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Diseases of the tongue

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Abstract The tongue is a complex organ involved in speech and expression as well as in gustation, mastication, and deglutition. The oral cavity, along with the tongue, are sites of neoplasms, reactive processes, and infections, and may be a harbinger of systemic diseases. This review includes both common and rare diseases that occur on the tongue, including: vascular and lymphatic lesions (infantile hemangiomas and oral varices), reactive and inflammatory processes (hairy tongue, pigmented fungiform papillae of the tongue, benign migratory glossitis, and fissured tongue), infections (oral hairy leukoplakia, herpes simplex and varicella-zoster virus infections, human papillomavirus, and candidiasis), premalignant lesions (leukoplakia and erythroplakia), malignant lesions (squamous cell carcinoma, Kaposi sarcoma, and lymphoproliferative diseases), and signs of systemic disease (nutritional deficiency and systemic amyloidosis).

Introduction

The tongue is a complex organ involved in speech and expression as well as in gustation, mastication, and deglutition. The oral cavity and the tongue are sites of neoplasms, reactive processes, and infections and may be a harbinger of systemic diseases.[1] The tongue is a complex set of sensory papillae and muscles (Figure 1). Taste buds are distributed along the dorsal surface of the tongue. There are three forms of taste buds: fungiform (anterior), circumvallate (posterior dorsum), and foliate papillae (posterior lateral). The filiform papillae are devoid of sensory fibers and are not true taste buds. There is no submucosa on the tongue, and muscle is present superficially. Lingual tonsils are present at the posterior dorsum as well as the posterior lateral tongue. Lingual salivary glands are located in the anterior ventral (glands of Blandin-Nuhn) and posterior dorsal tongue (glands of von Ebner). These glands are often surrounded by muscle. Long, tortuous sublingual veins are located on the ventral surface of the tongue.

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Vascular and lymphatic lesions

Infantile hemangiomas

Infantile hemangiomas (IHs) are benign vascular neoplasms and are the most common soft tissue tumors in childhood. In white, non-Hispanic infants, IHs are seen in 1-2% of newborns and 10-12% of 1 year olds.[2] They are more prevalent in girls and most commonly affect the head and neck region. Risk factors include low-birth-weight infants, multiple gestation, and placental abnormalities. IHs proliferate during the first year of life, and 90% involute by 10 years of age.[3] The majority of growth of IHs is seen in the first 2 months of life.[4] Most IHs are simple and run a benign course with involution and minimal cosmetic disfigurement. Although oral IHs are rare relative to the skin, they represent one of the most

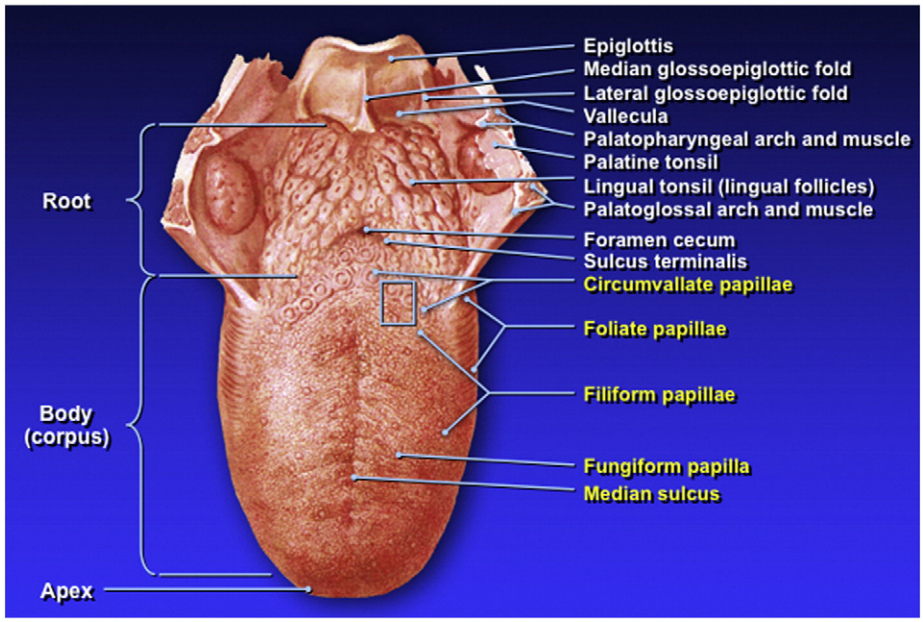

Fig. 1 General anatomy of the tongue.

common lesions in the oral cavity of children and often affect the tongue, buccal mucosa, and lips.[5–7] The oral IHs are of particular concern due to frequent trauma, the risk of bleeding, and the possibility of airway compromise.[8]

IHs come in three general varieties: superficial, deep, and mixed pattern. Superficial IHs are characterized by frambesiform, red papules, with lobulated plaques and nodules. Deep IHs are often a blue, subcutaneous papule or nodule with overlying telangiectasia or veins. The clinical differential diagnosis is dependent on the tumor depth and includes pyogenic granuloma, angiosarcoma, and other vascular tumors. Fully formed tumors at birth are more likely to be a noninvoluting congenital hemangioma (NICH), rapidly involuting congenital hemangioma (RICH), or partially involuting congenital hemangioma (PICH). The clinical course as well as GLUT-1 negativity, found in NICH, RICH, and PICH, will help differentiate these from IHs.

