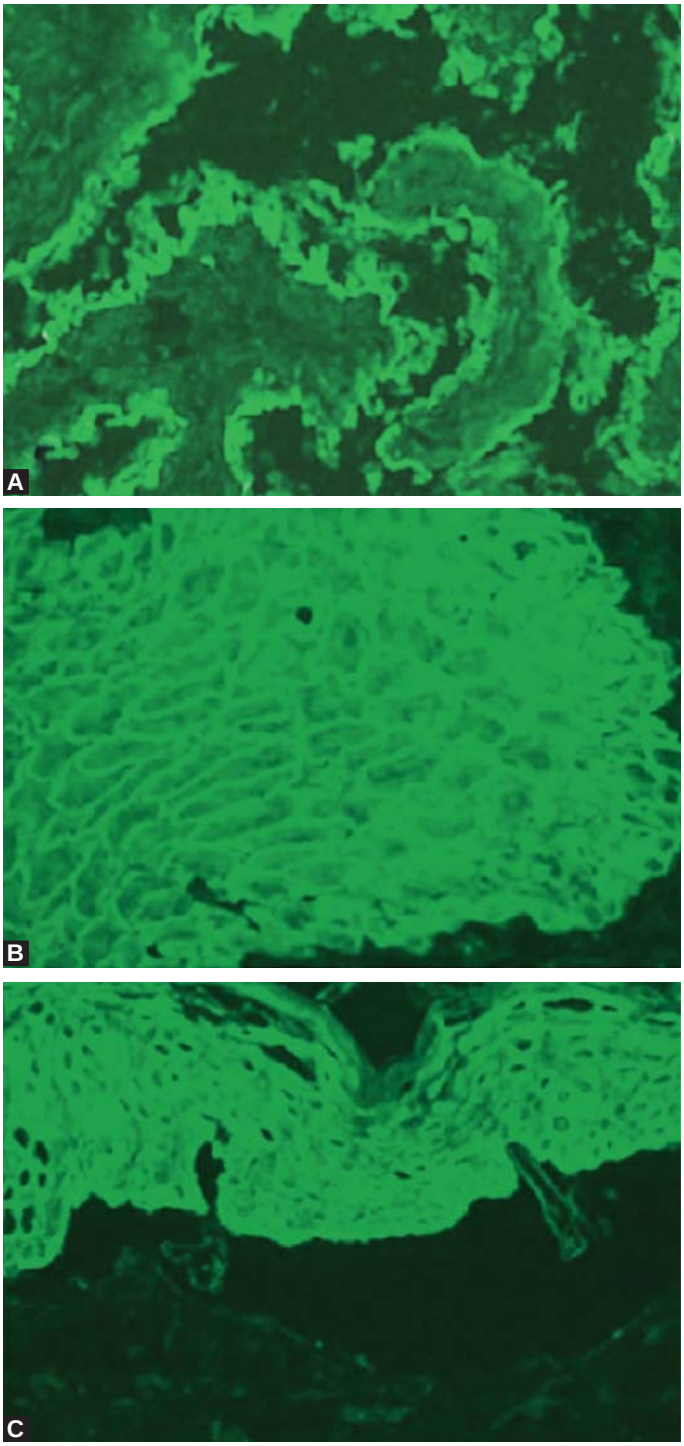
Direct immunofluorescence shows intercellular deposition of IgG and complement, but, in addition, a granular deposition of complement occurs at the basement membrane zone. Indirect immunofluorescence testing using rat bladder transitional epithelium is highly specific for this disease (Figs 12.8A, B and C). The antibodies react with 250-kD (desmoplakin I), 230-kD (BPAgI), 210-kD (desmoplakin II), and 90-kD proteins.

EPIDERMOLYSIS BULLOSA ACQUISITA

Clinical Presentation and Pathogenesis

Epidermolysis bullosa acquisita is another B cell mediated autoimmune disease that affects the basement membrane zone. Epidermolysis bullosa acquisita is the acquired or nonhereditary type of epidermolysis bullosa and should not be confused with the several hereditary types seen in children and caused by genetic defects in the basement membrane zone. Instead, epidermolysis bullosa acquisita is an IgG-mediated autoantibody disease that begins in mature to elderly adults.

Epidermolysis bullosa acquisita will present mostly with skin bullae and vesicles and only rarely with oral vesicles (Fig. 12.9). The skin bullae will be larger and more dominant. The bullae and vesicles are well known to emerge after minor trauma or simple skin contact. Patients will note skin fragility. The oral mucosa is equally fragile and, when involved, will form large hemorrhagic bullae, usually seen on the buccal mucosa. Both the skin and oral lesions will heal with scar formation.



Figs 12.8A to C: Indirect immunofluoresence assays, revealing cell surface staining of rodent bladder substrate with IgG (1:5 dilution; magnification: ×20) (A), staining of monkey esophagus substrate (serum, 1:20; magnification: ×40) (B), and staining of split-skin substrate (epidermis separated from dermis after NaCl incubation) (serum, 1:10; combined [epidermal and dermal] pattern; magnification: × 20). Epidermis and dermis correspond to top and bottom, respectively in (C)

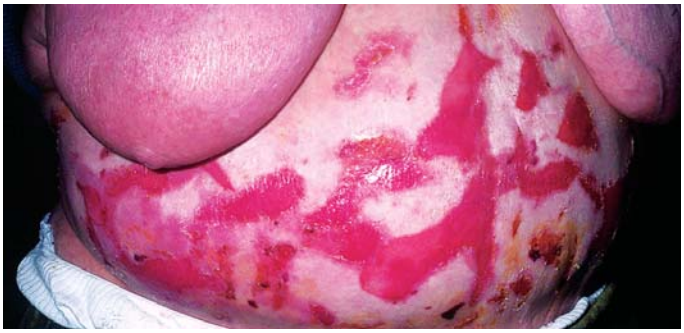


Fig. 12.9: Epidermolysis bullosa acquisita

Differential Diagnosis

Epidermolysis bullosa acquisita should not be confused with its hereditary counterpart, epidermolysis bullosa, because the former occurs exclusively in older adults, whereas the latter is seen in early childhood. However, cutaneous pemphigoid and cicatricial pemphigoid with some skin lesions will appear similar. In addition, pemphigus vulgaris may also form large skin bullae and oral vesicles. Because of the advanced age of most affected patients, a paraneoplastic pemphigus also bears some consideration.

Diagnostic Work-up

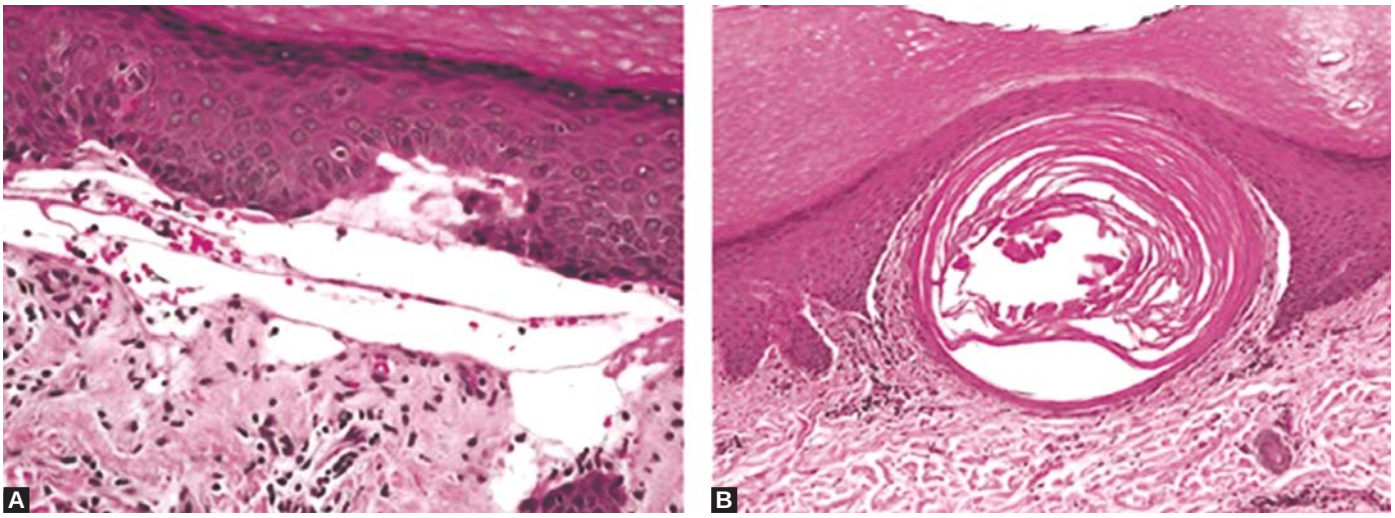
The disease may be anticipated by the age of the patient and the extreme fragility of both skin and mucosa; however, a biopsy either of mucosa or of skin is required to establish the diagnosis. The biopsy may include part of a vesicle, but it should also include adjacent normal appearing tissue. Routine formalin fixed H&E specimens and Michel's medium or frozen fixed direct immunofluorescence specimens are required for diagnosis.

Histopathology

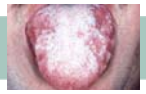
Bullae form below the basal lamina (Figs 12.10A and B). Some forms are non inflammatory, but more frequent is a lymphocytic and neutrophilic infiltrate that is perivascular and infiltrates the dermal papillae. Eosinophils may be present. By direct immunofluorescence, perilesional tissue will show linear deposits of IgG and complement at the basement membrane zone. Circulating IgG antibodies are seen in about 50% of cases. In this disease, antibody is directed to type VII collagen so that the anchoring fibrils are affected. Separation occurs in the upper lamina densa, so that the lamina densa is seen on the roof of the blister. While electron microscopy will be diagnostic, the use of salt split skin (skin biopsy treated with salt to effect a split within the basement membrane zone) for diagnosis is most helpful and distinguishes this condition from cutaneous pemphigoid. In epidermolysis bullosa acquisita, IgG is seen on the floor of the vesicle, whereas in cutaneous pemphigoid it is on the roof.

Treatment And Prognosis

Treatment responses are minimal. Although systemic corticosteroids with and without immunosuppressive drugs, as in the systemic corticosteroid regimens IIIA and IIIB, have been used, as have various chemotherapeutic agents often reserved for malignancies, the response is inconsistent and incomplete. Patients are, therefore, treated with adjusted doses of prednisone, dapsone, retinoids (such as Accutane, Roche), or beta carotene and further supported



Figs 12.10A and B: Epidermolysis bullosa acquisita: Histopathology reveals a subepidermal bulla with fibrin and a paucity of inflammatory cells



with protective clothing and an effort to avoid skin and mucosal friction or trauma.

EPIDERMOLYSIS BULLOSA

Clinical Presentation and Pathogenesis

Epidermolysis bullosa is a set of hereditary diseases that result in defective components of collagen and other proteins of the basement membrane zone. There are several inheritance patterns and, therefore, several clinical presentations, but each will have the general manifestation of skin, oral, and sometimes other mucosal vesicles and bullae. The five recognized types are epidermolysis bullosa simplex, epidermolysis bullosa simplex with muscular dystrophy, epidermolysis bullosa atrophicans generalisata graves, epidermolysis bullosa dominant dystrophic/hypertrophic form, and scarring epidermolysis bullosa with dermolytic vesicles.

Epidermolysis Bullosa Simplex

Epidermolysis bullosa simplex clinically presents in neonates and infants. The nails, feet, hands, and neck develop vesicles and small bullae, presumably in response to friction (Fig. 12.11). Oral vesicles are mild and small but do occur. The vesicles are located within the epithelium and, therefore, heal without scarring.

Epidermolysis Bullosa Simplex with Muscular Dystrophy

An autosomal recessive disorder, epidermolysis bullosa simplex with muscular dystrophy appears at birth with multiple bullae and frequently includes oral mucosa. Extremities seem to develop more numerous bullae, which result in scarring and eventuate into muscular dystrophy with deformity. The muscular dystrophy may not be noted at birth but will be noted later with weakness and reduced strength.

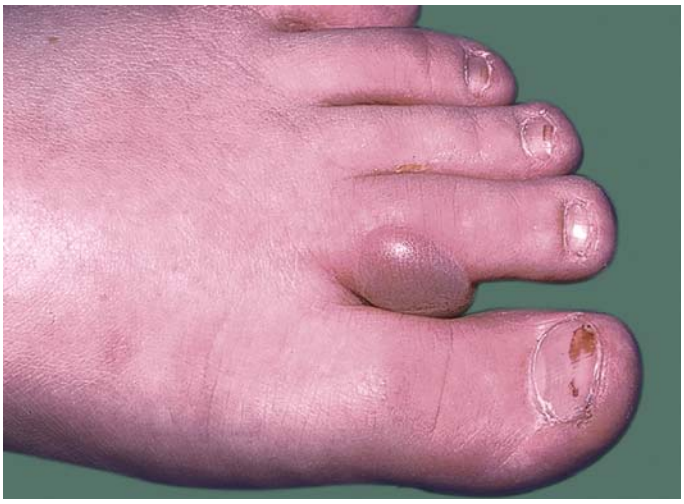


Fig. 12.11: Epidermolysis bullosa simplex

Epidermolysis Bullosa Atrophicans Generalisata Graves

A severe clinical disease expression of autosomal recessive inheritance, epidermolysis bullosa atrophicans generalisata graves develops in neonates within hours after birth and in infants. The nail beds are usually the first area of involvement; shedding of the nail is common. The remainder of the skin surface progressively develops bullae with the exception of the palms and soles. Many infants die within a few months. Survivors have nail distortion, growth retardation, anemia, scarring, and continued excoriated skin lesions. Oral lesions are found in almost all patients. Large, fragile vesicles and bullae are common, particularly on the posterior hard palate mucosa and soft palate. Teeth may be affected by enamel hypoplasia and enamel pits, leading to caries. Perioral hemorrhagic and crusting lesions around the alar base and commissures are particularly noted to develop between 6 and 12 months of age.

Epidermolysis Bullosa Dominant Dystrophic/Hypertrophic Form

The dominant dystrophic/hypertrophic form of epidermolysis bullosa is a mild form of autosomal dominant inheritance. It does not appear at birth, and only 20% of individuals develop manifestations before 1 year of age. Once vesicles or bullae begin to develop, they will gradually lessen with age. This type of epidermolysis bullosa is noted for scar formation. After bullae heal, they develop characteristically thick scars. Dystrophic nails also will develop. In addition, scarring of the skin at prominent areas of occurrence, such as the ankles, knees, hands, and elbows, will produce a thick skin pad in these locations (Fig. 12.12). Teeth are not affected by this form of epidermolysis bullosa, but thick white mucosal pads and white mucosal epithelial inclusion cysts may be seen on the tongue, buccal mucosa, and palatal mucosa.

Scarring Epidermolysis Bullosa with Dermolytic Vesicles

Scarring epidermolysis bullosa with dermolytic vesicles is autosomal recessive. It appears shortly after birth with skin bullae on the feet, fingers, buttocks, back, and occiput. Slight trauma or friction provokes bullae as it does in all forms of epidermolysis bullosa. This form seems to be somewhat more painful than most others and forms significant scarring, even keloid-like scars in some cases. This is thought to be caused by the deeper level of bullae formation, essentially on the dermal side of the basement membrane zone.

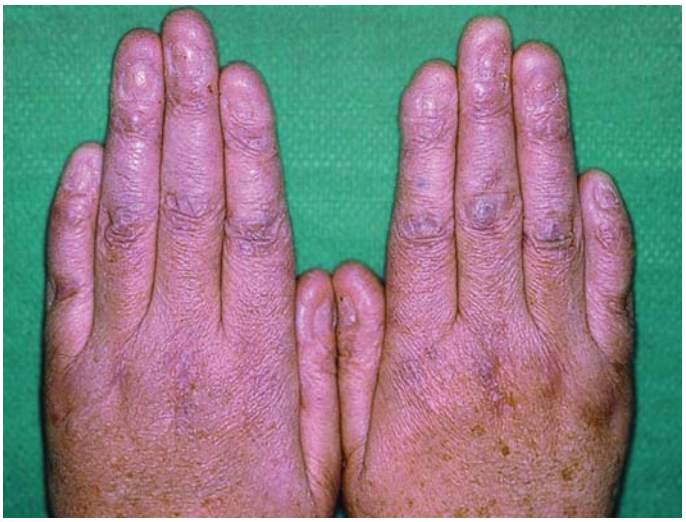


Fig. 12.12: Epidermolysis bullosa dominant dystrophic type

Oral vesicles develop with the skin bullae and are just as prone to scar formation. Ankyloglossia or mucogingival scar bands in the vestibule may result. Commissures may develop scarring as well, causing a restriction of opening similar to that seen in scleroderma. Teeth will demonstrate pits and enamel hypoplasia, leading to caries.

Differential Diagnosis

Epidermolysis bullosa is highly suggested by its familial inheritance, age of onset, and clinical picture. Only a few serious considerations on a differential diagnosis are warranted, including bullous impetigo, dermatitis herpetiformis, pemphigus vulgaris, and erythema multiforme. Any of these may form significant bullae and cause scar formation and may occur in infants and young children.

Diagnostic Work-up

The diagnosis of epidermolysis bullosa is mostly by history and clinical presentation. However, a biopsy of a vesicle and adjacent normal tissue is needed to rule out specific autoimmune based diseases such as pemphigus and to assess for the ultrastructural changes associated with some of the epidermolysis bullosa types. Therefore, the clinician should plan for a sufficient specimen size and prepare it for routine H&E sections, direct immunofluorescence and electron microscopy.

Histopathology

The light microscopic findings of these diseases are nonspecific. They are all characterized by subepidermal bullae, which initially show little inflammation (Fig. 12.13). Precise diagnosis requires electron microscopy and immunofluorescence mapping. From a histopathologic perspective, three types are recognized and will relate to certain clinical types:

Types

Epidermal Type

Separation occurs through the basal cell layer. There is intracellular edema below the nuclei with subsequent vacuolation and disruption of the plasma membrane of the basal cell. This is seen in the simplex types.

Junctional Type

Separation occurs in the lamina lucida, secondary to decreased numbers of hemidesmosomes and abnormal hemidesmosomes due to poorly developed attachment plaques and sub-basal dense plates. Affected teeth show abnormal enamel formation. The initial layer of enamel matrix is laminated, but the remainder is globular. The underlying problem is akin to that occuring in the skin, as vesicles form between the ameloblasts and the odontoblasts with the basement membrane remaining attached to the odontoblasts. It appears that ameloblasts develop normally or until the time of dentin formation when the cells form a little enamel matrix and then undergo squamous metaplasia. The dentin surface is irregular but not otherwise affected. This type is seen in epidermolysis bullosa atrophicans generalisata graves and the dominant dystrophic/hypertrophic types.

Dermal Type

Separation occurs deep to the lamina densa where the anchoring fibrils appear rudimentary and are decreased in number in both lesional and non-lesional tissue. In addition, fibroblasts form excessive amounts of collagenase, and a defect of a lamina densa protein has been noted. Dental findings are similar to those in the junctional form with enamel hypoplasia due to absence of the enamel's normal prismatic structure. Overproduction of poorly calcified cementum has also been described. This type is seen in the scarring types of epidermolysis bullosa.

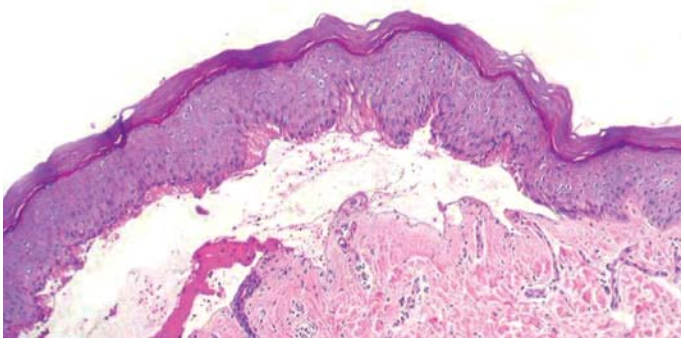


Fig. 12.13: Histology of epidermolysis bullosa showing subepithelial bullae

Immunomapping

Immunomapping requires fresh, artificially induced blisters, such as suction blisters, as these are devoid of secondary changes. Cryostat sections of the tissue are then exposed to specific antisera against type IV collagen (found in the lamina densa and basal lamina), laminin (in the lower lamina lucida), and cutaneous pemphigoid antigen (BPAg) (in the upper lamina lucida). In the epidermal form, all antigens are at the base of the blister. In the junctional form, type IV collagen and laminin are on the floor, and BPAg is on the roof. In the dermal form, all of these antigens are on the roof.

Treatment

Treatment is frustrating for the patient and clinician because at this time no treatment can alter the defective basement membrane zone proteins, which are produced by mutations in specific genes. Because these epidermolysis bullosa types are not autoimmune diseases, as is epidermolysis bullosa acquisita, systemic corticosteroids are not as effective. Systemic corticosteroid regimens such as regimen I, IIIA, and IIIB are used, but they only reduce secondary inflammation and scarring and do not alter the course of the disease. In addition, dapsone, 50 to 100 mg per day; retinoic acid A, 30 to 60 mg per day; and beta carotene, 30 mg four times per day, may also have some beneficial results.

PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA) AND THE CREST SYNDROME

Clinical Presentation and Pathogenesis

Progressive systemic sclerosis (PSS) is an autoimmune disease that produces systemic cellular damage focused on connective tissues that leads to fibrosis in the dermis of the skin and in internal organs. Like any autoimmune disease, it results from a cellular component that becomes antigenic. In the case of scleroderma, one or several ribonucleic proteins, most commonly (55%) the SCL-70 protein, is the antigenic focus. In a milder PSS variant of scleroderma known as the CREST (calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasias) syndrome, the cytoplasmic organelle, the centromere, is the antigen. Because several different antigenic nuclear proteins may be involved, some of which may stimulate a more intense antibody response than others, a spectrum of severity ranging from localized sclerosis to CREST syndrome to widespread systemic sclerosis to a rapidly progressive and fatal systemic sclerosis is to be expected.

Localized Systemic Sclerosis

This milder variant is limited to the skin and will involve one side more than the other. Women are affected more than men (4:1). Although this variant does not include all of the components of the CREST variant, Raynaud phenomenon is an early finding or one that may precede skin involvement. The skin involvement will be in either plaque or linear form.

CREST Syndrome

The CREST syndrome is a less progressive, lifelong, chronic form of PSS. Individuals with the CREST variant may show radiographically apparent calcification (calcinosis) at the finger tips (Fig. 12.14) or in the subcutaneous tissues over the bony prominences of the femur, the iliac crest the elbows, or the knees. Raynaud phenomenon is present in almost all forms of PSS, and the CREST variant is no exception.

Raynaud phenomenon is a vasospastic response brought on by cold. It is the initial clinical manifestation of all forms of PSS in 50% of cases. It can be brought about by immersing the individual's hands in cold water. Raynaud phenomenon occurs in three stages: the first is pallor (white), which is due to vasospasms that are painful and paresthetic; the second is cyanosis (blue), which heralds relaxation of the vasospasm and is caused by pooling of venous blood; and the third is hyperemia (red), in which the relaxation of the vasospasm creates a reactive hyperemia that actually represents a mild reperfusion injury. Because the red, white, and blue are often seen together, Raynaud phenomenon is known as the "patriotic sign".

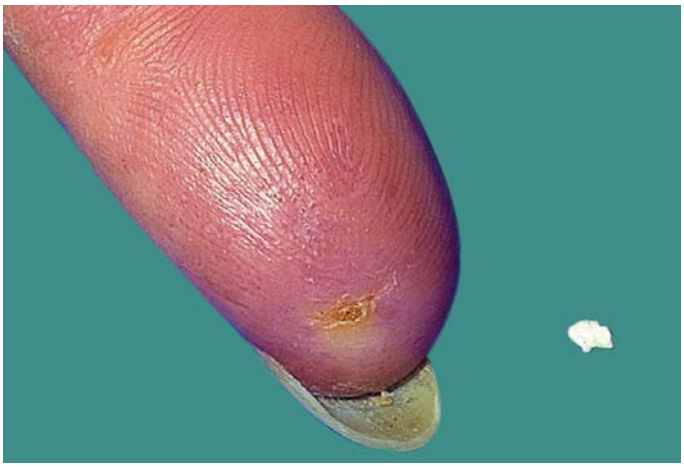


Fig. 12.14: Calcinosis is one of the typical features of CREST syndrome. Occasionally, calcified material may be transepidermally eliminated from dystrophic fingertip skin, as shown in this case

Esophageal hypomotility is caused by fibrosis and atrophy of the smooth muscles of the entire gastrointestinal tract. The esophageal involvement is most easily recognized, however, and often requires nasogastric or gastrostomy tube feedings.

Sclerodactyly is the dermal fibrosis involving the skin around each finger, causing the finger to appear narrow and pointed. The fingertips may be narrowed with ulcerations or loss of the nail. The skin will be noticeably tight and telangiectasias on the skin of the fingers are common.

Telangiectasias in the CREST variant have a unique morphology (Fig. 12.15). They are flat and mat like with irregular edges. They are most commonly seen on the skin of the hands, fingers, face, and back and on the mucosa of the tongue and lips. Like all true telangiectasias, they do not blanch.

Diffuse Progressive Systemic Sclerosis

The diffuse type of PSS is the form previously referred to as scleroderma. This type is diagnosed by the clinical identification of either one major criteria or two or more minor criteria as defined by the American Rheumatism Association. The single major criterion, proximal sclerosis, is sclerosis proximal to the knees and elbows. Minor criteria include sclerodactyly, loss of finger pads or pitting of the fingertips, and pulmonary fibrosis.

Diffuse PSS will initially present with either Raynaud phenomenon or a thickening of the skin on the hands and fingers (Fig. 12.16). Nonspecific joint pains, weakness, weight loss, and muscle aches may also be seen. As the disease progresses, more obvious signs develop. The skin becomes overtly firm and bound down and possibly hyperpigmented. In addition, hair loss and dryness of the skin will develop because of fibrosis around skin appendages. The fingers and wrists may eventually undergo a flexion deformity resulting from a greater quantity of muscle and tendon in the flexors versus the extensors. The oral and maxillofacial specialist may observe a somewhat limited mouth opening due to tightness at the commissures and a stiff, thin lip quality. Radiographs may show a symmetric widening of the periodontal membrane space or bony resorption at the angle and posterior ramus. This resorptive pattern has been termed the "tail of the whale" deformity because the thinned ramus resembles the base of a whale's tail and the condyle and coronoid process resemble the flutes of the tail. In addition, fibrosis often produces a retrognathia of the mandible and an absolute transverse deficiency in the maxilla. The overall appearance will usually be that of a skeletal Class II with a high arched palate.

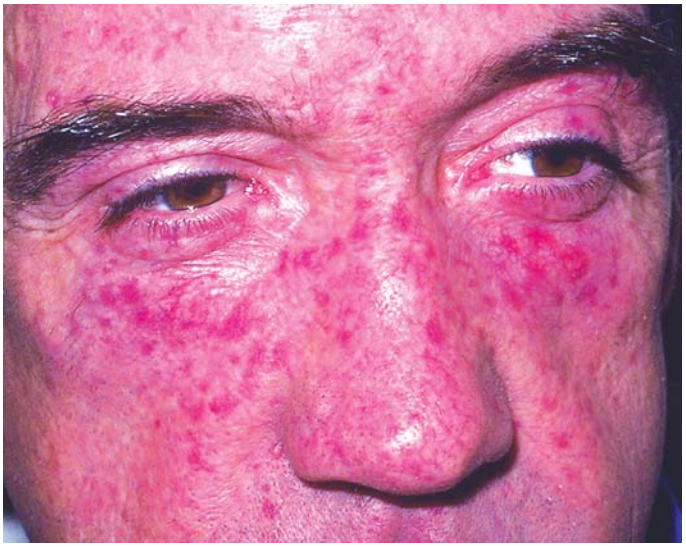


Fig. 12.15: CREST syndrome with telangiectasia of the face

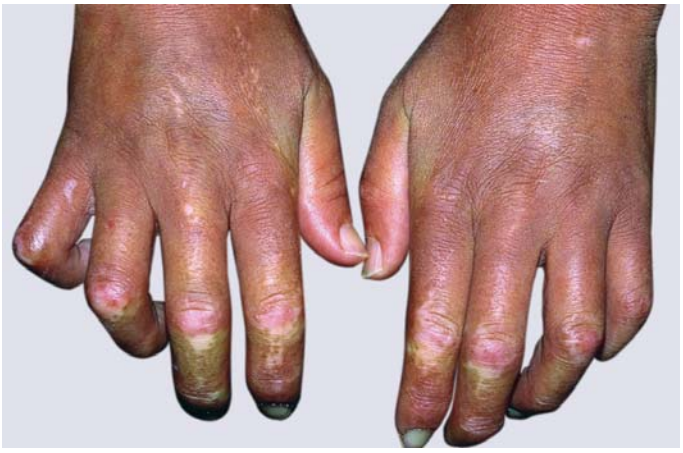
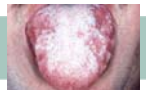


Fig. 12.16: Digital ulceration may occur in CREST or systemic sclerosis, may affect either the skin over joints or the finger pulps, and often leads to further tightness and pigment change if it heals

Differential Diagnosis

Progressive systemic sclerosis and its variants are difficult to diagnose in their early stages but become more apparent as the disease develops. If Raynaud phenomenon is the first manifestation, similar autoimmune diseases such as systemic lupus erythematosus, Sjögren syndrome, and mixed connective tissue disease would be considered. If nonspecific arthralgias, muscles aches, and thickening of the skin are the first signs, Hashimoto thyroiditis, eosinophilic fasciitis, dermatomyositis, and chemical induced scleroderma like conditions would be the considerations. Agents such as bleomycin, pentazocine, and vinyl chloride produce significant fibrosis, which may mimic scleroderma. In the CREST variant, the



telangiectasias may initially mimic hereditary hemorrhagic telangiectasia, and the esophageal hypomotility may mimic Plummer-Vinson syndrome.

Diagnostic Work-up

The work-up should include a physical examination guided by knowledge of the manifestations of PSS. Once all positive physical findings are noted, a panoramic radiograph, a chest radiograph, a barium swallow, an arterial blood gas, pulmonary function tests, a serum creatinine, and antibody tests for the general antinuclear antibody (ANA) as well as the more specific SCL-70 and anti-centromere antibody are recommended. A panoramic radiograph may identify widened periodontal membrane spaces and angle resorption. The chest radiograph is needed to assess for pulmonary fibrosis, which will be confirmed by the arterial blood gas and pulmonary function tests. In PSS, the vital capacity is often < 50% of predicted and the PaO_2 < 70 mm Hg. The barium swallow will identify esophageal hypomotility. The creatinine will assess for possible renal fibrosis. The ANA is positive in 96% of PSS cases and the anti-centromere antibody test is positive in 96% of the CREST variants. The SCL-70 antibody is positive in 55% of PSS cases.

Histopathology

Within the skin, there is initial edema, which is followed by induration due to an increase in collagen deposition within the reticular dermis. This is accompanied by a thinning of the epidermis with loss of rete ridges and atrophy of dermal appendages. Mild mononuclear T - cell infiltrates occur within the subcutaneous tissue and around vessels. Hyalinization and obliteration of arterioles may be seen. Within the collagen, calcific deposits may form. Similar changes can be seen in other organ systems. Vascular changes are prominent in the kidney with luminal narrowing and fibrosis. The lungs show diffuse interstitial fibrosis, and the esophagus may undergo atrophy of smooth muscle with fibrosis. Interstitial fibrosis and acinar atrophy may also affect salivary glands.

Treatment and Prognosis

There are few effective therapies to reverse or even significantly slow the progress of PSS. Like most autoimmune diseases, PSS will progress at a predetermined rate. Those with early and progressive internal organ involvement of the lungs, heart, or kidneys succumb to the disease often in their 30s or 40s. Most individuals with more slowly progressive PSS live into their 60s and 70s. In the past, attempts to halt the progression with steroids, azathioprine, chlorambucil, cyclophosphamide, and colchicine have proven ineffective. However, penicillamine, which blocks the cross-linking in collagen synthesis in dosages of 500 to 1500 mg per day, has some therapeutic benefit. It reduces skin thickness and slows the progression of internal fibrosis. As part of the overall management of PSS, physical therapy to maintain joint motion and mouth opening is recommended. The oral and maxillofacial specialist should not hesitate to prescribe such physical therapy as well devices such as the Therabite (Therabite) to resist further limitation of jaw opening. The oral and maxillofacial surgeon also may be called upon to accomplish a bilateral commissurotomy to improve jaw opening. Such surgery can be accomplished without wound healing complications and the need for hyperbaric oxygen, although it will not increase the absolute interincisal opening. This is due to the fibrosis, which is not only within the commissures but also within the buccinator, cheek, and pterygomasseteric sling.

KAWASAKI DISEASE (MUCOCUTANEOUS LYMPH NODE SYNDROME)

Kawasaki disease is a complex of clinical signs and symptoms in which mucocutaneous lesions and cervical lymphadenopathy are the two central findings and are often responsible for bringing it to the attention of the oral and maxillofacial specialist.

Although the syndrome suggests a bacterial etiology, none has been found. Its mechanism is thought to be related to a subtle staphylococcal infection or colonization. This produces an exotoxin, which in turn acts as a potent antigen. This toxin antigen subsequently stimulates a profound T cell response that produces the observed signs and symptoms of the syndrome.

Clinical Presentation

Kawasaki syndrome is most often seen in children younger than 10 years and of Asian heritage. Occasionally adults and rarely non-Asian children are seen with Kawasaki syndrome. Fever is the most common finding combined with a variable mucous membrane presentation of inflamed tongue (the so-called strawberry tongue) (Fig. 12.17), pharyngitis, cracked and fissured lips (Fig. 12.18), and bilateral nonsuppurative conjunctivitis. The cervical lymphadenopathy is mildly tender with multiple palpable lymph nodes of about 1.5 cm. These findings are coupled with extremity signs consisting of either edema, erythema, and/or a desquamation of skin.

The most serious complication of Kawasaki syndrome is coronary arteritis, which occurs in 25% of untreated cases. This has caused coronary artery aneurysms and even myocardial infarction in children, making Kawasaki

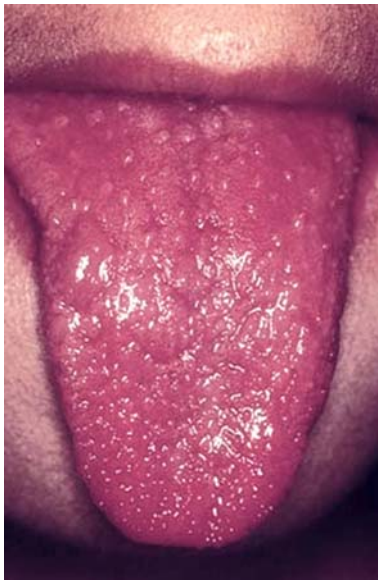


Fig. 12.17: Kawasaki disease- The 'strawberry' appearance of the tongue at presentation

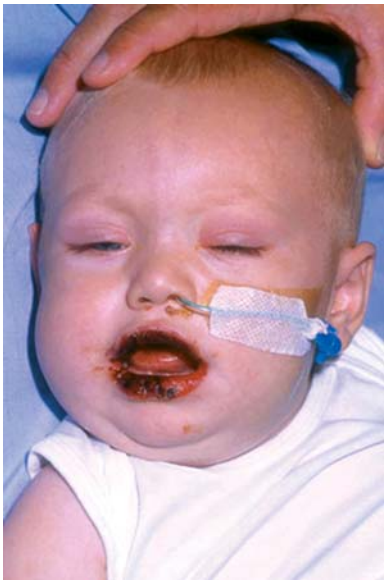


Fig. 12.18: Kawasaki disease with lip involvement

syndrome one of the more common causes of acquired pediatric heart disease in the United States.

Differential Diagnosis

The presentation of oral mucosal infections, fever, pharyngitis, and cervical lymphadenitis is suggestive of several specific diseases such as streptococcal pharyngitis, diphtheria, and infectious mononucleosis. In addition, HIV-related lymphadenopathy and tuberculosis lymphadenitis in an HIV-positive child are considerations in certain individuals. Once extremity signs or symptoms related to coronary arteritis such as chest pain and tachycardia develop, a serious consideration for rheumatic fever is warranted. Mild cases will mimic nonspecific viral influenza.

Diagnostic Work-up

The diagnosis of Kawasaki syndrome is made by the clinical correlation of signs and symptoms and only after rheumatic fever and streptococcal pharyngitis have been ruled out. Therefore, throat cultures are recommended with a specific attention to group D hemolytic streptococci. Otherwise, a complete blood count with a differential white blood cell count and c-reactive protein are recommended. Kawasaki syndrome usually will be associated with leukocytosis and an elevated c-reactive protein. In cases where extremity involvement is significant or oral/pharyngeal lesions are severe, a cerebrospinal fluid test will reveal a leukocytosis.

Histopathology

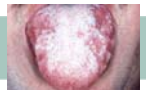
Mucocutaneous lesions show only a nonspecific perivascular infiltration of lymphocytes and histiocytes. The cutaneous lesions show changes similar to those found in polyarteritis nodosa, including a panarteritis and perivascular infiltrates of neutrophils. The lymph nodes may show localized necrosis, small thrombi, and inflammation of small vessels with a proliferation of immunoblast like cells around postcapillary venules.

Treatment

The management of Kawasaki syndrome has focused on reducing the fever and the inflammation. This is usually accomplished with aspirin, 80 to 100 mg/kg per day in divided doses, coupled with intravenous immune globulin in high doses. In refractory cases, plasmapheresis is used. Corticosteroids are not recommended to treat Kawasaki syndrome because of the fear of further weakening coronary artery walls and thus increasing the likelihood for coronary artery aneurysms or worsening those already present. In rare cases where coronary artery aneurysms obtain a size of 6.5 mm or larger, anticoagulation with Coumadin (DuPont) is recommended.

Prognosis

Prompt recognition and treatment leads to recovery without sequelae. However, uncommon refractory cases or those left untreated can lead to severe cardiac disabilities and even death.



DERMATITIS HERPETIFORMIS

Clinical Presentation and Pathogenesis

Dermatitis herpetiformis is a papulovesicular disease associated with gluten hypersensitivity. Eighty five percent of affected individuals have a gluten- sensitive enteropathy associated with very pruritic skin lesions. The skin lesions are broad areas seen most commonly on the knees, elbows, buttocks, posterior neck, and scalp. The disease has only rare oral involvement. When it does, the lesions appear as discrete vesicles on the palate or buccal mucosa (Fig. 12.19).

The disease process is not herpes related; it derives its name from the appearance of the skin lesions, which resemble those seen in herpes zoster. The pathogenesis relates to IgA antibody production, which collects at and apparently produces inflammation around the dermal papillae. The collections of IgA are granular-focal as opposed to the linear IgA disease or those seen at the basement membrane zone in the spectrum of pemphigoid diseases. The role of gluten may involve the inducement of antigluten antibodies, which become fixed to gluten attached to gut mucosa and the dermal papillae, or perhaps gluten-altered intestinal permeability, which allows other dietary products to enter the circulation as larger molecules and therefore become antigenic.

Differential Diagnosis

Skin lesions closely resemble psoriasis and skin lichen planus because of their broad crusty papules and pruritus. Their raised nature and distinctive rolled borders may also suggest sarcoidosis. Because of the pruritus and redness of the lesions, the erythrodermic stage of the cutaneous lymphoma mycosis fungoides is a concern. Early cases may seem to arise over a single dermatome. Because the clinical lesion resembles a herpes skin eruption (hence its name), herpes zoster becomes a consideration.

Diagnostic Work-up

Dermatitis herpetiformis can be distinguished from all of the other entities on the differential diagnosis by a direct immunofluorescence biopsy. A representative biopsy specimen of the lesion's edge, along with clinically normal appearing skin, is diagnostic. Unlike several other immune-based diseases, such as pemphigus vulgaris and cicatricial pemphigoid, in which direct immunofluorescence is optional and required only in equivocal cases, direct immunofluorescence is required in all cases suggestive of dermatitis herpetiformis. Therefore, biopsy specimens should be sent both in 10% neutral-buffered formalin for routine H&E slides and in Michel's medium for direct immunofluorescence. As an alternative to Michel's medium, the tissue specimen can be frozen with liquid nitrogen or sent fresh within 4 hours. Because circulating anti-endomysium antibodies can be detected in all cases of dermatitis herpetiformis, this should be tested if the laboratory has that capability.

Histopathology

The early erythematous lesions of dermatitis herpetiformis show an infiltrate of neutrophils in the tips of connective tissue papillae (Fig. 12.20). These develop into microabscesses, and an influx of eosinophils ensues. Vesicles form as separation occurs over the tips of the papillae. Initially multilocular, the lesion becomes unilocular as the separation widens. The deeper tissue contains perivascular in filtrates of mononuclear cells. Early lesions show that separation occurs above the lamina lucida, but that in more advanced lesions there is destruction of the lamina densa. By means of direct immunofluorescence, IgA may be demonstrated in the basement membrane zone, usually in a granular pattern over the tips of the papillae, although deposits may occur throughout the papilla. This may be

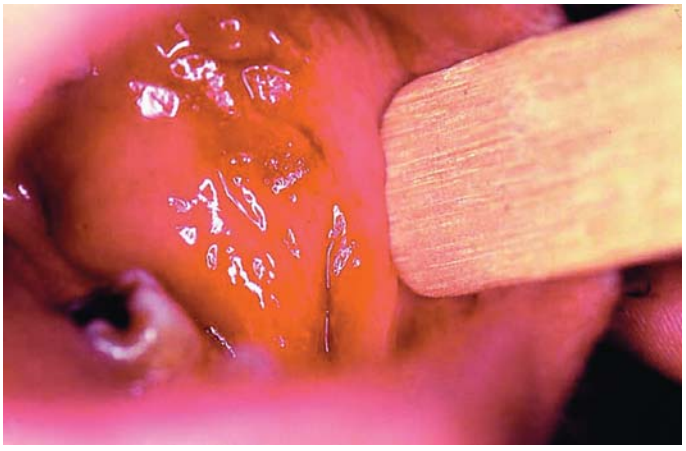


Fig. 12.19: Dermatitis herpetiformis rarely affects the mouth; when it does, lesion is generally purpuric

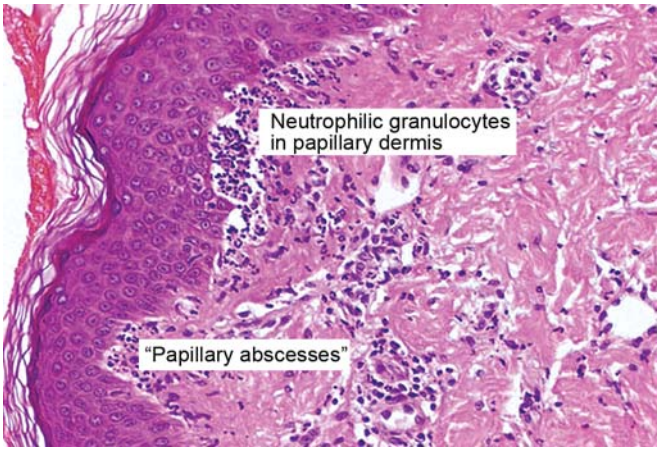


Fig. 12.20: Histology of dermatitis herpetiformis

seen in both lesional and nonlesional tissue. Circulating IgA antibodies may be present.

The enteric component involves the jejunum with atrophy of villi and lymphocytic infiltration of the epithelium.

