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Review

Diagnosis of oral pigmentations and malignant transformations

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ABSTRACT

Background: Oral pigmentation is a common finding in the mouth. Pigmentation can be either normal or abnormal discoloration of oral mucous membrane. The purpose of this review mainly focuses on the main oral pigmented lesions, in order to help the clinicians establish a better approach towards the patients with pigmented oral lesions and to provide thorough knowledge regarding such lesions for patient reassurance, early definitive diagnosis and prompt treatment.

Methods: Relevant data concerning oral pigmented lesions, clinical features and the possibility of malignant transformation of such lesions were reviewed thoroughly from pubmed literature published in English. Pigmented lesions affecting the skin were not included in our review.

Results: Few pigmented lesions have been identified and their tendency to become malignant has been reported in the literature. The oral lesions showing malignant transformation reported were mostly case series. Unfortunately, due to lack of long-term studies, follow ups and randomized controlled studies in this respect it was difficult to draw a statistical analysis. This information is quite crucial for general dental practitioners to improve their understanding regarding oral lesions and to differentiate between normal and diseased conditions, so that they can master the skill of differential diagnosis, definitive diagnosis and prompt treatment.

Conclusion: Oral pigmentation may present as focal, multifocal or diffused macular or tumefactive lesions. They may greatly vary in color as blue, purple, brown, gray or black depending on the quantity and site of melanin in the tissues [1]. Etiology of pigmentation can be multi factorial. Mostly pigmentation is physiologic but at times it can be a precursor of severe diseases.

Lesions may be caused by localized harmless accumulations of melanin, hemosiderin or exogenous metals or they may be a sign of underlying systemic or genetic disease. A few lesions may be associated with life-threatening medical conditions that require immediate intervention. The differential diagnosis for any pigmented lesion is extensive, as it includes examples of endogenous and exogenous pigmentations. Although biopsy is a helpful and necessary aid in

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the diagnosis of focally pigmented lesions, with diffuse pigmentation lesions require a thorough dental and medical history and laboratory investigations.

Contents

Introduction

Pigmented lesions of the oral mucosa

Oral mucosa is not uniformly colored. The color varies in different physiological and pathological conditions [1–6]. Physiological pigmentation is frequent in Asians, Africans and Mediterranean people [3]. The color change of the oral mucosa could be due to accumulation of one or more pigments in tissues. Pigments associated with mucosal discoloration could be classified as endogenous (e.g. melanin and blood-related pigments) and exogenous (e.g. metals and drug-related pigments). Melanin-associated lesions are most common pigmentations. They may present as benign melanocytic nevi or extremely aggressive neoplasm as mucosal melanoma [1–7]. Benign melanin-associated pigmentations of the oral mucosa includes racial pigmentations, melanotic macules, oral melanocytic, naevi (OMNs), melanoacanthoma, post-inflammatory pigmentations and so-called smoker's melanosis [1–6]. Several systemic diseases such as Peutz–Jeghers, Laugier–Hunziker syndromes as well as the Addison's disease are also characterized by the presence of benign melanin-associated lesions of the oral and perioral tissues. Non-melanin associated pigmentations may be caused by blood-related entities (bilirubin and biliverdin, iron-containing ferritin and hemosiderin) and metal pigments (e.g. silver, gold, lead and mercury) [1–6]. Among these, the most frequent is amalgam pigmentation (amalgam tattoo). Several drugs have been reported to induce mucosal discoloration through direct deposition on oral surfaces, local accumulation after systemic absorption, stimulation of melanin-related pathways and bacterial metabolism [1–6].

It is important to have a thorough checkup of all the systems of the body and to study the previous medical and surgical history to determine the presence of any atypical, unstable or malignant skin lesions. Similarly a positive family history of oral pigmentation or hereditary systemic diseases is crucial in the overall evaluation of the patient. For clinical assessment good lighting and a mouth mirror or magnifying glass should be used. Examination of the mouth should begin with the evaluation of pigmentation of facial skin, especially the perioral region, followed by labial vermilion border and mucosal surfaces, the mucogingival junction as well as the attached gingiva.