The treatment of IHs is dependent on the risk of compromise of vital organs and structures as well as cosmesis. Oral propranolol is now Food and Drug Administration approved for IHs and has become the gold standard for treatment.[9] Response rates for propranolol are 98% with a goal dose of 2 mg/kg/day and 6 months of therapy. Although laser therapy is effective for treating IHs, it may not be appropriate for intraoral disease.[10] Other treatment options include corticosteroids, interferon alpha, and vinca alkaloids.

Oral varices

Oral varices are a common developmental anomaly noted in older adults.[11] The etiology of oral varicosities remains unknown. Although the data are controversial, there may be an association with old age, smoking, and cardiovascular disease.[12] When seen in younger individuals, one should think of Fabry disease, as well as hereditary hemorrhagic telangiectasia. Oral varicosities most commonly involve the ventral tongue and are characterized by tortuous, asymptomatic, compressible veins (Figure 2). Thrombosis has been rarely reported within the varices and may result in episodic pain and erythema.[13,14] Oral varices are commonly seen on the lip, as venous lakes, but are rare on the buccal mucosa. Treatment is not necessary; however, conservative excision of cosmetically concerning varices is often effective. Due to venous drainage of the tongue into the internal jugular, sclerotherapy should not be used.

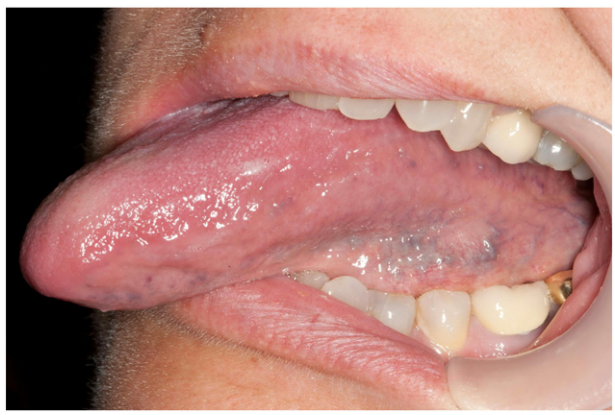

Fig. 2 Vascular anomalies: oral varices. Oral varices are most commonly seen sublingually and are characterized by asymptomatic, tortuous vessels.

Reactive and inflammatory processes

Hairy tongue

Hairy tongue (HT), also known as furred tongue, is the result of retention hyperkeratosis of the filiform papillae on the anterior two thirds of the dorsal aspect of the tongue.[15] HT is variably reported in the literature with rates as low as 0.5% and as high as 11.3%.[16] There appears to be a male predominance, as high as 3 to 1, and increased prevalence in older individuals, 40% in those older than 60 years.[16] Normal papillae are 1 mm in length; however, in HT there is defective desquamation of cells in the central column of the filiform papillae, causing an increase in length 10 to 20 times normal[17] (Figure 3, a). Black HT, seen in the spectrum of HT, occurs when bacteria are trapped in the filiform papillae and produce porphyrins causing a brown or black color. The presence of other microbes, such as *Candida*, can exacerbate this condition. Solid food acts to naturally debride the tongue, whereas irritants stimulate hyperplasia of the tongue. HT is more common in those with poor oral hygiene, smokers, drug users, mouth breathers, those on low-fiber diets, and febrile patients. Interestingly, HT has rarely been reported in patients with HIV infections, graft-versus-host disease, or internal malignancies.[18–20] HT can be exacerbated by drugs, the most common being antibiotics and medications that induce xerostomia, including atypical antipsychotics, antidepressants, and anticholinergics.[18]

Clinically, HT is characterized by hairlike projections on the dorsal tongue that can be scraped off. Although the original name, black HT, implies that the tongue is black, the color can range from black-brown to green-yellow. Due to the previously stated risk factors and the overgrowth of microbes, it is not surprising that HT is associated with halitosis.

The differential diagnosis of HT includes: pseudo–hairy black tongue, oral hairy leukoplakia, premalignant leukoplakia and squamous cell carcinoma, pigmented fungiform papillae of the tongue, acanthosis nigricans, and, rarely, hypertrophic herpes simplex virus infections. Pseudo–hairy black tongue is often secondary to bismuth salicylate (Figure 3, b). Oral hairy leukoplakia (OHL) is strongly associated with immunosuppression and has adherent plaques. Unless there are stigmata of underlying disease or symptoms, such as pain, no additional workup is needed. In refractory or atypical cases, a biopsy and cultures or polymerase chain reaction testing for bacteria, fungus, and herpes simplex virus may be warranted.