Treatment

Both the enteropathy and the skin lesions resolve when a gluten-free diet has been followed for 4 to 36 months and will recur if gluten is reintroduced. The skin lesions respond well to drug therapy, but the enteropathy does not. The drug of choice is either dapsone, 100 mg per day (range, 50 to 400 mg per day), or sulfadiazine, 500 mg twice per day (range, 500 to 1,000 mg per day). With the use of either of these, most if not all of the skin lesions will resolve. Dapsone is the treatment of choice if the patient can tolerate it. In the 22% who develop side effects, or in the elderly patients who develop dapsone-induced hemolysis, sulfamethoxypyridazine is the drug of choice.

Prognosis

Disease control with diet alone and/or diet and drugs is excellent. Diet control is ideal because it is the only known means of controlling the small bowel changes. However, because an absolutely gluten-free diet is difficult to maintain, most patients require intermittent drug therapy.

DERMATOMYOSITIS

Clinical Presentation and Pathogenesis

Dermatomyositis is a disease of unknown etiology, but probably represents an autoimmune disease of striated muscle. It produces inflammation followed by degenerative changes in the larger (proximal) muscles first, followed by weakness in all muscle groups. Women are affected twice as commonly as men, and it is found in individuals of all ages. Initial symptoms are weakness at the pelvis or shoulder girdle areas. Patients may not be able to rise from a sitting position or lift their arms above their head. Pain is usually not a significant part of the presentation although mild discomfort does occur.

A skin rash that is characteristically dusky red may mimic the butterfly rash more commonly associated with either type of lupus erythematosus (Fig. 12.21). A periorbital purplish edema over the upper eyelids is characteristic (Fig. 12.22), as are scaly patches, called Gottron sign (Fig. 12.23), over the dorsum of the proximal interphalangeal and metacarpophalangeal joints. The skin rash usually precedes the development of muscle weakness.

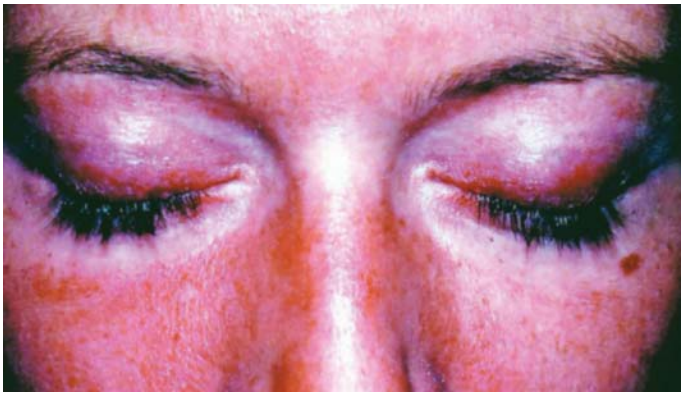


Fig. 12.21: Dermatomyositis showing the violaceous heliotrope rash, in these cases predominantly affecting the upper eyelid

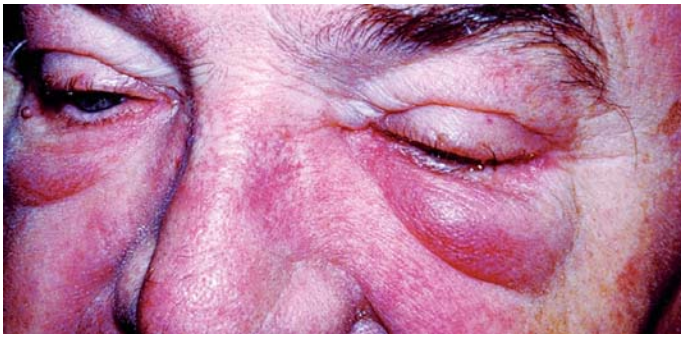


Fig. 12.22: Eyelid edema may be an early and dramatic sign in dermatomyositis

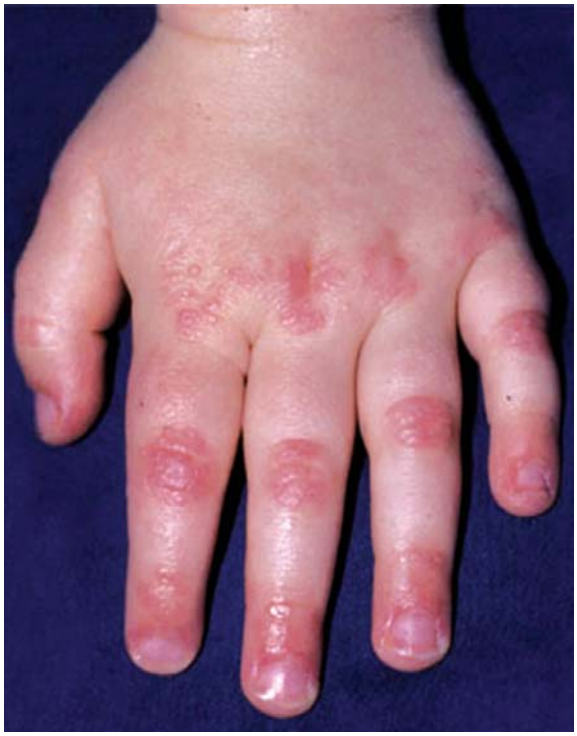


Fig. 12.23: Gottron's papules

In the oral and maxillofacial area, the flexor muscles of the neck are especially weakened, leading to an upward facial gaze. Involvement of the pharyngeal and esophageal musculature often leads to dysphagia and silent regurgitation. Laryngeal muscle weakness will produce a coarse or raspy voice.

Dermatomyositis is a combined cell-mediated and humoral immune-based disease. The specific antigen or stimulus remains unknown. There is a noted association with malignancy and it tends to precede infection, which implies either that it may offer the immune system an antigen similar to a muscle component or that it may alter a normal muscle component to make it antigenic. In either case, the full array of inflammatory cells proceed to degrade muscle fibers, producing clinical fatigue and decreased strength. If and when cardiac muscle is attacked, the prognosis dramatically worsens because arrhythmias and heart blocks develop.

Differential Diagnosis

Like dermatomyositis, both hypothyroidism and hyperthyroidism are noted for muscle weakness together with elevated levels of creatinine phosphate kinase (CPK). Careful examination of the type, distribution, and character of the skin rash will, however, distinguish dermatomyositis from either of the two. Multiple sclerosis and myasthenia gravis are also known for muscle weakness but will have a distinctly different electromyographic pattern from that of dermatomyositis. Additionally, many drugs, including alcohol, glucocorticoids, and penicillamine, can produce a drug induced polymyositis. In particular, HIV-infected individuals on zidovudine (AZT) frequently develop a polymyositis.

Diagnostic Work-up

Four components should be included in a work-up to rule out dermatomyositis. The first is measurement of serum CPK, which is indicative of muscle degeneration. The second is an ANA test, which is a nonspecific screening test for autoimmune disease; over 70% of dermatomyositis patients have positive results. The third component is electromyographic testing, which can help distinguish dermatomyositis from other diseases that cause muscle weakness. Characteristically, dermatomyositis will show high frequency action potentials in a pattern of polyphasic potentials and fibrillation. The fourth is a muscle biopsy of a clinically involved muscle. Often the muscle biopsy is from the hip or shoulder girdle, but if the flexors of the neck are involved, the sternocleidomastoid muscles serve as readily accessible muscle biopsy sites. If jaw closure reveals clinical weakness, the anterior border of the masseter muscle can be accessed from a transoral approach.

Dermatomyositis is associated with a general increased risk for malignancy. The general physical examination should specifically look for and include diagnostic tests for malignancy common to the age, sex, and other risk factors of the individual.

Histopathology

Skin lesions may show a nonspecific inflammatory infiltrate, but very often the changes are akin to those of SLE (Fig. 12.24). They show perivascular lymphoid infiltrates, connective tissue edema, liquefaction degeneration of epithelial basal cells, and PAS-positive deposits in the basement membrane zone and around capillaries. However, there is no deposition of immunoglobulins at the epidermal-dermal junction. The changes within muscle consist of scattered degeneration and regeneration of muscle fibers. These areas, as well as blood vessels, may be surrounded by mononuclear infiltrates. Because these inflammatory components are focal, they may be missed on biopsy. A typical degenerative regenerative reaction may be seen at the periphery of muscle fascicles. In older lesions, muscle fibers may be replaced by fibrotic tissue. The mononuclear infiltrates are predominantly activated T cells that show sensitization to muscle antigens and natural killer cells, which are cytotoxic to muscle fibers.

Treatment

Most patients respond to prednisone. Systemic corticosteroid regimen I or IIIA is used most often. Systemic corticosteroid regimen IIIB is used rarely and only in refractory cases.

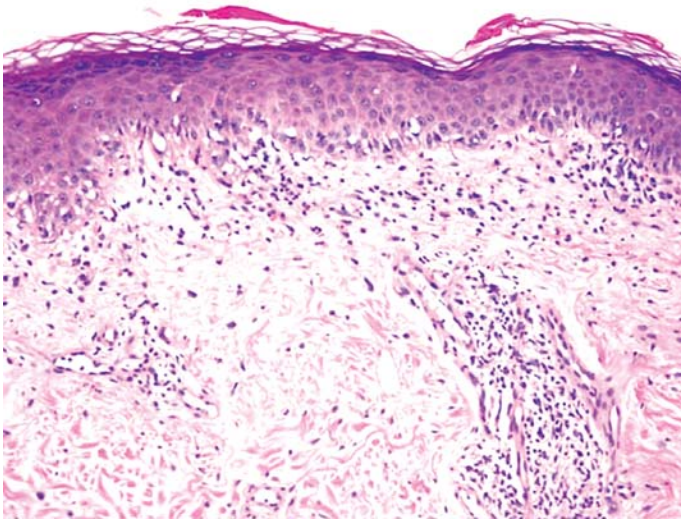


Fig. 12.24: Histopathology of dermatomyositis showing superficial and mid-perivascular infiltrate predominantly of lymphocytes

Prognosis

Long-term use of prednisone is often needed, and exacerbations after discontinuation are common. CPK serum levels are indicative of disease activity and are a part of the follow-up assessment. Patients with an associated malignancy do not respond as well to treatment and have a poorer prognosis. However, treatment of the malignancy alleviates the dermatomyositis. Children respond much better than do adults, and many achieve permanent drug-free remissions.

ECTODERMAL DYSPLASIA

Clinical Presentation and Pathogenesis

Ectodermal dysplasia is a syndrome characterized by the clinical findings of hypodontia (missing and/or conical teeth), hypotrichosis (missing and/or sparse hair), and hypohidrosis (dry skin). It is primarily an inherited X-linked recessive trait associated with the repressed expression of a gene on the X chromosome in the positions from q13 to q21. Consequently, it is more common in men. Women often represent asymptomatic or only mildly affected carriers; however, some women have a fully expressed ectodermal dysplasia thought to be related to an autosomal recessive form indistinguishable from the more common X-linked form seen in men.

The individual will be missing numerous teeth, especially the molar teeth, and may even be edentulous. The teeth that are present, most likely incisors and canines (Fig. 12.25), will have conical crowns and roots and may also have shortened roots due to the effects of this gene loss on both the full development of the enamel organ and Hertwig root sheath. Because of these effects on the teeth, most individuals will have a reduced alveolar bone, a reduced vertical dimension, and consequently a pseudoprognathism with an everted lower lip. There may also be some xerostomia related to hypoplasia of minor salivary glands.

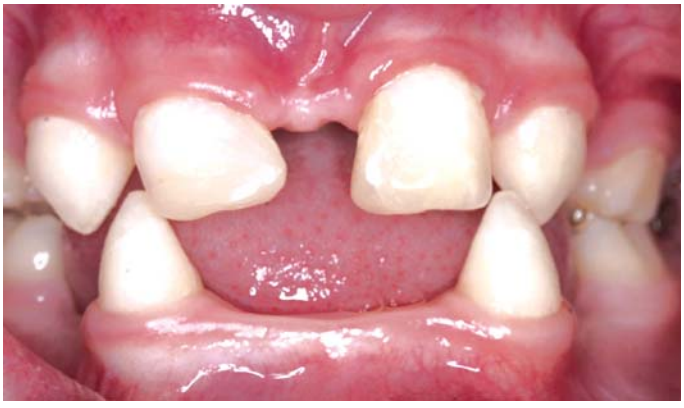


Fig. 12.25: Ectodermal dysplasia showing cone shaped teeth

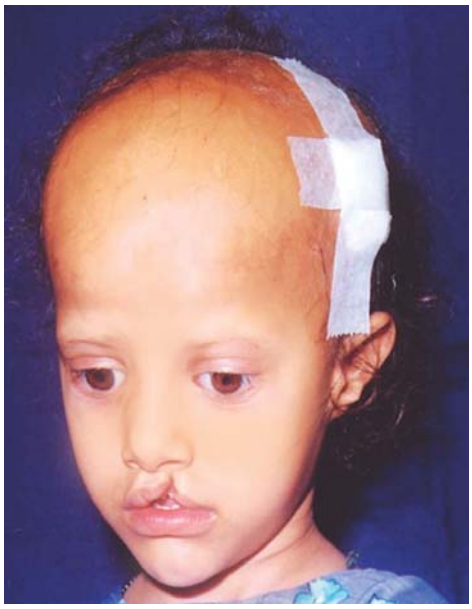


Fig. 12.26: Ectodermal dysplasia associated with sparse hair

The facial appearance will be one of prognathism and prominent brow ridges. The eyebrows, facial hair, and scalp hair are usually thinned but may be absent in severe cases (Fig. 12.26). The skin is soft, thin, and dry. There may be mild xerophthalmia if the lacrimal gland is hypoplastic, which will be worsened by the loss of meibomian glands. There is usually some corneal thinness as well.

The dryness of the skin and inability to sweat may produce fevers of unknown origin particularly in infants or children in whom the syndrome has not yet been diagnosed. Since both sweat and sebaceous glands are significantly reduced in about 65% of individuals, they will also develop eczema. The nails are usually normal.

Differential Diagnosis

Ectodermal dysplasia is a distinctive clinical recognition diagnosis, particularly if all three components are present. However, it may be confused with other entities that resemble a single component of ectodermal dysplasia. Isolated oligodontia is the most apparent. The lip scarring of rhagades and the saddle nose deformity in congenital syphilis may resemble the facial picture of ectodermal dysplasia. Congenitally missing teeth are found in the rare Witkop tooth-nail syndrome, and conical teeth are found in acrodental dysostosis. Trichodental syndrome, an autosomal-dominant trait, produces congenitally missing teeth and fine, sparse hair and eyebrows, but no dry skin. This syndrome will resemble ectodermal dysplasia more closely than any other.

Diagnostic Work-up

A panoramic radiograph is recommended to confirm the true absence rather than the lack of eruption of teeth and to assess their root shape and development. The remaining work-up consists only of a careful topographic examination. If the hypohidrosis is equivocal, it can be assessed by means of the starch iodine test that is used on the face to detect sweating from aberrant reinnervation of sweat glands after surgery for Frey syndrome, using a 5-mg pilocarpine iontophoresis challenge.

Histopathology

Both hidrotic and anhidrotic types demonstrate hypoplasia of hair and sebaceous glands. Their numbers and size are reduced, and their maturation is affected. In the anhidrotic form, the endocrine glands are also affected. They may be completely absent or present in a few areas in a hypoplastic form.

Salivary glands may be hypoplastic, and minor salivary glands may even be absent, resulting in xerostomia. Hypoplasia of nasal and pharyngeal mucous glands can cause rhinitis and pharyngitis.

Treatment and Prognosis

Because of its genetic basis, there is no treatment to alter the course of ectodermal dysplasia. Symptom related treatments that may be used include pilocarpine, 5 mg by mouth twice or three times a day, to improve xerostomia, xerophthalmia, and the ability to sweat in the facial skin area but not in other areas. This improved sweating ability from pilocarpine will be limited to the facial skin area because only the sweat glands located in the facial skin are innervated by sympathetic nerves, which have cholinergic receptors rather than the usual adrenergic receptors. The missing teeth may be replaced with overdentures or removable partial dentures if the conical teeth can be crowned to improve retention. Since the bone is normal, dental implants are an ideal dental replacement concept in individuals with ectodermal dysplasia.

WHITE SPONGE NEVUS

Clinical Presentation

White sponge nevus is an autosomal dominant disease producing a soft, spongy type of clinical leukoplakia. These white, asymptomatic, folded lesions usually develop in the preteen years and reach a plateau in early adulthood. White folded areas are most prominent on the buccal mucosa and the lateral border of the tongue (Fig 12.27).

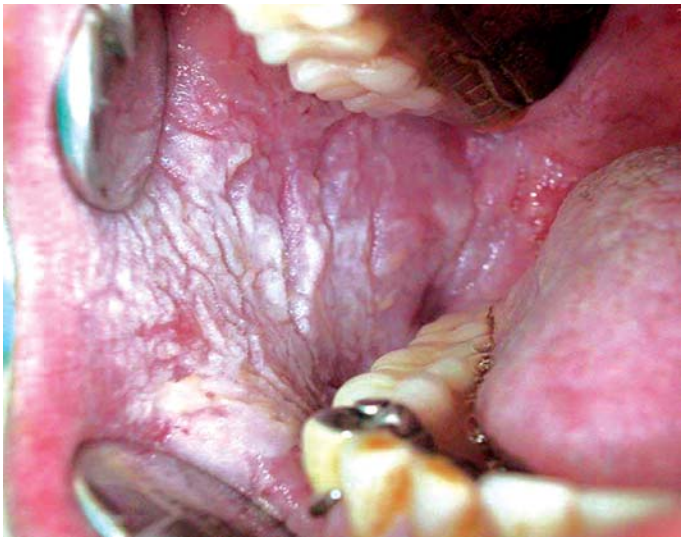


Fig. 12.27: White spongy nevus

Differential Diagnosis

White sponge nevus is essentially a leukoplakia, that is, a white patch. Its main differential lesions are a benign hyperkeratosis and a dysplastic or premalignant lesion, which may also present as clinical leukoplakia. In addition, hereditary benign intraepithelial dyskeratosis, which is another autosomal-dominant trait, causes identical white oral lesions but has concomitant conjunctival plaques with hyperemia. Lichen planus is a more common disease that produces white oral lesions, particularly on the buccal mucosa and tongue; however, lichen planus is a disease of adults and is not usually seen in the preteen and teen years. Candida of the hypertrophic type, which will not come off on scraping, is also a consideration. Lastly, the two pachyonychia congenita syndromes, Jadassohn-Lewandowsky syndrome and Jackson-Lawler syndrome, produce similar white oral patches; however, each also shows palmar and plantar hyperkeratosis and nail bed elevations, which distinguish them from white sponge nevus.

Diagnostic Work-up

A mucosal biopsy is indicated to confirm the diagnosis and distinguish this condition from the other more serious diseases in the differential diagnosis.

Histopathology

There is a thickening of the epithelium due to hyperparakeratosis, acanthosis, and intracellular edema of prickle cells (Fig. 12.28). The change in the prickle cells may

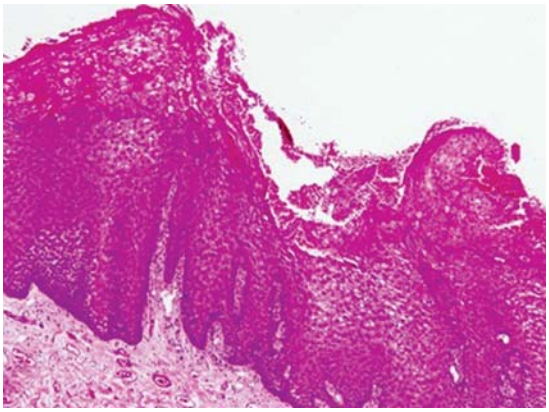


Fig. 12.28: Histology of white spongy nevus

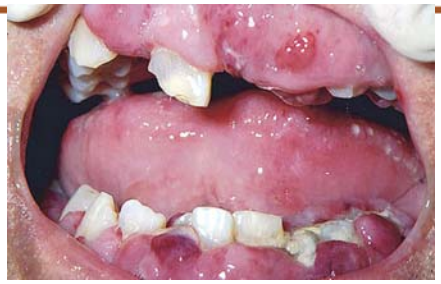
affect all layers, and the nuclei are also pyknotic. The basal cells are unaffected. Parakeratotic plugs may extend into the prickle cells, giving a so-called basket weave appearance to the epithelium. The underlying connective tissue is unremarkable.

Treatment

No specific treatment is necessary. Reassurance should be given to the patients and their families that the lesions do not represent a premalignant condition and that transformation to a malignancy does not occur.

13

Diseases of Blood and Blood Forming Organs



PERNICIOUS ANEMIA

(Vitamin B_{12} ***deficiency, Addisonian anemia,*** **Biermer anemia,** ***Hunter-Addison*** **anemia,** ***Lederer anemia, Biermer-Ehrlich anemia,*** **Addison-***Biermer disease).*

Pernicious anemia is a relatively common chronic hematologic disease. It is an adult form of anemia that is associated with gastric atrophy and loss of intrinsic factor production in gastric secretions and a rare congenital autosomal recessive form in which intrinsic factor (IF) production is lacking without gastric atrophy. The term pernicious anemia is reserved for patients with vitamin B12 deficiency due to a lack of production of IF in the stomach. Intrinsic factor in gastric secretions is necessary for the absorption of dietary vitamin B_{12}'. Vitamin B_{12}, a substance now thought to be synonymous with erythrocyte maturing factor' or 'hemopoietic principle' and present in many foods particularly liver, beef, milk and *dairy* products. Body stores of the vitamin usually exceed 1000 mcg and the daily acquirement is about 1 mcg.

Pernicious anemia probably is an autoimmune disorder with a genetic predisposition and the disease is associated with human leucocyte antigen (HLA) types A2, A3 and B7 and A blood group. Antiparietal cell antibodies occur in 90 percent of patients with pernicious anemia but in only 5 percent of healthy adults. Similarly, binding and blocking antibodies to IF are found in most patients with pernicious anemia. A greater association than anticipated exists between pernicious anemia and other autoimmune diseases, which include thyroid disorders, type I diabetes mellitus, ulcerative colitis, Addison disease and acquired agammaglobulinemia. An association between pernicious anemia and helicobacter pylori infections has been postulated but not clearly proven.

Clinical Features

Pernicious anemia is rare before the age of 30 years and increases in frequency with advancing age. In the United States, males are affected more commonly than females. In other countries, notably Scandinavia, females are more commonly affected. No apparent racial predilection is noticed.

The disease is often characterized by the presence of a triad of symptoms: generalized weakness, a sore, painful tongue and numbness or tingling of the extremities. In some cases the lingual manifestations are the first sign of the disease. Other typical complaints are easy fatigability headache. Dizziness, nausea, vomiting, diarrhea, loss of appetite, shortness of breath, loss of weight, pallor and abdominal pain. Patients with severe anemia exhibit a yellowish tinge of the skin and sometimes of the sclerae. The skin is usually smooth and dry. Nervous system involvement is present in over 75 percent of the cases of pernicious anemia, and this consists of sensory disturbances including the paresthetic sensations of the extremities described above, weakness, stiffness and difficulty in walking, general irritability, depression or drowsiness as well as incoordination and loss of vibratory sensation. These nervous aberrations are referable to the degeneration of posterior and lateral tracts of the spinal cord with loss of nerve fibers and degeneration of myelin sheaths. Degeneration of the peripheral nerves also occurs.

Oral Manifestations

Glossitis is one of the more common symptoms of pernicious anemia. The patients complain of painful and burning lingual sensations which may be so annoying that the dentist is often consulted first for local relief.

The tongue is generally inflamed, often described as 'beefy red' in color, either in entirety or in patches scattered over the dorsum and lateral borders. In some cases, small and shallow ulcers resembling apthous ulcers occur on the tongue. Characteristically, with the glossitis, glossodynia and glossopyrosis, there is gradual atrophy of the papillae of the tongue that eventuates in a smooth or 'bald' tongue which is often referred to as Hunter's glossitis or Moeller's glossitis and is similar to the 'bald tongue of Sandwith' seen in pellagra. Loss or distortion of taste is sometimes reported accompanying these changes. The fiery *red* appearance *of the tongue may* undergo periods of remission, but recurrent attacks are common. On occasion, the inflammation and burning sensation extend to involve the

entire oral mucosa but, more frequently, the rest of the oral mucosa exhibits only the pale yellowish tinge noted on the skin. Millard and Gobetti have emphasized that a non-specific persistent or recurring stomatitis of unexplained local origin may be an early clinical manifestation of pernicious anemia. Not uncommonly the oral mucous membranes in patients with this disease become intolerant to dentures.

Farrant and Boen and Boddington have reported that cells from buccal scrapings of patients with pernicious anemia presented nuclear abnormalities consisting of enlargement, irregularity in shape and asymmetry: These were postulated to be due to a reduced rate of nucleic acid synthesis with a reduced rate of cell division. These epithelial cell alterations are rapidly reversible after administration of vitamin B_{12}.

Laboratory Findings

Blood

This chronic disease often exhibits periods of remission and exacerbation, and the blood changes generally parallel these clinical states. The red blood cell count is seriously decreased, often to 1,000,000 or less per cubic millimeter. Many of the cells exhibit macrocytosis; this, in fact, is one of the chief characteristics of the blood in this disease, although poikilocytosis, or variation in shape of cells, is also present. The hemoglobin content of the red cells is increased, but this is only proportional to their increased size, since the mean corpuscular hemoglobin concentration is normal. A great many other red blood cell abnormalities have been described, particularly in advanced cases of anemia, including polychromatophilic cells, stippled Cells, nucleated cells, Howell-Jolly bodies and Cabot's rings punctate basophilia. Leukocytes are also often remarkably reduced in number, but are increased in average size, in number of lobes to the nucleus (becoming the so-called macropolycytes), and anisopoikocytosis. Mild-to-moderate thrombocytopcnia is noticed. Coexistent iron deficiency is common because achlorhydria prevents solublization of dietary ferric iron from foodstuffs. Striking reticulocyte response and improvement in hematocrit values after parenteral administration of cobalamin is characteristic (Fig. 13.1).

Serum

The indirect bilirubin may be elevated because pernicious anemia is a Hemolytic disorder associated with increased turnover of bilirubin. The serum lactic dehydrogenase usually is markedly increased. The serum potassium. cholesterol, and skeletal alkaline phosphatase often are decreased. Serum antibodies for If are highly specific.

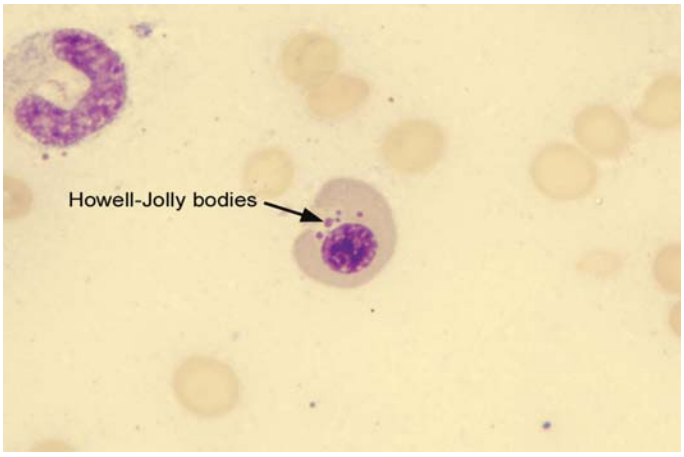


Fig. 13.1: Pernicious anemia
(orthochromatic megaloblast with Howell-Jolly bodies)

Gastric Secretions

Total gastric secretions are decreased to about 10 percent of the reference range. Most patients with pernicious anemia are achlorhydric, even with histamine stimulation. If is either absent or is markedly decreased.

Bone Marrow

The bone marrow biopsy and aspirate usually are hypercellular and show trilineage differentiation. Erythroid precursors are large and often oval. The nucleus is large and contains coarse motley chromatin clumps, providing a checkerboard appearance. Nucleoli are visible in the more immature erythroid precursors. Imbalanced growth of megakaryocytes is evidenced by hyperdiploidy of the nucleus and the presence of giant platelets in the smear. Lymphocytes and plasma cells are spared from the cellular gigantism and cytoplasmic asynchrony observed in other cell lineages. The bone marrow histology is similar in both folic acid and cobalamine *deficiency*

Treatment

The treatment of pernicious anemia consists of the administration of vitamin B_{12}, and folic acid. Early recognition and treatment of pernicious anemia provides a normal, and usually uncomplicated, lifespan. Delayed treatment permits progression of the anemia and neurological complications. The mental and neurological damage can become irreversible without therapy.

CELIAC SPRUE

(Celiac disease, nontropical *sprue, gluten-sensitive enteropathy, Gee-Herter disease)*

Sprue is one disease of a large group which constitutes the 'malabsorption syndrome'. It is a chronic disease of the

digestive tract that interferes with the absorption of nutrients from food. Sprue is not basically an anemic disorder): It is considered here, however, because it presents so many signs and symptoms in common with pernicious anemia that the differentiation is often difficult. This disease, also called 'idiopathic steatorrhea' to distinguish it from steatorrhea resulting from fibrocystic disease of the pancreas with resultant decrease in pancreatic enzyme secretion.

People with celiac sprue cannot tolerate gluten, a protein commonly found in wheat, rye, barley, and sometimes oats. When affected individuals ingest gluten, the mucosa of their small intestine is damaged by an immunologically mediated inflammatory response, resulting in maldigestion and malabsorption. Genetics play an important role in celiac sprue. The incidence of disease in relatives of celiac sprue patients is significantly higher than in the general population. The prevalence in first-degree relatives of celiac sprue patients is approximately 10 percent. Concordance for the disease in HLA identical siblings is about 30 percent and that for identical twins approaches 70 percent. Strong association exists between the disease and to human leukocyte antigen (HLA) haplotypes, DR3 and DQW2.

Clinical Features

Sprue occurs both in tropical countries and in temperate zones in persons of all ages, including infants. For example, the frequency of the disease is between 1 in 250 persons and 1 in 300 persons in Italian and Irish populations. In comparison, the disease is rare in Africans or Asians. The symptoms of untreated celiac sprue divided into gastro extra intestinal Symptoms.

Gastrointestinal symptoms include diarrhea, which is the most common symptom in untreated celiac sprue due to maldigestion and malabsorption of nutrients. Malabsorption of dietary treatment leads to remission of the oral lesions.

Laboratory Findings

The blood and bone marrow changes are often identical with those of pernicious anemia and include a macrocytic anemia and leukopenia. Hypo chromic microcytic anemia occasionally occurs. A low serum iron level is common. The prothrombin time (PT) might be prolonged because of malabsorption of vitamin K. The patients do not usually exhibit achlorhydria nor is the 'intrinsic' factor absent.

Small intestinal biopsy along with appropriate serum antibodies. Usually will establish the diagnosis.

Histologic Findings

Celiac sprue primarily involves the mucosa of small intestine. The submucosa, muscularis and serosa usually are not involved. The villi are atrophic or absent and crypts are elongated. The cellularity of the lamina propria is increased with a proliferation of plasma cells and lymphocytes. The number of intraepithelial lymphocytes per unit length of absorptive epithelium is increased (Fig. 13.2).

Treatment

Sprue responds well in most cases to the administration of vitamin B_{12} and folic acid. Although the diet must be carefully supervized and supplemented with vitamins and minerals. Use of food grains containing gluten should be avoided. A small percentage of celiac sprue patients fail to respond to a gluten free diet. In some patients who are refractory, corticosteroids might be helpful. The patients who fail to respond to corticosteroids, other conditions such as lymphomas of the small intestine should be suspected.

APLASTIC ANEMIA

Aplastic anemia is a bone marrow failure syndrome characterized by peripheral pancytopenia and general lack of bone marrow activity. It may affect not only the red blood cells but also the white cells and platelets, resulting in a pancytopenia. The clinical manifestations of the disease vary according to the type of cell chiefly affected. Paul Ehrlich, MD introduced the concept of aplastic anemia in 1888 when he studied the case of a pregnant woman who died of bone marrow failure. However, it was not until 1904 when this disorder was termed aplastic anemia by Chauffard.

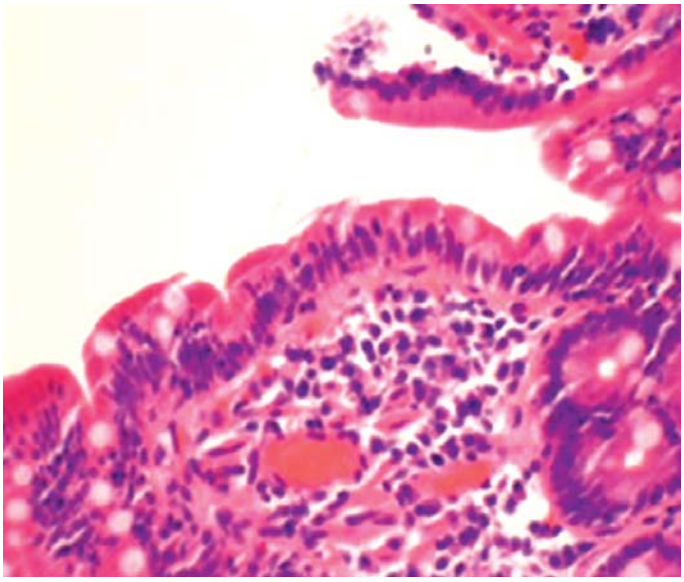


Fig. 13.2: Celiac sprue showing atropic villi with increased cellularity of lamina propria

It is common to recognize two chief forms of aplastic anemia, primary and secondary. **Primary aplastic anemia** is a disease of unknown etiology which occurs most frequently in young adults, develops rapidly and usually terminates fatally: A disease known as Fanconi's syndrome consists of congenital, and sometimes familial. Aplastic anemia associated with a variety of other congenital defects including bone abnormalities, microcephaly, hypogenitalism and a generalized olive-brown pigmentation of the skin.

Secondary aplastic anemia, on the other hand is of known etiology, occurs at any age and presents a better prognosis, particularly if the cause is removed. The etiology of this secondary anemia is the exposure of the patient to various drugs or chemical substances or to radiant energy in the form of X-rays, radium or radioactive isotopes. In many cases the development of aplastic anemia after exposure to the drug or chemical seems to be an allergic phenomenon, since the amount of the substance absorbed is too small to result in an actual poisoning or intoxication. The chemicals which have been found most frequently to cause the development of this condition are acetophenetidin, amidopyrine, organic arsenicals, particularly sulfarsphenamine, benzol, chloramphenicol, quinacrine hydrochloride (Atabrine), trinitrotoluene, dinitrophenol, colloidal silver, bismuth, mercury, sulfonamides and penicillin, although many others have also produced the disease. On few occasions aplastic anemia is preceded by infection by hepatitis viruses.

The role of an immune dysfunction was suggested in 1970, when autologous recovery was documented in a patient with aplastic anemia who had failed to engraft after marrow trans plantation. It was proposed that the immunosuppressive regimen used for conditioning promoted the return of normal marrow function. Subsequently, numerous studies have shown that, in approximately 70 percent of patients with acquired aplastic anemia, immuno suppressive therapy improves marrow function. Although the inciting antigens that breach immune tolerance with subsequent autoimmunity are unknown, HLA-DR2 is over represented among European and American patients with aplastic anemia.

Suppression of hematopoiesis likely is mediated by an expanded population of the cytotoxic T lymphocytes (CD8 and HLA-DR+), which are detectable in both the blood and bone marrow of patients with aplastic anemia. These cells produce inhibitory cytokines, such as gamma interferon and tumor necrosis factor, which are capable of suppressing progenitor cell growth. The cytokines suppress hematopoiesis by affecting the mitotic cycle and cell killing through induction of fas mediated apoptosis.

The effect of irradiation is usually more pronounced on the white blood cell series although the development of a aplastic after exposure to X-ray radiation is well recognized

Clinical Features

The clinical manifestations of aplastic anemia, are referable not only to the anemia. But also to the leukopenia and thrombocytopenia which are variably present. There are few differences in the clinical features of the primary and secondary forms of the disease except in the ultimate prognosis. The onset is insidious, with the initial symptom relating to anemia or bleeding, but fever or infections often are noted at presentation. Patients usually complain of severe weakness with dyspnea following even slight physical exertion and tingling of the extremities and edema are also encountered due to anemia. Petechiae in the skin and mucous membranes occur, owing to the platelet deficiency, while the neutropenia leads to decreased resistance to infection (Fig. 13.3).

Oral Manifestations

Petechiae purpuric spots or frank hematomas of the oral mucosa may occur a any site, while hemorrhage into the oral cavity especially spontaneous gingival hemorrhage, is present in some cases. Such findings are related to the development of ulcerative lesions of the oral mucosa or pharynx. These may be extremely severe and may result in a condition resembling gangrene because of the lack of cell inflammatory response.

Resistance to infection, and this is manifested by the development of ulcerative lesions of the oral mucosa or pharynx. These may be extremely severe and may result in a condition resembling gangrene because of the lack of inflammatory cell response.

Laboratory Findings

The red blood cell count is remarkably diminished, often to as low as 1,000,000 cells per cubic millimeter, with a

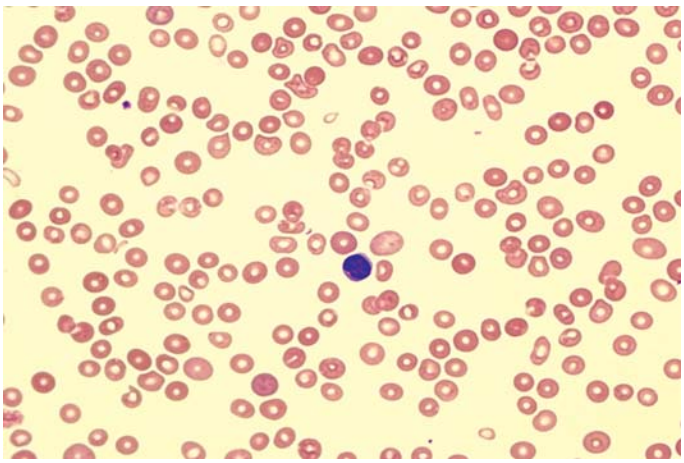


Fig. 13.3: Aplastic anemia

corresponding reduction in the hematocrit and hemoglobin levels. A paucity of granulocytes, monocytes and reticulocytes found. The thrombocytopenia results in a prolonged bleeding time. The clotting time remains normal. Clot retraction is poor and the tourniquet test is positive. The degree of cytopenia is useful in assessing the severity of aplastic anemia. The presence of tear drop poikilocytes and leukoerythroblastic changes suggest marrow aplasia from infiltrative and dysplastic causes.

Bone marrow smears exhibit variable findings depending on the extent of the anemia and panocytopenia. If only an anemia exists, there is erythropoietic depression. Occasionally, however the marrow appears normal or even hyperplasic.

THALASSEMIA

(Cooley's anemia, Mediterranean anemia, Erythroblastic Anemia)

Thalassemic syndromes are genetically determined disorders of hemoglobin synthesis with decreased production of either alpha or beta polypeptide chains of hemoglobin molecules, which results from markedly decreased amounts of globin messenger ribonucleic acid. Features first described by Thomas B Cooley in 1925 are seen primarily in Mediterranean populations, in races bordering the eastern Mediterranean sea or in families originating from these areas (thalassa means 'sea' in Greek).

Normal adult hemoglobin is a large complex molecule in which an iron-containing pigment (heme) is conjugated to a complex protein. (globin). The globin component consists two pairs of unlike polypeptide chains, alpha and non alpha chains (e.g. beta, gamma, delta). In the normal adult hemoglobin (HbA), which constitutes over 95 percent of the hemoglobin in normal persons older than one year. The globin component consists of two alpha and two beta chains. The thalassemia group of anemias is a heterogeneous group characterized by diminished synthesis of the alpha (a) or beta-globin chain of hemoglobin A. The disease is termed a thalassemia when there is deficient synthesis of the α-chain and β-thalassemia when the Ps chain is deficient. Thus, in P-thalassemia there is an excess of α-chains, producing 'unstable hemoglobins' that damage the erythrocytes and increase their vulnerability to destruction. In heterozygotes, the disease is mild and is called thalassemia minor or thalassemia trait. It represents both alpha-and beta-thalassemia. homozygous may exhibit a severe form of the disease that is called thalassemia major or *homozygous P- thalassemia, in which the* production *of* beta chains is markedly decreased or absent and a consequent decrease in synthesis of total hemoglobin occurs. This results in severe hypochromic anemia. Furthermore, excess α-chains, which synthesize at the normal rate, precipitate as insoluble inclusion bodies within the erythrocytes and their precursors. The presence of such intracellular inclusion bodies **(Fessas bodies)** leads to increased erythrocyte hemolysis and severe ineffective hematopoiesis. Approximately 70-85 percent of marrow normoblasts are destroyed in severely affected patients. These processes result in profound anemia and an associated increase in marrow activity which is estimated to increase 5 to 30 fold.

Two other forms of thalassemia major that represent α-thalassemia also exist. These are:

- Hemoglobin H disease which is a very mild form of the disease in which the patient may live a relatively normal life.
- Hemoglobin Bart's disease, with hydrops fetalis, in which the infants are stillborn or die shortly after birth.

Clinical Features

In high-risk areas (i.e. Greek and Italian islands), 10 percent of the population may have homozygous beta thalassemia; 5 percent in southeast Asian populations; and 1.5 percent in African and American black populations. The onset of the severe form of the disease (homozygous beta thalassemia) occurs within the first two years of life, often in the first few months. Siblings are commonly affected. The child has a yellowish pallor of the skin and exhibits fever, chills, malaise and a generalized weakness. Splenomegaly and hepatomegaly may cause protrusion of the abdomen. The face often develops mongoloid features due to prominence of the cheek bones, protrusion or flaring of the maxillary— anterior teeth, and the depression of the bridge of the nose which gives rise to the characteristic 'rodent facies'. The child does not appear acutely ill, but the disease follows an ingravescent course which is often aggravated by intercurrent infection. Some patients, however, die within a few months, especially when the disease is manifested at a very early age. Logothetis and his associates have shown that the degree of cephalofacial deformities in this disease (including prominent frontal and parietal bones, sunken nose bridge. Protruding zygomas and mongoloid slanting eyes is closely related to the severity of the disease and the time of insistution of treatment. Thalassemia minor is generally without clinical manifestations (Fig. 13.4).

Oral Manifestations

An unusual prominence the premaxilla has been described in cases of erythroblasic anemia such as reported by Novak and this results in an obvious malocclusion. The oral mucosa may exhibit the characteristic anemic pallor observed on the skin.

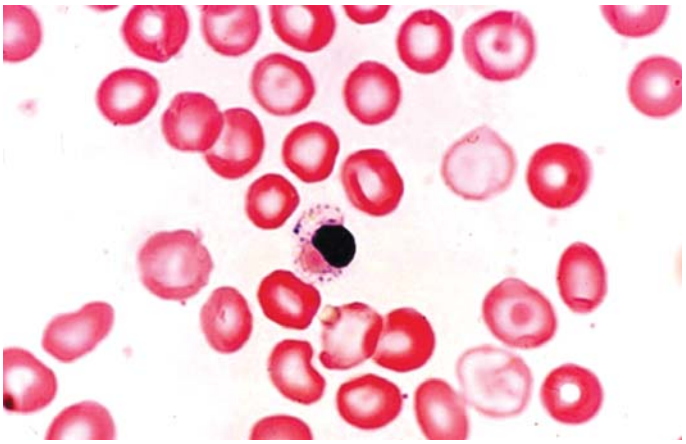


Fig. 13.4: Blood picture of beta thalassemia major

Laboratory Findings

The pronounced anemia is of a hypochromic microcytic type. The red cells exhibiting a poikilocytosis and anisocytosis. These cells are extremely pale but in some instances appear as 'target' cells with a condensation of coloring matter in the center of the cell. The presence of typical **'safety-pin'** cells and normoblasts or nucleated red blood cells in the circulating blood is also a characteristic feature. The white blood cell count is frequently elevated, often as high as 10,000 to 25,000 or more per cubic millimeter. Supravital staining (methyl violet) of peripheral blood can demonstrate inclusion bodies. Bone marrow smears show cellular hyperplasia with large numbers of immature, primitive and steno forms of red blood cells all indicating maturation arrest. The serum bilirubin in these patients also elevated indicative of the severe hemosiderosis which is almost invariably present. This systemic hemosiderosis has suggested a possible block in iron utilization with accumulation of iron pigment and subsequent inadequate formation of hemoglobin.