Classification of oral pigmentations

Kauzman et al. [8] proposed a *Classification based on the distribution of the pigmentation.*

Diffuse and bilateral

Early onset: physiological pigmentation, Peutzjegher's syndrome.

Predominantly adult onset.

With systemic signs and symptoms.

Addison's disease, heavy metal pigmentation, Kaposi's sarcoma.

No systemic signs and symptoms.

Drug induced pigmentation, post-inflammatory.

Smoker's melanosis.

Focal

Red, blue, and purple.

Blanching: hemangioma, varix.

Nonblanching: thrombosis, hematoma.

Blue-gray: amalgam tattoo, other foreign body tattoo, blue nevus.

Brown: melanotic macule, pigmented nevus, melanoacanthoma, melanomas.

The clinical features and presentation of most commonly found pigmented lesions in the oral cavity are as follows:

Physiologic Melanotic Lesions.

Physiologic Pigmentation (Racial).

Racial pigmentation of oral mucosa is the most common cause of oral pigmentation; however it is not directly related to the color of the skin [9–11]. The pigmentation is symmetrically distributed, especially on the gingival [Fig. 1] and buccal mucosa, on the hard palate, lips and tongue may also be seen as brown patches with well-defined borders. Gaeta et al. [3] stated that it is more common in African, Asian and Mediterranean populations. This increase in pigmentation is due to increase in melanocyte activity and not due to greater number of melanocytes. The degree of gingival pigmentation is directly related to skin pigmentation. In light skinned individuals gingiva is mostly non-pigmented but in dark skinned people the chance of having pigmented gingiva is extremely high [4]. It is seen during the first two decades of life but may not come to the patient's attention until later. The color ranges from light to dark brown. The attached gingiva is the most common site, where it appears as a bilateral, well-demarcated, ribbon-like, dark brown band that usually spares the marginal gingiva [1]. The pigmentation is asymptomatic therefore no treatment is required. Since these lesions are considered physiological so there are no chances of malignant transformation, having said this, it is critical to differentiate between normal and premalignant lesions.

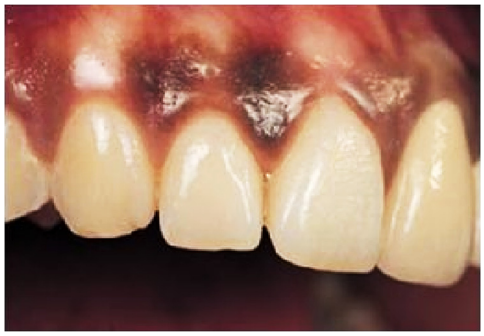

Fig. 1 – Shows physiologic (racial) pigmentation on the gingiva for black man.

Ephelides

Ephelides are common small, brown macules (5 mm) [8,9]. They appear on sun-exposed areas of the perioral skin and lips. These lesions darken after sun light exposure. It is a self limiting condition depending on the amount of exposure to the sun. There have been no reports on malignant transformation.

Melanotic macules

Weathers et al. [12] stated that the labial melanotic macule is a benign pigmented lesion that is common on the lower lip, and the oral melanotic macule is the same lesion seen inside the oral cavity, most commonly on the gingiva, buccal mucosa and palate. It is caused by increased melanin production without increase in the number of melanocytes. Melanotic macules are usually smaller than 1 cm in diameter and show a well-demarcated smooth border. They usually occur as single lesions, but multiple lesions are sometimes seen. The color is homogenous light or dark brown. Melanotic macules are more common in women and young adults [13]. Melanotic macules are benign and hardly ever transform into melanoma. For any melanotic macules seen on the palate that has been reported by the patient to increase in size, a biopsy should be performed. This was because is usually required to establish the diagnosis and to rule out melanoma, especially for lesions involving the palate, where malignant melanoma is most prevalent and malignant transformation of melanotic macules is rare [14]. No further treatment is required once the diagnosis has been established.

Heavy metal pigmentation

Increase in heavy metal (e.g. lead, bismuth, mercury, silver, arsenic and gold) levels in the blood leads to oral mucosal discoloration. It is mostly seen in individuals exposed to heavy metal vapors (occupational) or patients taking drugs containing heavy metals such as arsenic, previously used for the treatment of syphilis. Use of water or paints containing lead and drugs containing mercury or silver can also cause mucosal discoloration [8]. The pigmentation appears as a blue-black line along the gingival margin and seems to be proportional to the amount of gingival inflammation as stated by Esen et al. [15,16]. Other oral mucosal sites may also be involved [Fig. 2]. A variety of systemic signs and symptoms may be seen depending on the type of heavy metal exposure [15]. Malignant transformation of oral pigmentation due to heavy metal pigmentation has not been reported. Yet care should be taken regarding severe systemic toxicity.

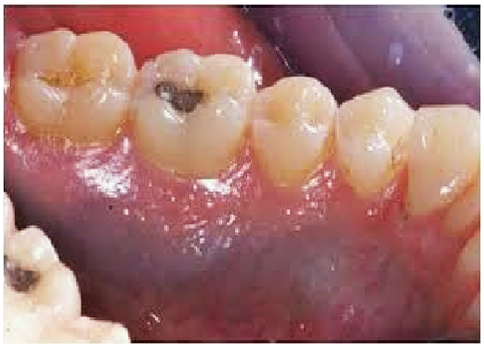

Fig. 2 – Shows heavy metal pigmentation on oral mucosa.

Kaposi's sarcoma

Kaposi's sarcoma (KS) is a multifocal vascular malignancy seen predominantly in HIV-infected individuals. The development of this tumor is considered diagnostic of AIDS progression. A human herpes virus (HHV-8, also called Kaposi's sarcoma-associated herpes virus) has been implicated as the cause. KS in the oral mucosa most commonly affects the hard palate, gingiva and tongue. It appears as a bilateral flat or slightly elevated brown to purple colored lesion in early stages. Advanced lesions may appear as dark red to purple plaques or nodules that may exhibit ulceration, bleeding and necrosis. A definitive diagnosis requires biopsy, which shows the proliferation of spindle-shaped cells, surrounded by poorly formed vascular spaces or slits with numerous extravasated red blood cells [15,16]. With new treatments for AIDS, KS has become less common in the United States, and it now occurs at a rate of about 6 cases per million people each year. In the United States, KS is much more common in men than in women, and it is rarely seen in children. It is also more common in African Americans than in whites in the United States.

Transplant recipients are another group that gets KS. About 1 in 200 transplant patients in the United States gets KS. Most people who develop Kaposi's sarcoma have been infected with the virus prior to organ transplantation. The drugs taken to suppress the immune system of the patient after transplantation is done, allows KS to develop. In areas of the world (such as Africa) where KSHV and HIV infection rates are high, both endemic and HIV-associated KS are seen, and KS occurs in men, women, and children. Early detection of HIV thorough investigations and management of the immune modulation will turn down further complications associated with HIV.

Post-inflammatory pigmentation

Long-standing inflammatory mucosal diseases, particularly lichen planus, can cause mucosal pigmentation [1]. This is seen more frequently in dark-skinned individuals. Clinically, multiple brown-black pigmented areas are noted adjacent to reticular or erosive lesions of lichen planus. Halder et al. mentioned that the pathogenesis of post-inflammatory pigmentation remains unclear [17]. Histologically, there is increased production of melanin by the melanocytes and accumulation of melanin laden macrophages in the superficial connective tissue. There is no literature on hand about its transformation into malignancy.