Roentgenographic Features

The skeletal changes in thalassemia are most striking and have been thoroughly described by Caffey. A frequent finding in rib has been referred to as the **rib within-a-rib'** appearance and is noted particular in the middle and anterior portions of the ribs. the finding consists (of a long linear density within or overlapping the medullary space of the rib running parallel to its long axis. In the skull, there is extreme thickening of the dipole (medulla) the inner and outer plates (cortices) poorly defined, and the trabeculae between the plates become elongated, producing a bristle like **'crew-cut'** or **'hair-on-end'** appearance of the surface of the skull because of lack of hematopoietic marrow the occipital bone usually not involved. Both the skull and long bones exhibit some degree of osteoporosis, but spontaneous fracture widening of the medulla with thinning of the cortices of the long bones. The bony changes may occur early in life and tend to persist. Particularly those in the skull, proliferation of marrow within the frontal and facial bones impedes pneumatization of the paranasal sinuses. This results in hypertrophy of osseous structures and a consequent prominence of the lateral margins of the malar eminences. Together with anterior and medial displacement of developing teeth. Characteristically, ethmoidal sinuses are not involved a factor attributable to the absence of red marrow in the sinus walls.

ERYTHROBLASTOSIS FETALIS

Congenital hemolytic anemia due to Rh incompatibility results from the destruction of fetal blood brought about by a reaction between maternal and fetal blood factors.

The Rh factor, named after the rhesus monkey, was discovered by Landsteiner and Wiener in 1940 as a factor in human red blood cells that would react with rabbit antiserum produced by administration of red blood cells from the rhesus monkey. The Rh factor, a dominant hereditary characteristic is present in the red blood cells of approximately 85 percent of die Caucasian population of the United States.

Pathogenesis

Erythroblastosis fetalis is essentially due to the inheritance by the fetus of a blood factor from the father that acts as a foreign antigen to the mother. The transplacental transfer of this antigen, actually transplacental leaks of red cells from the fetus to the mother results in immunization of the mother and formation of antibodies which, when transferred back to the fetus by the same route, produce fetal hemolysis. Occasionally the ABO system may produce a similar type of hemolysis and immunization. The basic inheritance of the Rh factor is relatively simple. If both parents are homozygously Rh-positive (have the Rh factor), the infant will be Rh-positive, but maternal immunization cannot occur. Since both mother and fetus have the same antigen, the mother is homozygously positive, but the father Rh-negative, the same situation: actually exists, since both the mother and the foetus; have the same antigen and no immunization can occur. If the father is Rh-positive and the mother Rh-negative. However, the fetus inherits the paternal factor, which may then act as an antigen to the mother and immunize her with resultant antibody formation.

The problem is complicated, however, by the occurrence of numerous immunologically Rh antigens. The strongest of these antigens have been termed C, D and E. And the presence any of one of them constitutes an Rh-positive per-

son. Each of these antigens is normally present in a specific gene, but, if absent; their place is taken by less potent Hr antigens, known as c, d and e. Thus, three Rh or Hr genes are inherited from each parent, constituting three pairs of factors. Any combination of C, D, E and c, d, e is therefore possible, but the only combination producing an Rh negative person is cde-cde. The D antigen, by far the strongest, is most frequently responsible far Tc the clinical manifestations of erythroblastosis fetalis is and the 85 percent of the population generally, considered Rh-positive actually have the d antigen homozygously or heterozygously. The 15 percent who are Rh-negative have the dl, w antigen homozygously (d-d). Mathematically, according to the laws of random mating, there should be 10 cases of erythroblastosis fetalis in every 100 pregnancies. Clinically, it has been found that only one case in every 200 pregnancy occurs. There are several possible explanations for this discrepancy.

In some cases the mother may he unable to form antibodies even though immunized.

- By the Rh positive fetus Even though the fetus is Rh-positive, Transplacental transfer of the antigen does not occur, so that there is no maternal immunization. Immunization may occur, but its level is so low as to be clinically insignificant. Recent evidence has shown that, in general, women have a reduced immunologic responsiveness during pregnancy. Subsequent pregnancies might cause further immunization with increased antibody formation, so that in ensuing pregnancies clinical hemolysis does occur. This latter explanation is plausible since it explains adequately why the first pregnancy is often uneventful, While erythroblastosis frequently occurs in succeeding pregnancies.

It is of great interest to note that the frequency of erythroblastosis fetalis of Rh incompatibility has shown a dramatic decrease in the past few years and that the eventual elimination of the disease through immunization prevention techniques is a probability. At present, Rh-negative mothers are being given anti-D gamma globulin to prevent immunization, since it binds to antigenic receptor sites on fetal red cells, making them non immunogenic (Fig. 13.5).

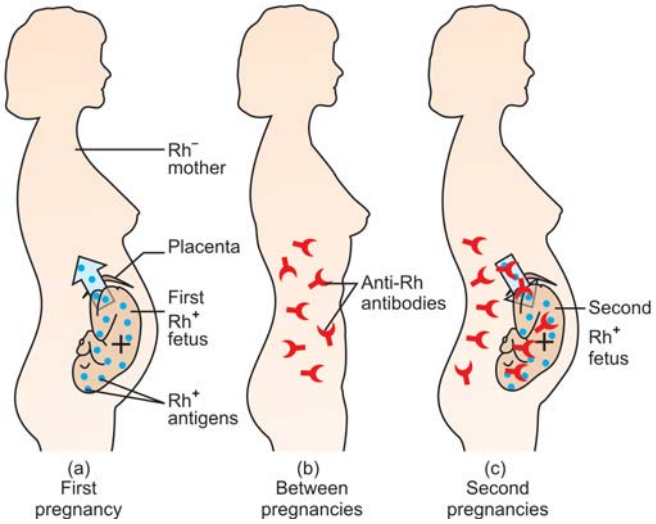


Fig. 13.5: Erythroblastosis fetalis – Pathogenesis

Clinical Features

The manifestations of the disease depend upon the severity of the hemolysis. Some infants are stillborn. Those that are born alive characteristically suffer from anemia with pallor, jaundice, compensatory erythropoiesis, both medulla' and exramedullary', and edema resulting in fetal hydrops. It is of considerable interest that the severe anemia and jaundice do not begin to develop until at least several hours after birth and frequently not for several days. The most important aid in diagnosis of the disease is a positive direct Coombs test on cord blood.

Oral Manifestations

Erythroblastosis fetalis may be manifested in the teeth by the deposition of blood pigment in the enamel and dentin of the developing teeth, giving them a green, brown or blue hue. Ground sections of these teeth give a positive test for bilirubin. The stain is intrinsic and does not involve teeth or portions of teeth developing after cessation of hemolysis shortly after birth.

Enamel hypoplasia is also reported occurring in some cases erythroblastosis fetalis. This usually involves the incisal edges of the anterior teeth and the middle portion of the deciduous cuspid and first molar crown. Here a characteristic ring-like defect occurs which has been termed the **'Rh hump'** by Watson.

Many infants with this disease are stillborn but an increasing number of those born alive have survived after a total replacement of their blood by transfusion at birth. Thus, the dentist may expect to see more children with the peculiar pigmentations of teeth characteristic of the condition and should be aware its nature.

Laboratory Findings

The red blood count at birth may vary from less than 1,000,000 cells per cubic millimeter to near a normal level. There are characteristically large numbers of normoblasts, or nucleated red cells, in the circulating blood. Ultimately, severe anemia usually develops within a few days. The icterus index is invariably high and may reach a level of 1(U) units.

Treatment

No treatment for tooth pigmentation is necessary since it affects only the deciduous teeth presents only a temporary cosmetic problem.

IRON DEFICIENCY ANEMIA AND PLUMMER-VINSON SYNDROME (PATERSON-BROWN KELLY SYNDROME, PATERSON-KELLY SYNDROME, SIDEROPENIC DYSPHAGIA)

Iron deficiency is an exceedingly prevalent form of anemia, particularly in females. Iron deficiency is the most prevalent single deficiency state on a worldwide basis. It has been estimated that between 5 and 30 percent of women in the United States are iron deficient, while in some parts of the world. This may reach 50 percent. Men are only rarely affected. In healthy people, the body concentration of iron (approximately 60 parts per million) is regulated carefully by absorptive cells in the proximal small intestine, which alter iron absorption to match body losses of iron. Persistent errors in iron balance lead to either iron deficient anemia or hemosiderosis.

The iron deficiency leading to this anemia usually arises through:

- Chronic blood loss (as in patients with a history of profuse menstruation,
  - inadequate dietary intake,
  - faultyiron absorption or
- Increased requirements for iron, as during infancy, childhood and adolescence and during pregnancy.

An adult male absorbs and loses about 1 mg of iron from a diet containing 10 to 20 mg of iron daily. During childbearing years, an adult female loses an average of 2 mg of iron daily (extra 500 mg of iron with each pregnancy, menstrual losses are highly variable is about 4 to100 mg of iron) and must absorb a similar quantity of iron in order to maintain equilibrium. Growing children must obtain approximately 0.5 mg more iron daily.

The Plummer-Vinson syndrome is one manifestations of iron deficiency anemia and was first described by Plummer in 1914 and by Vinson in 1922 under the term 'hysterical dysphagia'. Not until 1936, however, was the full clinical significance of the condition recognized. Ahlbom then defined it as a predisposition for the development of carcinoma in the upper alimentary tract. It is, in fact, one of the few known predisposing factors in oral cancer. It is thought that the depletion of iron-dependent oxidative enzymes may produce myasthenic changes in muscles involved in the swallowing mechanism, atrophy of the esophageal mucosa, and formation of webs as mucosal complications. It is also thought to be an autoimmune phenomenon as the syndrome is seen in association with autoimmune conditions such as rheumatoid arthritis, pernicious anemia, celiac disease, and thyroiditis. Other factors such as nutritional deficiencies, genetic predisposition are thought to play roles in the causation of this disease.

Clinical Features

While an iron-deficiency anemia may occur at any age, the Plummer-Vinson syndrome occurs chiefly in women in the fourth and fifth decades of life. Presenting symptoms of the anemia and the syndrome *are cracks or fissures* at the corners of the mouth (angular cheiiitis), a lemon-tinted pallor of the skin, a smooth, red, painful tongue (glossitis) with atrophy of the filliform and later the fungiform papillae, and dysphagia limited to solid food resulting from an esophageal stricture or web. These oral findings are reminiscent of those seen in pernicious anemia. The mucous membranes of the oral cavity and esophagus are atrophic and show loss of normal keratinization. Koilonychia (spoon-shaped fingernails) or nails that are brittle and break easily have been reported in many patients; splenomegaly has also been reported in 20-30 percent of the cases.

The depletion of iron stores in the body; manifested as iron-deficiency anemia, may be the direct cause of the mucous membrane atrophy, since the integrity of epithelium is dependent upon adequate strum iron levels. The atrophy of the mucous membranes of the upper alimentary tract predisposes to the development of carcinoma in these tissues. This relationship was first noted by Ahihorn, who reported that half of all women with carcinoma of the hypopharynx and upper part oldie esophagus seen at Radiumhemmet in Stockholm suffered from Plummer-Vinson syndrome. Subsequently the predisposition to the development of oral carcinoma was also established.

Laboratory Findings

Blood examination reveals a hypochromic microcytic anemic of varying degree, while sternal marrow examination shows no megaloblasts typical of pernicious anemia. The red blood cell count is generally between 3,000,000 and 4,000,000 cells per cubic millimeter, and the hemoglobin is invariably low that the anemia is of an iron-deficiency type can be confirmed by lack of a reticulocyte response following administration of vitamin B_{12}. A low serum iron and ferritin with an elevated total iron binding capacity (TIBC) are diagnostic of iron deficiency there is an absence of free hydrochloric acid in the stomach (Fig. 13.6). The achlorhydria is generally the cause of the faulty absorption of iron. Since the absence of hydrochloric acid

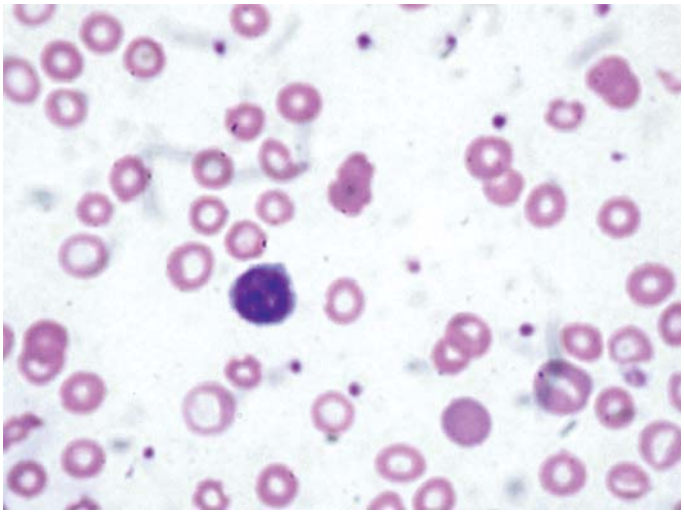


Fig. 13.6: Iron deficiency anemia blood picture shows microcytic hypochromic, few fragmented forms, polychromasia

prevents the conversion of unabsorbable dietary ferric iron to the absorbable ferrous state. The absence of stainable iron in a bone marrow aspirate is further diagnostic of iron deficiency: Unusual alterations in exfoliated squamous epithelial cells of the tongue in cases of severe iron-deficiency anemia have been reported by Montn and his associates. These changes consisted of a deficiency of keratinized cells, a reduced cytoplasmic diameter of cells with a paradoxical enlargement of the nucleus, and abnormal cellular maturation characterized by a disturbed nuclear pattern, an increase in nucleoli, presence of double nuclei and karyorrhexis. Testing stool for the presence of hemoglobin is useful in establishing gastrointestinal bleeding as the etiology of iron deficiency anemia; however, they produce a high incidence of false-positive results in people who eat meat.

Treatment

Anemia respond well to iron therapy and high protein diet, because of the predisposition to the development of carcinoma of oral mucous membranes, it is essential that the diagnosis be established early so that treatment may be instituted as soon as possible, dysphagia may improve with iron replacement alone, particularly in patients whose webs are not substantially obstructive. Dysphagia caused by more advanced webs is unlikely to respond to iron replacement alone and thus is managed with mechanical dilation.

POLYCYTHEMIA

Polycythemia is defined as an abnormal increase in the number of red blood cells in the peripheral blood. usually with an increased hemoglobin level. Three forms of the disease are recognized: relative polycythemia; primary polycythemia or erythremia (polycytltentia rubra vera) of unknown etiology; and secondary polycythemia or crythroocytosis, due to some known stimulus.

Relative polycythemia is an apparent increase in the number of circulating red blood cells that occurs as a result of loss of blood fluid with hemo concentration of cells, and is seen in cases of excessive loss of body fluids such as chronic vomiting, diarrhea, or loss of electrolytes with accompanying loss of water. This increase in the number of red blood cells in only relative to the total blood volume, and therefore, is not a true polycyrhemia.

Primary polycythemia, or polycythemia **rubra vera,** is characterized by a true idiopathic increase in the number of circulating red blood cells and of the hemoglobin level. It is characterized by bone marrow with an inherent increased proliferative activity (Fig. 13.7).

Secondary polycythemia is similar to primary polycythemia except that the etiology is known. Secondary polycythemia is caused due to absolute increase in red blood cell mass resultant to enhanced stimulation of red blood cell production. In general, the stimulus responsible toe producing a secondary polycythemia is either bone marrow anoxia or production of an 'erythropoietic stimulating factor. Bone marrow anoxia may occur in numerous situations such as pulmonary dysfunction, heart disease, habitation at high altitudes or chronic carbon monoxide poisoning. Erythropoietic stimulatory factors include a variety of drugs and chemicals.

Oral lesions are present in certain diseases that are characterized by a reduction in the number of white cells. These lesions are related to the inability of the tissues to react in the usual manner to infection or trauma. Because of the dangerous sequelae which may result if the disease

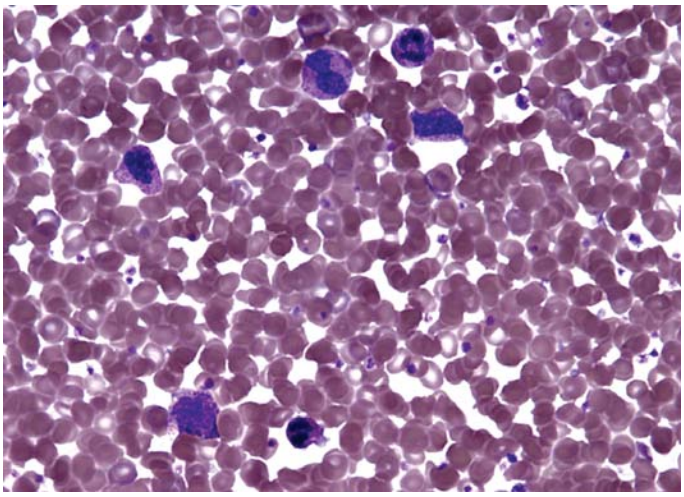


Fig. 13.7: Polycythemia characterized by too many red blood cells

is not recognized. The dentist must be fully acquainted with each disorder and its serious consequences.

AGRANULOCYTOSIS

(Granulocytopenia, *agranulocytic* angina, malignant leukopenia or neutropenia**)**

Agranulocytosis is a serious disease involving the white blood cells. It is characterized by decreased number of circulating granulocytes. It is often classified with reference to etiology as primary or secondary in type, primary agranulocytosis being that form of the disease in which the etiology is unknown, and secondary agranulocytosis being that form in which the cause is recognized. Since the clinical and laboratory findings, both forms are identical, the disease will be discussed here as a single entity.

Etiology

The most common known cause of agranulocytosis is the ingestion of any one or a considerable variety of drugs and infections. Those compounds chiefly responsible for the disease are also those to which patients commonly manifest idiosyncrasy in the form of urticaria, cutaneous rashes and edema. For this reason and because often only small amounts of these drugs are necessary to produce the disease, it appears that the reaction may be an allergic phenomenon, although attempts to demonstrate antibodies in affected patients have not been successful. Moreover, in the case of some of the drugs, the disease occurs only after continued administration. The risks of agranulocytosis associated with select drugs are given in Table 13.1.

Kracke in 1931 was one of the first to point out that a rapid increase in the number of cases of agranulocytosis occurred at the time of the introduction of certain coaltar derivatives for use in therapy. The following drugs and compounds are some of those which have been reported to produce agranulocytosis in some persons:

Amidopyrine	Promazine, mepazine,
Barbiturates	Prochlorperazine and
(including amobarbital)	Imipraimine)
and phenobarbital)	Phenylbutazone
Benzene	Quinine
Bismuth	Sulfonamides
Chloramphenicol	including
Cinchophen	Sulfanilamide,
DDT	Sulfapyridine,
Dinitrophenol	Sulfathiazole and
Gold salts	Sulfadiazine)
Organic arsenicals	Thioglycoic acid
Phenacetin	Thiouracil
phenothiazines and	Tolbutamide
related compounds	Trimethadione
(including	Tripelennamine chlorpromine

Table 13.1: Risks of agranulocytosis associated with select drugs

Drug	RR	Excess risk
Antithyroid drugs	97	5.3
Macrolides	54	6.7
Procainamide	50	3.1
Aprindine	49	2.7
Dipyrone	16	0.6
Trimethorpin-sulfamethoxazole	16	2.4
Thenalidine	16	2.4
Carbamazepine	11	0.6
Digitalis	2.5-9.9	0.1-0.3
Indomethacin	**6.6**	0.4
Sulfonylureas	4.5	0.2
Corticosteroids	4.1	
buta Zones	3.9	0.2
Dipyridamole	3.8	0.2
β-Lactams	2.8	0.2
Propanolol	2.5	0.1
Salicylates	2.0	0.0006

The mechanism that causes agranulocytosis is not understood completely. In drug-induced agranulocytosis, the drug may act as a hapten and induce antibody formation. Thus produced antibodies destroy the granulocytes or may form immune complexes which hind to the neutrophils and destroy them. Auto immune neutropenia due to antineutrophil antibodies is seen in few cases.

Other uncommon causes of agranulocytosis include **Kostmann syndrome** (severe congenital neutropenia) which is most often inherited in autosomal recessive pattern. Autosomal dominant and sporadic cases have also been reported, most often due to mutations in the granulocyte colony-stimulating factor (G-CSF) receptor.

Chronic severe neutropenia has an underlying unknown cause. Myeloid dysplasia occurs in early infancy and is associated with recurrent infections. The condition is due to accelerated apoptosis and decreased expression of bcl-x in neutrophil precursors.

Clinical Features

Agranulocytosis can occur at any age, but is somewhat more common in adults, particularly women. The disease frequently affects workers in the health professions and in hospitals (e.g. physicians, dentists, nurses, hospital orderlies, and pharmacists) Probably because they have easy access to the offending drugs and often use drug samples injudiciously.

The disease commences with a high fever, accompanied by chills and sore throat. The patient suffers malaise,

weakness and prostration. The skin appears pale and anemic, or in some cases, jaundiced. The most characteristic feature of the disease is the presence of infection, particularly in the oral cavity, but also throughout the gastrointestinal tract, genitourinary tract, respiratory tract and skin. Regional lymphadenitis accompanies the infection in any of these locations. If treatment is not promptly instituted, the infection progresses to generalized sepsis, which may be life threatening.

The clinical signs and symptoms develop rapidly in the majority of cases, usually within a few *days, and death may occur* within a week.

Oral Manifestations

The oral lesions constitute an important phase of the clinical aspects of agranulocytosis. These appear as necrotizing ulcerations of the oral mucosa, tonsils and pharynx. Particularly involved are the gingiva and palate. The lesions appear as ragged necrotic ulcers covered by a gray or even black membrane usually no purulent discharge is noticed. Significantly there is little or no apparent inflammatory cell infiltration around the periphery of the lesion, although hemorrhage does not occur especially from the gingival in addition the patient often manifests excessive salivation (Fig. 13.9).

Histologic Features

The microscope appearance of sections through the ulcerated oral lesions is a pathogonomic one and accounts for certain clinical features of the disease since essential fault is the lack of developement of normal granular leucocytes, the ulcerted areas exhibit no polymorpho nuclear reaction to the bacteria in the tissue, and rampant necrosis ensues (Fig. 13.8).

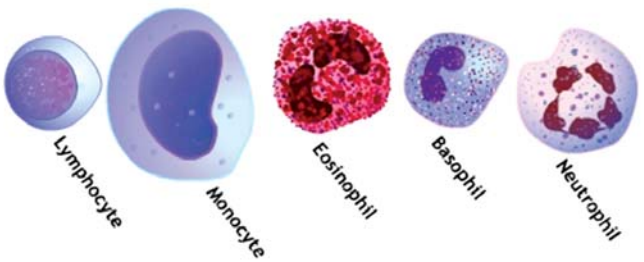


Fig. 13.8: The granulocytes includes neutrophils, eosinophils and basophils, have granules in their cell cytoplasm. Monocyte and lymphocyte are agranulocytes

Labortary Findings

Absence of a defense mechanism. With return of the neutrophil count to normal, the gingiva assumes a nearly normal clinical appearance. In children the repeated insult of infection often leads to considerable loss of supporting bone around the teeth. The widespread severe ulceration usually seen in agranulocytosis does not often occur. However, isolated painful ulcers may occur which persist for 10-14 days and heal with scarring. On this basis, it has been suggested by Gorlin and Chaudhry that some cases diagnosed clinically as periadenitis mucosa necrotica recurrens may actually be cyclic neutropenia.

Roentgenographic Features

The intraoral roentgenograms typically exhibit mild to severe loss of superficial alveolar bone, even in children, as a result of the repeated cyclic gingivitis, advancing to periodontitis. In children, this loss of bone around multiple teeth has sometimes been termed 'prepubertal periodontitis' and it is frequently indicative of a serious systemic disease. Cohen and Morris have discussed the periodontal manifestations of cyclic neutropenia.

Laboratory Findings

Cyclic neutropenia is an unusual disease which manifests the clinical signs and symptoms and blood changes in a

Table 13.2: Infection associated with neutropenia

Viruses and viral illness	Bacterial
Colorado tick fever	Brucellosis
Cytomegalovirus	Gram-negative septicemia
Denguefever	Paratyphoid fever
Epstein-Barr virus	Tuberculosis
Hepatitis virus	Tularemia
Herpes simplex virus	Typhoid fever
Human immunodeficiency Virus type	**Fungal** Histoplasmosis
Influenza A and B	**Protozoal**
Measles	Leishmaniasis
Mumps	Malaria
Parvovirus	Rickettsia
Poliomyelitis	Rickettsial pox
Psittacosis	Rocky Mountain
Respiratory syncytial virus	Spotted fever
Roseola	Typhus fever
Sandfly fever	
Small pox	
Varicella	
Yellow fever	

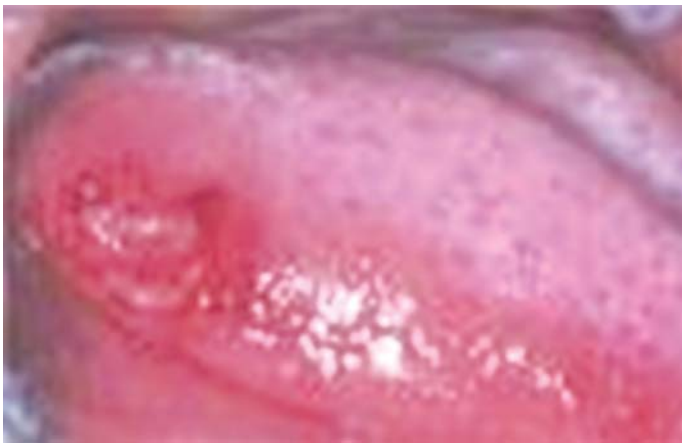


Fig. 13.9: Ulceration of the tongue in agranulocytosis

periodic fashion. The cycle commonly occurs every three weeks, although in some cases it may be several months or even longer in duration. The patient may exhibit a normal blood count which, over a period of four to five days. Begins to show a precipitous decline in the neutrophil count compensated 1 an increase in monocytes and lymphocytes. At the height of the disease, the neutrophils may completely disappear for a period of one or two days. Soon, however, the cells begin to reappear, and within four to five days the blood cell count and differential count are essentially normal.

The infection associated with neutropenia and its differential diagnosis are given in Tables 13.2 and 13.3 respectively.

Treatment and Prognosis

There is no specific treatment for the disease, although some instances splenectonomy has proved beneficial, death occasionally results, usually from intercurrent infection, but the prognosis is generally far better than in typical agranulocytosis. The patients may suffer from their periodic disease for years.

CHEDIAK-HIGASHI SYNDROME

(Beguez Cesar **syndrome,** Chediak-Steinbrinck-**Higashi syudrorrre)**

Chediak-Higashi syndrome (CHS) was described by Beguez Cesar in 1943, Steinbrinck in 1948, Chediak in 1932, and I ligashi in 1954. Cliediak-Higashi syndrome is an autosomal recessive immunodeficiency disorder characterized by abnormal intracellular protein transport.

The Chediak-Higashi syndrome gene was characterized in 1996 as the LYST or CHS1 gene and is localized to bands 102-43 which encodes a lysosomal trafficking regulator. The CHS gene affects the synthesis and/or maintenance of storage or secretory-granules in these cells, e.g. lysosomes of leukocytes and fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils, and melanosomes of melanocytes. The impaired function in the polymorphonuclcar leukocytes may be due to abnormal microtubular assembly. Defective melanization of melanosomes, i.e. autophagocytosis of melanosomes results in oculocutaneous albinism in CHS.

Table 13.3: Differential diagnosis of neutropenia

- Pseudoneutropenia
- Acquired neutropenia
- Infections
  - Bacterial
  - Viral
  - Protozoal
  - Rickettsial
  - Fungal
- Drugs and chemicals
- Nutritional
  - Cachexia and debilitated states
  - B_{12} and folate deficiencies
  - Copper deficiency
- Immune neutropenia
  - Isoimmune neonatal neutropenia
  - Chronic autoimmune neutropenia
  - T lymphocytosis
  - Miscellaneous immunologic neutropenia
- Felty syndrome
- Neutropenia *associated with* complement activation
- Dialysis, bypass
  - Extracorporeal membrane oxygenation
  - Anaphylactoid shock
- Spienic sequestration
- Congenital or chronic neutropenias
  - *Severe* congenital neutropenia (IKostrnann syndrome)
  - Cyclic neutropenia
  - Chronic benign neutropenia
    - Familial
    - Nonfamilial (chronic granulocytapenia of childhood)
    - Idiopathic chronic severe neutropenia
  - Neutropenias associated with congenital immune defects
    - Neutropenia with immunoglobulin abnormality
    - Neutropenia with detective cell-mediated immunity
  - Reticular dysgenesis
  - Neutropenias associated with phenotypic abnormalities
  - Shwachman syndrome
    - Cartilage-hair hypoplasia
    - Dyskeralosis congenita
    - Barth syndrome
    - Chediak-Higashi syndrome
  - Myelokathexia

Clinical Features

Chediak-Higashi syndrome affects all races and usually appears soon after birth or in children younger than five years. This disease is characterized by immune deficiency; partial oculocutaneous albinism; easy bruisability and bleeding as a result of deficient platelet dense bodies:

recurrent infections with neutropenia, impaired chemotaxis, and bactericidal activity; and abnormal natural killer (NK) cell function.

The disease is often fatal in childhood as a result of terminal phase characterized by nonmalignant lymphohistiocytic lymphoma like infiltration of multiple organs that occurs in more than 80 percent of patients. This stage is precipitated by virus infection, particularly by the Epstein-Barr virus. It is associated with anemia, bleeding episodes, and overwhelming infections leading to death. Infections secondary to abnormal functioning of polynorphonuclear leukocytes commonly involve die skin. the lungs, and the respiratory tract. Infections are usually caused by *Staphylococcus aureus, Streptococci's pyogenes*, and *Pneumococcus* species. Very few patients live to adulthood and in these patients, a progressive neurologic dysfunction may be the dominant feature. Neurologic involvement is variable but often includes peripheral neuropathy.

Oral Manifestations

Ulcerations of the oral mucosa, severe gingivitis, and glossitis are the commonly described oral lesions, as in the case report of Gillig and Caldwell, hamilton and Giansanti have pointed out that periodontal break down, probably related to defective Ieukocyte function, may also be a common oral feature.

Laboratory Findings

Hematologic studies show that the patients classically exhibit giant abnormal granules in the peripheral circulating leukocytes, in their marrow precursors, and in many other cells of the body as well, these granules are the hallmark of the syndrome and are invariably present. They are thought to represent abnormal lysosomes and bear resemblance cotoxic granulations and Dohle bodies. Pancytopenia is sometimes present. Ultrastructurally viable dividing bacteria, along with abnormal granules, are found in the cytoplasm of periodontal polymorphonuclear leukocytes.

Treatment and Prognosis

There is no specific treatmcnt for the disease. It is often fatal. with death occuring before the child reaches the age of 10 years.

LEUKOCYTOSIS

Leukocytosis is defined as an abnormal increase in the number of circulating white blood cells. This condition is usually considered to be a manifestation of the reaction of the body to a pathologic situation. Any increase in the number of circulating white blood cells. Particularly when involving only one type of cell, should prompt suspicion of and investigation for a particular disease, especially when the laboratory- findings are correlated with the clinical findings in the patient. Care must be exercised in separating an absolute from a relative leukocytosis. But this should offer little difficulty.

A tabulation of the various conditions in which a pathologic increase in the number of each form of white blood cell is found has been compiled by Wintrobe. In addition, a transient peripheral plasmacytosis, a cell not normally seen in circulating blood, may be found occasionally in a variety of pathologic situations or conditions listed in.

INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER)

Infectious mononucleosis was first described by Sprunt and Evans in the *johns Hopkinsmedical* Bulletin in 1920. These authors described the clinical characteristics of Epstein-Barr virus (EBL) infectious mononucleosis. and. at the time, their paper was entitled 'Mononuclear leukocytosis in reaction to acute infection (infectious mononucleosis)', Since the 1800s, infectious mononucleosis has been recognized as a clinical syndrome consisting of fever, pharyngitis, and adenopathy. The term glandular fever was first used in 1889 by German physicians and was termed drusenfiber.

The disease occurs chiefly in children and *voting adults.* It *has been* transmitted experimentally to monkeys by the administration either of emulsified material from lymph nodes or of Seitz filtrate of the blood from affected human beings. EB virus is transmitted via intimate contact with body secretions, primarily oropharyngeal secretions and one important means is thought to he through 'deep kissing' or intimate oral exchange of saliva. For this reason, the condition has sometimes been called the 'kissing disease'. It is known that oral excretion of the EB virus may continue for as long as 18 months following onset of the disease. Although this excretion may be either constant or intermittent.

Clinical Features

Frequently seen in epidemic form infectious mononucleosis is characterized by fever, sore throat. headache. chills. cough, nausea or vomiting and lympadenopathy (bilateral and symmetrical). Splenomegaly and hepatitis also occur with considerable frequency. Most patients with EBY infections mononucleosis can be asymptomatic.

The cervical lymph nodes are usually the first to exhibit enlargement, followed by the nodes of the axilla and groin. Pharyngitis and tonsillitis are common, but not invariably present, and skin rash has occasionally been reported.

The majority of cases in children appear to be asymptomatic however, the peak incidence of the disease occurs in the 15-20-year-old age group. There does not appear to be a sex or seasonal predilection for recurrence.

Oral Manifestations

There are apparently no specific oral manifestations of infectious mononucleosis. Although secondary' lesions do occur. An excellent review of the literature read study of the oral lesions occurring in 140 patients with infections mononucleosis was reported by Fraser-Moodic. The oral manifestations consisted chiefly of acute gingivitis and stomatitis. The appearance of a white or gray membrane in various areas, palatal petechiae and occasional oral ulcers. Of his entire series of 140 patients. 32 percent exhibited oral manifestations. About one-third of the patients with the hemorrhagic tendency exhibited oronasopharnryngeal bleeding, including bleeding from the gingiva.

Laboratory Findings

The patient exhibits atypical lymphocytes in the circulating blood, as well as antibodies to the EB virus and an increased hetrophil antibody titer However. the increased heterophil is present only in a small minority of children with the disease. The normal titer of agglutinins and hemolysin in human blood against sheep red blood cells does not exceed 1:8. In infections monoucleosis. However, the titer may rise to 1:4096. This is referred to as a positive Paul-Bunnell test and is both characteristic and pathognomonic of the disease. Agglutination of horse RBCs on exposure to EB virus heterophile antibodies (Monospot test) is a highly *specific test-* in *acute infection.* The viral core antigen antibody of IgM class titer against EBV is increased. Later in the course of infection. the increase in IgM viral core-antigen (VGA) antibodies may be accompanied by an increase in IgG VGA antibodies and an increase in IgG EBNA (EBV nuclear antigen antibodies), EBNA appears after one to two months and persists throughout lire. Thus, the presence of this antibody suggests previous exposure to the antigen. The erythrocyte sedimentation rate is elevated in most patients with EBV infectious mononucleosis. An increase in the white blood cell count also common, and this is almost invariably a lymphocytosis. In fact, infectious mononucleosis is defined partly on the basis that the patient **has** more than a 50 percent lymphocytosis of which 10 percent of which 10 percent or more are the atypical forms these a typical forms consists of either oval horse shaper shoe shaped or intended nuclei with dense irregular Or vacuolated cytoplasm. A thrombocytopenia present in some patients. It is an interesting finding that during the acute phase of infectious mononucleosis, patients frequently have **a normal,** sedimentation rate (Fig. 13.10).

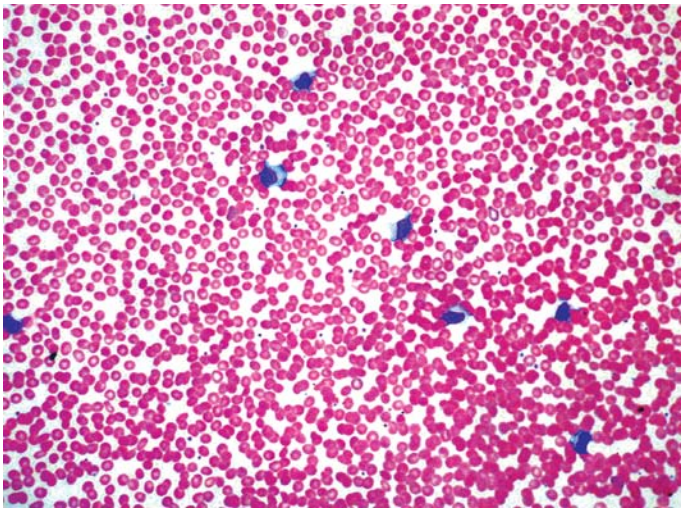


Fig. 13.10: Infectious mononucleosis peripheral smear, low power showing lymphocytosis

Treatment

There is no specific treatment for **this** disease. The various antibiotics have been **used** without great success. Bed rest and adequate **diet** are probably of as great a benefit as any other **form** of therapy. Short-term steroid therapy has **occa**sionally been used, but the results have **bitter** somewhat inconsistent, the disease generally noire its course in two to four nee, and there **seldom** are complications.

LEUKEMIA

Leukemia is a disease characterized by the progessive overproduction of white blood cells which usually appear in the circulating blood in an immature form. This proliferation of white blood cells or their precursors occurs in such an uncordinated and independent fashion that leukemia is generally considered a true malignant neoplasm, particularly since the disease is so often fatal. Any of the white blood cells may be involved by this disorder, and for this reason the disease is often classified according to the following types:

I. Lymphoid (lymphoblastic, lymphocytic leukemia—involving the lymphocytic series.

Myeloid (myelogenous) leukemia—involving progenitor cell that gives rise to terminally differentiated cells of the myeloid series (erythrocytes, granulocytes, monocytes and platelets), e.g. acute myelogenous leukemia, acute promyelocytic leukemia, acute monocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia.

This classification may be modified to indicate the course of the disease by application of the terms *'acute'*, 'subacute,' *and 'chronic.' An acute* form of leukemia is one in which survival is less than six months; chronic leukemia implies a survival of over one year, and the subacute form lies between these two. In general, the course of disease closely parallels the degree of anaplasia of the malignant cells; thus, the more undifferentiated the cell, the more acute is the course. The relation of the leukemias to other malignant disease of the lymphoid tissues is discussed under the section dealing with the malignant lymphomas.

Etiology

The etiology of leukemia is unknown certain aspects of the disease have suggested a infectious origin to some investigators, but a specfic causative organism has never been isolated. *Of these, viruses have* been suspected for many years of being most closely related to this disease it has been recognized for many years that a variety of animal leukemias were almost certainly of viral origin. It has been shown by Stewart and Eddy that the 'polyoma' virus is capable of producing numerous different types of neoplasms in a variety of animals, one of these neoplasms being leukemia.

It is rather well accepted by most workers in the field of viral oncology today that avian, feline and murine leukemia are caused by leukemogenic viruses, however, the animals must be rendered immunologically vulnerable and it is possible that in the human as well as in the experimental animal, radiation and a variety of chemicals, both of which have been closely associated with leukemia many years, may be at least one key to this immunologic susceptibility. Not only is the incidence of leukemia among radiologists approximately 10 times higher than among general practitioners of medicine, but also the data indicate a general rise in the incidence of this disease among the Japanese exposed to the atomic bombblasts at Hiroshima and Nagasaki. In addition, chronic exposure to benzol, aniline dyes and related chemicals has been recognized for many years as being associated with the development of leukemia.

The Epstein-Barr (EB) virus, a herpes like virus, has been implicated as being the most likely leukemogenic virus in humans because of the high antibody titer against this virus in leukemic patients, as well as the finding in leukemic cells of viruses with a morphogenic similarity to the E13 virus. human T-cell leukemia virus-1 (HTLV-I) is known to be associated with a form of T-cell leukemia/lymphoma that is endemic in certain parts of Japan and the Caribbean basin. It is also recognized that chronic abnormalities commonly occur in leukemic patients. One such abnormality is the finding of the Philadelphia chromosome in between 85 and 95 percent of patients with chronic myeloid leukemia. This Philadelphia chromosome, at one time thought to be a partial deletion of the long arm of chromosome 22, is now recognized as a translocation of chromosomal material from chromosome 22 to chromosome 9. In about 5 percent of cases the translocation occurs to other chromosomes. It is interesting to note that this chromosome disappears from the circulation during remission of the disease in many cases but will reappear when there is a relapse. In addition. a variety of other chromosomal abnormalities also have been recognized as occurring in over 50 percent of patients with different forms of poorly differcntiated leukemia.

It should be remembered that mongolism or Down syndrome is due to a defect or trisomy of chromosome 21. Interestingly, it has been found that the incidence of leukemia in mongoloids is between three and 15-2 (1 times that of the general population. However this type of leukemia in; mongoloids is generally an acute form of leukemia in contrast to the chronic leukemia associated with the importance of various cofactors or predisposing characteristics, such as genetics, age, hormones, immune competence and stress, must all be considered in determining the susceptibility to tumor development of an individual infected with an oncogenic virus. Only when this has been accomplished can there be *any* attempt *at specific* cure or even prevention of the disease.

Clinical Features

The age of the patients affected by leukemia varies remarkably but generally rarely correlated with the course of the disease. Thus acute leukemia occurs more common in children and young adults, while chronic leukemias are most frequently seen in adults or middle age or older. There are however, many exceptions to this general rule. There is some difference in die gender predilection, males being affected more often than females. No notable differences exist in the clinical manifestations of the morphologic forms of leukemia except that most cases of acute leukemia in adults are of the monocvtic variety: thus all types of acute leukemia present a similar clinical picture and cannot be differentiated without recourse to laboratory' studies. The same is true for chronic leukemia. For this reason the clinical features of leukemia can be discussed under the general categories of acute and chronic forms of the disease.

Acute Leukemia

The development *of acute* leukemia is sudden , characterized by weakness, fever, headache, generalized swelling of lymph nodes, petecheal or ecchymotic hemorrhages in the skin and mucous membranes and evidence of anemia. The lymphadenopathy is often the first sign of the disease.

although many cases are recorded in which the oral lesions were the initial manifestation. In a survey of chlildren with acute lymphoblastic leukemia. White has shown that in at least two thirds of the cases, cervical lymph nodes are palpable before diagnosis and treatment of the disease have been established (Fig. 13.11).

Numerous organs, such as die spleen, liver and kidney, become enlarged. owing to leukemic infiltration, especially in cases of long duration. In the fulminating variety of the disease there is not time for gross pathologic changes to develop, Hemorrhages are common due to the decrease in platelets incident to involvement of the bone marrow and decrease in megakaryocytes. Terminal infection is frequent and may be related to the crowding out of myeloid tissue which ordinarily produces granulocytes.

Chronic Leukemia

In contrast to acute leukemia, chronic leukemia develops so insidiously that the disease may be present for months or even several years before the symptoms lead to discovery, it is not unusual for this form of leukemia to he found by **a** routine hematologic examination in which an unexplained leukocytosis is noted.