Chemically induced melanosis

Smoker's melanosis

Hedin et al. stated that smoking may cause oral pigmentation in light-skinned individuals and accentuate the pigmentation of dark skinned patients [18]. There is increased production of melanin, which may provide a biologic defense against the noxious agents present in tobacco smoke [19]. Smoker's melanosis occurs in up to 21.5% of smokers [20]. It is proved that the intensity of the pigmentation is related to the duration and amount of smoking [20,21]. Women are more commonly affected than men, which suggest a possible synergistic effect between the female sex hormones and smoking [20]. According to them, the brown-black lesions most often involve the anterior labial gingiva, followed by the buccal mucosa [20]. Smoker's melanosis usually disappears within 3 years of smoking cessation. Zaraa et al. [15] mentioned that biopsy should be performed if there is surface elevation or increased pigment intensity or if the pigmentation is in an unexpected site. There is no evidence supporting the malignant transformation of smoker's melanosis, but caution should be taken about other systemic complications associated with smoking. Smoker's melanosis can be used as a clinical finding to identify the smoking history [21].

Amalgam tattoo and other foreign-body

Pigmentation

Amalgam tattoo is one of the most common causes of intraoral pigmentation [22]. It presents clinically as a localized flat, blue-gray lesion of variable dimensions [Fig. 3]. The gingiva and alveolar mucosa are the most common sites, but these lesions may also involve the floor of the mouth and the buccal mucosa. No signs of inflammation are present at the periphery of the lesion. Diascopy is a test whether lesion is vascular or nonvascular or hemorrhagic by applying pressure with a finger glass slide and observing color changes [23]. A negative response was seen with diascopy. In some cases, especially when the amalgam particles are large enough, they can be seen in intraoral radiographs as fine radiopaque granules. In these circumstances, the diagnosis of amalgam

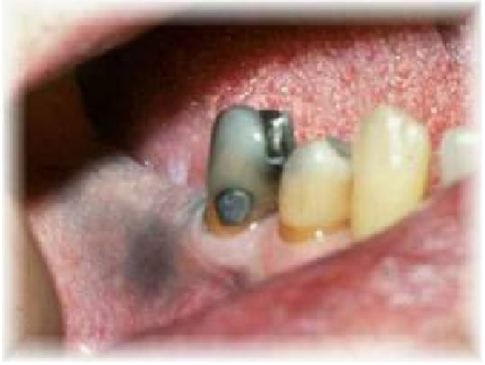

Fig. 3 – Shows amalgam tattoo as blue-gray lesion on alveolar mucosa. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tattoo can be made on the basis of the clinical and radiographic findings. In case of doubt, a biopsy should be performed to demonstrate the presence of amalgam particles in the connective tissue [8]. Graphite may be introduced into the oral mucosa through accidental injury with a graphite pencil. The lesion occurs most frequently in the anterior palate of young children, appearing as an irregular gray to black macule. A history of injury confirms the diagnosis; otherwise, a biopsy should be performed to exclude the possibility of melanoma. As amalgam fillings still are ubiquitous and amalgam tattoos remain one of the most common causes of intraoral pigmentation, we consider amalgam tattoos to be an important differential diagnosis consideration, when assessing patients suspected for mucosal melanoma of the oral cavity. Information regarding previous prosthetic dental work should be included in the patient's medical history, and an X-ray showing metal deposits in the mucosa can safely rule out mucosal melanoma. But when in doubt, we recommend a diagnostic biopsy for histopathological examination [8]. This lesion is just a localized reaction to metal deposition in the mucosa.