The patient may appear in excellent health or exhibit features such as an anemic pallor and emaciation *suggestive of a* chronic debilitating disease. Lymph node enlargement is common in chronic lymphatic leukemia, but uncommon *in* myeloid leukemia, as might be expected, particularly in the early stages of the disease. The protracted course of the disease allows sufficient rime for full development of splenomegaly and hepatomegaly. Enlargement of the salivary glands and tonsils also may occur. Owing to leukemic infiltration, and this results in xerostomia.

The skin is frequently involved in chronic leukemia and may manifest petechiae or echymoses. In other instances there may be leukemids, papules, pustules, bullae, areas of pigmentation, herpes zoster. itching and burning sensations or a variety of other disturbances. Finally, nodule lesions composed of leukemic cells may occur on the skin.

Destructive lesions of bone are reported in some cases of chronic leukemia, and these may result in pathologic fracture or osteomyelitis (Fig. 13.12).

Laboratory Findings

Hematologic examination constitutes the basis for the final diagnosis of any type of leukemia. It is recognized, however, the 'subleukemic' or `aleukemic' forms of the disease exist in which the white blood cell count of the peripheral blood is normal or even subnormal and in which these are or are not abnormal or immature leukocytes present.

Acute Leukemia

Anemia and thrombocytopenia are both characteristic of acute leukemia. As a result, in some instances, both bleeding time and coagulation time are prolonged. The tourniquet test is usually positive.

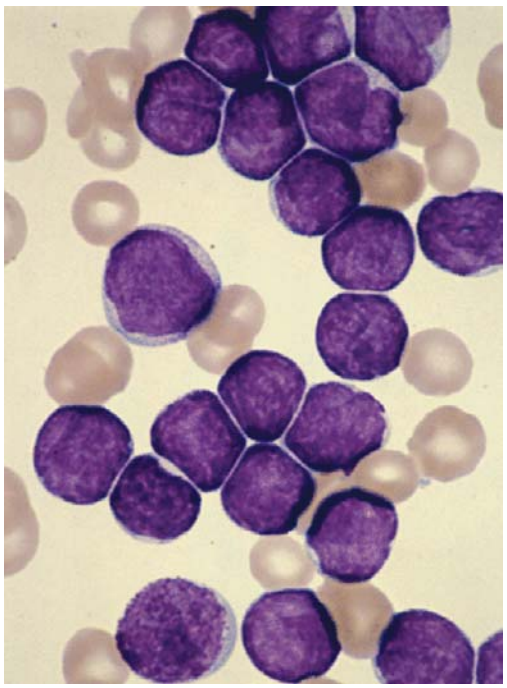


Fig. 13.11: Acute lymphoid leukemia (All) - Marked proliferation of small lymphoblasts

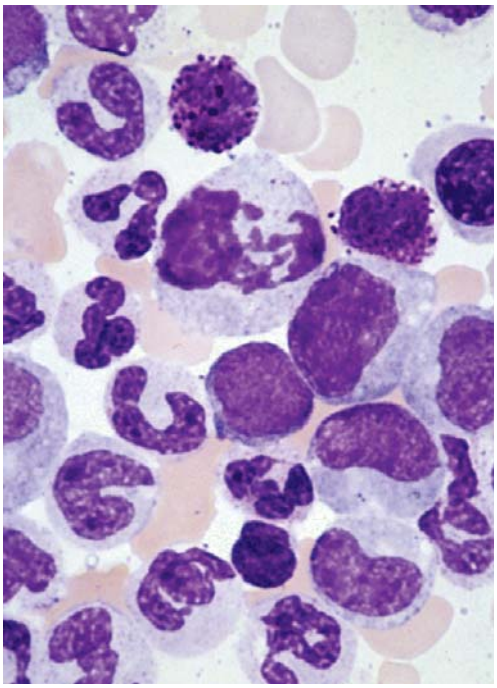


Fig. 13.12: Chronic myeloid leukemia (CML)- Marked proliferation of granulocytes at various stages of maturation

The leukocyte count may be subnormal, particularly in the early stages of the disease, but it usually rises in the terminal stages to 100,000 or more cells per cubic millimeter, and there is a corresponding increase in the proportion of the involved cell in the differential count. This increase in cells is due to a single cell type, usually very immature. In myeloid leukemia the predominant cell often resembles the myeloblast, or undifferentiated myelocyte. The cells of lymphoid leukemia may exhibit considerable variation in degree of differentiation. Monocytic leukemia also manifests poorly differentiated cells.

In many instances, it is difficult if not impossible for even an experienced hematologist to distinguish the exact type of acute leukemia. The term 'stem cell leukemia' is sometimes applied to those types in which the leukemic cells are highly undifferentiated. Such cases are most difficult to diagnose.

Chronic Leukemia

Anemia and thrombocytopenia are also common in the chronic form of leukemia. The leukocytosis may be great, an white blood cell counts of over 500,000 cells per cubic millimeter are not uncommon. On the other hand very low white blood cell counts also occur. In all forms of the chronic dyscrasia the differential count is elevated in the cell type involved, and often over 95 percent of the total number of cells are leukemic cells.

Oral Manifestations

Oral lesions occur in both acute and chronic forms of all types of leukemia: myeloid, lymphoid and monocytic. These manifestations are far more common. However, in the acute stage of the disease, and according to Burket, are most common in monocytic leukemia. In a series of cases he reported oral lesions in 87 percent of patients with monocytic leukemia, in 40 per cent of patients with myeloid leukemia and in 23 percent of those with lymphoid leukemia. Osgood found a similar high incidence of oral manifestations in monocytic leukemia, reporting that 80 percent of affected patients exhibited gingiyal hyperplasia. An 80 percent incidence of positive oral findings was reported in a series of 38 leukemic patients by Duffy and Driscoll. Interestingly, those patients not manifesting oral lesions were either very young children or edentulous persons. In a study of 292 children with leukemia of different types, Curtis found that only slightly less than 30 percent had oral findings suggestive of leukemia. He pointed out that this infrequency of oral manifestations in childhood leukemia is due primarily to the high incidence of acute lymphocytic leukemia in this age group, since this type is least likely to produce oral lesions.

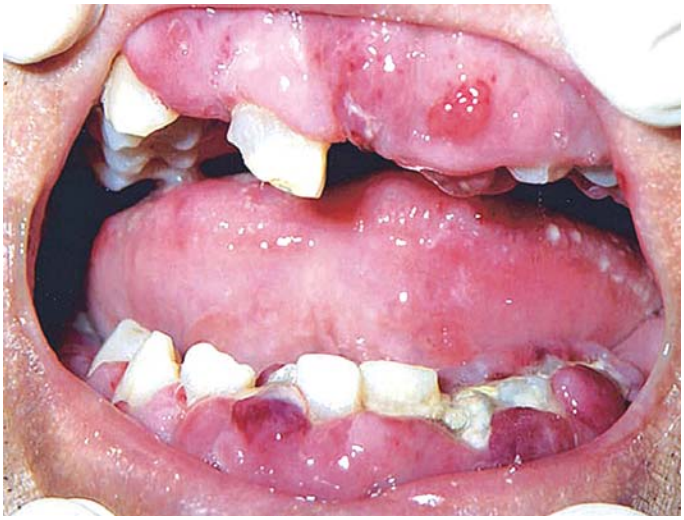


Fig. 13.13: Diffusely swollen gums and infiltration by leukemic cells is common in acute myelomonocytic or monocytic leukemia

Often a patient with leukemia presents himself to his dentist for treatment of oral lesions, not suspecting that they are more than local in nature. These primary clinical manifestations of the disease may consist of gingivitis, gingival hyperplasia, hemorrhage, petechiae and ulceration of the mucosa (Fig. 13.13).

The gingival hyperplasia, which may be one of the most constant features of the disease except in edentulous patients is usually generalized and varies in severity. In severe cases the teeth may be almost completely hidden. The gingiva are boggy, edematous and deep red. They bleed easily. The gingival swelling is due to the leukemic infiltration in areas of mild chronic irritation. Purpuric lesions of the oral **mucosa analogous** to the cutaneous ecchymoses may also be seen. The gingival hemorrhage which commonly occurs is due to ulceration of the **sulcus** epithelium ***and necrosis*** underlying tissue. Since the normal white blood cells distribution is greatly disturbed, a normal inflammatory response to even a mild infection is impossible. For this reason severe ulceration of the oral mucosa and even the development of a noma-like condition is not unusual. Thrombosis of gingival vessels appears to contribute to this phenomenon.

Rapid loosening of the teeth due to necrosis of the periodontal ligament has been reported, and destruction of alveolar bone also occurs in some cases. The use of panoramic radiographs in a study of 214 children with acute leukemia has been reported by Curtis to be useful in demonstrating previously overlooked changes in the jaws. Of this group, approximately 63 percent exhibited osseous changes in the jaws, including alterations in developing tooth crypts, destruction of lamina dura, displacement of

teeth and poor radiographic definition of bone, sometimes extending to the crest of alveolar bones, with destruction of the bone in this area.

It is imperative that the dentist maintain a high index of suspicion in cases of periodontal lesions with a somewhat unusual appearance. The complaint of a patient that he has experienced sudden gingival bleeding or gingival hyperplasia should suggest the possibility of leukemia. As Michaud and her coworkers have indicated in a study of 77 children with the disease, the oral manifestations of acute leukemia may be varied; they are not pathognomonic. Any disease that causes immunosuppression, bone marrow suppression, and disease of the blood-forming organs may have one or more of the oral findings of acute leukemia at the time of its initial diagnosis.

Treatment

Spectacular advances have been made in the treatment of the leukemias over the past few years. At one time, the prognosis for this disease was almost hopeless. Today a wide array of chemotherapeutic drugs, radiation therapy and corticosteroids under certain circumstances offer prolonged remissions and apparent cures in at least some forms of the disease. For example, the most common form of leukemia in children, acute lymphocytic leukemia, once almost always fatal within a few months, now has a prolonged remission and a probable cure rate approaching 50 percent. Because this area of treatment is changing so rapidly *with the* introduction of new drugs and new techniques, to cite data on therapeutic responses would not be meaningful. It is sufficient to note that while leukemia is still a serious disease, the outlook for the leukemic patient today is far more promising than it was only a few decades ago and will probably continue to improve.

DISEASE INVOLVING BLOOD PLATELETS

Blood platelets have a variety of unique and very necessary functions which include: Adhesion to a variety of substances, primarily collagen fibrils in the damaged vessel wall, which initiates a secretory process in which there are extruded from the cell (release reaction) granules including serotonin, adenosine triphosphate (ATP) and adenosine diphosphate (ADP). ADP can directly aggregate platelets, thus accounting for the primary and temporary arrest of bleeding after vascular wall disruption.

Participation in the blood-clotting mechanism by providing a lipid or lipoprotein surface that may catalyze on or more reactions in the conversion of prothrombin to thrombin. This thrombin, in addition to converting fibrinogen to fibrin, can also aggregate platelets. An additional function, recently discovered, is their synthesis of certain prostaglandins which act as potent inhibitors of platelet aggregation in normal blood flow.

Table 13.4: Etiology classification of secondary thrombocytopenia

Conditions associated with a reduction of platelet production
A. Hypopiasia or aplasia of megakaryocytes
   1. Ionizing radiation
   2. Drugs and chemicals (e.g. certain oncolytic compounds, organic solvents, chemotherapeutic agents, antibiotics, anticonvulsants, antihistamines, sedatives and tranquilizers, heavy metals, hair dyes and shoe polishes, insecticides, antithyroid drugs, antidiabetic drugs and a variety of others)
   3. Congenital hypoplastic anemia
   4. Fanconi's familial anemia
   5. Congenital thrombocytopenia with absent radii
   6. Aplastic anemia with thymoma
   7. *Agnogenic* myeloid metaplasia
   8. 'idiopathic'
B. Infiltration of marrow by abnormal cells
   1. Leukemia
   2. Metastatic tumors
   3. Multiple myeloma
   4. The histiocytoses
C. Megaloblastic anemia
D. Metabolic disorders
   1. Azotemia
   2. Hypothyroidism
E. Infection (e.g. many bacterial diseases, including pneumococcal pneumonia, meningococcal infection, erysipelas, scarlet fever, diphtheria tuberculosis, bacterial endocarditis and others; certain spirochetal infections, including syphilis; certain rickettsial infections; many viral infections, including measles, chickenpox, mumps, influenza, smallpox, cat-scratch fever, infectious hepatitis and infectious mononucleosis; certain protozoan and metazoan diseases).

There has been very extensive research within the past two decades to clarify our understanding and secondary, which may be due to a wide variety of situations listed in Table 13.4. One subtype, thrombotic thrombocytopenic purpura, will be discussed separately because of its unusual clinical and histologic features.

Primary Thrombocytopenia (Werlhrof's disease, purpura hemorrhagica and idiopathic purpura)

This is thought by some investigators to be an autoimmune disorder in which a person becomes immunized and develops antibodies against his own platelets. The discovery in the serum of thrombocytopenic patient of an antiplatelet globulin which results in a decrease in the number of circulating platelets when administered to normal patients has given credence to this theory, however, some cases appear due to the absence of a platelet-stimulating or megakaryocyte-ripening factor. The acute

form of the primary type of disease commonly occurs in children, often following:

1. Sensitivity to drugs (e.g. certain sedatives, antipyretics, chemotherapeutic agents, cardiac therapeutic agents, antihistaminics, antidiabetic drugs and a variety of others).
2. Experimental anaphylaxis
3. Infections (same as those listed in 1, E **above)**
4. Hemolytic anemias (e.g. acute idiopathic hemolytic anemia, toxemia of pregnancy, incompatible transfusion reactions)
5. *Systemic* lupus erythematosus
6. Thrombotic thrombocytopenic purpura
7. Idiopathic thrombocytopenic purpura

B. Diseases resulting in platelet sequestration or utilization at an excessive rate

1. Splenomegaly (e.g. congestive splenamegaly. Gaucher's disease, sarcoidosis, miliary tuberculosis)
2. Platelet sequestration (e.g. congenital hemangiomatosis. Kaposi's sarcoma, experirnental hypothermia)
3. Intravascular coagulation: amniotic fluid embolism.

Thrombocytopenia due to dilution of platelets by transfusion of platelet-poor blood IV. Conditions in which thrombocytopenia is of idiopathic pathogenes is infections (same as those listed in I, E above)

- Congenital thrombocytopenia with eczema **and** repeated infections
- Familial thrombocytopenia
- Onyalai
- Thermal burns
- Heat stroke
  - Kwashiorkor
- Macroglobulinemia
- Hypofibrinogenemia with carcinoma, **premed** separation of placenta, etc.
- Paroxysmal nocturnal hemoglobinuna certain viral infections, white the chromic type occurs most frequently in adults, especially women of childbearing age. The various manifestations of primary and secondary thrombocytopenic purpura are nearly identical, and for this reason, may be described together.

Clinical Features

Thrombocytopenic purpura is characterized by the spontaneous appearance of purpuric or hemorrhagic lesions of the which vary in size from tiny, red pinpoint petechiae to large purplish ecchymoses and even massive hematomas. The patient also exhibits a bruising tendency:

Epistaxis, or bleeding from the nose, is a common manifestation of the disease, as are bleeding in the urinary tract, resulting in hematuria, and bleeding in the gastrointestinal tract, producing melena or hematemesis. A possible complication is intracranial hemorrhage, which may result in hemiplegia. The spleen is usually not palpable. If it is palpable, leukemia should be suspected instead of thrombocytopenic purpura.

According to Wintrobe and his associates. over 80 percent of cases of primary thrombocytopenic purpura occur before the age of 30 years, with the greatest incidence before 10 years. Many patients present a familial history of purpura. Secondary thrombocytopenia has no particular age predilection.

Oral Manifestations

One of the prominent manifestations of thrombocytopenic purpura is the severe and often profuse gingival hemorrhage which occurs in the majority of cases. This hemorrhage may be spontaneous and often arises in the absence of skin lesions.

Petechiae also occur on the oral mucosa, commonly on the palate, and appear as numerous tiny, grouped clusters of reddish spots only a millimeter or less in diameter. Actual ecchymoses do occur occasionally.

The tendency for excessive bleeding contraindicates any oral surgical procedure. particularly tooth extraction, until the deficiency has been compensated.

Laboratory Findings

The thrombocytopenia may be exceptionally severe, and the platelet count is usually below 60,000 platelets per cubic millimeter. As a consequence. the bleeding time is prolonged, often to one hour or more. The coagulation time is normal, although the clot does show failure of retraction. As might be expected from the clinical findings, the capillary fragility is increased and the tourniquet test is strongly positive. The red and white blood cell counts are normal unless secondarily disturbed by frequent episodes of hemorrhage or drug or X-ray-induced pancytopenia. Giant platelets on peripheral smear suggest congenital thrombocytopenia.

It is important to understand the basic mechanisms underlying the determination of bleeding and clotting times. Cessation of bleeding as measured by the bleeding time, depends upon the physical blockade of severed capillaries by platelets as long as the number of platelets present in the blood stream is normal and the platelets aggregate properly. There is no alteration in bleeding time. But if the number of circulating platelets is decreased. the normal platelet plugging of the capillaries occurs more slowly and the bleeding time is consequently prolonged. On the other hand, the role of the platelets in the blood clotting mechanism is through release of a thromboplastic

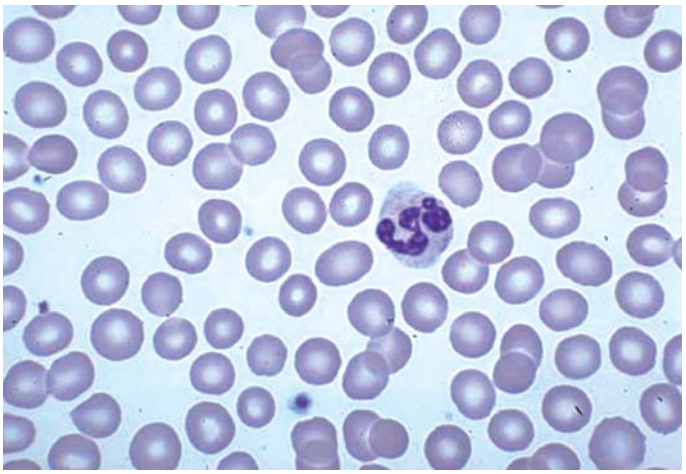


Fig. 13.14: Thrombocytopenia. Fewer platelets seen

factor from agglutinated platelets. This is present in sufficiently large quantities so that, even when there is a reduction in the number of circulating platelets sufficient thromboplastic substance is released to maintain normal coagulation. Therefore, in thrombocytopenia. the coagulation time remains normal.

The blood platelets *are* probably also related to capillaty fragility although the exact mechanism is unknown. It has been suggested that all capillaries undergo daily wear and tear with minor injuries to their walls which are normally plugged by the platelets. It the platelets are diminished, however there is failure of this maintenance of capillary integrity, resulting in an apparent increase in the capillary fragility (Fig. 13.14).

Treatment and Prognosis

There is no specific treatment for this disease, although splenectomy probably has proved more beneficial than any other form of therapy aside From symptomatic relief such as transfusions and bed rest. Corticosteroids have been used in many cases with excellent results, although remissions may be temporary. The prognosis for patients with *this* disease is fairly good. Since remissions are common. Unfortunately, exacerbations are also common, when death ensues, it is usually from sudden severe hemorrhage.

In secondary thrombocytopenia, correction or removal of the etiologic factor is essential.

THROMBOTIC THROMBOCYTOPENIC PURPURA

(Moschcowitz disease, *TTP)*

Thrombotic thrombocytopenic purpura (TTP), an uncommon form of thrombocytopenic purpura, is a life-threatening multisystem disorder of an obscure nature but may be immunologically mediated. It was first described by Eli Moschcowitz in 1924. TTP and hemolvtlc uremic syndrome (HUS) are thrombotic microangiopathies characterized by microvascular lesions with platelet aggregation.

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome share the same pathophysiological etiology and may be varied expressions of the same underlying disease process. TTP is more common in adults and is associated with pregnancy; diseases such as HIV, cancer, bacterial infection, and vasculitis; bone marrow transplantation: and drugs. The TTP syndrome is characterized by microangiopathic hemolysis and platelet aggregation/hyaline thrombi in microcirculation, whose formation is unrelated to coagulation system activity. The thrombi partially occlude the vascular lumina with overlying proliferative endothelial cells. The endothelia of the kidneys and brain are particularly vulnerable to TTP No inflammatory changes are seen but the partial occlusion causes fragmentation o erythrocytes and hemolysis.

Clinical Features

The disease generally occurs in young adults and is more common in females than in males. It is characterized by thrombocytopenia, hemolytic anemia, fever transitionary neurologic dysfunction and renal failure.

Histologic Features

The major findings in this disease are the widespread microthrombi in the arterioles, venules, and capillaries in all tissues and organs throughout the body. These intravascular thrombi are composed of loose aggregates of platelets that become organized into amorphous plugs, which are then replaced by fibrin. All of the clinical features can be traced to the thrombosed microcirculation.

It has been reported by Goldenfarh and Finch that biopsy of gingival tissue in patients suspected of having this *disease* will frequently confirm the diagnosis. Although tissue from many other sites may be used. they believe that gingival tissue is preferable because of its accessible to rapid hemostasis. The characteristic microscopic gingival changes are described as occlusive subintimal deposits of PAS (periodic acid-Schiff)-positive material at arteriolocapillary junctions.

Laboratory Findings

On blood examination at thrombocytopenia and anemia can be noted. Fragmented RBCs (schistocytes) consistent with hemolvsis are noticed in peripheral smear. Reticulocyte count is also elevated in few cases. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are within normal limits. LDH levels are increased. Indirect bilirubin is elevated due to

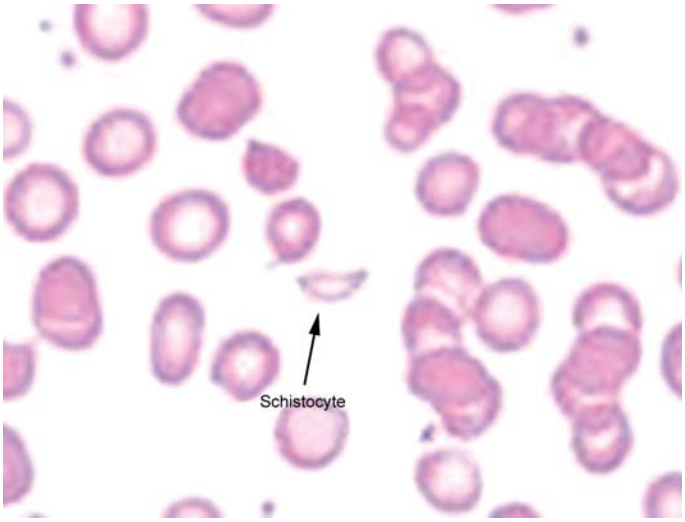


Fig. 13.15: Thrombotic thrombocytopenic purpura

extensive hemolysis. Urine analysis shows proteinuria and microscopic hematuria (Fig. 13.15).

FAMILIAL THROMBASTHENIA (GLANZMANN THROMBASTHENIA OR DISEASE)

Familial thrombasthenia is a hereditary; chronic hemorrhagic disease transmitted as an autosomal recessive trait. There appear to be at least several varieties or forms of Glanzinann disease, thus accounting for the heterogeneous nature of various descriptions of the condition and the bewildering array of biochemical alterations cited.

Clinical Features

Patients with this disease exhibit the usual characteristics of excessive bleeding, either spontaneous or following minor traumatic injury. Both genders may be affected, And in females, the onset of menarche may be a critical event. Purpuric hemorrhages of skin are common, as are epistaxis and gastrointestinal bleeding, hemarthrosis has also been reported.

Oral Manifestations

Spontaneous bleeding from the oral cavity, particularly gingival bleeding, is often seen in these patients as are palatal petechiae.

Laboratory Findings

The bleeding time is prolonged in familial thrombasthenia, while clot retraction characteristically is impaired. However, the platelet count is normal, as is the clotting time. The aggregation of platelets by epinephrine, ADP and thrombin is defective. In addition, it is now recognized that there are reduced amounts of certain membrane glycoproteins on the surface of platelets in this disease. This membrane abnormality may be at least partly responsible for the hemostatic defect.

Treatment

There is no specific treatment. However, Perking and his coworkers have discussed this disease and reported two cases of patients requiring oral surgery who Ivere treated with a microfibrillar collagen preparation and with a fibrinolytic inhibitor, caminocaproic acid, to control postoperative hemorrhage.

THROMBOCYTOPATHIC PURPURA *(THROMBOCYTOPATHIA)*

Thrombocytopathic purpura is a group of rare diseases of unknown etiology in which the patient manifests a bleeding tendency referable to qualitative defects in the blood platelets. It is not related to thrombocytopenic purpura, since the platelet count is usually normal, although the two diseases have been reported to occur simultaneously. It is clinically indistinguishable from thrombasthenia. All acquired form is also recognized associated with a variety of disease conditions such as uremia.

Clinical Features

Patients with thrombocytopathic purpura have a severe bleeding tendency and bruise easily after only minor trauma. Spontaneous ecchymoses are common, although petechial hemorrhages are rare. Epistaxis and bleeding into the gastrointestinal tract are frequent clinical findings. In some cases, menstrual bleeding has been a severe as to require blood transfusions.

Oral Manifestations

The oral manifestations are those that might he expected in such a hemorrhagic disorder. Spontaneous gingival bleeding is common while mucosal ecchymoses occasionally occur. Excessive and prolonged bleeding from dental extractions may be a serious management problem.

Treatment

There is no satisfactory treatment far this disease, although conventional hemostatic agents and blood transfusions aid in controlling the severe hemorrhage. Apparently, death due to prolonged bleeding is rare, but obviously could occur.

THROMBOCYTHEMIA *(THROMBOCYTOSIS)*

Thrombocythemia is a condition characterized by an increase in the number of circulating blood platelets. As in thrombocytopenia, two forms are recognized: primary (or 'essential') and secondary. The etiology of primary thrombocythemia is unknown. Secondary thrombocythemia may occur after traumatic injury, inflammatory conditions, surgical procedures or parturition. In addition, a number of cases have been reported to occur in association with polycythemia and myeloid leukemia, anemia, tuberculosis and sarcoidosis, hyperadrenalism, rheumatoid arthritis and bronchial carcinoma syitli osseous metastases. Secondary thrombocytosis may be due to the overproduction of proinflammatory cytokines, such as IL-1, IL-6, and IL-11, that occurs in chronic inflammatort infective, and malignant states. The presence of elevated IL-I, IL-6. Creactive protein, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) in individuals with this condition suggests that these cytokines may be involved in reactive thrombocytosis.

Clinical Features

No gender or age predilection is seen. Patients with thrombocythemia almost invariably show a bleeding tendency inspite of the fact that their platelet count is elevated. Epistaxis and bleeding into the gastrointestinal tract as well as bleeding into the genitourinary tract and central nervous system are common. Hemorrhage into the skin is also found. Few patients can be asymptomatic and are identified on routine blood counts.

Oral Manifestations

Spontaneous gingival bleeding is one of the more commonly reported findings in cases of thrombocythemia, but petechiae arc rare. Excessive and prolonged bleeding also frequently occurs after dental extractions. Pogrel has discussed this disease as a cause of oral hemorrhage.

Laboratory Findings

The platelet count in thrombocythemia is greatly increased, and it has been suggested that this high concentration interferes with the formation of thromboplastin. One case reported in the literature showed 14.000,000 platelets per cubic millimeter by a method where-by the normal value was approximately 250.000. In addition, there is abnormal platelet aggregation in response to several aggregating agents. The clotting time, prothrombin time, clot retraction and tourniquet test are all normal, although the bleeding time is frequently prolonged. In primary thrombocythemia, both the red and white blood cell counts are normal. But in secondary thrombocythemia, there may be alterations in the red and white cell counts. depending upon the associated condition.

Treatment

The most common treatment has been the administration of radioactive phosphorus (P32) and blood transfusions in cases of severe hemorrhage. Certain cytotoxic drugs, heparin during thrombotic episodes, corticosteroids and aspirin have also been used with some degree of success.

DISEASES INVOLVING SPECIFIC BLOOD FACTORS (HEMOPHILIA) (BLEEDER'S DISEASE, DISEASE OF THE HAPSBURGS, THE DISEASE OF KINGS)

Hemoplilia is a blood disease with a long and interesting history. It is characterized by a prolonged coagulation time and hemorrhagic tendencies. The disease is hereditary: the defect being carried by the X chromosome. It is transmitted as a gender-linked Mendelian recessive trait, thus hemophilia occurs only in males, but is transmitted through an unaffected daughter to a grandson. The sons of a hemophiliac are normal and are not carriers of the trait: the heterozygous daughters carry the defect to half of their sons and as a recessive trait to half of their daughters. The occurrence of hemophilia is theoretically possible in a homozygous female and occasional rare cases have been recorded.

Etiology

There are a number of different types of hemophilia, and there has been extensive investigation and clarification of this disease in recent years. In light of our present knowledge, three chief forms of hemophilia be described. Hemophilia A (classic hemophilia). B, and C Each of these differs from others only in the particular deficiency of the blood clotting factor involved:

Type	Clotting Factor deficiency
Hemophilia A	Plasmathromboplastinogen (Antihemophilicglobulin,AHG) factor VIII
Hemophilia B	plasma thromboplastin component PTC, factor IX
Hemophilia C	Plasma thrmboplasin antecedent (PTA. factor XI)

The *genes for factor* VIII *and factor IX are* located on the long arm of the X chromosome in bands q28 and q27, respectively Genetic abnormalities include deletions of variable size, abnormalities with stop codons, and frameshift detects. Recent data suggest that four percent the cases

Table 13.5: Characteristics of the hemophilioid disorders

Disorder	*Mode of inheritance*	*Prothrombin time (PT) time (P7T)'*	*Partial thromboplastin*	*Bleeding time*
Hemophilia A	Sex-linked recessive	Normal	Prolonged	Normal
Hemophilia B	Sex-linked recessive	Normal	Prolonged	Normal
Vascular hemophilia	Autosomal dominant	Normal	Usually prolonged	Prolonged
Factor II deficiency	7	Prolonged	Prolonged	Normal
Factor V deficiency	Autosomal recessive	Prolonged	Prolonged	Normal
Factor VII deficiency	Autosomal recessive	Prolonged	Prolonged	Normal
Factor X deficiency	Autosomal recessive	Prolonged	Prolonged	Normal
PTA deficiency	Incomplete recessive	Normal	Slightly prolonged	Normal
Fibrnogen deficiency	Autosomal recessive	Prolonged (or incoagulable)	Prolonged (or incoagulable)	Normal+
Factor X deficiency	Autosomal recessive	Normal	Normal	Normal

Classification of hemophilia

Classification	Factor	Cause of hemorrhage
Mild	>5	Major trauma or surgery
Moderate	1-5	Mild-to-moderate trauma
Severe	¢1	Spontaneous, hemoarthrobleeding

of severe hemophilia A result from an inversion mutation. In hemophilia B several mutations such as partial and total deletions, missense mutations that result in the decrease or absence of factor IX or the production of an abnormal molecule. The factor XI gene is located on chromosome 4. Mutations of factor gene cause failure, reduced production of the active protein, and rarely production of an abnormal molecule result in factor XII deficiency.

A deficiency of AI-IC (factor VIII) results in the occurrence of hemophilia A, which is the most common type of hemophilia. However, recent studies now show that factor VII is a glycol protein which contains three distinct components:

1. A clot-promoting factor that corrects the coagulation detect in patients with classic hemophilia.
2. A factor VIII antigen that is present in patients with classic hemophilia but deficient in those with von Willebrand's disease.
3. A component called the von Willebrand factor that is synthesized by endothelial cells that will correct the platelet adherence defect in von Willebrand's disease.

Therefore, in hemophilia A (classic hemophilia), there is only an absence of the clot-promoting factor. **Hemophilia B,** due to a PTC deficiency; is also known as Christmas disease (named after the first patient in whom it was described). Apparently two forms of hemophilia B exist: one in which there are apparently normal levels of the inactive protein, another in which there are deficient levels of the coagulant factor. A PTA deficiency is the cause of hemophilia C. Despite the fact that different blood components are involved in each of the diseases, their clinical and oral manifestations are identical. They will therefore he described together as a single disease. In addition, some of the characteristics of the various hemophiliod disorders are shown, following even slight trauma that produces the mildest of abrasions or cuts. Hemorrhage into the subcutaneous tissues, internal organs, and joint is also a common feature and may result in massive hematoma. It is of interest, though still unexplained, that there is a wide range in the degree of severity of factor VIII deficiencies, with some patients showing only rare and mild bleeding.

Hemophilia C can be distinguished from hemophilias A and B by the absence of bleeding into joints and muscles and by its occurrence in individuals of either genders.

The characteristics of the hemophilioid disorders are given in Table 13.5.

Oral Manifestations

Hemmorrhage from many sites in the oral cavity is a common finding in hemophilia, and gingival hemorrhage may be massive and prolonged. Even the physiologic processes of tooth eruption and exfoliation may be attended with severe prolonged hemorrhage. The oral manifestations of the various forms of hemophilia have been discussed by Spiegel and by Steg and his coworkers. In addition, mandibular 'pseudotumor' of hemophilia has been reported by Stoneman and Beier a condition in which there is subperiosteal bleeding, with reactive new bone formation causing tumor-like expansion of the bone. The problem of dental extractions is a difficult one in

hemophiliacs. Without proper premedication even a minor surgical procedure may result in death from exsanguination. Tooth extraction by means of rubber bands has often been used successfully, the rubber band being placed around the cervix of the tooth and allowed to migrate apically, causing exfoliation of the tooth through pressure necrosis of the periodontal ligament.

Laboratory Findings

The characteristic defect of hemophilia is a prolonged coagulation time. The bleeding time is normal as is the prothrombin time and platelet aggregation. Usually; the activated partial thromboplastin time (aPTT) is prolonged: however, normal aPTT does not exclude mild or even moderate disease. Functional assay of factors is useful in diagnosing hemophilia caused due to dysfunction of coagatletion factors. The combination of low factor VIII and low von Willebrand's factor indicate von Willebrand's disease. *In vitro* the deficiency of the clot-promoting factor in the plasma of hemophiliacs impairs clotting because it appears to retard development of the substance responsible for conversion of prothrombin to thrombin. Separation of the various forms of hemophilia and proper diagnosis depends upon demonstration that the plasma of a patient with known form of hemophilia doesnot correct the plasma clotting defect in the patient under observation.

Treatment

There is no effective treatment for parahemophilia. Transfusion, as well as freshly frozen plasma, are given to replace blood lost through hemmorrage or prior to a necessary surgical procedure. The prognosis is good although a few deaths have been reported as a result of the hemorrhage.

AFIBRINOGENEMIA AND HYPOFIBRINOGENEMIA

Afibrinogenemia is an uncommon disease in which the patient has little or no fibrinogen present in either his plasma or tissues. For time reason die blood cannot clot, even after the addition of thrombin.

A fibrinogen deficiency may be either congenital or acquired. Congenital afibrinogenemia is a rare hereditary disease probably an autosomal recessive trait, occurring in both genders, but with some predilection for males. It is present from the time of birth and appears to be due to an inability of the patient to synthesize fibrinogen rather than any excessive destruction of fibrinogen.

Acquired hypofibrinogenemia generally *occurs* secondary to detective fibrinogens formation, to an increase in fibrinogen consumption during intravascular clotting, or to destruction or digestion of fibrinogen by fibrinolytic or proteolytic enzymes circulating in the blood stream. It may also occur in extravascular sequestration of the protein, in loss of blood through hemorrhage in transfusion reaction and in association with other conditions, including amyloidosis, polycythemia, certain neoplasms and pregnancy.

There *is generally not a complete absence of* fibrinogen in the acquired form of the disease as there is in the congenital type, and this accounts for the difference in use of the terms afibrinogenemia' and 'hypofbrinogenemia,' But since the clinical features in both forms of the disease are almost identical, they will be described together.

Clinical Features

Patients with hypofibrinogenemia or afibrinogenemia exhibit severe bleeding episodes, throughout their lives in the congenital type, and the disease is clinically indistinguishable from hemophilia. However, characteristically in the congenital type, the patients may have long periods of freedom from bleeding. Epistaxis, bleeding into the gastrointestinal tract and central nervous system, and cutaneous echvmoses and hematomas are all common, hemarthrosis is not as prominent as in hemophilia. In affected females, menstrual bleeding is usually normal.

Oral Manifestations

The oral manifestations of congenital afibrinogenemia have been reviewed by Kaanz and Ruff, and those of rile acquired type by Rose. These consist of spontaneous gingival bleeding and prolonged and excessive bleeding following dental extractions. Petechiae of the oral mucosa are rare.

Laboratory Findings

Patients with congenital afibrinogenemia have normal red blood cell, white blood cell and platelet counts, although thrombocytopenia has been occasionally reported. The bleeding time may be normal or slightly prolonged. The most dramatic feature is that the clotting time and prothrombin time are infinite, although this is not necessarily the case in hypofibrinogenemia. The peripheral blood fails to clot even faster the addition of thrombin. The tourniquet test in these patients is normal. Finally, the erythrocyte sedimentation rate is zero, the cells remain suspended even after 24 hours.

Treatment

There is no specific treatment for the disease except for transfusions, particularly for concentrated fibrinogen, during bleeding episodes. Occasional patients develop antibodies against the administered fibrinogen, thus disrupting therapy. Unfortunately, the prognosis is poor, and many patients die of hemorrhage during infancy or early childhood. Some patients do reach adult life. The acquired form of the disease is less serious if recognized in time.

DYSFIBRINOGENEMIA

This is a congenital disease probably transmitted as an autosomal dominant characteristic which appears to represent a group of familial disorders rather than a single entity. For example, there may be impairment of the rate at which thrombin cleaves fibrinopeptides from fibrinogen. There may be replacement of one amino acid residue by another in the NH2 terminal part of the A< chain of fibrinogen, as in fibrinogen , which arginine replaces serine. In fibrinogen Philadelphia. The abnormal protein is catabolized at an accelerated rate.

Fibrinogen is usually present in normal amounts in this disease, but is detective in its structure and coagulability so that the aggregation of fibrin monomers is impeded. In one variant, the abnormality of fibrinogen appears to be one manifesting defective cross-linking between fibrin strands after clotting has occurred.

Acquired dysfibrinogenemias, often called dysfibrinogenemia of liver disease commonly due to severe liver disease secondary to cirrhosis, hepatoma, or hepatitis exhibit bleeding complications.

The disease manifests itself clinically by a mild to severe bleeding tendency although, interestingly, paradoxical thrombosis has also been reported. (Fibrinogen also is an abnormal fibrinogen that is associated with thromboembolic complications. The abnormal fibrinogen in these patients forms a fibrin clot that is resistant to fibrinolysis by plasmin).

Laboratory Findings

Prothrombin time (PT) is prolonged (the most sensitive screening test). Activated partial thromboplastin time (aPTT) may be prolonged.

Treatment

Medical treatment is not required in majority of patients. Fresh frozen plasma or cryoprecipitate may be transfused in case of bleeding.

FIBRIN-STABILIZING FACTOR DEFICIENCY

(Factor XIII deficiency)

Congenital Factor XTTT or fibrin-stabilizing factor (factor XIII) deficiency, originally recognized by Duckert in 1960 is a rare autosomal recessive disease, with a high incidence of consanguinity. Acquired factor XIII deficiency has been described in, association with hepatic failure. Inflammatory bowel disease, and myeloid leukemia.

Inherited factor XIII deficiency is usually due to mutations in the gene encoding the catalytic subunit located on chromosome 6. More than 40 different mutations have been identified, half of which are missense Mutations. In patients homozygous for this defect, the a subunit is absent in plasma, platelets, and monocytes, result*ing in a severe* bleeding diathesis: the *concentration of subunits is* relatively normal. Biochemically, thrombin appears *to* activate *factor* I II Irons an inactive precursor fibrin This activated factor XIII then cross-links fibrin or stabilizes it by transamtidation. In the absence of this factor, there is failure of permanent peptide bonds between fibrin molecules so that the fibrinogen monomer aggregates (fibrins) break up under certain conditions. Factor:III covalently binds fibronectin. 2-plasmin inhibitor, and other molecules to the fibrin plug this enhances adherence to the wound site, resistance to fibrinolysis, and wound healing.

Clinical Features

Patients with this deficiency have severe postsurgical bleeding episodes which are typically delayed for 24-36 hours, hemarthrosis and defective wound healing. Bleeding and clotting times are both normal. Bleeding from the stump of the umbilical cord within the first days to week of life is a characteristic sign that occurs in 80 percent of affected individuals. Soft tissue bleeding and bruising are very common as is bleeding into the mouth and gums during teething.

Laboratory Findings

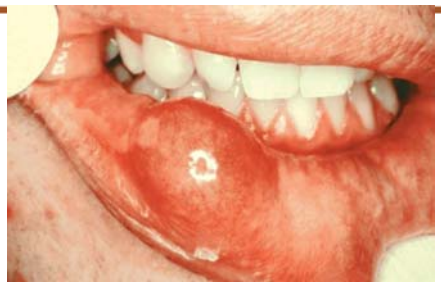
Measurement of clot stability is the most commonly used screening test for factor XIII deficiency. In the absence of factor XIII the clot dissolves in minutes to hours. Factor XIII ct and factor XIII J3 antigen levels can be quantified by means enzyme-linked immunosorbent assay (ELISA) techniques.

Treatment

Plasma cryoprecipitate, and factor XIII concentrates have been used for replacement of factor XIII and the treatment of bleeding.

14

Physical and Chemical Injuries of the Oral Cavity



BRUXISMS *(Night-grinding, Bruxomania)*

Bruxism is the habitual grinding of the teeth, either during sleep or as an unconscious habit during waking hours. This term is generally applied both to the clenching habit, during which pressure is exerted on the teeth and periodontium by the actual grinding or clamping of the teeth and also to the repeated tapping of the teeth (Fig. 14.1).

Etiology

The causes of bruxism have been described as: (1) local (2) systemic (3) psychological, and (4) occupational.

Local Factors

Local factors are generally associated with some form of mild occlusal disturbance, which produces mild discomfort and chronic, even though unrecognized, tension. It has been suggested that in many cases bruxism becomes a firm habit as a result of an unconscious attempt by the patient to establish a greater number of teeth in contact or to counteract a local irritating situation. In children, the habit is frequently associated with the transition from the deciduous to the permanent dentition and may result from an unconscious attempt to place the individual tooth planes so that the musculature will be at rest.

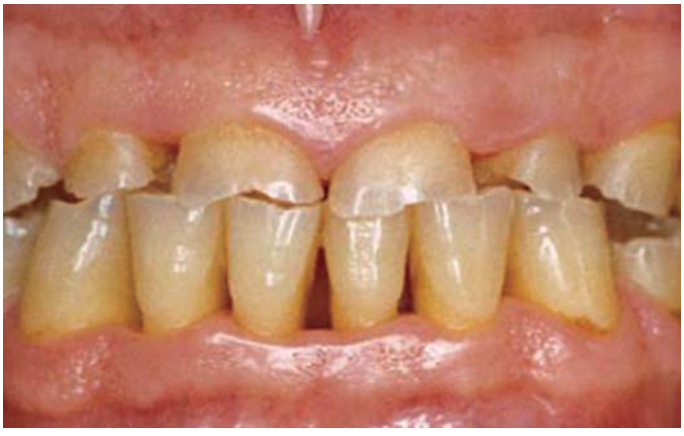


Fig. 14.1: Bruxism

Systemic Factors

Systemic factors have been proposed as etiologically significant but the role of most of these is difficult to assess. Gastrointestinal disturbances, subclinical nutritional deficiencies and allergy or endocrine disturbances have all been reported as causative factors. It is also seen in cases of acrodynia.

Psychological Factors

Psychological factors are believed by some investigators to be the most common cause of bruxism. Emotional tension may be expressed through a number of nervous habits, one of which may be bruxism. Thus, when a person suffers from fear, rage, rejection or a variety of other emotions which he is unable to express, these become hidden in the subconscious but are expressed periodically by numerous means. Bruxism is a manifestation of nervous tension in children also and may be related to chronic biting or chewing of toys.

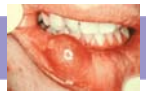
Occupations

Occupations of certain types favor the development of this habit. Athletes engaged in physical activities often develop bruxism, although the exact reason for this is uncertain. Occupations, in which the work must be unusually precise, such as that of the watchmaker, are prone to cause bruxism. Voluntary bruxism is also recognized in those persons who habitually chew gum, tobacco, or objects such as toothpicks or pencils. Although voluntary, this too is a nervous reaction and may lead eventually to involuntary of subconscious bruxism.

Clinical Presentations

The person who engages in bruxism performs the typical grinding or clenching motions during sleep or subconsciously when awake. These may be associated with a grinding or grating noise. The symptomatic effects of this habit have been divided them into six major categories:

- Effects on the dentition,
- Effects on the periodontium,



- Effects on the masticatory muscles.
- Effects on the temporomandibular joint,
- Head pain, and
- Psychological and behavioral effects.

When the habit is firmly established, severe wearing or attrition of the teeth may occur, not only occlusally, but also interproximally. On both surfaces, actual facets may be worn in the teeth.

As the bruxism continues, there may be loss of integrity of the periodontal structures, resulting in loosening or drifting of teeth or even gingival recession with alveolar bone loss. Temporomandibular joint disturbances are also reported to occur as a result of the traumatic injury of continuous tooth; impact without normal periods of rest. Hypertrophy of the masticatory muscles, particularly the masseter muscle, may interfere with maintenance of the rest position, cause trismus, and alter occlusion and the opening and closing pattern of the jaws.

Finally, while it has been suggested that bruxism may give rise to facial pain and headache as well as psychological and behavioral effects, these are very difficult manifestations to evaluate and correlate.

Treatment and Prognosis

If the underlying cause of the bruxism is an emotional one, the nervous factor must be corrected if the disease is to be cured. Removable splints to be worn at night may be constructed to immobilize the jaws or to guide the movement so that periodontal damage is minimal. If the disease is left untreated, severe periodontal and/or temporomandibular disturbances may result.

FRACTURES OF TEETH

Tooth fracture is a common injury, which may arise in a variety of situations, the most frequent of which is sudden severe trauma. This is usually a fall, a blow, an automobile accident, or any of a large number of incidents in which children especially are frequently involved. Some cases of fracture occur when a tooth is weakened as by a large restoration, particularly MOD (mesial-occlusal-distal) fillings in premolars, leaving thin walls or unsupported cusps which give way under the stress of mastication. A similar weakening and subsequent fracture occur also in cases of internal resorption of teeth. Endodontically treated teeth are often described as being somewhat brittle and susceptible to fracture. Teeth affected by dentinogenesis imperfecta or other congenital or acquired conditions that affect the integrity of the tooth structure may also be prone to fracture.

Clinical Presentations

Although fracture of teeth may occur at any age, children are especially prone to sustain this type of injury. The prevalence of tooth fracture is difficult to assess or evaluate, particularly since minor chipping of teeth is common.

As might be expected, boys are more frequently involved than girls. There is a definite predilection for involvement of maxillary teeth with between 75 and 90 percent of fractures occurring there.

There are several classifications of fractured teeth, the simplest being only whether or not the fracture line involves the pulp. A more detailed classification is that of **Ellis**, who divides all traumatized anterior teeth (for these constitute the vast majority of such injuries) into nine classes:

Class 1. Simple fracture of the crown involving little or no dentin.
Class 2. Extensive fracture of the crown involving considerable dentin but not the dental pulp.
Class 3. Extensive fracture of the crown, involving considerable dentin and exposing the dental pulp.
Class 4. The traumatized tooth becomes nonvital, with or without loss of crown structure.
Class 5. Teeth lost as result of trauma.
Class 6. Fracture of the root, with or without loss of crown structure.
Class 7. Displacement of a tooth without fracture of crown or root.
Class 8. Fracture of the crown en masse and its replacement.
Class 9. Traumatic injuries to deciduous teeth.

The clinical manifestation as well as the treatment and prognosis of the fractured tooth depend chiefly upon whether the dental pulp is pierced by the fracture and whether the crown or the root of the tooth is involved. If there is crown fracture without pulp involvement, vitality of the tooth is usually maintained, although there may be mild pulp hyperemia even when the overlying dentin is relatively thick. If the dentin over the pulp is exceedingly thin, bacteria may penetrate the dentinal tubules, infect the pulp and produce pulpitis leading to death of the pulp. When vitality is maintained, usually a layer of secondary dentin is deposited over the involved dentinal tubules. The tooth may be sore and slightly loose because of the traumatic injury, but severe pain is usually absent.

A fractured tooth crown, which exposes the pulp, is a more serious problem, but pulp exposure does not necessarily imply that death of the pulp will occur. In some cases, the exposure can be tapped by calcium hydroxide

and a dentinal bridge will form as a part of the healing reaction. Pulpotomy or pulpectomy may often be necessary, however, since the pulp becomes infected almost immediately after the injury.

Root fractures are somewhat uncommon in young children since their tooth roots are not completely formed and the teeth have some resilience in their sockets. When fractures do occur, they are mostly horizontal fractures in the middle third of the root. The second most common root fracture occurs in the apical third of the root. Most teeth become nonvital immediately when root fracture occurs. Some root fractures may heal by forming an inner layer of reparative dentin on the pulpal wall, or they may replace the hard tissue along the fracture line with granulation tissue that progresses to mature connective tissue. Some root fractures remain vital and proceed to round off the sharp fracture edges, separating the two fragments becoming surrounded by granulation tissue, which usually results in extensive resorption with eventual tooth loss. The chances of tooth resorption are minimized if the tooth is immobilized for a time.

Cemental tears result if the traumatic event is not forceful enough to fracture the tooth. Cemental tears are small fractures of cementum, usually the result of sudden torsional (rotational) forces.

Histologic Features

Healing in such cases may be of several types. The most satisfactory form of healing is the union of the two fragments by calcified tissue and this is analogous to the healing of a bony fracture. The clot between the root fragments is organized and this connective tissue is subsequently the site of new cementum or bone formation. There is nearly always some resorption of the ends of the fragments, but these resorption lacunae ultimately are repaired. If the apposition between the two fragments is not close, the union is by connective tissue alone.

TOOTH ANKYLOSIS

Ankylosis between tooth and bone is an uncommon phenomenon in the deciduous dentition and even more rare in permanent teeth.

Ankylosis ensues whenever the connective tissue of the periodontal ligament is lost allowing cementum and/or dentin to come in direct contact with alveolar bone, leading to fusion of these two opposing calcified structures. Ankylosis is also found when the normal physiologic resorption of the roots of deciduous teeth is interrupted or curtailed. When this occurs, the granulation tissue surrounding the resorbing roots reverts to a fibrous tissue that eventually goes on to become bone and fuses with the surrounding alveolar bone. Ankylosis does occur rather frequently after acute or chronic trauma to a tooth leading to inflammation and destruction of the periodontal ligament. Autoimplanted or reimplanted avulsed teeth in which the periodontal ligament has been destroyed usually undergo some degree of ankylosis if they are not lost by external resorption.

Clinical Presentations

Ankylosis of the deciduous teeth leads to 'submerged' teeth. Ankylosis of the permanent tooth seldom manifests clinical symptoms unless there is a concomitant pulp infection, which may be the underlying cause. If there is an extensive area of the root surface involved, the tooth may give a dull, muffled sound on percussion rather than the normal sharp sound. The fact that this condition exists may become apparent only at the time of extraction of the tooth. when considerable difficulty will be encountered, sometimes necessitating surgical removal.

Roentgenographic Features

If the area of ankylosis is of sufficient size, it may be visible on the roentgenogram as a loss of the normal thin radiolucent line that represents the periodontal ligament, with a mild sclerosis of the bone and apparent blending of the bone with the tooth root.

Histologic Features

Microscopic examination reveals an area of root resorption, which has been repaired by a calcified material, bone, or cementum, which is continuous with the alveolar bone. The periodontal ligament is completely obliterated in the area of the ankylosis.

Treatment

There is no treatment for ankylosis, although any infection present should be treated by appropriate measures. Ankylosed teeth have a good prognosis, and unless removed for some other reasons, should serve well.

EOSINOPHILIC ULCERATION

(Traumatic granulaoma, traumatic ulcerative granuloma with stromal eosinophilia [TUGSE], eosinophilic granuloma of tongue)

Eosinophilic ulceration is a histologically unique type of chronic ulceration of the oral mucosa characterized by a deep pseudoinvasive inflammatory reaction and is typically slow to resolve. The cause is unknown but a traumatic background has been suggested. Trauma may be due to missing. malposed teeth, partial denture, or more

commonly, erupting teeth during nursing which result in sublingual ulcerations in infants. The latter characteristic ulcerations of infancy are referred to as *Riga-Fede disease.*

Eosinophilic ulcerations not associated with trauma do occur rarely, with an inflammatory infiltrate suggestive of neoplastic process. These lesions are termed as *atypical eosiniphilic ulcerations (atypical histiocytic granuloma)* are believed to represent the oral counterpart of a T-cell cutaneous lymphoproliferative disorder that also exhibits sequential ulceration, necrosis, and self-regression.

Clinical Presentations

Eosinophilic ulcerations are commonly observed in all age groups, with a significant male preponderance. They are usually seen in the anteroventral and dorsal surfaces of the tongue even though lesions may also be observed in other sites such as the gingiva, the palate, and the mucobuccal fold. The ulcerations usually persist up to a week or even up to eight months. They resemble the simple traumatic ulcerations, appearing as area of erythema surrounding a central removable yellow fibropurulent membrane. Further, rolled borders of hyperorthokeratosis may develop immediately adjacent to the area of ulceration. The proliferation of the underlying granulation tissue can lead to raised lesion resembling pyogenic granuloma.

Riga-Fede disease appears in infancy between one week and one year of life. Lesions are usually observed on the anteroventral surface of the tongue. caused by contact with the mandibular incisors. Lesions do occur on the anterodorsal surface of the tongue associated with the maxillary incisors. These associated teeth are natal or neonatal teeth in most instances.

Atypical eosinophilic ulceration presents commonly as surface ulceration of the tongue in older individuals, usually above 40 years of age.

Histologic Features

Eosinophilic ulcerations are similar to simple traumatic ulcerations in histologic pattern except for features like deeper extension of the inflammatory infiltrate, presence of sheets of lymphocytes and histiocytes along with eosinophils, and hyperplasia of the vascular connective tissue leading to elevation of the surface ulceration.

It has been suggested that the ulceration resulting from trauma permits the ingress of microorganisms, toxins and foreign proteins into the connective tissue. In predisposed persons, these substances induce a severe inflammatory response resulting from an exaggerated mast cell-eosinophil reaction similar to that noticed in the pathogenesis of bronchial asthma.

The histologic appearance in atypical eosinophilic ulceration is similar to eosinophilic ulcerations, except few striking features like replacement of deeper tissues by a highly cellular proliferation of large lymphoreticular cells which show features of mitosis and are pleomorphic, along with mature lymphocytes and eosinophils. These large atypical cells have been identified as T-Iymphocytes, the majority of which react with CD 30 (Ki-I).

Treatment and Prognosis

Treatment of eosinophilic ulcerations is similar to simple traumatic ulcerations. Even large eosinophilic ulcerations heal rapidly after a biopsy. Even though extraction of the involved teeth solves the problem in Riga-Fede disease, the teeth should be retained if they are stable. In atypical eosinophilic ulcerations, the presence of lymphomas elsewhere in the body should he ruled out. There is no evidence of dissemination of this condition even though recurrences are common.

MUCOCELE

(Mucous extravasation phenomenon, mucous escape reaction)

The mucocele is a common lesion of oral mucosa involving salivary glands and their ducts (Fig. 14.2). They result from traumatic severance of a salivary duct, such as that produced by biting the lips or check, pinching the lip by extraction forceps, and the like, leading to spillage of mucin into the surrounding tissues. As these cysts lack an epithelial lining, they are not true cysts.

Clinical Presentations

Mucoceles are most commonly found on the lower lip. Less common sites include buccal mucosa, anterior ventral tongue (involving the glands of Blandin-Nuhn), and floor of the mouth (ranula).

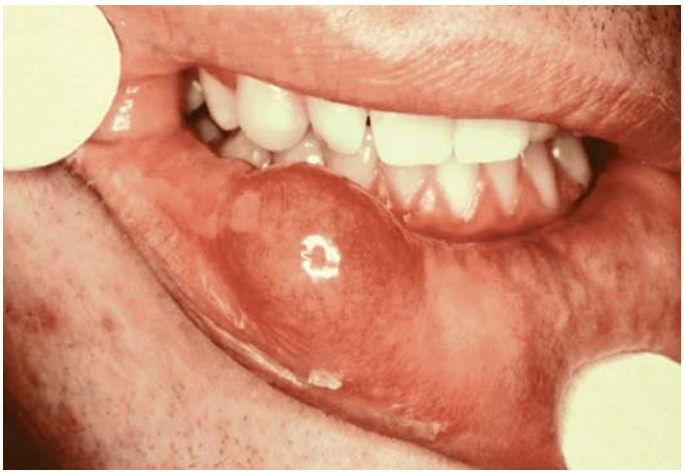


Fig. 14.2: Mucocele

Mucoceles are commonly observed in all decades of life, with increased predilection in children and young adults, possibly because of the higher chance of trauma in the latter age group.

Clinically, mucoceles appear as raised dome-shaped vesicles, ranging in size from 1 or 2 mm to several centimeters. There might be a history of rupture, collapse, and refilling which may be repeated.

Superficial mucocele, a variant of mucocele is commonly seen in soft palate, retromolar area, and posterior buccal mucosa, presenting as single or multiple tense vesicles measuring 1-4 mm in diameter. The vesicle appearance is created by the superficial nature of mucin spillage, resulting in a separation of epithelium from the underlying connective tissue. The vesicles often rupture, leaving shallow, painful, ulcers that heal within few days.

Histologic Features

Mucoceles consist of a circumscribed cavity in the connective tissue and submucosa, producing an obvious elevation of the mucosa with thinning of the epithelium as though it were stretched. The wall of the cavity is made up of a lining of compressed fibrous connective tissue and fibroblasts. Sometimes these cells may be mistaken for flattened epithelial cells. The connective tissue wall is essentially granulation tissue, but in any event it usually shows infiltration by abundant numbers of polymorphonuclear leukocytes, lymphocytes, and plasma cells. The lumen of the cyst-like cavity is filled with the spilled mucin containing variable numbers of cells, chiefly leukocytes and foamy histiocytes (macrophages).

Occasional mucoceles demonstrate an intact, flattened epithelial lining. It is probable that this simply represents the portion of the excretory duct bordering the line of severance, if severance is actually the manner in which these lesions develop. The flattened epithelial lining has been referred to as epithelium of the 'feeder duct'. In other instances, the epithelium-lined mucocele represents a mucous retention cyst.

The salivary gland acini, which lie adjacent to the area of the mucocele and are associated with the involved duct, often show alterations. These may consist of interstitial inflammation or sialadenitis, dilatation of intralobular and interlobular ducts with collection of mucus, and breakdown of individual acinar mucous cells resulting in the formation of tiny areas of pooled mucus.

Treatment and Prognosis

Treatment of the mucous retention phenomenon is excision. If the lesion is simply incised, its contents will be evacuated, but it will be rapidly filled again as soon as the incision heals. There is occasional recurrence after excision, but this possibility is less likely if the associated salivary gland acini are removed also.

RANULA

The ranula is a form of mucocele that specifically occurs in the floor of the mouth (Fig. 14.3). The name is derived from the Latin word ***rana***, which means frog, because the swelling may resemble a frog's translucent underbelly. The term ranula also has been used to describe other similar swellings in the floor of the mouth including true salivary duct cysts, dermoid cysts, and cystic hygromas.

Clinical Presentations

Ranulas usually appear as dome-shaped, fluctuant swellings in the floor of the mouth with a translucent blue color. Deeper ranulas are normal in color. This lesion, which is rare compared to the conventional mucocele, develops as a slowly enlarging painless mass located lateral to the midline of the floor of the mouth. This feature may help to distinguish ranulas from a midline dermoid cyst. The large ranulas may be several centimeters in diameter, filling the floor of the mouth and elevating the tongue. A rare suprahyoid type of ranula, termed plunging or cervical ranula, occurs due to herniation of spilled mucin through the mylohyoid muscle, producing swelling within the neck.

Histologic Features

The microscopic appearance is similar to that of the smaller mucoceles that occur in other locations. The spilled mucin elicits a granulation type of response that typically contains foamy histiocytes.

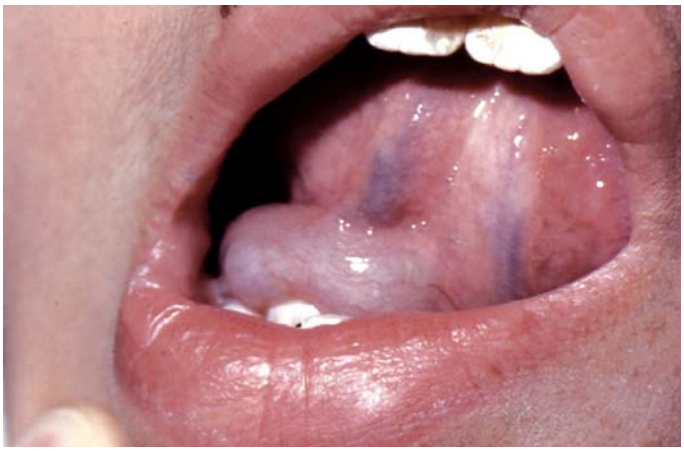
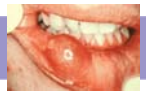


Fig. 14.3: Ranula



Treatment and Prognosis

The treatment and prognosis are also the same except that some operators prefer only to unroof the lesion rather than to excise it totally. Occasionally the lesion recurs. Some prefer initially to excise the entire sublingual gland.

MAXILLARY ANTROLITHIASIS *(ANTRAL RHINOLITH, ANTROLITH)*

Maxillary antrolithiasis is a relatively rare condition which is defined as a complete or partial calcific encrustation of an antral foreign body, either endogenous or exogenous, which serves as a nidus.

An endogenous nidus may consist of a dental structure such as a root tip or may simply be a fragment of soft tissue, bone, blood, or mucus. Exogenous nidi are uncommon, but may consist of such materials as snuff or paper.

Clinical Presentations

The antrolith may occur at any age in either gender. There may be a complete absence of symptoms, although some cases are marked by pain, sinusitis, nasal obstruction, and/or foul discharge, and epistaxis. Some cases are discovered accidentally during roentgenographic examination in which an opaque mass is evident in the sinus.

Treatment

The antrolith should be surgically removed.

RHINOLITHIASIS

Rhinolithiasis is a condition analogous to antrolithiasis, except that the calcification of the foreign body occurs intranasally. The rhinolith might be present for years and frequently gives rise to odorous discharge and symptoms of nasal obstruction, as well as pain and epistaxis.

X-RAY RADIATION

The general term 'radiation' is applied to two different forms of energy:

- That derived from electromagnetic radiation, and
- That derived from particle radiation.

Electromagnetic radiation consists of a continuous spectrum of varying wavelengths ranging from long electrical and radiowaves down through Infrared, visible light, ultraviolet light, roentgen rays, and gamma rays. Particle radiation is generated through spontaneous decay of various natural and artificial radioactive materials. Accelerating deuterons, electrons and so forth, in devices such as the cyclotron and the betatron, may also generate particles.

Certain natural radioactive elements such as radium and thorium give off radiant energy spontaneously in their decay process. A portion of this is electromagnetic or gamma rays, but most of the radiation consists of alpha and beta particles. Alpha particles, which are helium nuclei in rapid motion, have little ability to penetrate tissues and thus give up their energy in a **very** short distance. Beta particles, which are negatively charged electrons in rapid motion, have a greater penetrating power than alpha particles, but lose their energy *in a few* millimeters *of tissue.* Alpha *and* beta particles actually have little use in medical therapy and are important chiefly as hazards.

The half-life of these radioactive isotopes ranges from a fraction of a second to centuries. In recent years, many of these radioactive isotopes have found use in medicine as tracer substances, therapeutic agents and diagnostic agents, as well as in many areas of research.

These different types of radiant energy or radiation are sometimes spoken of as 'ionizing radiation'. This term refers to rays which carry enough energy to produce ionization in materials which absorb them, including living tissues. The most commonly used unit of measure of x-ray and gamma ray exposure is the roentgen(r). Another important unit of radiation measurement is the rad or radiation absorbed dose.

A roentgen and a rad are roughly equivalent, although they can very markedly depending upon the type of tissue or material involved. In contrast to these precise *physical measures of* exposure *and* absorbed dose, there is no adequate unit of biologic measurement of dosage, the most closely approaching this being the 'skin erythema dose' (SED). This is often used to indicate the exposure just sufficient to produce reddening of the skin. Unfortunately, it varies widely among different persons.

General Effects of Radiation on Tissue

The exact means by which radiation exerts its effect on cells and tissues is unknown. Most investigators believe that it is related to the mechanism of ionization, localized injures being produced in single cells. The cellular injury has been postulated to be due to a number of possible factors. These include:

- Toxic effect of protein breakdown products.
- Inactivation of enzyme systems,
- Coagulation or flocculation of protoplasmic colloids, or
- Denaturation of nucleoproteins.

There is great variation in the radiosensitivity of different types of living cells despite the fact that it is possible to kill any living thing with sufficiently large doses of radiation (Table 14.1). In general, embryonic immature, or poorly differentiated cells are more easily injured than differentiated cells of the same type. Significantly all cells

Table 14.1: Radiosensitivity of normal cells and tissues

1. **Radiosensitive** (2500 r or less kills or seriously injures many cells)
   - Lymphocytes and lymphoblasts
   - Bone marrow (myeloblastic and erythroblastic cells)
   - Epithelium of intestine and stomach
   - Germ cells (ovary and testis)
2. **Radioresponsive** (2500-5000 r kills or seriously injures many cells)
   - Epithelium of skin and skin appendages
   - Endothelium of blood vessels
   - Salivary glands
   - Bone and cartilage (growing)
   - Conjunctiva, cornea and lens of eye
   - Collagen and elastic tissue (fibroblasts themselves are resistant)
3. **Radioresistant** (over 5000 r necessary to kill or injure many cells)
   - Kidney
     - Liver
     - Thyroid
   - Pancreas
     - Pituitary
     - Adrenal and parathyroid glands
     - Mature bone and cartilage
     - Muscle
     - Brain and other nervous tissue

show increased vulnerability to radiation injury at the time of mitotic division. Furthermore, if cells are irradiated during the resting phase, mitosis is delayed or inhibited.

Latent tissue injury is one of the most unusual phenomenon related to X-ray or gamma radiation and refers to residual tissue damage after the initial radiation reaction has subsided. Furthermore repeated exposure to small doses of radiation, no one of which is sufficient to evoke a perceptible reaction, may in the aggregate produce serious latent damage. Thus the biologic effects of radiation are cumulative, but show incomplete summation.

Effects of Radiation on Oral and Paraoral Tissues

The common treatment of neoplasms in and about the oral cavity by X-ray radiation with inadvertent radiation of adjacent structures necessitates an understanding of the possible forms of damage, which may result. Actually, radiation effects are dependent upon a great number of factors such as the source of the radiation, the total amount of radiation administered, the period of time over which the radiation was administered (fractionation), the type of filtration used and the total area of tissue irradiated. The changes to be described here are those frequently seen after delivery of local therapeutic doses of X-ray radiation in the treatment of neoplasms of the head and neck. They are in no way related to the use of the diagnostic X-ray machine.

Effects on Skin

The effect of heavy therapeutic dose of radiation on the skin are well documented, although variable among patients. Erythema is the earliest visible reaction and begins within a few days after irradiation. The original erythema fades sickly only to reappear within two to four weeks. The secondary erythema fades slowly; often leaving the skin permanently pigmented a light tan shade. After heavy irradiation, the secondary erythema may be accompanied by edema with desquamation epithelial cells resulting in denudation of the surface. Re-epithelization occurs in 10-14 days. The early effects are caused by direct injury of the radiated cells and tissues, while the later effects are brought about chiefly by changes in the vascular bed and in the intercellular material.

Alterations in the sebaceous gland activity, evidenced by a reduction in secretion with dryness of the skin may occur within a week after the begin-mg of irradiation. The hair follicles are also sensitive to this type of radiation and epilation, either temporary or permanent, may be produced. The sweat glands are similarly disturbed so that their absence or secretion contributes to the dryness and scaling of the skin.

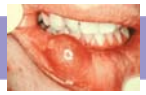
Eventually the epithelium becomes thin and atrophic and the superficial blood vessels become telangiectatic or occluded. The telangiectasis may persist for months or even years as evidence of the effect of X-rays. Other evidence of vascular damage includes thickening of the intima and in some cases, thrombosis. Some veins and arteries show subintimal fibrosis thickening of the wall at the expense of the lumen. Endophlebitis and phlebosclerosis may be particularly evident.

Effects on Oral Mucosa

The changes occurring in the oral mucosa after X-ray radiation are essentially the same as those in the skin and are related to the dose and the duration of therapy. The erythema may develop at a somewhat lower dose of X-ray; and the mucositis, which occurs after therapeutic radiation, is evoked somewhat earlier than the analogous dermatitis.

Radiation induced Mucositis

The earliest manifestation of radiation-induced mucositis is the development of a whitish discoloration due to the lack of sufficient desquamation of keratin (Fig. 14.4). This is replaced by atrophic mucosa, which is erythematous, edematous and friable. Subsequently; the mucosa became denuded, ulcerated, and covered with a removable



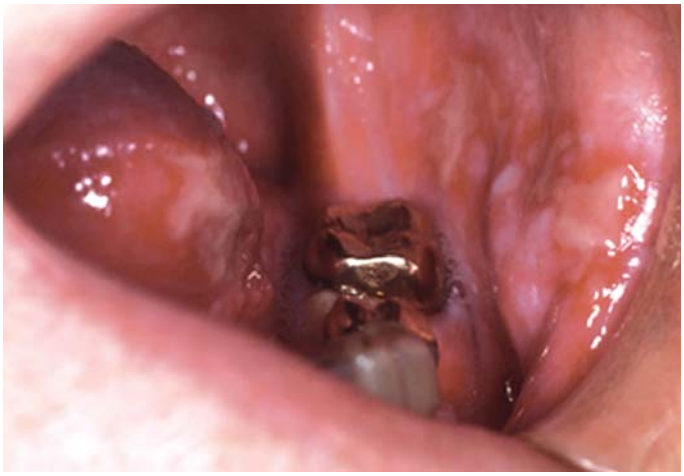


Fig. 14.4: Mucositis affecting the buccal tissues and tongue

yellowish, fibropurulent surface membrane. Great discomfort, which is intensified by contact with coarse or highly seasoned foods, is commonly present. The mucositis persists throughout radiotherapy and for several weeks thereafter. In many patients, a lidocaine mouth rinse before mealtimes is necessary to produce topical anesthesia so that eating is possible. When pain and dysphasia cannot be controlled with local anesthetics and analgesics, nasogastric tube feeding is necessary.

Patients undergoing radiotherapy for oral cancer also quickly lost their sense of taste, probably because of damage to the microvilli and outer surface of the taste cells. The effect is usually transitory and taste acuity is restored within 60-120 days after completion of the radiotherapy.

Effects on Salivary Glands

Xerostomia

Xerostomia, or dryness of the mouth, is one of the earliest and most universal of complaints of patients receiving therapeutic radiation about the head and neck. Alterations in the salivary glands, characterized by diminution or even complete loss of secretion, may occur with in a week or two after the beginning of radiation. There is some obvious damage of the acinar cells, chiefly a decrease in the number of secretory granules present with congestion, edema and inflammatory cell infiltration of the interstitial connective tissue. There are no remarkable changes in the ducts of the salivary glands.

The serous glands are more radiosensitive than mucous glands and thus the parotid glands are adversely and irreversibly affected. Besides the lack of lubrication associated with the decreased salivary flow other complications include a significant decrease of the bactericidal action and self-cleansing properties of saliva.

One interesting feature of acute postirradiation sialadenitis is the elevation of serum and urinary amylase, the source of this amylase being the salivary glands. This is one of the few biochemical changes that occur early and consistently following irradiation. Direct exposure of the salivary glands is necessary to provoke this change and that the serum amylase response is related to the dose of irradiation.

Effects on Teeth

Erupted teeth are often affected in patients who have received X-ray radiation about the head and neck. The most common manifestation of the injury is a peculiar destruction of tooth substance, resembling dental caries and sometimes called 'radiation caries', which often begins at the cervical area of the teeth. Teeth often seem brittle and pieces of the enamel may fracture away from the tooth (Fig. 14.5).

The primary cause of the condition lies in alterations of the saliva induced by either direct or indirect radiation of the salivary glands. The xerostomia of varying degrees certainly favors the collection of debris on the teeth and ensuing caries. There is a sharp decrease in the total daily output of caries-protective salivary electrolytes and immunoproteins. The microbial, chemical, immunologic, and dietary changes produce an enormous increase in the caries challenge.

Developing teeth are also particularly sensitive to X-ray radiation. Ameloblasts appear to be considerably more resistant to radiation than odontoblasts. Radiation of developing teeth in human beings sometimes occurs and if it is at a sufficiently young age, manifestations of the injury may be obvious. Such radiation is usually administered for the treatment of a tumor about the head and neck, frequently a hemangioma. Depending upon the

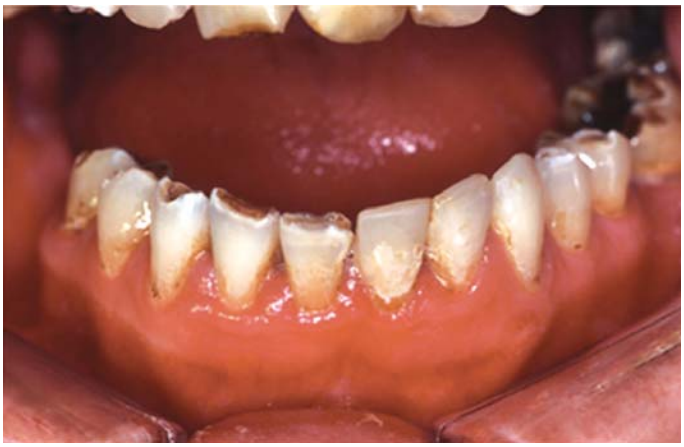


Fig. 14.5: Radiation caries affecting the incisal edge, neck of teeth

age of the patient at the time of the irradiation, there may be complete cessation of odontogenesis resulting in anodontia in the involved area or simply a stunting of the teeth.

Radiation of developing teeth in human beings sometimes occurs and if it is at a sufficiently young age, manifestations of the injury may be obvious. Such radiation is usually administered for the treatment of a tumor about the head and neck, frequently a hemangioma. Depending upon the age of the patient at the time of the irradiation, there may be complete cessation of odontogenesis resulting in anodontia in the involved area or simply a stunting of the teeth.

Effects on Bone

Bone itself is relatively resistant to X-ray radiation. Although osteoblasts are sensitive. If the radiation has been sufficiently intense, the normal balance between bone formation and bone resorption is disturbed; general bone vitality is decreased and localized osteoporosis may result.

The greatest clinical significance of bone, which has been irradiated, lies in the inability of this bone to react in the normal fashion to infection. This is related, at least in part, to the damage of the vascular bed with subsequent disturbance of the typical inflammatory response. This may occur in the maxilla and mandible.

An experimental study of the effects of radiation on extraction wound healing in rats has been reported by Stein and coworkers. They found that when radiation shortly followed tooth extraction, there was retardation of surface closure of the wound leaving an open pathway for tissue infection. The healing response was poor and slow. As the interval between tooth extraction and radiation was increased, impairment of healing decreased. In general, the longer the interval between tooth extraction and initiation of radiation, the less possibility is there of healing complications.

OSTEORADIONECROSIS

Osteoradionecrosis is a radiation- induced pathologic process characterized by a chronic and painful infection and necrosis accompanied by late sequestration and sometimes, permanent deformity. This is one of the most serious complications of radiation to the head and neck, seen less frequently today because of better treatment modalities and prevention.

Radiation causes a proliferation of the intima of the blood vessels (endarteritis obliterans) leading to thrombosis of the end arteries. This results in non vital bone. The altered bone becomes hypoxic, hypovascular and hypocellular. Histologically, there is destruction of osteocytes, absence of osteoblasts, and lack of new bone or osteoid formation. The walls of the regional blood vessels are thickened by fibrous connective tissue. They are also the seat of endarteritis and periarteritis. The loose connective tissue, which usually replaces the bone marrow, is infiltrated by lymphocytes, plasma cells and macrophages. Osteoradionecrosis is the result of nonhealing, dead bone. This devitalized bone may undergo sequestration, although there is no clear line of demarcation between vital and non-vital bone. The necrotic process may extend throughout the radiated bone. Although the exact pathogenesis is not completely understood, it is generally agreed that there are three factors involved: radiation, trauma and infection.

The mandible is affected by osteoradionecrosis more frequently than the maxilla (Fig. 14.6). After infection has gained entry to the bone following traumatic injury extraction, pulp infection or even severe periodontitis, there is a relatively diffuse spread of the process. There is minimal localization of the infection and there may be necrosis of a considerable amount of bone, periosteum, and overlying mucosa. Sequestration eventually occurs, but this may be delayed for many months or several years, during which time the patient usually suffers intense pain.

Osteoradionecrosis in a 56-year-old Man with a History of Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma (Fig. 14.7)

Affected areas of bone reveal ill-defined areas of radiolucency that may develop areas of relative radiopacity as the dead bone separates from the residual vital areas. Intractable pain, cortical perforation, fistula formation, surface ulceration, and pathologic fractures are the common symptoms and signs associated with osteoradionecrosis.

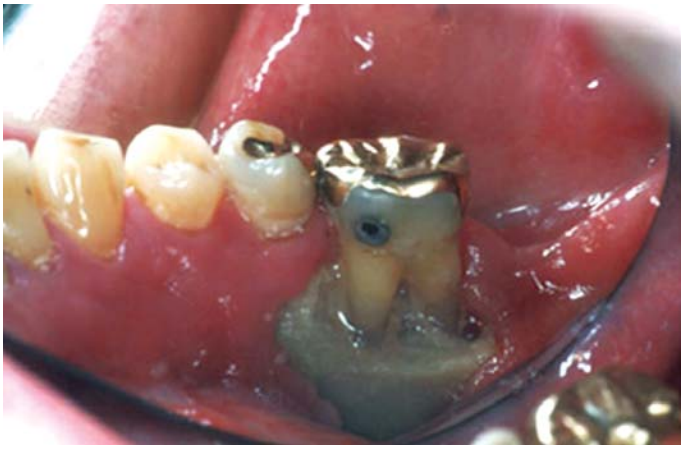


Fig. 14.6: Osteoradionecrosis involving mandible

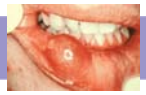


Fig. 14.7: Osteoradionecrosis

The occurrence of osteoradionecrosis is unpredictable and it may arise even without gross infection or trauma. Factors leading to osteoradionecrosis were listed as:

- Irradiation of an area of previous surgery before adequate healing had taken place.
- Irradiation of lesions in close proximity to bone.
- A high dose of irradiation with or without proper fractionation.
- Use of a combination of external radiation and intraoral implants.
- Poor oral hygiene and continued use of irritants.
- Poor patient cooperation in managing irradiated tissues or fulfilling home care programs.
- Surgery in the irradiated area.
- Indiscriminate use of prosthetic appliances following radiation therapy.
- Failure to prevent trauma to irradiated bony areas. Presence of numerous physical and nutritional problems prior to therapy.

Patients are most vulnerable to osteoradionecrosis of the jaws in the two years following radiotherapy.

LASER RADIATION

Lasers were first developed in the 1960s by Theodore H Maiman, is short form of 'light amplification by stimulated emission of radiation'. It is an electrooptical device which, upon stimulation, can convert jumbles of light waves into an intense, concentrated, uniform, narrow beam of monochromatic light with an energy source of great intensity and exceptional flexibility. The radiation may be continuous or modulated, or the emission may occur in short pulses. Application of lasers to biology and medicine *began* shortly after 1960.

Lasers in Dental Soft Tissue Treatment

Specific laser devices are cleared for a number of soft tissue applications, including intraoral soft tissue surgery (ablating, incising, excising, coagulating), sulcular debridement, treatment of aphthous ulcers and herpetic lesions, removal of coronal pulp and pulpotomy and coagulation of extraction sites.

Lasers in Dental Hard Tissue Treatment

'Optical drilling' of teeth, which includes caries removal-cavity preparation, selective caries removal in enamel, enamel roughening, tooth preparation to obtain access to the root canal cleaning, and root canal preparation, including enlargement, apicectomy, bone cutting, shaving, contouring, and resection.

It is also used as an aid in diagnosis of dental caries, illumination of caries detection and endodontic orifice location and blood flow measurements.

Effects on Teeth

The effects of laser on teeth were first reported by Stern and Sognnaes, who found that exposure of intact dental enamel, caused a glasslike fusion of the enamel, whereas dentin exposed to laser exhibited a definitive charred crater. A study on argon laser irradiation in root surface caries was investigated. In a continuous artificial caries attack, argon irradiation of sound root surfaces significantly increased the resistance of cementum and underlying dentin to demineralization. The anticaries effect of laser energy is one of the most exciting aspects of dental practice.

Effects on Pulp

The pulps of teeth in animals subjects to laser radiation shows severe pathologic changes, including hemorrhagic necrosis with acute and chronic inflammatory cell infiltration. The odontoblastic layer also underwent coagulation necrosis, although the severity of the response varied with the amount of radiation.

Effect on Soft Tissue

When directed at soft tissue, laser radiation has the ability to produce non-specific ulceration of the epithelium with acute purulent inflammation.

ELECTRICAL BURNS

Electrical burns of the oral cavity are seen with an unpleasant common frequency in children and constitute approximately 5 percent of all burns cases (Fig. 14.8). Such electric burns can be of the contact or the arc type. In the contact type, electric current passes through the body from

Fig. 14.8: Electric burns

the point of contact to the ground site and can cause death due to cardiopulmonary arrest. The arc type of-electric burns is commonly seen in the oral cavity wherein saliva acts as a conducting medium and an electrical arc flows between the electrical source and the mouth. Significant tissue destruction will usually result due to extreme heat that is produced at times up to 3000°C. Most of these cases invariably result from an accident in which the child chews on an electrical cord, break the insulation, and contacts the bare wire or sucks on the socket end of an extension cord.

Clinical Presentations

The resulting burn of the lips, and sometimes of the gingiva and tongue, usually begins as a painless, charred, yellow area that exhibits little to no bleeding. Often large areas usually feel 'cold' because normal-appearing tissue surrounding the crater is usually rendered ischemic. Edema develops within few hours of the injury and may persist up to two weeks. Around the fourth day, significant necrosis and sloughing of the affected area proceeds with considerable loss of tissue. Bleeding due to exposure of the underlying vasculature is an important complication to be monitored during this period. Adjacent teeth may occasionally become nonvital, with or without necrosis of the surrounding alveolar bone. Developing tooth germs or buds are often destroyed in the accident with permanent cosmetic disfigurement. This type of wound heals relatively slowly.

The involvement of lips and angle of the mouth, if untreated, may lead to the development of deformities such as microstomia, mucosal-alveolar adhesions and morphologic alterations in the shape of the lips.

Treatment and Prognosis

The nature of the wounds due to electric burns frequently requires interdisciplinary efforts and comprehensive core because of the variety of potential problems which ultimately may develop, such as bleeding, secondary infection, contracture of mouth during healing, scarring, and disfigurement. Tetanus immunization and prophylactic antibiotic are common treatment options.

THERMAL BURNS

Thermal burns of the oral cavity result from intake of hot foods or fluids. Most serious thermal burns occur during dental procedures when hot instruments accidentally contact the oral tissues. Burns can also be caused by overheated hydrocolloid impression material.

Clinical Presentations

The lesions commonly present as zones of erythema and ulceration often exhibiting remnants of necrotic epithelium at the periphery. Pain and a burning sensation are the presenting symptoms. The anterior tongue, the palate, and the posterior buccal mucosa are the common sites involved. Burns from hot dental instruments are commonly located on the lips and commissure of the lips. Overheated impression materials cause burns on the gingiva and can be diffuse and painful.

Treatment and Prognosis

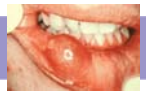
Most thermal burns resolve without treatment.

CERVICOFACIAL EMPHYSEMA

Emphysema is a swelling due to the presence of gas or air in the interstices of the connective tissue.There have been numerous cases of emphysema reported involving the cervicofacial and even mediastinal areas following a variety of dental and oral procedures like dental extraction, blowing of compressed air into a root canal during endodontic treatment or into a periodontal pocket, blowing of air from a high-speed-air-rotor machine, following middle-face fractures, or spontaneously as a result of the patient's breathing actions following some type of surgical procedure, with a break in the tissue permitting air to enter connective tissue spaces.

Clinical Presentations

Most cases develop during surgery or within the first postoperative hour. The emphysema manifests itself as a unilateral soft tissue enlargement of the face and/or neck,



which occurs very rapidly. Pain is usually minimal during the first few days and crepitus is usually detected on palpation. The enlargement increases and spreads due to secondary inflammation and edema. This phase may be accompanied by variable pain, facial erythema, and mild fever. Spread into the mediastinum results in dysphonia, dysphagia, or dyspnea. Crepitus synchronous with the heartbeat (*Hamman's crunch*) is heard on cardiac auscultation in mediastinal involvement.

Treatment and Prognosis

Unfortunately, venous air embolism is an unusual but often fatal complication of this condition. If the entrance of air into the venous circulation can be recognized promptly, resuscitation may prevent death. A second complicating factor is the possibility of bacterial infection in the emphysematous connective tissue, microorganisms being carried into the tissues with the air. In such instances, antibiotic therapy is recommended. Aside from this, there is no particular treatment indicated and the condition will generally resolve within a week.

PNEUMOPAROTID

Pneumoparotid is a condition analogous to emphysema resulting from air entering the parotid duct, leading to enlargement of the parotid gland caused by air insufflation. This can be accidental, self-induced, or occupational (such as in glass-blowers). Even though the Stenson's duct is protected by redundant mucosal folds and by the contraction of the buccinator muscle, dramatic increases in intraoral pressures can lead to air entering the Stenson's duct.

The common clinical presentation is that of a unilateral swelling in the parotid region demonstrating crepitus on palpation. The duct produces frothy air-filled saliva instead of the typical clear, waterlike secretion.

Management consists of altering the inciting occupational events to prevent air from entering the duct. Acute cases can be managed by administering antibiotics, massages, hydration, sialogogues, and warm compresses.

ANESTHETIC NECROSIS

On rare occasions, administration of the local anesthetic can result in ulceration and necrosis at the site of the injection. The necrosis results from local ischemia. The exact cause for this phenomenon is unknown. Suggested causes include subperiosteal injection, excessive injection of solution, rapid injection or the epinephrine in the anesthetic solution.