Drug-induced pigmentation

A number of medications may cause oral mucosal pigmentation such as Antimalarials (quinacrine, chloroquine, hydroxychloroquine, Quinidine, Zidovudine (AZT), Tetracycline, Minocycline, and Chlorpromazine), Oral contraceptives, Clofazimine, and Ketoconazole. The pathogenesis of drug-induced pigmentation varies, depending on the causative drug. It may involve accumulation of melanin, deposits of the drug or its metabolites, synthesis of pigments under the influence of the drug or deposition of iron after damage to the dermal vessels [9]. Chloroquine and other quinine derivatives are used in the treatment of malaria, cardiac arrhythmia and a variety of immunologic diseases including systemic and discoid lupus erythematosus and rheumatoid arthritis. Mucosal discoloration associated with these drugs mostly involves the hard palate only and appear as blue-gray or blue-black in color [9,10,24]. Laboratory studies have shown that these drugs may produce a direct stimulatory effect on the melanocytes [25]. However, the reason why this effect is limited to the palatal mucosa is not understood. Minocycline is a synthetic tetracycline used in the long term treatment of refractory acne vulgaris. It can cause pigmentation of the alveolar bone, which can be seen through the thin overlying oral mucosa (especially the maxillary anterior alveolar mucosa) as a gray discolouration [26]. Minocycline has also been reported to cause pigmentation of the tongue mucosa. [27]. Drug induced lesions are local reactions which are seen in oral cavity and no reports of malignant transformation have been reported in this regard.

Disease-associated melanosis

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome is a rare genetic disorder and is characterized by pigmented mucocutaneous macules, intestinal hamartomatous polyposis and increased risk of cancer in many organs, including the small intestine, colon, stomach, pancreas, breast and genital tract [4–6]. The melanotic spots of Peutz–Jeghers syndrome are characteristically small and multiple, and are very obvious around the lips. Pigmented spots also occur inside the mouth, in the mucosa of the nose, conjunctiva and rectum, and on the skin of the extremities [7]. The melanotic spots do not require treatment and are not associated with increased risk of melanoma. However, the patient should be monitored for the development of internal malignancies. Such oral lesions help in early diagnosis and should alert the clinician to prompt the patient to screen for cancers in organs implicated in this syndrome.

Addison's disease

Oral mucosal pigmentation associated with Addison's disease develops and progresses during adult life and is usually accompanied by systemic manifestations including weakness, nausea and vomiting, abdominal pain, constipation or diarrhea, weight loss and hypotension. Addison's disease, or primary hypoadrenalism, is due to progressive bilateral destruction of the adrenal cortex by autoimmune disease, infection or malignancy [11]. The lack of adrenocortical hormones in the blood stimulates production of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. The increased production of ACTH induces melanocyte-stimulating hormone, which results in diffuse pigmentation of the skin and oral mucosa. Oral involvement presents as diffuse brown patches on the gingiva, buccal mucosa, palate and tongue, which may resemble physiologic pigmentation [15]. However patients presenting with these features should be sent for medical evaluation and laboratory tests to assess levels of ACTH, plasma cortisol and serum electrolytes. Addison's disease can be fatal if left untreated. Management involves treatment of the underlying cause and corticosteroid replacement therapy. No cases of malignant transformation have been reported.

Melanocytic nevi

Pigmented nevi are a rare cause of focal oral pigmentation. They present as either brown or blue lesions. Histologically, nevi are composed of an accumulation of nevus cells in the basal epithelial layers, the connective tissue or both. As such, they are classified as junctional, intradermal or intramucosal, and compound nevi. Junctional nevi are flat and dark brown in color because the nevus cells proliferate at the tips of the rete pegs close to the surface. Intramucosal and compound nevi are typically light brown, dome-shaped lesions. Blue nevi are characterized by proliferation of dermal melanocytes within the deep connective tissue at some distance from the surface epithelium, which accounts for the blue color. Buchner et al. [28] stated that intramucosal nevus is the most common type and is seen most frequently on the buccal mucosa. The blue nevus is the second most common type, occurring most commonly in the palate [28]. It may be difficult to differentiate clinically between a nevus and an early lesion of mucosal melanoma, especially in the palate, the most common site for both lesions. Although transformation of oral pigmented nevi to melanoma has not been well documented, it is believed that nevi may represent precursor

lesions to oral mucosal melanoma [29]. It is therefore recommended to completely excise these lesions and submit it for histopathologic examination.

Oral melanoacanthoma

Oral melanoacanthoma is uncommon benign pigmented lesion of the oral mucosa, characterized by proliferation of dendritic melanocytes dispersed throughout the thickness of an acanthotic and hyperkeratotic surface epithelium [15,30]. Clinically, the lesion appears hyper pigmented black or brown, flat or slightly raised. This lesion, in contrast to most of the benign pigmented lesions discussed above, has a tendency to enlarge rapidly, which raises the possibility of a malignant process in the clinical differential diagnosis [31]. However its tendency to occur in young black females distinguishes it from melanoma, which is uncommon in this age and racial group. Goode et al. stated that the buccal mucosa is the most common site of occurrence, which may be related to greater frequency of trauma in this area [30]. Oral melanoacanthoma appears to be a reactive lesion with no malignant potential. In some cases, the lesion disappears after incisional biopsy or removal of the offending stimulus [31].

Oral melanoma

Oral mucosal melanoma is rare. It accounts for less than 1% of all oral malignancies. It is characterized by proliferation of malignant melanocytes along the junction between the epithelium and connective tissue or may occur deep inside the connective tissue. The palate is the most common site, which account for about 40% of cases, and gingival account for one third of case [29]. Other oral mucosal sites may also be affected [Fig. 4]. Oral melanoma is generally encountered between the fourth and seventh decades of life, with a greater incidence in men than women [32]. Clinically; oral melanoma may present as an asymptomatic, slowly-growing brown or black patch with asymmetric and irregular borders or as a rapidly enlarging mass associated with ulceration, bleeding, pain and bone destruction. A few oral melanomas are non-pigmented (amelanotic). Although oral mucosal melanomas are rare, they represent a serious and often fatal disease. Internationally, oral melanoma is more common in the Japanese than in other groups. In Japan, oral melanomas account for 11–12.4% of all melanomas, and males may be affected slightly more than females. This percentage is higher than the 0.2–8% reported in the United States and Europe. Although occurrence of cutaneous melanomas is less common in dark skinned races, these races have a greater relative incidence of oral mucosal melanomas. Oral mucosal melanoma tends to be more aggressive than its cutaneous counterparts and is mostly presented at a later stage of the disease. Treatment involves radical surgical excision with clear margins. This may be difficult to accomplish because of anatomic constraints and proximity to vital structures. Radiation and chemotherapy are ineffective, which further makes the management of this malignancy complicated. The prognosis for patients with oral melanoma is poorer than those with cutaneous lesions, and the overall 5-year survival rate is 15%. The best way to improve prognosis is early diagnosis [29,33]. Primary oral mucosal melanomas are biologically aggressive malignancies though they are rare. Oral melanoma clinically mimics many other pigmented lesions of the oral cavity. It is essential to include oral examination as a part of full body examination along with skin examinations, dentures should be removed for examination. Suspicious pigmented and non-pigmented lesions should be biopsied appropriately. Early diagnosis and intervention result in a better prognosis [8].

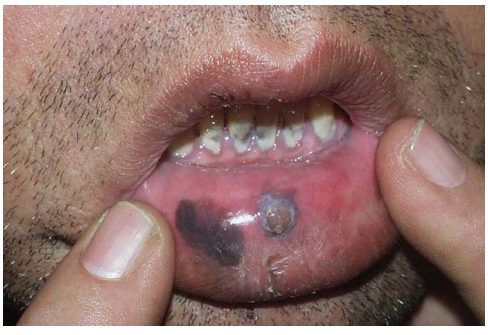

Fig. 4 – Shows oral melanoma on lips.