This lesion usually appears several days after the procedure characteristically in the hard palate as a well-circumscribed area of ulceration.

Treatment is not required unless the ulcer fails to heal as seen in some cases.

HUMAN BITE (*MORSUS HUMANUS*)

The human bite is a potentially serious injury, which may occur in a variety of situations including quarrels, children's play, child abuse, mental derangements, and sexual assaults or related activities. While the bite may involve any part of the body, the extremities are most frequently involved.

There is great potential for serious infections as well as marked disfigurement from the human bite. The infections are usually of mixed types of microorganisms and can be difficult to treat, especially since patients frequently delay seeking treatment for several days after the incident because of the embarrassing circumstances involved.

The human bites also has assumed a very important role in forensic medicine and forensic dentistry, especially in murder, rape, or assault cases in which legal identification of the guilty party has been made through a set of characteristic tooth imprints in bite marks (qv) on the involved area.

POISONING

Lead

Lead poisoning (plumbism) occurs chiefly as an occupational hazard today, but occasionally because of some other accidental exposure of either an acute or chronic nature. In adults, the chief means of poisoning is through inhalation of lead vapor or dust. In infants, most cases result from ingestion by the child while chewing on wood painted with lead-containing paint. Many other unusual sources of lead may also result in poisoning.

Clinical Presentations

Acute lead intoxication is manifested by serious gastrointestinal disturbances, which include nausea, vomiting, abdominal colic, and constipation, along with anemia (hypochromic anemia with basophilic stippling of the red blood cells), fatigue, irritability, and weakness. A peripheral neuritis also develops which may produce the characteristic wrist-drop or foot-drop. Encephalopathy and renal dysfunction may also occur. Chronic lead poisoning leads to dysfunction of the nervous system, kidneys, bone, and joints, along with symptoms such as fatigue, musculoskeletal pain, and headache. Skeletal changes due

to deposition of lead in growing bone occur in children and are demonstrable on the roentgenogram.

Oral Manifestations

The formation of a 'lead line' (halo saturninus or Burtonian's line) similar to the `bismuth line' occurs in lead poisoning. This gray or bluish black line of sulfide pigmentation occurs in the gingiva, but is somewhat more diffuse than that of bismuth. It is also found occasionally in other areas of the oral cavity. Ulcerative stomatitis is an additional reported finding.

Excessive salivation, metallic taste, swelling of the salivary glands, advanced periodontal disease, and tremor of the tongue on thrusting are the other common complaints.

Altshuller and his associates have reported that lead is deposited in the deciduous teeth of children suffering from lead poisoning and that these teeth may serve as an index of the body burden of lead.

Treatment and Prognosis

Treatment of the oral lesions is secondary to systemic treatment, and the prognosis depends upon the systemic condition of the patient.

Mercury

Mercury poisoning may be acute or chronic, but the systemic reactions in the acute form are so serious that the oral features need not be considered. Chronic mercurialism occurs after prolonged contact with mercurial compounds in a variety of situations, including therapeutic use of these compounds and as an occupational hazard. Elemental mercury is harmless. But mercury vapor is very hazardous, with a high rate of absorption and systemic retention. Ingestion of mercury salts is also associated significant adverse reactions. Exposure to mercury has been reported with the use of teething powders, cathartic agents, and antihelminthic preparations that contain mercury (Fig. 14.9). The level of mercury released from amalgam restorations does not appear sufficiently high to cause disease.

Clinical Presentations

Mercury poisoning may be acute or chronic. Abdominal pain, vomiting, diarrhea, thirst, and pharyngitis are commonly seen in acute poisoning. Chronic mercurialism is characterized by gastric disturbances, diarrhea, excitability, insomnia, headache and mental depression. The patients frequently have fine tremors of the fingers and limbs as well as of the lips and tongue. In addition, a desquamative dermatitis occurs in some persons. Nephritis is common in acute mercurial poisoning, but does not occur in severe form in the chronic type.

Oral Manifestations

The oral cavity suffers seriously in mercurialism and evidences numerous characteristic but not necessarily pathognomonic signs and symptoms. There is a remarkably increased flow of saliva (ptyalism) and a metallic taste in the mouth due to excretion of mercury in the saliva. The salivary glands may be swollen and the tongue is also sometimes enlarged and painful. Hyperemia and swelling of the gingiva are occasionally seen.

The oral mucosa is prone to ulcerations on the gingiva, palate, and tongue. Bacterial action on the metal liberates mercuric sulfide. In severe cases, pigmentation of the gingiva similar to the bismuth and lead lines may occur as a result of deposition of this dark sulfide compound. Mercuric sulfide also causes significant destruction of the alveolar bone with resultant loosening and exfoliation of the teeth.

A toxic reaction from absorption of mercury in dental amalgam has been reported on a number of occasions. The amount of estimated exposure to mercury from dental amalgam is not sufficient to cause mercury poisoning in the conventional sense. Nevertheless, this exposure may suffice to bring about allergic manifestations in patients sensitive to the mercury.

Treatment and Prognosis

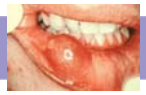
This treatment of the oral lesions in chronic mercurialism is supportive only and is secondary to the treatment of the poisoning itself. The prognosis is usually good, although severe periodontal destruction and loss of teeth may occur.

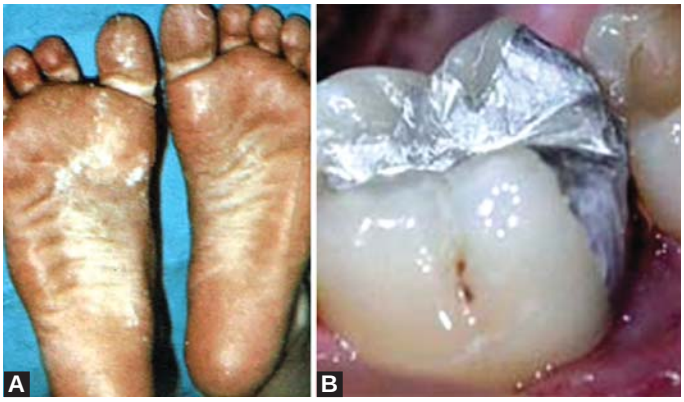
Acrodynia (Pink Disease, Swift's Disease)

Acrodynia is an uncommon disease with striking cutaneous manifestations (Fig. 14.9A). The cause of the disease has been established as a mercurial toxicity reaction, either actual mercury poisoning or more likely an idiosyncrasy to the metal. The source of the mercury is usually a teething powder (Fig. 14.9B), ammoniated mercury ointment, calomel lotion or bichloride of mercury disinfectant.

Clinical Presentations

Acrodynia occurs most frequently in young infants before the age of two years, although children are occasionally affected up to the age of five or six years. The skin, particularly of the hands, feet, nose, ears, and cheeks becomes red or pink and has a cold, clammy feeling. The appearance has been described as resembling raw beef. The skin over the affected areas peels frequently during the course of the





Figs 14.9A and B: (A) Acrodynia, (B) Mercury poisoning

disease. The patients also have a mucopapular rash, which is extremely pruritic. Severe sweating is an almost constant feature of acrodynia. Other features are a state of extreme irritability, photophobia with lacrimation, muscular weakness, tachycardia, hypertension, insomnia, gastrointestinal upset, and stomatitis. The children will frequently tear their hair out in patches.

Oral Manifestations

Patients with acrodynia exhibit profuse salivation and often much dribbling. The gingiva becomes extremely sensitive or painful and may exhibit ulceration. Bruxism is a common finding and loosening and premature shedding of teeth often occur. Many times, the child will extract loose teeth with his fingers. Mastication is difficult because of the pain.

Treatment and Prognosis

The discontinuance of possible exposure to mercury is a necessity, and the administration of BAL (British anti-lewisite; dimercaprol) has proved successful in most cases unless the disease is of long duration. Although recovery is the common outcome, patients occasionally die of this disease.

Silver (Argyria, Argyrosis)

Chronic exposure to silver compounds may occur as an occupational hazard or as the result of therapeutic use of silver compounds such as silver arsphenamine or silver nitrate. Silver is disseminated throughout the body with substantial amounts accumulating as subepithelial deposits in the skin. These deposits result in a diffuse grayish-black pigmentation, occurring primarily in sun exposed areas. The sclera and nails are also pigmented. One of the earliest signs of argyria is the appearance of a slate-blue silver line along the gingival margins, arising due to the deposition of metallic silver and silver sulfide pigments. There is also diffuse bluish-black discoloration of the oral mucosa. There are usually no other signs or symptoms, either local or systemic, associated with argyria.

Amalgam Tattoo (Fig. 14.10)

Accidental implantation of silver-containing compounds into the oral mucosal tissue usually results in a permanent grayish-black pigmentation, commonly referred to as amalgam tattoo. They are named so as the most common source of embedded silver compounds is amalgam. It is the most commonly used restorative material for dental restorations at present and is composed of a mixture of silver, mercury and tin. It may enter the oral mucosa in any of the following ways:

- From condensation in gingiva during amalgam restorative work.
- From particles entering mucosa lacerated by revolving instruments during removal of old amalgam restorations.
- From broken pieces introduced into a socket or beneath periosteum during tooth extraction.
- From particles entering a surgical wound during root canal treatment with a retrograde amalgam filling.
- From amalgam dust in the oral fluids entering through previous areas of abrasion.

Clinical Presentations

Amalgam tattoos appear as macules, or rarely as slightly raised lesions. The borders can be well defined, irregular, or diffuse. The most common locations for amalgam tattoos are gingiva (28 percent), buccal mucosa (23 percent), and alveolar mucosa (19 percent). Amalgam tattoos have frequently been mistaken for melanin-pigmented lesions and in some cases, biopsy is necessary to differentiate if the amalgam fragments are too small or diffuse to be visible on the dental roentgenogram. When the amalgam

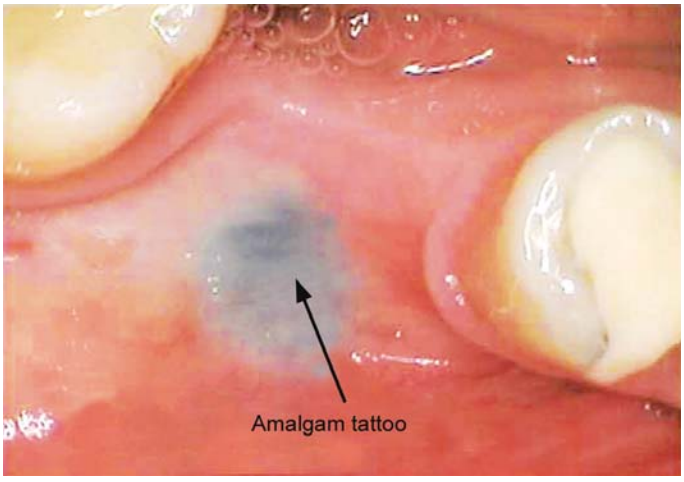


Fig. 14.10: Amalgam tattoo

fragments are embedded within bone, they may be mistaken for a variety of other foreign bodies.

Histologic Features (Fig. 14.11)

Microscopically, the size and quantity of the amalgam particles determine the histologic presentation. Larger particles evoke granuloma formation consisting of multinucleated paneth cells, lymphocytes, and increased fibrosis surrounding the foreign material. Smaller dustlike particles are likely to be engulfed by individual macrophages without the formation of individual granulomas. The fine particles of amalgam can also be found within the cytoplasm of a large number of cells and tissues, including muscle, nerve, blood vessel walls and collagen. Tissues like elastic fibers and the basement membrane chemically interact with amalgam incorporating the liberated silver as a fine linear deposit of brown precipitate.

The amalgam fragments appear as black or olive-brown granules or even as macroscopic pieces of material which can be seen plainly in the paraffin-embedded specimen as silver-gray flecks in the tissue. These granules are prominently arranged in a linear fashion along collagen fibers and around blood vessels. In addition, they are found around nerve sheaths and striated muscle fibers and alone the basement membrane of mucosal epithelium.

Tetracycline

Discoloration of either deciduous or permanent teeth may occur as a result of tetracycline deposition during prophylactic or therapeutic regimens instituted either in the pregnant female or postpartum in the infant. Tetracycline and its homologues have a selective affinity for deposition in bone and tooth substance, possibly through the formation of a complex with calcium ions in the surface of the microcrystals of hydroxyappetite.

That portion of the tooth stained by tetracycline is determined by the stage of tooth development at the time of drug administration. Since tetracycline does cross the placental barrier, it may involve those deciduous teeth developing antepartum, although the discoloration itself depends upon the dosage, the length of time over which administration occurred, and the form of the tetracycline. Moffitt and his coworkers have emphasized that the critical period for tetracycline-induced discoloration in the deciduous dentition (the period of mineralization of the first millimeter of dentin nearest the dentinoenamel junction) is four months *in utero* to three months postpartum for maxillary and mandibular incisors and five months in utero to nine months postpartum for maxillary and mandibular canines. The period for permanent maxillary and mandibular incisors and canines is three to five months postpartum to about seven years of age. The age at which tetracycline administration occurred can easily be pinpointed by reference to a chart on the chronology of odontogenesis.

According to Grossman and his associates, the use of oxytetracycline, or possibly doxycycline, may diminish tooth discoloration if tetracycline therapy is indicated in the pregnant female or during the first six to seven years of life. After this age, the probability of discoloration need not be considered since the cosmetically important anterior teeth have completed their formation.

Clinical Presentations (Fig. 14.12)

The teeth affected by tetracycline exhibit yellowish or brownish-gray diffuse bands of discoloration that are located within the tooth structure and not on the surface.

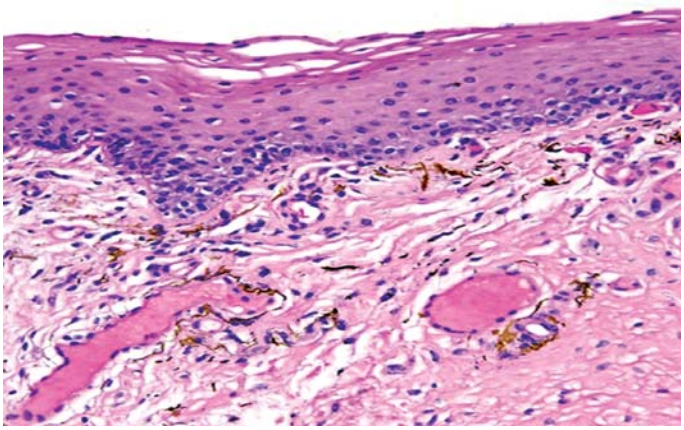


Fig. 14.11: In the lamina propria there is a finely granular black/brown pigment that encases el astic fibers and the basement membrane of superficial capillaries, it is within the cytoplasm of histiocytes

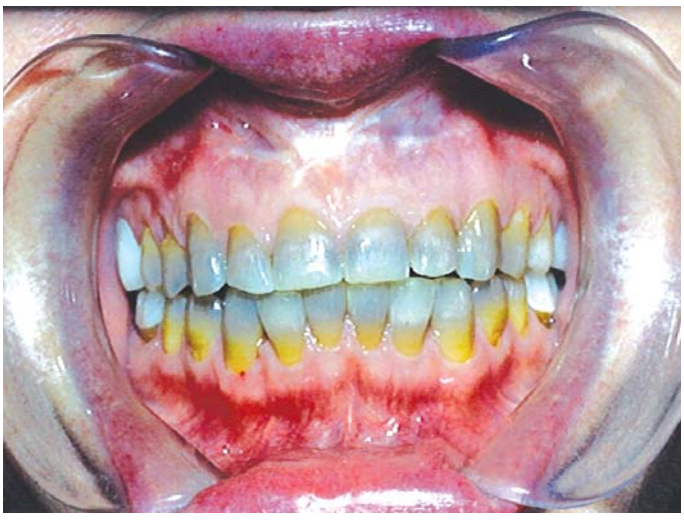
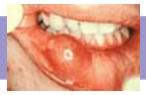


Fig. 14.12: Teeth affected by tetracycline



The discoloration is most pronounced at the time of eruption of the teeth. This discoloration gradually becomes more brownish after exposure to light. Chlortetracycline tends to cause a brownish-gray color, whereas oxytetracycline and tetracycline give a yellowish color. Tetracycline itself fluoresces under ultraviolet light, and accordingly, the teeth involved by its discoloration also fluoresce a bright yellow under ultraviolet light. However, in time, this fluorescence gradually diminishes. When tetracycline stained teeth are sectioned and examined microscopically with ultraviolet light, narrow bands or rings are seen coinciding with the part of tooth development at the time of administration of the drug.

Minocycline hydrochloride staining is commonly observed in the skin, nails, sclera, conjunctiva, thyroid, bone and teeth. The dark color of the underlying bone may show through the thin, translucent oral mucosa imparting to the palate or the anterior alveolar mucosa, a blue-gray appearance. The teeth reveal varying patterns of discoloration, the crown exhibiting blue-gray discoloration of the incisal three-fourths, more severely in the middle third, the exposed roots of erupted teeth revealing dark green discoloration, and the roots of developing teeth demonstrating a dark black color. The discoloration of the dentition remains after discontinuance of the medication, even though the cutaneous staining fades away.

CANCER CHEMOTHERAPEUTIC AGENTS

A chemically very diverse group of drugs and agents are used for the treatment of certain malignant neoplastic diseases. Their chief function is the destruction of malignant cells. Most of these cytotoxic agents exert their effect preferentially against cells in mitosis. Unfortunately, in addition to neoplastic cells, which undergo rapid division, certain normal cells including the cells of the oral and gastrointestinal mucosa, bone marrow and skin also exhibit a similar degree of mitotic activity and are especially prone to manifest the toxic and damaging effects of the antineoplastic agents.

Various Cancer Chemotherapeutic Agents are:

Alkylating agents
- Busulfan (Myleran)
- Chlorambucil (Leukeran)
- Cyclophosphamide (Cytoxan)
- Melphalan (Alkeran; L-PAM)
- Triethylenethiaphosphoramide (Thio-TEPA)

Antimetabolites
- Capecitabine
- Cladribine
- 6-Mercaptapurine (5-MP)
- 6-Thioguanine (6 -TG)
- Methotrexate (MTX)
- Fluorouracil (5-F U)

Antitumor antibiotics
- Actinomycin-D (Dactinomycin)
- Bleomycin (Blenoxane)
- Daunorubicin (Daunomycin)
- Doxorubicin (Adriamycin)
- Irinotecan
- Mitomycin-C (Mutamycin)

Plant alkaloids
- Vinblastine (Velban)
- Vincristine (Oncovin)

Nitrosureas (Halogenated N-alkyl-N-nitrosureas)
- Carmustine (BCNU)
- Lomustine (CCNU)

Enzymes
- L-Asparaginase (Elspar)

Hormonally active agents
- Antiandrogen
- Antiestrogen
- Progestins
- Adrenocorticosteroids
- Gonadotrophin-releasing hormones agonises
- Aromatase inhibitor

Miscellaneous
- Arsenic trioxide
- Hydroxyurea (Hydrea) Imatinib
- Mitotane
- Mitoxantrone

Clinical Presentations

Because the major effect of these materials on cells and tissues is similar, regardless of each agent's specific mechanisms of action, there are a few general manifestations of the group as a whole that can be emphasized.

These are:
- Alopecia due to arrest of mitosis of the rapidly geminating hair roots.
- Stomatitis, which may take a variety of forms.
- Radiation recall or radiation sensitization, a reactivation of radiation reaction within the field of radiation following administration of certain of the antineoplastic agents.

Oral Manifestations

The most common oral reaction is mucosal erosion and ulceration, frequently diffuse and multiple. This is often related to the neutropenia produced by the drug but occasionally occurring in its absence. Also the ulcers and erosions may occur anywhere in the mouth but is most likely to be seen on the lips, tongue and buccal mucosa.

Hemorrhage is also a common manifestation resulting from the thrombocytopenia secondary to the drug therapy. These reactions do not occur following use of all cancer chemotherapeutic agents but are especially common with the alkylating antimetabolite, and antitumor antibiotic groups.

Another oral finding in patients undergoing this type of therapy is the presence of any one of a variety of specific or nonspecific infections (commonly herpes simplex infection, *Candida* infection, or infection by staphylococcal or streptococcal organisms), especially since many of these patients are also immunosuppressed.

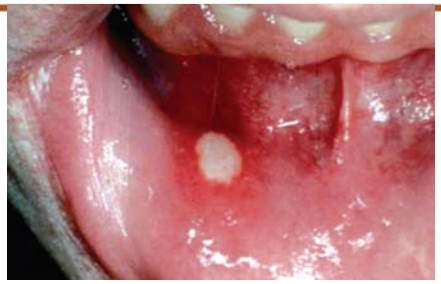
Finally, hyperpigmentation of oral mucosa has been reported occasionally, especially in patients receiving alkylating agents and antitumor antibiotics.

Treatment

There is no specific treatment for the oral lesions, which although severe, must be considered, of only secondary importance to the patient's major problem.

15

Allergic and Immunologic Diseases of the Oral Cavity



Allergy is a term used generally to encompass the hypersensitivity state acquired by exposure to a specific material and the altered capacity of the living organisms to react upon re-exposure to it. Allergic reactions can be: Immediate reactions, delayed reactions.

APHTHOUS STOMATITIS (FIG. 15.1)

It is a common disease characteristic by development of painful, recurring solitary or multiple ulcerations of the oral mucosa.

Clinical Presentation and Pathogenesis

Aphthous ulcers, well known to health care providers, are known as "canker sores" to the layperson. Aphthous ulcers are divided into two types: minor and major. Minor aphthous ulcers appear as single discrete ulcers or in groups of two or more. They are characteristically found on the free movable oral mucosa rather than the attached mucosa. The formed ulcers are discrete with a white-yellow base, which is a fibrinous slough, and a distinct irregular border with a red halo. The lesions emerge in four stages. In the first or prodromal stage, the individual will experience a tingling or burning pain in a clinically normal-appearing site; during the second or pre ulcerative stage, red oval papules appear and the pain intensifies; in the third or ulcerative stage, the classic ulcer appears; it will measure between 3 and 10 mm and may last 7 to 14 days. The fourth stage is the healing stage in which granulation tissue followed by epithelial migration incurs healing without scar.

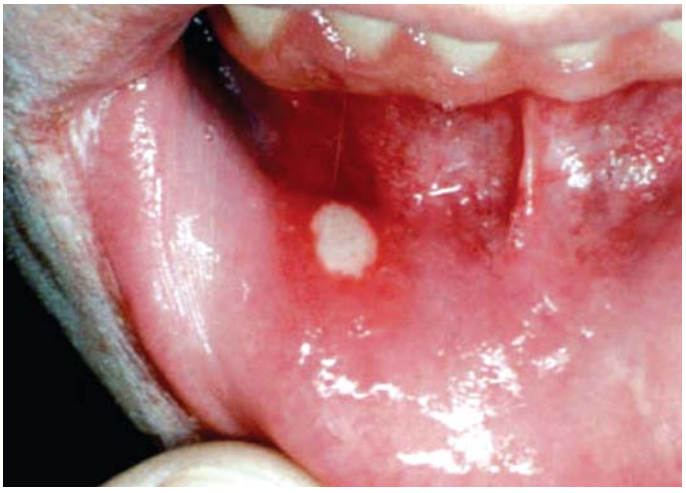


Fig. 15.1: Aphthous stomatitis

Major aphthous ulcers are identical in their developmental stages and their general appearance except that they are larger (exceeding 10 mm), deeper (extending into the deep layers of the submucosa and into underlying muscle at times), and longer lasting (up to 6 weeks). Most individuals with major aphthous ulcers harbor at least one or two lesions at all times.

The pathogenesis of aphthous stomatitis remains unknown. The theories are even more numerous than its suggested treatment schedules. The most plausible theory explaining most clinical observations is that of an immune-based leukocytoclastic vasculitis. In this theory, either autoantibodies to oral mucous membrane epithelium or circulating antibodies to the microorganism *Streptococcus sanguis* form antigen-antibody complexes within local vessel walls. These immune complexes together with complement initiate an intense cascade of inflammation mediated mostly by neutrophils. The secretion of cytopathic enzymes by neutrophils and other leukocytes causes the tissue destruction and necrosis of epithelium recognized as an aphthous ulcer.

Differential Diagnosis

Aphthous stomatitis is somewhat distinctive. However, minor aphthae will often be confused with recurrent herpes lesions. This similarity is sufficient to compel some authors to distinguish yet another type of aphthous ulcer, the so called herpetiform aphthous ulcer; however, there is no real distinction. The lesions of Behçet syndrome will look very much like those of major aphthous stomatitis and will

require that the clinician examine for iritis-hypopyon and similar-appearing genital skin lesions characteristic of Behcet syndrome. The oral lesions of hand foot and mouth disease will also resemble aphthae. However, a close examination of fingers, toes, and palms will confirm or rule out this entity.

Diagnostic Work-up

No specific work up is required. Aphthous stomatitis is clinically recognized.

Histopathology

Histological examination is not usually indicated for aphthous ulcers, although it is sometimes helpful for difficult clinical cases. The findings are rather nonspecific. The ulcer often appears punched out and the epithelial margins show no significant change, although occasionally edema may cause a slight separation of the epithelium from the underlying connective tissue. There may be some spongiosis, and there is usually an intense inflammatory infiltrate at the base. While neutrophils are typically seen on the surface of the ulcer, lymphocytes and macrophages are the major component. Major aphthae show changes identical to those in the minor form, but the inflammatory infiltrate extends more deeply. Because this often involves underlying mucous glands, it is understandable that at one time major aphthae were thought to be associated with salivary glands, hence the term periadenitis mucosa necrotica recurrens. The depth of the involvement is also responsible for the chronicity and scarring of these ulcers. Studies have indicated that aphthae may be the consequence of an immune complex vasculitis. This is supported by the fact that foci of extravasated erythrocytes are seen and that perivascular aggregates of neutrophils are found. The development of the lesion may relate to a lymphocytotoxic process because early lesions contain predominantly T4 lymphocytes before ulceration. In the ulcerative phase, most are T8 lymphocytes, while during healing the T4 cells again dominate.

Treatment

Because there is no known single effective treatment for aphthous stomatitis, there is a plethora of published and unpublished treatment schedules and drugs. They include antibiotics; vitamins; zinc; levamisole as an immune stimulant; and either topical, intralesional, or systemic corticosteroids. In addition, chlorhexidine gluconate 0.12%, sulfones, and iron therapy, among other treatments, have been recommended.

A rational approach to aphthous stomatitis requires an understanding that minor aphthous ulcers are few and of short duration. No specific therapy is ideal. It is reasonable to simply reassure the patient and provide no specific treatment. Single or small groups of ulcers that are uncomfortable may be directly cauterized with silver nitrate ($AgNO_3$) or phenol, thereby avoiding systemic side effects.

For aphthous ulcers that are numerous and frequent enough to debilitate patients, a trial with antibiotics is useful before resorting to systemic corticosteroids. The three most effective antibiotic regimens are: (1) erythromycin, 250 mg by mouth four times daily; (2) tetracycline (Achromycin, Lederle), 250 mg by mouth four times daily; and (3) a mixture often called "tetranydril elixir," which consists of 250 mg tetracycline and 12.5 mg diphenhydramine hydrochloride (Benadryl, Warner Lambert) per 5 ml of Kaopectate (Pharmacia and Upjohn). The patient is instructed to use 1 tsp at a time and swish, hold the solution in their mouth as long as possible, and swallow, three times daily. These regimens have been variably useful in controlling the number, frequency, and duration of lesions.

If these antibiotic regimens fail, systemic corticosteroids are the treatment of choice. Topical corticosteroids have little effect on major lesions. Most lesions that seem to benefit from topical treatment may not warrant any treatment. The corticosteroid of choice is prednisone and should follow the systemic corticosteroid regimen.

Prognosis

Aphthous stomatitis is most active in young adulthood. There may be a period of 10 to 15 years in which intermittent flare-ups occur where lesions appear more frequently and are more intense. The treatment schedules described attenuate and control the lesions and will likely alleviate their symptoms. With time and advancing age, the condition becomes less intense and usually remits altogether.

Behçet Syndrome

Beçhet's syndrome is a disease of uncertain etiology that may resemble an infectious disease and in the past has been suggested to be caused by pleuropneumonia- like organisms (PPLO) or more frequently by a virus.

Clinical Presentation and Pathogenesis

Behçet syndrome most often presents in young men with oral lesions identical to large aphthous ulcers. The syndrome is said to include ocular and genital lesions, so that, in addition to recurrent oral lesions, recurrent aphthous-looking lesions also appear on the skin around the penis and scrotum. In women, lesions occur on the labia

and vulva. Specifically, the ocular lesions comprise inflammation of the iris and uveal tracts (iritis and uveitis), which will produce a level of pus in the anterior chamber (hypopyon). Because the basis of this disease seems to be a vasculitis, red-nodular skin lesions (erythema nodosum) and a non-rheumatoid (sero negative) arthritis appear in two thirds of patients (localized to the knees and ankles). In one variant of Behçet syndrome, termed MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome, auricular and nasal cartilage is targeted along with the other manifestations. In rare severe cases, the vasculitis may cause vascular thrombosis, cranial nerve palsies, and encephalitis.

The oral lesions are usually the feature that brings the individual to seek medical attention. The lesions are painful and are usually 2 to 10 in number. They often precede the iritis, or the iritis is present but subclinical at the time of presentation.

The cause of Behçet syndrome is still unknown. It is currently believed to represent an autoimmune vasculitis in susceptible individuals related to HLA-B51 as a part of a recently recognized class of diseases referred to as leukocytoclastic diseases.

Differential Diagnosis

Behçet syndrome initially resembles an aphthous stomatitis, making it incumbent on the clinician to search for other features of this syndrome. Conversely, reactive arthritis may present with arthritis and a conjunctivitis resembling Behçet syndrome, but the oral lesions are not aphthous-like and are nonpainful. If skin lesions are prominent and include skin outside the genital area, erythema multiforme also must be considered.

Diagnostic Work-up

Behçet syndrome requires only a recognition of its clinical symptom complex. However, a complete ophthalmologic examination is indicated to assess the degree of uveitis.

Histopathology

Behçet syndrome may show the same histologic features as noted for aphthous stomatitis. Although the lesions may show only diffuse infiltration of neutrophils or mononuclear cells, there is often a vasculitis that may be lymphocytic or leukocytoclastic and in which fibrin is deposited in the wall of small blood vessels.

Treatment

Prednisone is the treatment standard for Behçet syndrome. Systemic corticosteroid regimen I or III is most commonly used.

Prognosis

Behçet syndrome is difficult to control even with systemic corticosteroids. Cytotoxic drugs such as cyclophosphamide (Cytoxan, Mead Johnson), 50 mg twice daily, or azathioprine (Imuran, GlaxoSmithKline), 50 mg twice daily, as in systemic corticosteroid regimen III, are frequently required or, alternatively, chlorambucil may be used. The disease course is most active in youth, and exacerbations are frequent. As the patient ages, the disease becomes more controllable and often goes into permanent remission.

WEGENER'S GRANULOMATOSIS

It is disease of unknown etiology, which basically involves the vascular, renal and respiratory system.

Clinical Presentation and Pathogenesis

Wegener's granulomatosis is a rare idiopathic vasculitis of small arterioles and capillaries. Consequently, it attacks the lungs, kidneys, and oral regions, all of which have numerous small arterioles and capillaries.

Wegener's granulomatosis usually presents with a 4 to 12 month onset of upper respiratory tract symptoms in an adult between 30 and 50 years of age. These may include nasal congestion, sinusitis, otitis media, cough, dyspnea, or hemoptysis. Oral symptoms and signs may include a painful cobblestone or ulcerative appearance of the palatal mucosa or the gingiva. Fever, weight loss, and fatigue are common. Palatal bony erosion has been overstated; even severe cases, in which much of the palatal mucosa is lysed, rarely if ever exhibit perforation of the palate into the nasal cavity.

Wegener's granulomatosis is an immune based disease. Antibodies develop to cytoplasmic components in the neutrophil; these are known as cANCA, which stands for cytoplasmic pattern antineutrophil cytoplasmic antibodies. pANCA, which stands for perinuclear antineutrophil cytoplasmic antibodies, relates to antibodies that develop to the myeloperoxidase granules, and are located in the cytoplasm of neutrophils in a perinuclear pattern. Wegener's granulomatosis has a 70% positivity for cANCA and a 20% positivity for pANCA. In either, the antibody is thought to lyse the neutrophil, releasing its multiple enzymes and proteases, which induce further inflammation and directly necrose local tissues.

Differential Diagnosis

The picture of a chronically ill or anemic individual with respiratory tract symptoms and the more common presentation of palatal granulation tissue and ulcers is also

suggestive of systemic fungal diseases such as histoplasmosis, coccidioidomycosis, and blastomycosis, as well as local fungal diseases such as mucormycosis and an aspergillus infection. Mucormycosis and aspergillosis are usually associated with a significant immune compromise, such as uncontrolled diabetes, HIV infection, or immunosuppressive therapy. Mucormycosis will cause bone necrosis, whereas Wegener granulomatosis should not. Both fungal diseases render tissue black, mucormycosis by avascular necrosis of bone and aspergillosis by virtue of the black appearance of its organismal colonies. Histoplasma, Coccidioides, and Blastomyces species will appear in the biopsy specimen, as will Mucor and Aspergillus species. A PAS or methenamine silver stain is useful in identifying these organisms in tissue.

In addition to these infectious diseases, the more common oral squamous cell carcinoma should be considered in the presence of a palatal ulceration. If the granulation tissue and inflammation are submucosal with an intact surface, a non-Hodgkin lymphoma of the mucosal type bears consideration, as might the more rare angiocentric T cell and natural killer cell lymphoma formerly termed midline lethal granuloma.

Diagnostic Work-up

Because Wegener granulomatosis produces a normochromic, normocytic anemia, leukocytosis, and thrombocytosis, a complete blood count is recommended. A chest CT scan is preferred over a plain radiograph because of the multiple patterns that may be seen, ranging from infiltrates to nodules to thickening of alveoli to large cavities. Because of the possibility of renal disease, a urine analysis and serum renal function test are indicated. The oral and maxillofacial area is also best studied with a CT scan to assess sinus, nasal, mastoid, and middle ear involvement.

A definitive diagnosis requires a biopsy, which should show an intense necrotizing vasculitis of small vessels and a positive serum ANCA determination. It is recommended to test for both cANCA and pANCA, although a positive cANCA is more closely associated with Wegener granulomatosis.

The oral biopsy offers a straightforward opportunity to make an important diagnosis. It should sample a large portion of the clinically apparent lesion. Because several fungal diseases are part of the differential diagnosis, this tissue will require cultures in Sabouraud medium for fungi, as well as both aerobic and anaerobic cultures. It is advisable to include areas that are not necrotic since the preponderance of organisms will be found at the edge of viable and necrotic tissue.

Histopathology

The characteristic change is a necrotizing vasculitis of small vessels, in which there is an infiltration of neutrophils, and fibrinoid necrosis. This type of necrosis appears as an eosinophilic, structureless mass that stains positive for fibrin. There may be thrombosis of vessels with ulceration. The second major histologic finding is formation of necrotizing granulomas, which tend to have necrotic centers surrounded by neutrophils, lymphocytes, and plasma cells. Epithelioid cells are uncommon, but multinucleated giant cells of Langerhans and/or foreign-body type are usually prominent. These may be seen within, adjacent to, or at some distance from vessel walls. Gingival lesions do not usually demonstrate necrotizing vasculitis, although vessel damage probably results in the inflammatory infiltrate and hemorrhages that are seen. The gingiva will often show a reactive epithelial hyperplasia, and the epithelium may be infiltrated by neutrophils. The connective tissue usually contains infiltrates of neutrophils and eosinophils with formation of microabscesses. Plasma cells and lymphocytes may also be present, and multinucleated giant cells are seen. Sometimes, however, the clinical changes are accompanied by a nonspecific inflammatory reaction.

Treatment and Prognosis

Without treatment, Wegener granulomatosis is fatal in less than 1 year. Prompt treatment is essential to prevent involvement of the kidneys or to reverse kidney involvement to avoid renal failure, which is the most common cause of death.

The treatment of choice is cyclophosphamide (Cytoxan, Mead Johnson), 50 mg orally twice daily, combined with prednisone, 20 to 60 mg per day orally. The dosages of each are then adjusted to prevent recurrence at the lowest dose. Once the disease is under control, oral methotrexate, 25 mg per week, is a reasonable substitute for cyclophosphamide to maintain a remission. In addition, the antibiotic trimethoprim sulfamethoxazole (Bactrim, Roche) can also maintain a remission and allow for a discontinuance of cyclophosphamide and prednisone.

The prognosis is good with treatment. However, delayed treatment or severe disease may result in death. Most patients experience long-term remissions. Some require repeated treatments or ongoing maintenance therapy. The cANCA levels do not correlate well with disease activity and are not recommended for planning changes in treatment.

ANGIOEDEMA (ANGIONEUROTIC EDEMA)

Angioedema is a diffuse edematous swelling of the skin, mucosa and submucosal connective tissues.

Causes

- Allergic angioedema
- Associated with the use of angiotensin-converting enzyme (ACE) inhibitors
- Activation of the complement pathway
- Due to the presence of high levels of antigen-antibody complexes (e.g. in lupus erythematosus, bacterial or viral infections)
- In patients with grossly elevated peripheral blood eosinophil counts

Clinical Features

Angioedema manifests as a soft, nontender, diffuse, edematous swelling of rapid onset, which may be solitary or multiple, most commonly involving the face around the lips, chin, eyes, tongue, pharynx and larynx. Sometimes the hands, arms, legs, genitals and buttocks are involved. A feeling of tenderness or an itchy or prickly sensation sometimes precedes the urticarial swelling. The skin may be of normal color or slightly pink. Perioral and periorbital edema are characteristic of allergic edema.

The enlargement usually resolves within 24 to 72 hours, although some cases persist for several days.

Treatment and Prognosis

When the etiologic agent, such as food, can be discovered, its elimination from the diet will prevent recurrent attacks. Once developed, the edema can be treated by antihistaminic drugs usually prompt relief.

DRUG ALLERGY (DRUG IDIOSYNCRASY)

Drug allergy includes a variety of sensitivity reactions following exposure to any one of a great many drugs and chemicals but is not related to any pharmacologic activity or toxicity of these materials.

Clinical Features

The various allergic reactions to systemic administration of a drug are seldom anaphylactic in suddenness of appearance, but instead occur several days or longer after the beginning of the drug administration. Occasionally an immediate severe reaction occurs. The common allergic reactions of systemic administration of a drug include skin lesions, arthralgia, fever, lymphadenopathy and rarely agranulocytosis. The allergic reaction of the skin is called dermatitis medicamentosa. Commonly drug such as aspirin, barbiturates, chloramphenicol, tetracycline, penicillin, streptomycin and sulfonamides are implicated in allergic drug reactions.

Oral Manifestations

An allergic reaction of the mucosa is called stomatitis medicamentosa. Common reactions produced in the oral cavity are stomatitis, ulceration and necrosis, hemorrhage, gingival hyperplasia, pigmentation, altered salivary function and altered taste sensation.

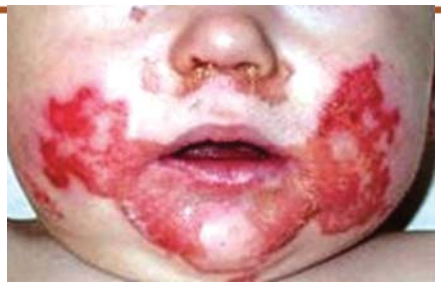
The most common type of allergic reaction of oral mucosa is erythema multiforme, characterized by multiple ulcerations of the tongue, palate, buccal mucosa and gingival. The other common patterns of oral mucosal disease are anaphylactic stomatitis, intraoral fixed drug eruptions, lichenoid drug reactions, lupus erythematosus-like eruptions, pemphigus-like eruptions and nonspecific vesiculoulcerative lesions.

Treatment and Prognosis

The signs and symptoms of drug allergy usually regress with discontinuance of the causative agent. The localized acute signs may be relieved by the administration of antihistamine drugs or cortisone.

16

Oral Aspects of Metabolic Diseases



DISTURBANCES IN MINERAL METABOLISM

Although hormones are the primary regulators of metabolism, they are ineffective without minerals and vitamins. Minerals are inorganic elements that are essential for life and provide both the structural and regulatory functions of the body. It is observed that there are at least 29 different elements in our body constituting about 4 percent of the body weight, concentrated mostly in the skeleton. The elements considered essential for normal growth and development of mammals are calcium, phosphorus, magnesium, potassium, sodium, chlorine, iodine, copper, iron, zinc, manganese, cobalt, chromium, selenium, and fluoride.

Minerals which are present in relatively high amounts in the body are referred to as macro minerals and those that are less than 0.005 percent of the body weight are called the micro minerals. Macro minerals or principal elements are nutritionally important minerals whose daily requirement is more than 100 mg. These include sodium, potassium, chloride, calcium, phosphorous, magnesium and sulfur. The micro minerals or trace elements are those found in tissues in minute amounts but are found to be essential to life. Their requirement is less than 100 mg/day and these include chromium, copper, cobalt, iron, iodine, manganese, selenium, fluorine, and zinc. The other trace elements which are possibly essential include cadmium, nickel, silicon, tin, and vanadium.

Inorganic and organic combinations of these elements are active in many physiologic processes. They constitute the basic structure of bone and teeth; help maintain the osmotic relations of the body fluids; regulate the acid – base equilibrium of the tissues; form part of hormones; are an integral part of some enzymes; serve as activators of certain enzymatic reactions; and they are an essential part of the oxygen – carrying pigments. Mertz's definition of 'essential' has been widely accepted. He stated that an element is considered essential when a deficient intake consistently results in suboptimal physiologic function that can be prevented or reserved by supplementation with physiologic levels of the element.

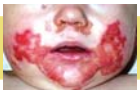
It is interesting that in many physiologic processes one mineral element may be substituted for another. For example, strontium or lead may replace calcium in the inorganic structure of bone. Rubidium may replace potassium in potassium deficient diet with the result that, even though the animals maintained on the diet die, the characteristic myocardial necrosis found in potassium deficiency will not occur. A thorough understanding of the normal processes of mineral metabolism and the effects of abnormal mineral metabolism is essential in pointing the way to the solution of many of the problems related to calcification of the teeth and jaws that constantly arise during the practice of dentistry.

Minerals

Although the literature concerned with calcium, phosphorus, and magnesium is voluminous, we still do not have a clear picture of the role of these elements in nutrition. The exact relation of magnesium to calcium and phosphorus metabolism is not known. For convenience, we shall discuss each element separately, trying to combine or integrate our knowledge whenever possible.

Calcium

Calcium is the fifth most abundant element in the body, and in crystalline form, with phosphorus, in a proteinaceous matrix, forms the major structural support of the body (bones). The total calcium in the body is 100-170 g, about 99 percent of which is found in bones existing as carbonate or phosphate of calcium while about 0.5 percent is present in soft tissue and 0.1 percent in extracellular fluid. The normal serum calcium level is about 9-11 mg/dl. The calcium in plasma is of three types: ionized calcium, protein bound calcium, and complexed calcium. About 40 percent of the total calcium is in ionized form, which is also physiologically active form of calcium. The level of the blood calcium is largely controlled by the action of the parathyroid glands, which are stimulated by low serum calcium levels and inhibited by high serum calcium levels.