Focal pigmentation

Hemangioma and vascular malformation

Hemangioma is a benign proliferation of the endothelial cells that line vascular channels [8]. Vascular malformation is a structural anomaly of blood vessels without endothelial proliferation. Both lesions are developmental abnormalities, characterized by onset during infancy. Hemangiomas regress as the patient ages, but vascular malformation persists throughout life. The multi nodularity is racemose and diffuse. Tongue angiomas frequently extend deeply between the intrinsic muscles of the tongue. The lip mucosa is another common site for hemangiomas in children; they appear mostly as localized, raised blue tumors.

Varix and thrombus

Pathologic dilatations of veins or venules are varices or varicosities, and the chief site of such involvement in the oral tissues is the ventral tongue [3–5]. Varicosities become progressively prominent with age, thus lingual varicosities are mostly seen in elderly individuals. Lingual varicosities appear as tortuous serpentine blue, red or purple elevations that course over the ventrolateral surface of the tongue, with extending anteriorly. Even though they may be quite striking in some patients, they represent a degenerative change in the adventitia of the venous wall and are of no clinical consequence. They are painless and are not subjected to rupture and hemorrhage. If the varix contains a thrombus, it presents as a firm bluish purple nodule that does not blanch on diascopy. Thrombi are more common on the lower lip and buccal mucosa [15].

Hematoma and other hemorrhagic lesions

As stated by Barker et al. [32]. Hematomas, petechiae, purpurae and ecchymoses are caused by extravasation of blood into the soft tissues. They may appear as nonblanching flat or elevated pigmented lesions. They may occur spontaneously in certain systemic conditions such as idiopathic thrombocytopenic purpura, or they may result from trauma [21]. The color produced due to degradation of hemoglobin to bilirubin and biliverdin, varies among red, purple, blue and bluish black depending on the length of time the blood has been present in the extravascular spaces. It may take up to 2 weeks for the color to become normal again. If hemorrhagic lesions occur in the absence of recent trauma, the patient should be investigated for platelet disorders and coagulopathies.

Discussion

Intraoral pigmentations could be focal, diffuse or multifocal. They may be black, gray, blue, purple or brown in color. They may be flat or swollen. They can be localized accumulations of melanin, hemosiderin, exogenous metal or some are even indications of an internal disease. The differential diagnosis can be lengthy in certain conditions with multiple and complex lesions with pigmentations. Although biopsy is a helpful aid to diagnosis for localized lesions, the more diffuse lesions will require a thorough history and laboratory studies in order to arrive at a definitive diagnosis [8]. Thorough examination of the oral pigmentation together with complete history and clinical findings are necessary for early diagnosis and prompt treatment. Even though only a few lesions are reported to undergo malignant transformation, yet this limited data regarding malignancy transformation in oral lesions cannot be simply ruled out. All general practitioners should have thorough knowledge in order to establish a probable differential diagnosis as well as definitive diagnosis for prompt treatment. In case of a doubt referral to specialist is recommended.

Conclusion

The diagnostic procedure of pigmented lesions of the oral cavity and perioral tissues is quite challenging. Clinicians may benefit to a certain extent from the available epidemiological data or they can make the diagnoses on clinical grounds alone; however such diagnosis will remain “provisional”. Histopathological evaluation of oral pigmentation is required for a definitive diagnosis. Unfortunately the available data based on randomized controlled trials is quite limited to draw a statistical analysis. We have tried to highlight the oral pigmented lesions that clinicians can most possibly come across during a routine checkup of the patients. The management of pigmented oral lesions varies greatly based on the diagnosis, understanding of the underlying causes of mucosal pigmentation and appropriate evaluation of the patient is therefore essential.

General dental practitioners can benefit from this review as it delineates the factors that will help them to differentially diagnose pigmented lesions of the oral cavity and also improve their understanding differentiate between normal and diseased conditions, so that they can master the skill of early definitive diagnosis and prompt treatment.

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