Requirements and Absorption

The Food and Nutrition board of the National Academy of Sciences, National Research Council, recommends a daily dietary calcium intake of 360 mg for newborn infants and 800 mg for children and adults. Adolescents and pregnant and lactating women are advised to increase their daily dietary calcium intake by 50 percent to 1,200 mg. Calcium is taken in diet principally as calcium phosphate, carbonate and tartarate. Unlike sodium and potassium which are readily absorbed, the absorption of calcium in man is an inefficient process. Only about one third of the daily dietary intake of calcium is absorbed under normal conditions about 40 percent of average daily dietary intake of calcium is absorbed from the gut, mainly from the duodenum and first half of jejunum against an electrical and concentration gradient.

Absorption

In well-balanced diets, the ratio of calcium to phosphorus is of little significance, but in less balanced diets, this ratio assumes considerable importance. Phytic acid, which is found in cereals, forms and insoluble calcium phytate with ingested calcium and renders it nonavailable. Since this substance of cereals and is hydrolyzed only to the extent of 30-60 percent in the alimentary tract, the phosphate – calcium ratio is thus upset, interefering with the normal absorption of calcium. Vitamin-D increases absorption of calcium from the intestine. Under normal metabolic conditions for fat has been found to aid calcium absorption, but in conditions in which there is excessive fat excretion, such as in sprue or idiopathic steatorrhea, calcium is lost in the feces as calcium soaps.

Citrates, which may lower the pH of the intestinal tract, form calcium citrate which is relatively soluble. The addition of citrates to a rachitogenic diet seems to render the diet nonrachitogenic and also aid calcification. It has therefore been suggested that the lowering of the intestinal PH aids absorption of calcium citrate ion. Though relatively soluble, aids the deposition of calcium in bones by raising the pH of the calcifying tissue or of the fluids surrounding the calcifying tissue. High protein diets have also been shown to increase calcium absorption, probably through the formation of soluble calcium compounds with the amino acids produced by the digestion of the protein.

Oxalic acid interferes with calcium absorption by forming an insoluble calcium oxalate. For example, spinach contains sufficient oxalic acid to render all its calcium nonavailable, with some oxalic acid to spare for other calcium which might be present in the diet. The presence of hypochlorhydria or achlorhydria also exerts an adverse influence upon calcium and phosphate absorption, since normal secretion of hydrochloric acid by the stomach is necessary for optimal absorption of calcium and phosphate.

Lactose or milk sugar increase calcium absorption in rats, presumably by increasing intestinal acidity. In the human, lactose increases the retention of calcium without materially affecting absorption.

Many factors affect the utilization of absorbed calcium and phosphorus. Obviously, conditions which produce profound disturbance of any vital metabolism may have an indirect influence upon the metabolism of these minerals. Those factors, however, which appear to have a well-defined effect on calcium and phosphorus metabolism, are the parathyroid hormone, vitamin D, thyroid, calcitonin, and the steroid hormones.

Excretion

Calcium is excreted in both the faces and the urine, with 80 percent of the total amount being excreted in the feces. Fecal calcium consists not only of unabsorbed calcium, but also of calcium which has been absorbed and re-excreted. Although the small intestine is the predominant site in which the calcium is re-excreted, all segments of the intestinal tract probably excrete some calcium. Unless there is excessive perspiration, the dermal losses do not exceed 50 mg/dl. The normal daily urinary calcium excretion in adults is less than 250 mg for women and 300 mg for men. The calcium in the urine is excreted mainly as calcium chloride and calcium phosphate. The rental threshold for calcium is approximately 7 mg/dl of serum calcium. The urinary excretion of calcium is increased by increased plasma calcium, deprivation of phosphate, excessive vitamin D, increased urinary excretion of sodium, immobilization corticosteroid administration, increased dietary calcium, metabolic acidosis, hyperthyroidism, and idiopathic whereas urinary excretion of calcium is decreased by decreased ultrafiltration rate, parathyroid hormone, decreased dietary calcium, increased dietary phosphate, increased calcium utilization as in growth, pregnancy, and lactation.

Function

Calcium plays a large role in the formation of bones and teeth, in the maintenance of skeletal structure, tooth structure, normal membrane permeability, normal heart rhythm and other neuromuscular excitability, in the coagulation of blood, muscle contraction and as a secondary or tertiary messenger in hormone action. Variations of serum calcium ion concentration from the limited optimal range of 9-11 mf/dl have profound effects. A low concentration of calcium ions about 8 mg/dl) produces hyperirritability and tetany laryngospasm and convulsions, while high concentration produce depressed nerve conductivity and muscle rigor.

Hypocalcemia is said to exist when serum calcium is less than 8.5 mg/dl. The commonest cause of hypocalcemia is hypoalbuminemia, closely followed by renal failure. The other common cause of hypocalcemia is surgically induced hypoparathyroidsm. Hypercalcemia occurs when serum calcium levels exceed 11.0 mg/dl and the most common cause is primary hyperparathyroidism, malignancy and endocrine causes such as acute adrenal insufficiency and renal failure.

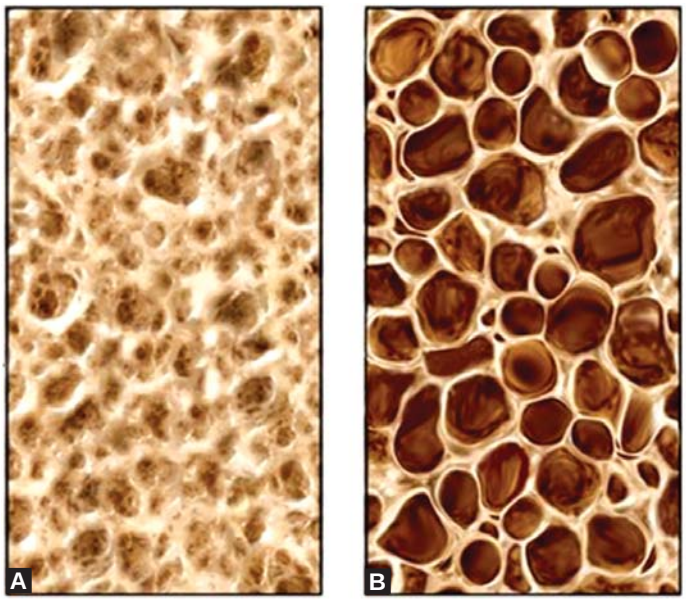
Experimental calcium deficiency in rats leads to a derangement of blood coagulation and of the integrity of the capillaries. Internal hemorrhages and generalized paralysis of the young born of calcium – deficient females are common. In addition, stomach ulcers have been described in rats, and lens opacities (cataracts) have been described in rabbits deficient in calcium. Hyperplasia and hypertrophy of the parathyroid glands of rats maintained on calcium – deficient diets have also been observed. In adult animals maintained on low calcium diets, sterility and reduction in lactation are frequently found. There are no descriptions of the teeth of animals maintained on a low calcium diet.

Osteoporosis and Calcium Deficiency

The etiology of osteoporosis was once thought to be a lack of adequate bone matrix. But evidences indicate that it may be due to a long-term negative calcium balance. Skeletal mass in old age is proportional to skeletal mass in old age is proportional to skeletal mass at maturity, indicating that infant and childhood calcium intake may play a major role in the occurrence and severity of the disease in later years. Based on these findings, the treatment of osteoporosis has changed over the years. Androgen and estrogen therapies have been replaced by increased calcium intake and strontitum and sodium fluoride ingestion. The role of strontium and fluoride in bone metabolism is not fully known, but they do act to sustain bone mass in elderly osteoporotic patients. Long-term metabolic balance studies indicate that in a majority of osteoporotic patients, calcium balance can be achieved with a high calcium intake. The importance of calcium strontium, and sodium fluoride in the prevention and treatment of senile osteoporosis have been found encouraging (Fig. 16.1).

Trace Elements

A large number of elements have been shown to occur in a wide range of animal tissues and fluids in such minute quantities that they are usually described as traces. Demonstration of a physiologic role for many of these elements has lagged far behind their mere detection in the living organism. It has been shown that both barium and strontium are essential for growth and especially for calcification of the bones and teeth of rats and guinea pigs. Mertz has reported silicon, vanadium, nickel, and arsenic to be essential in various animal species. However, no imbalances in humans have been reported.



Figs 16.1A and B: (A) Normal bone matrix, (B) Osteoporosis

Iodine

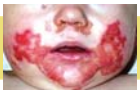
Iodine in small amounts is widely distributed in living matter. Sea foods are the best natural source and useful amounts may be present in vegetables and milk. The food color erythrosine is very rich in iodine. Normal whole blood contains an average of 8-12 µg/dl (range, 3-30 µg); protein – bound iodine varies from 3-8 µg/dl. The level of protein bound iodine is increased during pregnancy and in hyperthyroidism is essential for the formation of thyroid hormone. No other function for iodine in the nutrition of higher animals is known.

Iodine deficiency in man results in goiter. Iodine deficiency in experimental animals does not lead to colloid goiter. On the other hand, addition of iodine to the salt or water supply of endemic goiter areas has been successful in acting as a prophylactic in colloid goiter. About one third of the total body iodine is found in the thyroid concentrated iodine to colloid is unclear. However, thyroxin formation is intimately related to tyrosine metabolism.

The effects of the thyroid gland on oral structure will be considered in the section dealing with the endocrine glands. The ovaries also contain a high concentration of iodine.

Copper

Iron and copper have been *inextricably* involved in the development of all forms of life since the earth's



atmosphere dramatically changed from a reducing to an oxidizing environment. Copper deficiency in experimental animals leads to anemia. Adult humans contain 100-150 mg of copper, out of which approximately 65 mg is found in muscles, 23 mg in bones, and 18 mg in liver. Fetal liver contains approximately 10 times more copper than adult liver.

Requirement and Absorption

Copper requirements for infants and children are 0.05 mg/kg body weight per day, whereas adult requirement is approximately 2.5 mg/day. Ordinary diets consumed daily contain about 2.5-5.0 mg of copper. Acute copper deficiency in human beings has not been demonstrated.

The value of copper supplements, with and without iron, in the treatment of anemias of infancy and childhood and of secondary anemias of adults has been extensively studied. Copper is necessary for normal erythropoietin as well as or iron absorption. Copper deficiency produces microcytic hypochromic anemia, due to impairment of erythropoiesis and decrease in erythrocyte survival time, which cannot be corrected by administration of iron. Iron absorption is mediated by ceruloplasmin, which acts as a ferroxidase. Other metalloenzymes which require copper are cytochrome c oxides, superoxide dismutase, tyrosinase, and lysyl oxidase. Human copper deficiency diseases of importance are hepatolenticular degeneration (Wilson's disease) and Menkes' Syndrome (Steely – or Kinky – Hair Syndrome)

Iron

Iron is one of the most essential trace elements in the body. In spite of the fact that iron is the fourth most abundant element in the earth's crust, iron deficiency is one of the most important prevalent nutritional deficiencies in India. The total iron content in a human of 70 kg body weight varies approximately from 2.3 – 3.8 gm. The average iron content of adult males is about 3.8 gm and of females about 2.3 gm. There are two broad categories that are used to describe iron in the body. They are essential (or Functional) iron and storage iron. Essential iron is involved in the normal metabolism of cells whereas storage iron is present in two major compounds – ferritin and hemosiderin.

Requirement and Absorption

The requirement of iron varies according to age, gender, weight and state of health. An adult male requires approximately 10 mg/day and adult female 20 mg/day. Pregnancy and lactation demand or pregnant women require 10 mg/day and acting mother 25-30 mg/day. Children require 10-15 mg/day. Iron is absorbed in the upper portion of the duodenum, either as ferrous or as ferric salts, depending on the species studied. Absorption depends on the amount of the element that the organism has stored. If the tissues are depleted, iron is absorbed rapidly, if sufficient quantities are present, absorption is slight. Since little excretion of iron takes place either by the alimentary canal or by the kidneys, this element has been called a one – way substance'. Normally, the loss of iron from the body of man is limited to 1 mg per day.

Few studies have been reported on the histopathologic changes occurring in the tissues of human beings or experimental animals with iron deficiency anemias. Iron deficiency in the human being, particularly in women and children, however, is more common than has been realized. Changes in the resulting anemia include formation of an esophageal web in the Plummer – Vinson syndrome, Spooning of the nails (Koilonychia), normoblastic arrest in the bone marrow and microcytosis, anisocytosis, and hypochromia of the erythrocytes in the peripheral blood. Sore tongue, similar to that found in nicotinic acid and riboflavin deficiencies, has been described in the iron deficiency anemias. These anemias respond well to iron therapy. It is imperative to determine iron levels in all patients with anemias, since there are disorders such as thalassemias that may be present and misdiagnosed as iron deficiency.

Iron overload can occur in a number of conditions. Idiopathic hemochromatosis results in excessive iron absorption and is characterized by micronodular cirrhosis with marked brown pigmentation, diabetes mellitus, and skin pigmentation called as **'Bronze diabetes'.** Hemoglobinpatheis such as sideroblastic anemia and thalassemia can also cause iron overload. **Bantusiderosis,** a form of iron overload resulting from ingestion of home made beer fermented in iron pots, has been extensively described.

Zinc

The role of zinc as an essential nutrient is known for more than 100 years. Zinc is obtained from liver, milk and dairy products, eggs, unmilled cereals, legumes, pulses, oil seeds, and leafy vegetables. An average man has about 1.4 – 2.3g of Zinc in the body. The zinc is distributed in highest concentration in skin and prostate where it is about 70 – 80 mg/100g followed by bone and teeth where zinc concentration varies between 10-15 mg/100g. The concentration of zinc in enamel and dentin is about 0.02 percent, which is higher than in many other hard tissues of the body. Bone, nails and hair have a slightly lower concentrations.

Only a small percentage of dietary zinc is absorbed from duodenum and ileum. A low molecular weight zinc binding factor secreted by the pancreas, forms complex

with zinc and helps in its absorption. High amounts of dietary calcium and phosphates interfere with zinc absorption. In a normal healthy adult, approximately 9.0 mg of zinc is excreted through faeces and urine and only about 0.5 mg retained in the body. Adult men and women require about 15-20 mg as the recommended daily does is about 0.3mg/kg body weight.

Among many functions of zinc, the most important is its role in enzyme action as it forms an integral part of several enzymes are superoxide dismutase, carbonic anhydrase, and leucine aminopeptidase. Zn^{++} has been claimed to stimulate the release of vitamin A from the liver into the blood and thus increases its plasma level and its utilization in rhodopsin synthesis. Protamine zinc insulin and globin zinc insulin contain Zn^{++} for its functioning. Zinc content of pancreas also has been found to diminish in diabetes mellitus. Zinc is also necessary for the healing of wounds as zinc has been found to accumulate in granulation tissues and zinc deficiency delays wound healing.

In 1961, Prasad and his associates reported a symptom complex of dwarfism and hypogonadism in male Iranians which stemmed from a deficiency of zinc in the diet. This deficiency was thought to occur from zinc binding with phytates present in bread. Subsequent studies in Egypt by Prasad and his coworkers confirmed this impression. The zinc – deficient subjects appeared much younger than their stated age, lacked facial, axillary and pubic hair, had atrophic tests and small external genitalia and were retarded in bone age. The zinc content of the plasma, red blood cells and hair was consistently lower than in normal ethnically identical controls. Radioisotope studies demonstrated a significantly increased plasma zinc turnover and a decreased excretion of Zn 65 in the urine and stools of the dwarfs, indicative of zinc retention and conservation. A low plasma level of alkaline phosphates, a zinc – containing enzyme, was also found in these patients (Fig. 16.2).

Acrodermatitis enteropathica, a specific multiorgan disorder resulting from zinc deficiency, has been described. It is an autosomal recessive disorder in which the primary defect is in zinc absorption. Its symptoms include diarrhea and a wide range of mucocutaneous problems including vesicles, eczematoid, and glossitis. In leukemias, zinc content is almost reduced to 10 per cent of the normal amount. Zinc in leukocytes probably has immunologic function. Serum zinc levels are decreased in cirrhosis of liver and lower plasma levels of zinc has been noted in acute viral hepatitis which returns to normal level with recovery. Zinc deficiency in humans results in a number of disorders involving taste, keratogenesis, bone growth, wound healing, and reproduction.

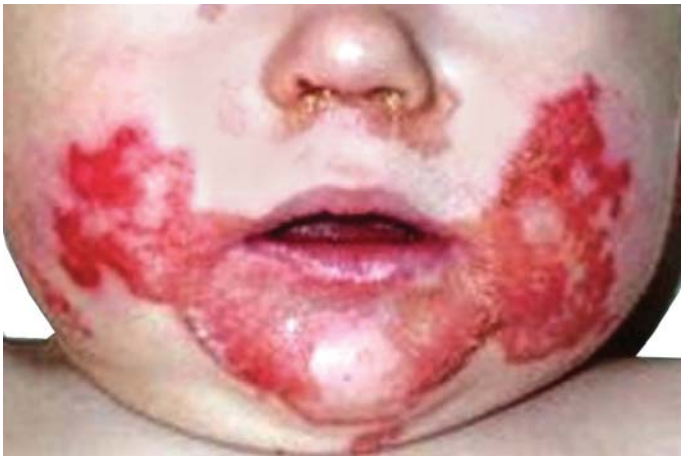


Fig. 16.2: Zinc deficiency

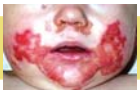
Manganese

Manganese is an essential element widely distributed in the crust of the earth. The total amount of manganese distributed in our body is in the range of 10-18 mg and is found in highest concentration in the kidney and liver. Manganese is obtained in diet principally from cereals vegetables, fruits, nuts and tea. Blood manganese is usually about 4-20 µg/100 ml. They are mainly in RBCs in combination with several porphyrins and are transported in the plasma in combination with a b1 globulin called transmaganin.

Manganese acts as a "Cofactor' or as an activator of many enzymes like arginase, isocitrate dehydrogenase (ICD), lipoprotein lipase, cholinesterase, and many others. Manganese may be be associated with mithochondrial respitratory chain enzymes and act as a cofactor of all hydrolases and decarboxylases. Manganese has also been shown to have a role in animal reproduction and plays a part in the synthesis of mucopolysaccharides in the cartilagenous matrices of long bones. Deficiencies in animals produce alteration of bones, ataxia, and infertility.

DISTURBANCES IN PROTEIN METABOLISM

Proteins are complex biologic compounds of high molecular weight containing nitrogen, hydrogen, oxygen, carbon and small amounts of sulfur. As the third principal group of organic compounds, they are much more complex in structure and have a larger range of functions than carbohydrates or lipids. All living tissues, whether plant or animal, contain proteins. The fundamental difference between the protein metabolism of plants and that of animals is the ability of plants to synthesize proteins from the nitrogen and sulfur of the soil and from the carbon, oxygen, and hydrogen of the air. Animals must ingest,



break down, absorb, and rearrange dietary proteins to form tissue proteins. The chemical process of digestion, which is essentially hydrolytic, is common to all heterotrophic organisms. Substances of high molecular weight – proteins, nucleic acids, and carbohydrates are hydrolyzed to yield smaller molecules which are absorbed and assimilated. A normal adult has about 12-18 per cent protein. Nitrogen balance studies are used to determine the lowest protein intake that will support homeostasis.

Protein Requirements

The accepted figure of 1 gm of protein for each kilogram of body weight is designed to give a factor of safety to cover individual difference in requirement. Protein is required in increased quantity in the last half of pregnancy and during lactation, and in even greater amounts in infancy, childhood, and adolescence. Proteins constitute the most important group of foodstuffs. In addition to contributing to cells and intercellular materials, proteins and their constituent amino acids are of importance in the formation of hormones, enzymes, plasma proteins, antibodies, and numerous other physiologically active substances.

Complete proteins contain sufficient amounts of the essential amino acids for normal metabolic reactions and these are usually found in foods of animal origin. Incomplete proteins are those that have insufficient quantities of one or more essential amino acids and among few are the corn protein which is low in lysine and legume protein that is low in methionine. Complementary proteins are proteins that, when ingested singly, are incomplete but, when combined provide sufficient essential amino acids.

Comparatively little is known of the processes by which digested protein is recombined to form body proteins. Build – up of body protein is particularly active during growth, late pregnancy, and lactation. There is apparently a constant flux of tissue breakdown and tissue formation, producing a dynamic equilibrium. Proteins have an important bearing on the pre-eruptive and post – eruptive effects on teeth. They form an integral component of cells necessary for the normal development of the tooth and specifically for the formation of the matrix of hard tissues of teeth. The chemical nature or protein foods can neutralize the acids produced by oral bacteria.

Protein Energy (Calorie) Malnutrition (PEM)

PEM is a spectrum of diseases with kwashiorkor whose essential feature is deficiency of protein at one end; and nutritional marasmus, which is total inanition of infant due to severe and prolonged restriction of all food at the other end. In the middle of the spectrum is marasmic kwashiorkor in which there are clinical features of both disorders. Some children adapt to prolonged energy and protein shortage by nutritional dwarfism. The most prevalent of all the varieties is mild to moderate PEM or the underweight Child. PEM, in its various forms, has a higher incidence in India, south east Asia, parts of Africa, the Middle East, the Caribbean Islands, and in south and Central America.

In some developing countries, marasmus is of greater clinical importance than kwashiorkor. The factors which predispose to marasmus are a rapid succession of pregnancies, and early and often abrupt weaning, followed by artificial feeding of infants in inadequate amounts. The two constant features of marasmus are retarded growth and wasting of subcutaneous tissues, giving the child an aged appearance. Marasmus is usually associated with energy deficiency and occurs in many pathologic states besides simple starvation. Protein deficiency is common in prolonged febrile illness, in massive burns and large chronic ulcers, in 'Stress' hyperthyroidism and other hypermetabolic states, in conditions interfering with digestion and absorption and in metabolic diseases which interfere with utilization. The other clinical findings in protein deficiency include loss of weight and of subcutaneous fat, wasting of muscles, pigment changes in the skin with hair loss, hypotension, weakness, and edema. Anemia is common. A decrease in serum proteins, hemoconcentration, and a decrease in blood volume are other frequent findings.

In Kwashiorkor, some amino acid or protein deficiency arises typically after prolonged breast-feeding and the child is weaned on to a low protein family diet. This combined protein – energy deficiency in children in many parts of the world, due to insufficient supply of amino acids, leads to inadequate protein synthesis, reduced synthesis of enzymes, and plasma proteins and impaired development of organs. The child's weight is usually well below standard for age but the deficit may be masked by edema often due to hypoalbuminemia. Impaired synthesis of digestive enzymes may be masked by edema often due to hypoalbuminemia. Impaired synthesis of digestive enzymes may be partially responsible for diarrhea which is so commonly present and which leads to loss of potassium and magnesium in the stools. The child is prone to infections due to Subnormal levels of immune responsiveness.

The oral lesions, when apparent, include a bright reddening of the tongue with a loss of papillae, bilateral angular cheilosis, fissuring of the lips, and a loss of circumoral pigmentation. In addition, the mouths of kwashiorkor patients have been described by van wyk as being dry, dirty caries free, and easily traumatized, with

the epithelium readily becoming detached from the underlying tissues, leaving a raw, bleeding surface. In oral cytologic smears from his patients, he described a perinuclear vacuolization or halo around the nucleus in a remarkable number of the epithelial cells present and interpreted this as a sign of epithelial atrophy.

King has pointed out that about half of the world's population lives in areas where the lack of milk, meat, poultry, fish, eggs, and so on, leads to early retardation of growth. Typically, children so retarded have edema, episodes of diarrhea, skin pigmentation, liver enlargement, alopecia, and poor resistance to infection, especially of the lungs and intestinal tract. The death rate may reach 25 times that considered normal for the age group those that survive show permanent physical stunting. This stunted condition is so general that it is often mistaken for a genetic phenomenon. In some areas 50 percent of the children die before school age. It is significant that most of the children exhibit a normal growth rate up to weaning time.

Frandsen and his coworkers, chawla and Glickman, Di Orio and coworker, Navia, Aponte – Merced and Navia, Menaker and navia, and Navia and coworkers have studied the effect of protein and Protein – energy deprivation on salivary glands and teeth and their supporting structures in experimental animals. Overall growth and growth of the jaws were decreased. Eruption was delayed, and incisor and molar growth was retarted. Radicular osteocementum was decreased. The enamel of affected incisors exhibited increased acid solubility. Increased dental caries was also reported. The gingiva and periodontal membranes exhibited varying degrees of degeneration. Salivary volume was decreased as were the DNA, RNA, and protein concentrations of affected animals. The severity of these changes was dependent on the degree of protein deprivation.

Some of the genetic disorders, where dietary modifications become important include, phenyl ketonuria (PKU), which is an inherited enzyme defect in which individuals cannot metabolize the phenylalanine found in nearly all proteins. Patients with this condition are prescribed a diet which is protein restricted, just enough to meet growth and maintenance needs. Gout is yet another disorder of protein metabolism which is characterized by excessive uric acid production leading to the formation of urate crystals deposited in joints. The treatment often includes restriction of protein to limit purine and uric acid production.

Protein needs increase during fever, after severe injury and surgery, intestinal malabsorption, increased protein loss from the kidneys, or diminished protein synthesis by the liver. Dietary protein must be restricted when the kidneys can no longer remove nitrogenous wastes from the body or in severe liver disease when the nitrogenous by products of protein catabolism can no longer be synthesized.

Individual Amino Acids

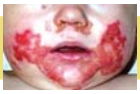
The inadequacy of zein as a sole source of protein in rat nutrition brought out the importance of the variations in amino acid content of different proteins and led to the work of rose and his collaborators and other on the essential and nonessential amino acids. The essential amino acids are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. This list of nine essential amino acids must not be accepted as final, however, more may have to be added and some may eventually be droped. The original concepts of essential and nonessential must be modified, since the determination of essentiality depends not only on the species studied, but also on the experimental criteria used (e.g nitrogen balance, growth) the age of the animal used and the presence or absence of vitamins in the diet. For example, arginine is nonessential in the adult. However, infants are incapable of producing sufficient amounts of arginine for normal physiologic functions. Therefore, arginine is considered essential in infants. It is unlikely, however, that a deficiency of a single essential amino acid occurs in humans.

Porphyria

Porphyria is a term which has been generally used to connote one of the inborn errors of porphyrin metabolism, characterized by overproduction of uroporphyrin and related substances. Not all cases of porphyria, however, represent a constitutional disturbance, since porphyria may appear as a sequel to some infections or intoxications. The classification of the porphyrins remains unsettled, although the most basic classification defines two types:

- Erythropoietic porphyria, characterized by early photosensitivity, splenomegaly, and excessive abnormal porphyrin formation in developing erythrocytes. Two subclasses, uroporphyria (Congential porphyria and protoporphyria, have been described based on their respective porphyrin precursor type.
- Hepatic porphyria, also a multisystem disorder, which has four subclasses; acute intermittent porphyria, porphyria variegate, porphyria cutanea tarda, and hereditary coproporphyria.

Heritable enzymatic effects have been indentified in uroporphyria, acute intermittent porphyria and porphyria cutanea tarda. An excellent review of the porphyries has been published by Elder and coworkers.



DISTURBANCES IN CARBOHYDRATE METABOLISM

Mucopolysaccharidoses

Mucopolysaccharidoses (MPS) result from abnormal degradation of glycosaminoglycans such as dermatan sulfate, keratin sulfate, heparin sulfate, and chondroitin sulfate resulting in organ accumulation and eventual dysfunction. Glycosaminoglycans or mucopolysacchaides are normally component of the cornea, cartilage, bone, connective tissue, and the reticuloendothelial system and are therefore target organs for excessive storage. The catabolic enzymes involved in the breakdown of glycosaminoglycans or mucopolysaccharides are deficient. Ten known enzyme deficiencies give rise to six distinct MPS.

The step-wise degradation of the glycosaminoglycans requires four glycosidases, five sulfatases, and one nonhydrolytic transferase. The mode of transmission is autosomal recessive except for MPS II, which is X – linked. A variety of mutations are described, and the correlation of genotype with disease severity is beginning to emerge from mutation analysis.

In genral, MPS are progressive disorders, characterized by the involvement of multiple organs, including the brain, liver, spleen, heart and blood vessels, many are associated with coarse facial features, clouding of the cornea, and mental retardation. Diagnosis can often be made by examination of urine, which reveals increased concentration of glycosaminoglycan fragments.

Clinical Presentation

MPS Type I includes **Hurler, Hurler – scheie,** and **Scheie syndromes. MPS type IH (Hurler syndrome)**. This form is intermediate between the Hurler syndrome and scheie syndrome.

MPS type IS (Scheie Syndrome)

Biochemical findings are identical to type I Hurler syndrome, but the clinical features are less severe.

Glycosaminoglycan fragments are generated by alternative pathways and are excreted in the urine. Simple enzyme assays are available for the diagnosis of MPS from fibroblast, leukocyte, or serum samples. Because heterozygous individuals are identified on the basis of enzyme activity, the diagnosis can be difficult. However, it is becoming more definitive as specific mutations are identified. Prenatal diagnosis is made by means of aminocentesis or chorionic villus biopsy **(Hurler syndrome).**

Clinical Features

The disease usually becomes apparent within the first two years of life, progresses during early childhood and adolescence and terminates in death usually before puberty. The head appears large and the facial characteristics are quite typical, consisting of prominent forehead, broad saddle nose and wide nostrils, hypertelorism, puffy eyelids with coarse bushy eyebrows, thick lips, large tongue, open mouth, and nasal congestion with noisy breathing. Progressive corneal clouding is a classic manifestation of the disease as is hepatosplenomegaly, resulting in a protuberant abdomen. A short neck and spinal abnormalities are typical, while flexion contractures result in the claw hand these dwarfed individual are mentally retarded

VITAMIN A

Clinical Features of Vitamin A Deficiency

If the deficiency is mild, the manifestations in man are night blindness, xerophthalmia, and keratomalacia. Hyperkeratotic changes in the oral epithelium of adults have been noted. Follicular keratotic changes have been described in naturally occurring vitamin A deficiency by Frazier and HU and by sweet and Kang. Hume and Krebs, and stiffens and humans and were able to produce cutaneous manifestations in only one patient.

As it progresses, kertinizing metaplasia appears in the trachea and bronchi, kidney, pelvis, conjunctiva, cornea, salivary glands, an genitourinary tract. Documented autopsy studies have been published by Wilson and Dubois and by Blackfan and Wolbach. If vitamin A deficiency were to cause changes in the human tooth bud, the deficiency state would have to occur before the sixth year of life, since by that time the crowns of all the teeth except the third molars are completely formed. The only cases of changes in human tooth buds attributable to vitamin A deficiency are those described by boyle and by Dinnerman. Their findings were similar to those described in the rat incisor tooth in vitamin A deficiency and its clinical implications may be found in the federation proceedings for 1958.

VITAMIN D DEFICIENCY RICKETS

Clinical Features of Rickets

Rat is the laboratory animal commonly used for the experimental investigation of rickets. The effects of rickets are reflected only in the bones and teeth of the afflicted animal. The changes in the bones are found in the epiphyseal plate, the metaphysic, and the shaft. Since the

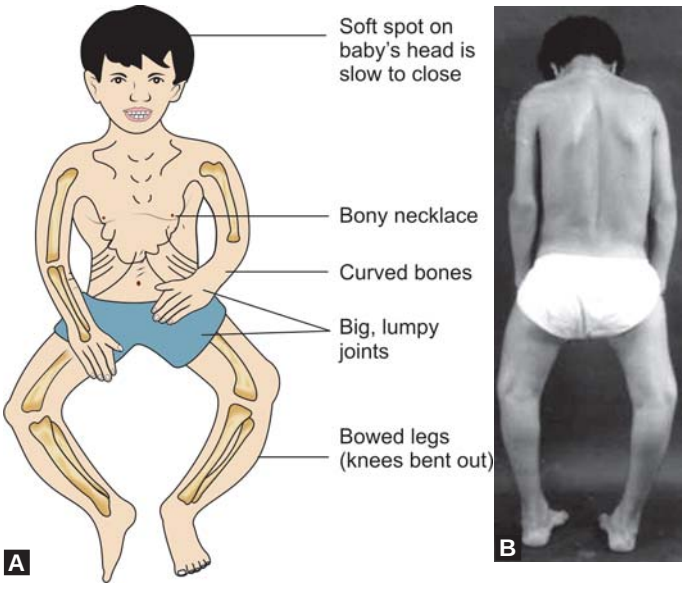
degree of change encountered depends on the rate of growth of the bones at the time of the deficiency young, animals are more seriously affected than older animals.

In young rats placed on rachitogenic diets, the first change seen is the cessation of calcification of their epiphyseal disks. Since the intercellular ground substance does not become calcified, the cartilage cells are not denied nutrition. Therefore, they do not die, and their continued growth and multiplication lead to an increase in the width of the disk. The disk thickens irregularly because some focal areas usually calcify. The osteoblasts continue to lay down osteoid around the bone and cartilage spicules in the metaphysic, as well as beneath the periosteum in the region of the metaphysic and other areas of the shaft. The changes in the ribs and long bones of children with rickets are essentially the same as those described for the rat. Since undermineralized bone is not as capable of supporting weight as normal bone, children with rickets show bowing of leg (Fig. 16.3).

HYPOPHOSPHATASIA

Clinical Features

On the basis of clinical manifestations and chronology of the appearance of bone disease, hypophosphatasia is divided into three clinical forms: infantile, childhood, and adult. The infantile form is manifested by severe rickets, hypercalcemia, bone abnormalities, and failure to thrive. Most of these cases are lethal. Hypophosphatasia of childhood is characterized by premature exfoliation of deciduous teeth, increased infection, growth retardation and rachitic-like deformities, including deformed extremities, costochondral junction enlargement (rachitic rosary), and failure of the calvarium to calcify. Pulmonary, gastrointestinal, and renal disorders are also present. The adult form includes spontaneous fractures, prior history of rickets and osseous radiolucencies (Fig. 16.4).



Figs 16.3A and B: (A) Signs of rickets deficiency, (B) Vitamin D resistant rickets. Note the deformities of legs (bow legs) and compromised height

CLINICAL FEATURES OF THIAMIN DEFICIENCY

In man, thiamin deficiency leads to beriberi, which is generally insidious in onset, chronic in course and sudden death may occur. Beriberi may be of two types: wet and dry. In either form, patients may complain of pain and paresthesia. Wet beriberi manifests with cardiovascular symptoms due to impaired myocardial energy metabolism, dysautonomia, cardiomegaly, high – output cardiac failure, peripheral edema, and peripheral neuritis. In dry beriberi, same symptoms occur but for the edema.

Alcoholic patients with chronic thiamin deficiency are having CNS mainfestaitions known as wernickes' encephalopathy, which consists of horizontal nystagmus, opthalmoplegia, cerebral ataxia, and mental impairment. Along with the above mentioned symptoms, if there is loss of memory and confabulatrory psychosis, it is known as Wernickes'-Korsakoff syndrome.

CLINICAL FEATURES OF RIBOFLAVIN DEFICIENCY

Riboflavin deficiency is particularly common among children who do not drink milk. In endemic areas, the incidence is greater during the spring and summer months than in other seasons.

A long period of vague, nondescript symptoms usually precedes the appearance of diagnostic lesions. The

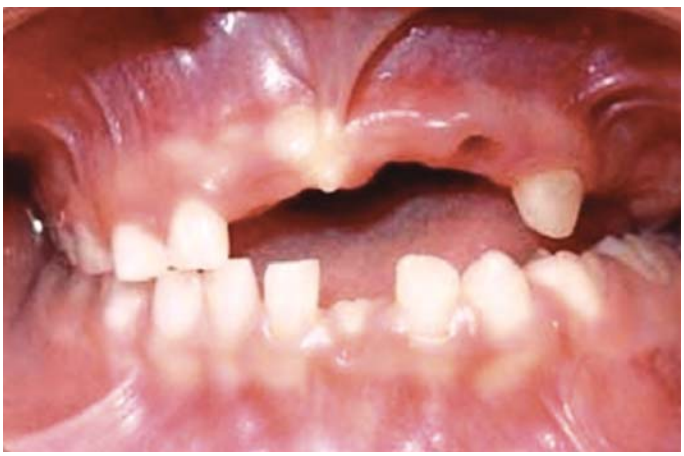
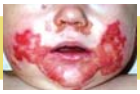


Fig. 16.4: Premature exfoliation of deciduous teeth in hypophosphatasia



diagnostic lesions of riboflavinosis are usually limited to the mouth and periroal regions. The oral manifestations of the disease are well recognized, since they have been experimentally produced by sebrell and Butler in 18 healthy women placed on ariboflavin – deficient diet. Although the exact mechanism involved in the production of the oral lesion is not understood, the clinical stages have been clearly defined.

In the mild deficiency state there is a glossitis which begins with soreness of the tip and/or the lateral margins of the tongue. The filliform papillae become atrophic, while the fungi form papillae remain normal or become engorged and mushroom shaped, giving the tongue surface a reddened, coarsely granular appearance. The lesions extend backward over the dorsum of the tongue. In severe cases the tongue may become glazed and smooth, owing to complete atrophy of all papillae. In many cases the tongue has a magenta color which can be easily distinguished from cyanosis.

Paleness of the lips especially at the angles of the mouth, but not involving the moist areas of the buccal mucosa, is the earliest sign of the deficiency disease. The pallor, which usually continues for day, is followed by cheilosis, which is evidenced by maceration and fissuring at the angles of the mouth. The fissures may be single or multiple. Later the macerated lesions develop a dry yellow crust which can be removed without causing bleeding. The lips become unusually red and shiny because of a desquamation of the epithelium. As the disease progresses, the angular cheilosis spreads to the cheek. The fissures become deeper, bleed easily and are painful when secondarily infected with oral and/or skin microorganisms. Deep lesions leave scars on healing. The gingival tissues are not involved.

Riboflavin deficiency also affects the nasolabial folds and the alae nasi, which exhibit a scaly, greasy dermatitis. A fine scaly dermatitis may also occur on the hands, vulva, anus, and perineum. Ocular changes, consisting of corneal vascularization, photophobia, and a superficial and interstitial keratitis, have also been described considering that flavoprotiens are widely distributed throughout the body, it is surprising that the lesions are so well localized.

In the differential diagnosis of ariboflavinosis, it is important to remember that bilateral angular cheilosis is a nonspecific lesion. Older people with greatly decreased vertical dimension, either through faulty dentures or through attrition of the natural dentition, frequently show the nonspecific angular cheilosis (Fig. 16.5).

HYPOPITUITARISM

In man, some indication of the role played by the pituitary in the development of the oral tissue can be gained from studies of hypopituitarism as well as hyperpituitarism. Hypopituitarism is caused by compression or atrophy of anterior pituitary cells or defect in the hypothalamic control of hormonal secretion. Before puberty, the hypofunctioning leads dwarfism, which mainly manifests with features of growth hormone deficiency. After puberty, it affects other endocrine glands also. Some of the common causes of hypopitutarism, which occur after puberty, are pituitary adenoma, simmonds disease or hypophyseal cachexia, and Sheehan's syndrome (pituitary infraction in the postpartum woman). Hypofunction of posterior lobe leads to deficiency of vasopressin, resulting in diabetes insipidus.

Clinical Features

The typical evidence of hypopituitarism resulting in pituitary dwarfism are a diminutive but well-proportioned body, fine, silky, sparse hair on the head and other hairy regions, wrinkled atrophic skin, and often, hypogonadism. The deficiency may be congenital, or it may be due to a destructive disease of the pituitary, such as an infarct occurring before puberty. There is no distinctive pattern to the basal metabolism in this disease.

In pituitary dwarfs the eruption rate and the shedding time of the teeth are delayed, as is the growth of the body in general. The clinical crowns appear smaller than normal because, even though eruption does occur, it is not complete. The dental arch is smaller than normal and therefore cannot accommodate all the teeth, so that a malocclusion develops. The anatomic crowns of the teeth in pituitary dwarfism are not noticeably smaller than normal, contrary to what might be expected in light of the animal experiments. There are no reports of a careful statistical study of crown size in dwarfism. The roots of the teeth are shorter than normal in dwarfism, and the supporting structures are retarded in growth. The osseous development of the maxilla is not as retarded as that of the mandible.

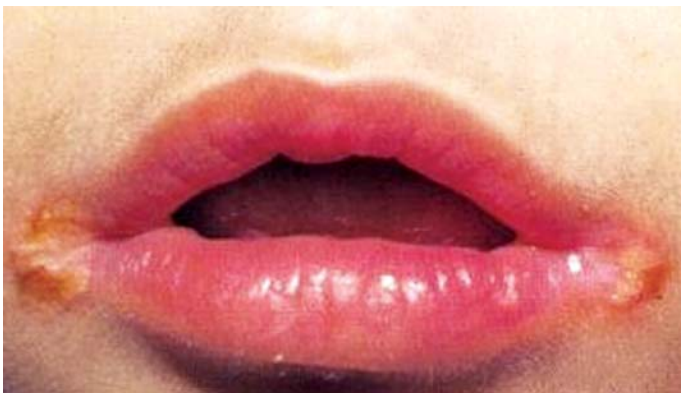


Fig. 16.5: Angular cheilitis in riboflavin deficiency

Hypopituitarism in the adult is usually due to an infraction of the pituitary called Simmonds diseases. It is characterized by loss of weight and diminished sexual function. The basal metabolic rate is markedly lowered, and since Simmonds disease represents a panhypopituitarism, there is a decrease in the activity of the many hormones of the pituitary gland and of those glands that are under pituitary regulation. In this disease, the skin shows atrophic alterations. Changes in the head include thin eyebrows, loss of eyelashes, sharp features, thin lips, and an immobile expression. There will be a decreased salivary flow due to hypofunctioning of salivary glands which leads to increased caries activity and periofontal disease.

HYPERPITUITARISM

Clinical Features

Gigantism is characterized by a general symmetric overgrowth of the body, some persons with this disturbance attaining a height of over 8 feet. Later in life such people usually show genital underdevelopment and excessive perspiration, and they complain of headache, lassitude, fatigue, muscle and joint pains, and hot flashes. It is also characterized by the presence of broad, enlarged nose, thick and furrowed oily skin. Organomegaly and hypertension is a common finding. Skeletal changes include frontal bossing and prognathic mandible. Increased glove, ring, and shoe size indicates the changes in the hands and feet. Patient may develop class II malocclusion with interdental spacing. Hypercementosis is a common finding in the introral radiographs.

The teeth in gigantism are proportional to the size of the jaws and the rest of the body. The roots may be longer than normal.

HYPOTHYROIDISM

Clinical Features

Congenital hypothyroidism, or cretinism, leads to mental defects, retarded somatic growth, generalized edema and other changes, depending on the severity of the deficiency of thyroid hormone. The dentofacial changes in cretinism are also related to the degree of thyroid deficiency. Usually, the base of the skull is shortened, leading to a retraction of the bridge of the nose with flaring. The face is wide and fails to develop in a longitudinal direction. The mandible is underdeveloped, and the maxilla is overdeveloped. The hair is sparse and brittle; the fingernails are brittle, and the sweat glands are atrophic.

The dental changes in juvenile hypothyroidism have been reviewed by Hinriches, who also presented 36 cases. He indicated that the longer the time between the onset of the disease and the institution of treatment, the greater is the likelihood that the developing dentition will be affected. However, with a few exceptions, he found no striking morphologic changes in the teeth of the patients in his series.

Characteristically, the tongue is enlarged by edema fluid. It may protrude continuously, and such protrusion may lead to malocclusion. The eruption rate of the teeth is delayed, and the deciduous teeth are retained beyond the normal shedding time. Myxedema, the disease produced by thyroid deficiency in adults or children is usually, caused by atrophy of the thyroid gland of unknown etiology. The metabolic rate is lowered, although this finding should not be used as a diagnostic test for myxedema. Concentration of serum protein-bound iodine and radioactive iodine uptake or excretion studies are the diagnostic tests of value.

The myxedematous swelling is probably an extravascular, extracellular accumulation of water and protein in the tissues. The protein has a greater osmotic effect than the serum proteins, accounting for the increased blood protein concentration and decreased plasma volume which are found in myxedema.

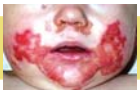
The clinical orofacial findings in myxedematous patients are apparently limited to the soft tissues of the face and mouth. The lips, nose, eyelids, and suborbital tissues are edematous and swollen. The tongue is large and edematous, frequently interfering with speech.

CUSHING'S SYNDROME

This syndrome is a result of hormonal excess resulting from any of the following:

- Hyperplastic adrenal cortices without any other clinically evident endocrine lesion.
- Adrenal cortical adenoma or carcinoma.
- Ectopically located adrenal – like tumor, for example, of an ovary.
- ACTH secreting tumor of the anterior pituitary associated with adrenal cortical hyperplasia.
- Nonpituitary carcinoma, for example, of a lung or the pancreas, with secretion of an ACTH–like material that induces adrenal cortical hyperplasia.

When the syndrome is associated with spontaneous bilateral adrenal hyperplasia, it is referred to the Cushing's disease. In adults, it is recognized that Cushing's disease represents approximately 75 percent of the cases of Cushing's syndrome. While Cushing's disease is uncommon in children, McArthur and his associates have



reported a series of 13 cases in patients under the age of 15 years. The pathogenesis of this disease has been reviewed by Hunder.

It is characterized by a rapidly acquired adiposity about the upper portion of the body, mooning of the face, a tendency to become round shouldered and develop a 'buffalo hump' at the base of the neck, alteration in hair distribution, a dusky plethoric appearance with formation of purple striae, muscular weakness, vascular hypertension, glycosuria not controlled by insulin, and albuminuria (Fig. 16.6).

The oral pathologist's primary concern with this peculiar disease state lies in the bone changes. In children there may be osteoporosis and premature cessation of epiphyseal growth, while in adults there is a severe osteoporosis.

The mechanisms for the bone changes is not well understood. Apparently, 11-desoxycorticosterone is relatively unimportant in the pathogenesis of Cushing's syndrome. Albright's explanation for the pathogenesis of the disease is based on the S-F-N (sugar-fat-nitrogen) hormone group of steroids in which the 'N' hormone is considered an anabolic one, stimulating osteogenesis and causing closure of the epiphysis, and the 'S' hormone is considered an ant anabolic one. The mechanism of osteoporosis is then explained on the basis of an excess of 'S' hormone, leading to a retardation of osteoblastic activity and reduction in matrix formation.

We appreciate the fact that a number of complex interrelations are concerned in the normal and abnormal control of bone growth and maturation. Considerable interest is now centering on these interrelations and on the precise metabolic or endocrine pathways by which particular hormones influence skeletal growth. Little definite evidence on these topics exists as yet, but some information is available on the effects of cortisone on bone growth. For example, Follis showed that cortisone injections in rats produced retardation and arrest of and interference with resorption of bone. In other species, only retardation of bone growth was found.

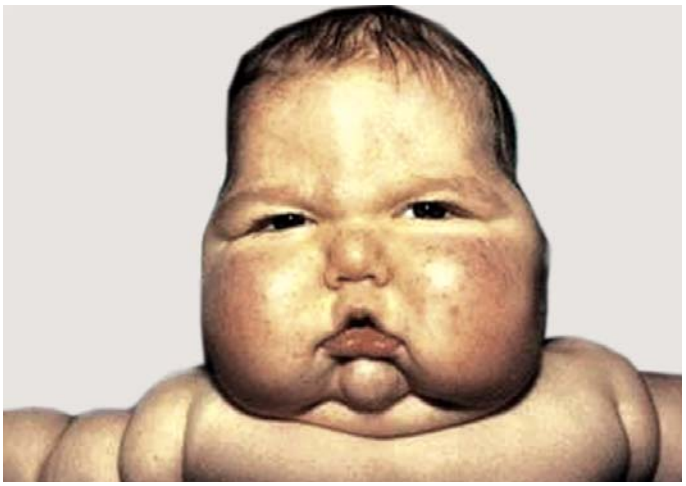


Fig. 16.6: Cushing's syndrome

Fraser and Fainstat demonstrated that in certain strains of mice the injection of cortisone into pregnant females produced a high percentage of cleft palates in the offspring. This effect was not due primarily to the inhibition of growth, since cleft palate was produced even when the cortisone was administered after the palate had already closed. Doig and Coltman reported several cases of cleft palate in children born of mothers who conceived while receiving injections of cortisone or who received injections of cortisone during the first three months of pregnancy. Obviously, more work is needed in this field before definite conclusions can be drawn.

STRESS AND THE ADAPTATION SYNDROME

The extensive studies of Hans Selye have done much to stimulate thinking and research in the area of 'stress' and the adrenal gland. He formulated a theory of response to prolonged stress as a part of the individual's adaptive mechanism which may lead to clinical signs and symptoms called the 'general adaptation syndrome'. This theory is controversial one, and much research is being done to clarify the points of controversy.

Any wasting disease produces atrophy of the adrenal cortex and loss of adrenal lipid. The mechanism for this finding is not known. Selye states that the adrenal changes are due to prolonged stress, with the mobilization of lipids and ultimate exhaustion atrophy of the cortical cells. Apparently, the hormones of the adrenal cortex are not necessary for cellular enzymes to catalyze the energy producing processes of cells. All 'stressor' agent such as cold, heat and trauma, increase the metabolic demands of the organism and stimulated adrenocortical function through stimulation of the pituitary to secrete ACTH. If the stress is continued, the pituitary and the adrenal cortex produce excessive amounts of hormones to increase resistance. Eventually pathologic changes occur in this tissues which respond to the hormonal stimulation, and the diseases of adaptation (hypertension periarteritis nodosa, and others) results.

Since there is a considerable amount of evidence against Selye's theory, and since the entire field of adrenal mechanisms in pathologic processes is in a state of flux, only a brief resume of Selye's theory will be presented. The reader is directed to Selye's original papers (1946, 1948) and to the excellent critical review by Sayers (1950) for a more comprehensive coverage of the subject.

Selye states that the 'stressed' person passes through a succession of stages. The first is the 'alarm reaction', which consists of a shock phase and then a countershock phase. The next is the adaptation stage' in which his resistance to the original stressor is greater, but his resistance to other stressor agents is lowered. If the stressor is continued, he eventually enters a stage of exhaustion and dies. If the stressor is removed, he enters a stage of convalescence and recovers and diagrammatically the control of adrenocortical activity.

Many people are receiving large doses of cortisone for the treatment of various diseases. We must remember that cortisone interferes with the formation of granulation tissue, proliferation of fibroblasts, and production of ground substance. Since these tissues and cellular products are essential to wound healing, it is important to recognize that surgery is hazardous in hyperadrenocorticism.

PANCREATIC HORMONE: INSULIN

Diabetes Mellitus

Diabetes is a biochemical lesion, and though no complete correlation exists between the occurrence of the disease and histologically demonstrable changes in the pancreas, the role of insulin in the control of the disease and historical considerations make it legitimate to discuss diabetes in the section on the pancreas. Because recent investigations have shown that other endocrine organs play a role in its production, many writers consider diabetes mellitus more generally a disease of metabolism.

Diabetes is a disorder of carbohydrate metabolism characterized by hyperglycemia and glycosuria, reflecting a disortion in the equilibrium between utilization of glucose by the tissues, liberation of glucose by the liver and production-liberation of pancreatic, anterior pituitary and adrenocortical hormones. This metabolic disorder lowers tissue resistance to infection.

It is a disorder caused by relative or absolute lack of insulin, and in the later stages of disease it provides multiple systemic complications. Recent evidences indicate that it is a multifactorial disease with genetic predisposition and destruction of the islet of langerhans cells.

It is classified into two types:

- Insulin Dependant Diabetes Mellitus (IDDM) (Juvenile onset or type I or brittle or ketosis prone or labile diabetes). It occurs as a result of immunologically mediated destruction of pancreatic beta cells.
- Non-Insulin Dependant Diabetes Mellitus (NIDDM) (Adult onset or type II or maturity onset diabetes).

IDDM is the less common form of diabetes, characterized by onset before age 20, with a thin body build, extreme thirst, hunger, constant urination, and weight loss. As there is no insulin secreted in these patients, daily injections of insulin are required to control the blood glucose level and also to prevent ketoacidosis. There is a positive family history for the disease with a weaker genetic tendency than type II diabetes mellitus.

Clinical Features

Patients manifest with glycosuria, polyuria, polydipsia, weakness, and weight loss. Abnormal and acclerated metabolism of amino acids and fats results in ketoacidosis.

The complications are microangiopathy and macroangiopathy which include atherosclerosis, retinopathy, neuropathy, renal failure, autonomic insufficiency, and susceptibility to infections.

Oral Manifestations

The oral manifestations are mainly due to inflammation and infection because of the abnormal neutrophil function, microangiopathy, and altered oral flora. Most of the patients present with a dry mouth, persistent gingivitis, multiple carious lesions, periodontal disease, and candidiasis.

Diabetic patients show an increased tendency towards delayed wound healing and dry socket formation.

Because of the lowered tissue resistance, patients with untreated or inadequately controlled diabetes sometimes exhibit a fulminating periodontitis with periodontal abscess formation and inflamed, painful and even hermorrhagic gingival papillae. Bernick and coworkers studied a series of 50 diabetic children and found that gingivitis was increased; however, the rate of caries formation was not related to the duration of the disease. Lin and colleagues noted a significant thickening of the basement membranes of gingival vessels and proposed that gingival biopsies may be useful as an adjunct in the diagnosis of diabetes. Because of excessive fluid loss, diabetic patients commonly complain of dry mouth. Even minor oral surgery is contraindicated in uncontrolled diabetic patients. Vascular changes in the dental pulp, gingival, and periodontal ligament have been reported in diabetic patients by Russell.

Controlled diabetic patients should undergo dental operations only after consultation with the physician who is treating the patient. There are no oral manifestations of controlled diabetes mellitus.

Diagnosis

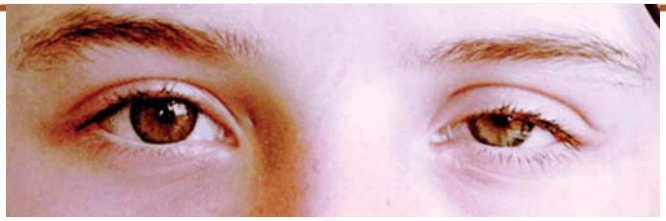
It is mainly based on clinical signs and symptoms. Blood sugar estimation and the glucose tolerance test are useful as confirmatory tests for diabetes.

Treatment

It is based on diet, oral hypoglycemic drugs, and insulin therapy.

17

Diseases of Nerves and Muscles



DISTURBANCES OF THE NINTH CRANIAL NERVE

Glossopharyngeal Neuralgia

Pain similar to that of trigeminal neuralgia may arise from the glossopharyngeal nerve. This condition is not as common as trigeminal neuralgia, but when it occurs, the pain may be as severe and excruciating.

Clinical Presentations

This neuralgia occurs without gender predilection in middle-aged or older persons and manifests itself as a sharp shooting pain in the ear, the pharynx, the nasopharynx, the tonsil or the posterior portion of the tongue. It is almost invariably unilateral, and the paroxysmal, rapidly subsiding type of pain characteristic of trigeminal neuralgia is also a feature here. Numerous mild attacks may be interspersed by occasional severe ones. The patient usually has a 'trigger zone' in the posterior oropharynx or tonsillar fossa. These zones are difficult to localize but can be found by careful probing. Because of the location of these trigger zones, certain actions are recognized as inciting the episodes of pain. These include such simple acts as swallowing, talking, yawning or coughing. The etiology' of glossopharyngeal neuralgia is unknown. Neural ischemia has been suggested, but without conclusive evidence (Fig. 17.1).

Treatment

The treatment of glossopharyngeal neuralgia has generally consisted in resection of the extracranial portion of the nerve or intracranial section. The injection of alcohol into the glossopharyngeal nerve has not been as widely accepted as has similar treatment in the case of trigeminal neuralgia. Periods of remission with subsequent recurrence are common in this disease.

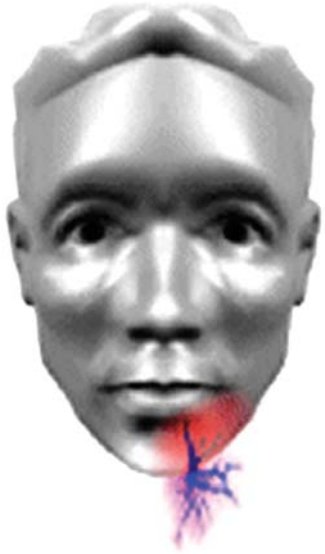


Fig. 17.1: Glossopharyngeal neuralgia

MISCELLANEOUS DISTURBANCES OF NERVES

Motor System Disease (Motor Neuron Disease, Amyotrophies)

Motor system disease constitutes a group of closely related conditions of unknown etiology which occur in three clinically variant forms usually referred to as progressive muscular atrophy, amyotrophic lateral sclerosis, and progressive bulbar palsy- They are called the motor system disease, since they all manifest corticospinal and anterior horn cell degeneration and exhibit either bulbar (tongue, pharyngeal, laryngeal) or limb muscle involvement.

Clinical Presentations

Progressive muscular atrophy is characterized by progressive weakness of the limbs with associated muscular atrophy,

reflex loss and sensor- disturbances. It shows a strong hereditary pattern, affects males more frequently than females and tends to occur in childhood. The initial symptoms usually consist of difficulty in walking, with leg pain and paresthesia. Atrophy of the foot, leg and hand muscles ultimately occurs with the appearance of a typical foot-drop, steppage gait and storklegs.

Amyotrophic lateral sclerosis generally occurs between the ages of 40 and 50 years and affects males more frequently. Precipitating factors include fatigue, alcohol intoxification, trauma and certain infections such as syphilis, influenza, typhus and epidemic encephalitis. The initial symptoms consist of weakness and spasticity of the limbs, difficulty in swallowing and talking with indistinct speech and hoarseness. Atrophy and fasciculations of the tongue with impairment or loss of palatal movements may occur.

Progressive bulbar palsy is characterized by difficulties in swallowing and phonation, hoarseness, facial weakness and weakness of mastication. It generally occurs in patients in the fifth and sixth decades of life with a familial pattern in some instances. The initial symptoms are gradual in onset and consist of difficulty in articulation, with impairment and finally loss of swallowing. Chewing is difficult as the facial muscles become weakened. These patients exhibit atrophy of the face, masseter and temporal muscles, and tongue with fasciculations of the face and tongue. There is also impairment of the palate and vocal cords.

Pseudobulbar palsy is a disease unrelated to the 'motor system disease. It results from loss or disturbance of the cortical innervation of time bulbar nuclei, usually seen in patients with multiple cerebral thrombi as a result of cerebral arteriosclerosis. The typical patient with pseudobulbar palsy has suffered a cerebrovascular accident with paralysis of one arm and leg but no swallowing difficulty. A subsequent 'stroke', however may result in paralysis of the opposite limbs with impairment of swallowing and talking, associated with loss of emotional control. In this disease there is hypertonia and failure of voluntary muscle control rather than spasticity.

Treatment and Prognosis

There is no specific treatment for motor system disease. In most instances, the disease is fatal, although temporary remissions sometimes occur.

Multiple Sclerosis (Disseminated Sclerosis)

Multiple sclerosis (MS) is an idiopathic inflammatory demyelinating disease of the central nervous system (CNS). Patients commonly present with an individual mixture of neuropsychological dysfunction, which tends to progress over years.

Etiology

Multiple sclerosis commonly is believed to result from an autoimmune process. What triggers the autoimmune process is not clear, but the nonrandom nature of its geographic distribution suggests an isolated or additive environmental effect and/or inadvertent activation and dysregulation of immune processes by a retroviral infection that was perhaps acquired in childhood. Some authorities implicate human herpes virus-6 (HHV-6), while others implicate *Chlamydia pneumonia* as causative agents (Fig. 17.2).

Clinical Presentations

Multiple sclerosis rarely occurs in those younger than 20 years or those older than 70 years. Onset of symptoms is most frequently seen between the ages of 20 and 40 years. There is a female gender predilection (2:1), and a familial incidence is often observed. The disease is characterized by:

- A variety of ocular disturbances, including visual impairment as a manifestation of retrobulbar neuritis, nystagmus and diplopia.
- Fatigability, weakness and stiffness of extremities with ataxia or gait difficulty involving one or both legs.
- Superficial or deep paresthesia.
- Personality and mood deviation toward friendliness and cheerfulness.

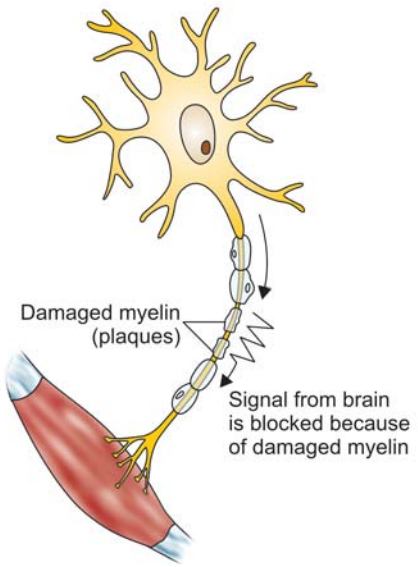


Fig. 17.2: Damaged myelin in multiple sclerosis

- Autonomic effector derangements, such as bladder and/or rectal retention or incontinence.

Charcot's triad is a well-known diagnostic triad characteristic of multiple sclerosis but not invariably present. It consists of intention tremor, nystagmus and dysarthria or scanning speech, an imperfect speech articulation.

Facial and jaw weakness occurs in some patients, and a staccato type of speech has been described. In addition, both Bell's palsy and trigeminal neuralgia have been reported in some patients with multiple sclerosis.

Treatment and Prognosis

There is no specific treatment for motor system diseases. In most of instances, the disease is fatal, although temporary remission sometimes occur.

Horner's Syndrome (Sympathetic Ophthalmoplegia)

Horner's syndrome is a condition characterized by:

- Miosis, or contraction of the pupil of the eye due to paresis of the dilator of the pupil.
- Ptosis or dropping of the eyelid due to paresis of the smooth muscle elevator of the upper lid.
- Anhidrosis and vasodilatation over the face due to interruption of secretomotor and vasomotor control (Fig. 17.3).

Its chief significance lies in the fact that it indicates the presence of a primary disease. The exact features of the syndrome depend upon the degree of damage of sympathetic pathways to the head and the site of this damage. Thus lesions in the brain stem, chiefly tumors or infections, or in the cervical or high thoracic cord occasionally will produce this syndrome. Preganglionic fibers in the anterior spinal roots to the sympathetic chain in the low cervical and high thoracic area are rather commonly involved by infection, trauma or pressure as by aneurysm or tumor to produce Horner's svndrome. Finally, involvement of the carotid sympathetic plexus by lesions of the gasserian ganglion or an aneurysm of the internal carotid artery may produce the typical facial sweating defect as well as facial pain and sensory loss.

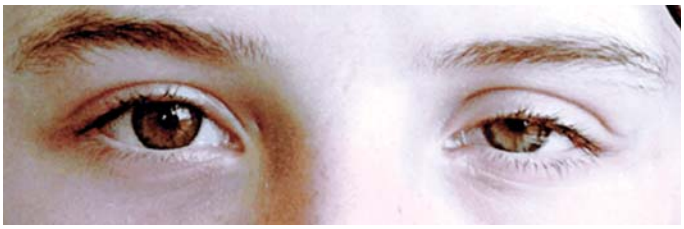


Fig. 17.3: Horner's syndrome —prominent ptosis, miosis and iris hypopigmentation of the left eye

Marcus Gunn Jaw-Winking Syndrome (Trigemino-oculomotor Synkinesis)

This interesting condition consists of congenital unilateral ptosis, with rapid elevation of the ptotic eyelid occurring on movement of the mandible to the contralateral side. It is commonly recognized in the infant by the mother when, on breastfeeding her baby, she notices one of its eyelids shoot up, as in the case reported by Smith and Gans.

At least some cases are hereditary, although it is reported that the phenomenon may begin in later life following an injury or disease. From reported cases, it appears that males are affected more frequently than females and the left upper eyelid is involved more frequently than the right.

Marcus Gunn Jaw-Winking is a form of synkinetic ptosis. An aberrant connection exists between the motor branches of the trigeminal nerve (CN V3) innervating the external pterygoid muscle and the fibers of the superior division of the oculomotor nerve (CN III) that innervate the levator superioris muscle of the upper eyelid.

An interesting condition known as the *Marin Amat syndrome* or inverted *Marcus Gunn phenomenon* is usually seen after peripheral facial paralysis. In this condition, the eye closes automatically when the patient opens his mouth forcefully and fully, as in chewing and tears may flow.

DISEASES OF THE MUSCLES

Diseases of the skeletal muscles of the face and oral cavity occur with sufficient frequency to be of considerable concern to the dentist. Many of these primary diseases manifest a generalized muscular involvement so that facial and oral manifestations constitute only a minor portion of the clinical problem. In other instances, the facial or oral manifestations represent a major feature of the disease, and these may present serious functional problems that must be met and solved. Secondary diseases of muscle are seen with somewhat greater frequency, and they also present difficulties in diagnosis and clinical management.

Classification of Diseases of Muscle

I. Primary myopathies, limited to or predominant in muscle
   - A. Dystrophies
   - B. Myotonias (dystrophic, congenital, acquired)
   - C. Hypotonias
   - D. Myasthenias
   - E. Myositis (including dermatomyositis and myositis ossificans)
   - F. Metabolic defects (glycolytic, myoglobinuria)
   - G. Miscellaneous (amyoplasias, contractures, degenerations)

II. Secondary myopathies, representing muscular reaction to primarily extramuscular disease
   A. Atrophy (traumatic, neuropathic secondary to metabolic, vascular, nutritional, infectious and toxic processes)
      1. Denervation
      2. Disuse and fixation
      3. Aging and cachexia
   B. Hypertrophy
      1. Developmental
      2. Functional
   C. Endocrine
   D. Internal environment
      1. Chemical
      2. Vascular
   E. Infection
      1. Specific (Trichinella, coxsackievirus)
      2. General (rickettsial, typhoid, pneumococcal pneumonia)
      3. Postinfectious asthenia.

Dystrophies

Muscular dystrophy is a primary progressive degenerative disease of skeletal muscle. The basic disorder lies within the muscle fiber itself, since the muscular nerves and nerve endings at the neuromuscular junction are normal. Actually, a number of different diseases fall within this category, all characterized by:

- Symmetric distribution of muscular atrophy,
- Retention of faradic excitability in proportion to the remaining power of contraction,
- Intact sensibility and preservation of cutaneous reflexes,
- Liability to hereditary familial incidence, and
- Unknown etiology.

The important forms of muscular dystrophy include:

- Severe generalized familial muscular dystrophy,
- Mild restricted muscular dystrophy;
- Myotonic dystrophy.
- Ophthalmoplegic dystrophy and
- Late distal muscular dystrophy.

Severe Generalized Familial Muscular Dystrophy (Pseudohypertrophic muscular dystrophy of Duchenne)

This disease is best described as a rapidly progressive muscle disease usually beginning in early childhood, presenting strong familial transmission usually through unaffected females, and occurring, predominantly in males, with or without pseudohypertroph. It is the most common form *of* muscular dystrophy.

Clinical presentations: Severe generalized familial muscular dystrophy begins in childhood, usually before the age of six years and rarely after- 15 years. The earliest signs are inability to walk or run, the children falling readily, with muscular enlargement and weakness. The muscles of the extremities are generally those first affected, but even the facial muscles may be involved. This muscular enlargement ultimately proceeds to atrophy how-ever, and the limbs appear flaccid. Atrophy from the onset of the disease is apparent in certain groups of muscles, chiefly those of the pelvis, lumbosacral spine and shoulder girdle. It is this atrophy which is responsible for the postural and ambulatory defects, such as the waddling gait.

The muscles of mastication, facial and ocular muscles, and laryngeal and pharyngeal muscles are usually involved only late in the course of the disease.

Histological features: There is gradual disappearance of muscle fibers as the disease progresses, until ultimately no fibers may be recognized, being replaced entirely by connective tissue and fat. Persistent fibers show variation in size in earlier stages of the disease, some being hypertrophic, but others atrophic.

Laboratory findings: The serum creatine phosphokinase level is elevated in all males affected by this disease and in about 70 percent of the female carriers as well. It is significant that this CPK elevation occurs prior to the clinical manifestations of the disease in the males.

Treatment: There is no treatment for this disease, and despite modern advances in gene therapy and molecular biology, the disease remains incurable. With proper care and attention, patients have a better quality of life, but most still die by the time they are 30 years of age, usually as a result of cardiopulmonary failure.

Mild Restricted Muscular Dystrophy (Facioscapulohumeral dystrophy of Landouzy and Dejerine)

Mild restricted muscular dystrophy is a slowly progressive proximal myopathy which primarily involves the muscles of the shoulder and face and has a weak familial incidence. It frequently presents long remissions and sometimes complete arrest.

Etiology: It is an autosomal dominant disease in 70-90 percent of patients and is sporadic in the rest. One of the causative genes has been localized to chromosome band 4q35.

Clinical Presentations: This disease begins at any age from 2-60 years, although the onset in the majority of cases is in

the first two decades of life. Frequency of occurrence is higher in males.

The earliest signs of the condition may be inability to raise the arms above the head and inability to close the eyes even during sleep as a result of weakness of facial muscles. The lips develop a characteristic looseness and protrusion which have been described as 'tapir-lips, a part of the 'myopathic facies' and the patients are unable to whistle or smile. The scapular muscles become atrophic and weak, with subsequent alteration in posture, as do the muscles of the upper arm.

Cardiac abnormalities, including cardiomegaly and tachycardia, are often present and many patients die of sudden cardiac failure.

Histological features: No specific microscopic findings are found in this disease. There is some variation in the size of muscle fibers and moderate infiltration of fiber bundles by connective tissue. Individual fibers ultimately become atrophic.

Treatment: There is no treatment for the disease. Some patients undergo temporary periods of remission or even complete arrest. There may be mild disability. The possibility of cardiac failure is always present.

Myotonias

Myotonia is a failure of muscle relaxation after cessation of voluntary contraction. It occurs in three chief forms: dystrophic, congenital, and acquired myotonia. Paramyotonia is a disorder related to the other myotanias, but differing from them in several important aspects.

Dystrophic Myotonia (Myotonic Dystrophy, Dystrophia myotonica)

Dystrophic myotonia has been described by Adams and his associates as a steadily progressive, familial, distal myopathy with associated weakness of the muscles of the face, jaw and neck, and levators of the eyelids, a tendency for myotonic persistence of contraction in the affected parts, and testicular atrophy. It is inherited as an autosomal dominant characteristic.

Clinical presentations: Atrophy of muscles is a characteristic feature of this disease, generally manifested first in the muscles of the hands and forearms. This muscular wasting does not appear usually until the third decade of life, but may be seen earlier, even in childhood.

Alterations in the facial muscles are one of the prominent features of the disease. These consist of ptosis of the eyelids and atrophy of the masseter and sternocleidomastoid muscles. The masseteric atrophy produces a narrowing of the lower half of the face which, with the ptosis and generalized weakness of the facial musculature, gives the patient a characteristic 'myopathic facies' and 'swan neck'. In addition, the muscles of the tongue commonly show myotonia but seldom atrophy.

Pharyngeal and laryngeal muscles in patients with dystrophic myotonia also exhibit weakness manifested by a weak, monotonous, nasal type of voice and subsequent dysphagia. Recurrent dislocation of the jaw is also reported to be common in this disease.

Other clinical features frequently associated with dystrophic myotonia include testicular atrophy, which is so common as to be considered an integral part of the syndrome, cataracts, even in a high percentage of young patients; hypothyroidism with coldness of extremities, slow pulse and loss of hair; and functional cardiac changes.

Histological features: Enlargement of scattered muscle fibers and the presence of centrally placed muscle nuclei in long rows have been described as being characteristic of atrophy. True hypertrophy of some fibers is almost invariably found, as well as isolated fibers which show extreme degenerative changes, including nuclear proliferation, intense basophilic cytoplasmic staining and phagocytosis.

Treatment and prognosis: There is no treatment for this disease. It progresses inevitably over a period of many years, producing disability and ultimately death.

Congenital Myotonia (Thomsen's Disease, Myotonia Congenita)

Congenital myotonia is an anomaly of muscular contraction in which an inheritance pattern has been established in about 25 percent of the reported cases. Thus, it is an autosomal dominant trait but with incomplete penetrance in some families. The characteristic feature of the disease is myotonia associated with muscular hypertrophy.

Clinical presentations: Congenital myotonia commences early in childhood and may be first noticed because of difficulties in learning to stand and walk. The degree of myotonia varies, but is generally severe and affects all skeletal muscles, especially those of the lower limbs.

Muscular contraction induces severe, painless muscular spasms, actually a delay relaxation. Electrical or physical stimultion of a muscle produces characteristic prolonged contraction or 'percussion contraction'.

The muscles of the thighs, forearms and shoulders are especially affected, as well as the muscles of the neck and the masseter muscles of the face. The muscles of the tongue are not reported to be affected by the hypertrophy although they may be involved by the myotonia.

Blinking with strong closure if the eyes will sometimes produce a prolonged contraction of the lids. Spasms of the

extraocular muscles may lead to convergent strabismus. Interestingly, a sudden movement such as sneezing often produces a prolonged spasm of the muscles of the face, tongue, larynx, neck and chest, and there may be respiratory embarrassment.

Histological features: Muscle biopsy reveals no alterations from normal except for hypertrophy of all muscle fibers.

Treatment and prognosis: There is no specific treatment of the disease but the prognosis is good. In fact, some regression of the disease occurs in occasional patients.

Hypotonias

Hypotonia is a reduction or complete absence of tones in muscles. There are many causes of hypotonia and delay in motor development in infants, so that this condition should be regarded only as a symptom which may be found in many diseases. Certain congenital diseases may result in hypotonias such as:

- Diseases of the central nervous system (e.g. atonic diplegia),
- Lipoid and glycogen storage diseases (e.g. Tay-Sachs disease),
- Mongolism,
- Cretinism, and
- Achondroplasia

Hypotonia also may result from strictly neu-romuscular diseases, however, including:

- Infantile muscular atrophy,
- Infantile muscular dystrophy,
- Amyotonia congenital,
- Congenital nonprogressive myopathy, and
- Neonatal myasthenia gravis.

Many of these latter diseases, all occurring in infancy, have certain features in common, including hypotonia, reduced tendon reflexes and muscular weakness. Because of the difficulty encountered in their separation, the term 'floppy infant syndrome' has sometimes been applied to describe the chief clinical manifestation of these unfortunate children. As the term would imply, these infants have a generalized weakness so that their bodies hang limply with inability to sit, stand or walk. The hypotonia involves the muscles of the face and tongue as well, but these findings are secondary to the generalized condition.

Myasthenias

Myasthenia is an abnormal weakness and fatigue in muscle following activity. The myasthenia constitute a group of diseases in which there is a basic disorder of muscle excitability and contractility and include myasthenia gravis, familial periodic paralysis and aldosteronism.

Myasthenia Gravis

Myasthenia gravis (MG) is an acquired autoimmune disorder characterized clinically by weakness of skeletal muscles and fatigability on exertion.

Etiology: Myasthenia gravis is idiopathic in most patients but autoimmunity is also implicated to be responsible. The antibodies in MG are directed toward the acetylcholine receptor (AChR) at the neuromuscular junction (NMJ) of skeletal muscles.

Clinical presentations: Myasthenia gravis *occurs* chiefly in adults in the middle-aged group, with a predilection for women, and is characterized by a rapidly developing weakness in voluntary muscles following even minor activity. Of interest to the dentist is the fact that the muscles of mastication and facial expression are involved by this disease, frequently before any other muscle group. The patient's chief complaints may be difficulty in mastication and deglutition, and dropping of the jaw. Speech is often slow and slurred. Disturbances in taste sensation occur in some patients.

Diplopia and ptosis, along with dropping of the face, lend a sorrowful appearance to the patient. The neck muscles may be so weak that the head cannot be held up without support. Patients with this disease rapidly become exhausted, lose weight, become further weakened and may eventually become bedfast. Death frequently occurs from respiratory failure.

The clinical course of patients with myasthenia gravis is extremely variable. Some patients enter an acute exacerbation of their disease and succumb very shortly, but others live for many years with only slightest evidence of disability. On this basis, two forms of the disease are now recognized: one, a steadily progressive type; the other, a remitting, relapsing type.

Histological features: There are usually no demonstrable changes in the muscle. Occasionally, focal collection of small lymphocytes, or 'lymphorrhages', are found surrounding small blood vessels in the interstitial tissue of affected muscles. In few cases foci of atrophy or necrosis of muscle fibers have been described.

Treatment: It is interesting that the drug of choice used in treatment of myasthenia gravis provides such remarkable relief of symptoms in such a short that it is commonly used as a diagnostic test for the disease. Physostigmine, an anticholinesterase, administered intramuscularly, improves the strength of the affected muscles in a matter

of minutes, although the remission is only temporary. No 'cure' for the disease is known even though the prognosis is good in the relapsing type.

Myositis

Myositis refers to an inflammation of muscle tissue and is entirely nonspecific, since a great many bacterial, viral, fungal, or parasitic infections, as well as certain physical and chemical injuries, may give rise to the condition. In addition, a variety of diseases of unknown etiology may produce or atleast be associated with mysositis.

Dermatomyositis (Juvenile Dermatomyositis, Childhood Dermatomyositis, Polymyositis)

Dermatomyositis (DM) is an idiopathic inflammatory myopathy (IIM) with characteristic cutaneous findings. Four of the five criteria are related to the muscle disease, and are followed by progressive proximal symmetrical weakness, elevated muscle enzymes, an abnormal finding on electromyogram, and an abnormal finding on muscle biopsy. The fifth criterion is compatible cutaneous disease.

Bohan and Peter (1975) suggested five subsets of myositis, as follows: dermatomyositis, polymyositis, myositis with malignancy, childhood dermatomyositis/polymyositis and myositis overlapping with another collagen-vascular disorder.

Etiology: The cause of DM is unknown. The pathogenesis of the cutaneous disease is poorly understood. DM is probably caused by complement-mediated (terminal attack complex) vascular inflammation, while PM is caused by the direct cytotoxic effect of CD8+ lymphocytes on muscle.

Clinical presentations: Dermatomyositis may occur in patients of any age from very young children to elderly adults, but the majority of cases occur in the fifth decade of life. There is no sex predilection in its occurrence.

The more acute form of the disease, seen more commonly in children, begins with an erythematous skin eruption, edema, tenderness, swelling and weakness of the proximal muscles of the limbs. Accompanying these manifestations are fever and leukocytosis. The skin lesions frequently calcify and form calcium carbonate nodules with a foreign body reaction. This is known as calcinosis cutis, whereas the term *calcinosis universalis* is applied when these calcified masses are found generalized throughout the soft tissues.

The chronic form of the disease is similar, but may not show dermal involvement (polymyositis only), although all gradations are present between the two extremes. In addition, Raynaud's phenomenon or paroxysmal digital cyanosis may be an early manifestation. The muscular stiffness and weakness are often symmetric in distribution.

The cutaneous lesions usually consist of a diffuse erythema with desquamation although other types of rashes have been described. This rash is most frequently seen on the face, eyelids, ears, anterior neck and overlying articulations.

Oral manifestations: The oral lesions, consisting of diffuse stomatitis and pharyngitis, are extremely common. Telangiectatic lesions of the vermilion border of the lips and cheeks may also occur. In addition, involvement of the muscles of the jaws, tongue and pharynx may pose problems in eating and phonation.

Histologic features: The muscle fibers in dermatomyositis exhibit widespread degeneration and hyalinization. In advanced cases the muscle fibers disappear, leaving only the fibrous stroma. Many fibers show vacuolization. granulation and fragmentation with phagocystosis of disintegrating fibers. Diffuse leukocytic infiltration is also frequently pronounced.

Laboratory findings: Patients with this disease sometimes manifest a mild anemia or leukocytosis. In addition, creatinuria is a constant finding, as well as elevated levels of serum transaminase and aldolase.

Treatment: There is no specific treatment for the disease, although symptomatic treatment may be of considerable benefit to the patient. In the more acute forms of the disease, death may occur rapidly.

Heterotopic Ossification

The term heterotopic ossification (HO) describes bone formation at an abnormal anatomical site usually in soft tissue. Stover et al. (1975) classify HO into the following three types: myositis ossificans progressive; traumatic myositis ossificans; and neurogenic heterotopic ossification.

Myositis Ossificans Progressiva

Generalized myositis ossificans is a disease of unknown etiology which affects the interstitial tissues of muscles as well as tendons, ligaments, fascia, aponeuroses and even the skin. Basically masses of fibrous tissue and bone occur within these structures with secondary atrophy and destruction of the associated muscles due to pressure and inactivity. The differential diagnosis for this condition includes calcinosis universalis, which usually occurs in relation to scleroderma or polymyositis. In calcinosis, calcium deposition is noted in the skin, subcutaneous tissues and connective tissue sheaths around muscles, as opposed to within muscles.

Clinical presentations: Generalized myositis ossificans usually occurs in young children or adolescents with the development of soft, fluctuant or firm nodular swellings anywhere on the body but frequently on the neck or back. These masses may develop spontaneously or after minor trauma. They vary considerably in size and shape and may disappear or become transformed into bony nodules. These are usually painless and are covered by a reddened skin which may ulcerate as a result of pressure from the underlying mass.

Any skeletal muscle may be affected, but those of the trunk and proximal limb are most frequently involved. Interestingly, certain muscles tend to escape involvement: the tongue, larynx, diaphragm and perineal muscles. Ultimately, entire groups of muscles become transformed into bone with resulting limitation of movement. The masseter muscle is often involved so that fixation of the jaw occurs. The patient becomes transformed into a rigid organism sometimes encountered in circuses as the 'petrified man'.

The differential diagnosis for this condition includes calcinosis universalis, which usually occurs in relation to scleroderma or polymyositis. In calcinosis, calcium deposition is noted in the skin, subcutaneous tissues, and connective tissue sheaths around muscles, as opposed to within muscles.

Histological features: The muscle in this disease is gradually replaced by connective tissue which undergoes osteoid formation and subsequently ossification. In some cases cartilage formation may also be evident. Characteristically, intact muscle fibers may be found within the bony tissue.

Treatment and prognosis: There is no treatment for the disease. It is progressive until death results, usually from a pulmonary infection secondary to the respiratory difficulties arising front involvement of the intercostal muscles.

Focal Myositis

Focal myositis is a benign inflammatory pseudotumor of skeletal muscle, first described by Heffiier and his associates in 1977 as a new and distinct clinicopathologic entity. The actual etiology is unknown but, even though a history of trauma is absent in most cases, it is speculated that a subclinical injury, such as a muscle tear, might initiate the condition.

Clinical presentations: Focal myositis presents as a rapidly enlarging mass within a single skeletal muscle. The most common sites reported are the lower leg, thorax, abdomen, and forearm; however, involvement of perioral musculature and submandibular and buccal mucosa has been reported by Ellis and Brannon.

There is no apparent gender predilection and the age range has been from 10 to over 65 years of age, with a mean of nearly 40 years of age. While lesions have a duration of only a few weeks, some lesions are present a year or longer. Some cases are asymptomatic; others are characterized by a dull, aching pain. There are not other local or systemic manifestations of disease present.

Histological features: There are microscopic changes in random muscle fibers, rather than grouped bundles, consisting of atrophy, hypertrophy, necrosis with phagocytosis, and regeneration. Lymphocytic infiltration is usually present in the interstitial tissue, as is an increase in fibrous connective tissue in endomysial and perimysial locations. It should be stressed that a careful consideration of both clinical and histologic findings is essential in order to establish a definitive diagnosis of focal myositis.

Treatment: The lesion should be excised; it does not recur.

Differential diagnosis: A variety of conditions, especially from the clinical aspect, must be considered in the diffrential diagnosis. These include a benign or malignant neoplasm within muscle, nodular fasciitis, proliferative myositis, myositis ossificans. polymyositis, and in the oral region, a salivary gland lesion.

Miscellaneous Myopathies

Congenital Facial Diplegia (Mobius syndrome)

Congenital facial diplegia is a nonfamilial deficient development of cranial muscles consisting official diplegia with bilateral paralysis of the ocular muscles particularly the abducens. Although von Graefc described a case of congenital facial diplegia in 1880, the syndrome was reviewed and defined further by Moline in 1888 and 1892. Because of these contributions. Mobius is now the eponym used to describe the syndrome. Mobius syndrome is due, in part, to loss of function of motor cranial nerves.

Etiology: Numerous theories exist concerning the primary underlying pathogenesis. Mobius believed that the condition was degenerative and involved the nuclei of the affected nerves. Some authors suggest that the underlying problem is congenital hypoplasia or agenesis of the cranial nerve nuclei. Approximately 2 percent of cases appear to have a genetic basis. Theories of vascular etiologies propose the disruption of now in the basilar artery or premature regression of the primitive trigeminal arteries. A second vascular theory is that of subclavian artery supply disruption sequence, which also involves an interruption of embryonic blood supply. Simultaneous occurrence of limb malformations with cranial nerve dysfunction suggests a disruption of normal morphogenesis during a

critical period in the development of the embryonic structures of these regions, most likely from four to seven weeks of gestation.

Clinical presentations: Congenital facial diplegia is usually manifested in infancy during the first few days of life by failure to close the eyes during sleep. Because of the partial or complete facial paralysis, the infant exhibits no change in facial expression even when crying or laughing. The prominent lips are often everted and the mouth may remain partially opened.

There is difficult in mastication; saliva frequently drools from the corners of the mouth, and speech is severely impaired.

The majority of patients have other associated congenital deformities, including external ophthalmoplegia, deformity of the external ears, deafness, defects of the pectoral muscles, paresis of the tongue, soft palate or jaw muscles, clubfoot, mental defects and epilepsy.

Histological features: There are no conclusive microscopic studies of muscle in patients with congenital facial diplegia.

Treatment: There is no treatment for the disease but the prognosis appears to be good, barring complications.

Atrophy of Muscle

Atrophy of muscle refers to a decrease in the size of individual muscle fibers which were once normal. The condition is entirely nonspecific, since it occurs in many situations, some of which have been previously described. A partial listing of some of the recognized causes of muscle atrophy is given below:

1. Disuse and fixation
2. Aging and cachexia
3. Denervation
4. Muscular dystrophies
5. Nutritional disturbances
6. Infections and toxins
7. Muscular hypotonias
8. Metabolic disturbances
9. Vascular changes.

Atrophy of muscle has been confused occasionally with aplasia or agenesis of muscles. Thus, some disease are a result of muscular aplasia, or actually hypoplasia, rather than an actual decrease in size of normal fibers. One form of muscle atrophy, facial hemiatrophy (q.v.).

Hypertrophy of Muscle

Hypertrophy of muscle refers to an increase in size of individual muscle fibers. This should be separated from pseudohypertrophy, in which the overall increase in the size of a muscle is due to an increase in interstitial connective tissue.

The causes of muscular hypertrophy are also nonspecific and occur in a variety of situations listed below:

1. Developmental defects
2. Functional disturbances
3. Inflammations and infections
4. Metabolic changes
5. Neoplasms.

Two forms of muscular hypertrophy are of interest to the dentist: macroglossia; and hypertrophy of the masseter muscle.

Masseteric hypertrophy occurs usually in two situations: congenital facial hemihypertrophy (qv): and functional hypertrophy as a result of unusual muscle function through habit or necessity after certain surgical procedures involving the jaws.

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