HT is commonly asymptomatic and self-resolving. Due to its unsightly appearance, patients often wish to pursue treatment. First-line treatment is aimed at reducing the risk factors and improving hygiene by regular brushing of the tongue with a simple dentrifice or using 1.5% hydrogen peroxide (5–10 strokes daily) with a hard toothbrush. Second-line therapies include topical retinoids, antifungals, and keratolytics.[21] Oral therapy with antifungals, antibiotics, and antivirals should be reserved for refractory cases with positive cultures. More importantly, when the disease is refractory or persistent, an alternative diagnosis, an associated systemic disease, or oral malignancy should be considered.

Pigmented fungiform papillae of the tongue

Pigmented fungiform papillae of the tongue (PFPT) is often confused with black HT. PFPT is normal variant most common in darkly pigmented individuals and has been reported in one fourth to one third of African Americans.[22] PFPT is thought to be secondary to pigment-laden macrophages in the fungiform papillae. The papules of PFPT are nonprogressive and appear in infancy. PFPT is characterized clinically by monomorphic brown papules on the tip and lateral aspects of the tongue (Figure 4). The areas of pigmentation are well demarcated and confined to the individual fungiform papillae. The differential diagnosis of PFPT includes amalgam tattoo, Peutz-Jeghers syndrome, chronic adrenal insufficiency,

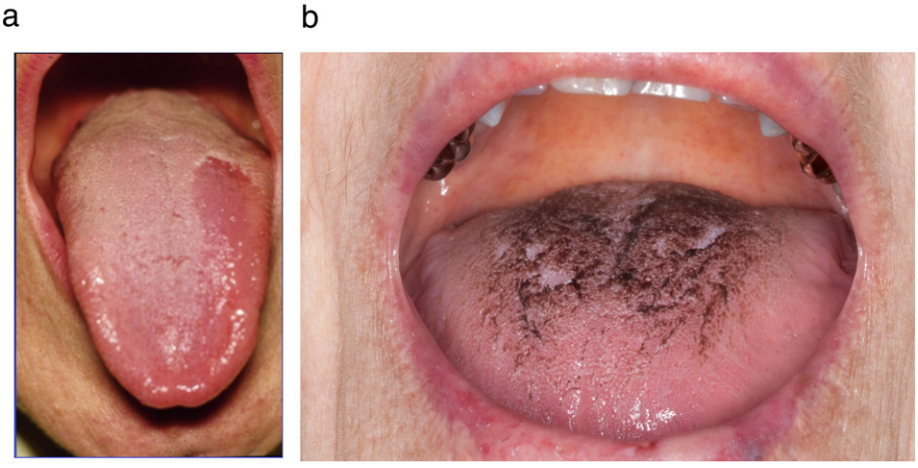

Fig. 3 a, Hairy tongue. Classic hairy tongue is characterized by elongation of the filiform papillae with furlike quality. b, Pseudo–hairy black tongue. Pseudo–hairy black tongue has similar black hyperpigmentation to classic black hairy tongue but lacks the elongation of the filiform papillae.

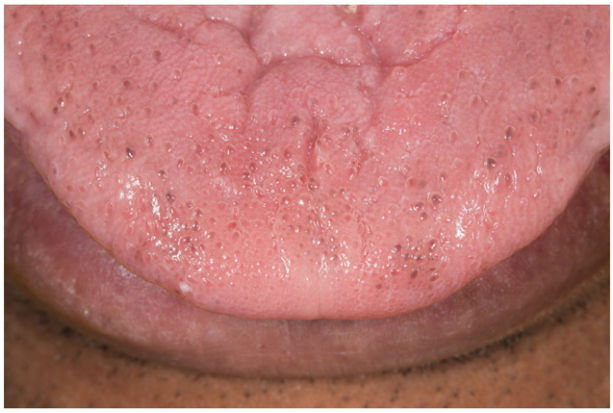

Fig. 4 Pigmented fungiform papillae of the tongue is characterized by monomorphic, darkly pigmented fungiform papillae.

neurofibromatosis type I, melanocytic nevus, melanoma, and black HT.[23] No treatment is necessary; patient reassurance of the benign nature of the condition is adequate.

Benign migratory glossitis

Benign migratory glossitis (BMG), also known as geographic tongue and annular transient patches of the tongue, is a benign, inflammatory condition that affects all age groups. BMG affects 1-2% of the population, is more common in young patients, and often diminishes with age.[24–27] The etiology of BMG remains elusive. BMG is more common in people with psoriasis, up to 14%, and some argue that BMG is an oral manifestation of psoriasis.[28–30]

BMG is characterized by an annular arrangement of alternating raised, hyperkeratotic plaques and smooth, atrophic patches[31] (Figure 5). Filiform papillae are absent in the atrophic, red patches.[32] The lesions are dynamic and change over hours, creating a "migratory pattern," and more often involve the dorsolateral aspect of the tongue.[31] BMG often has a waxing and waning course. Ectopic BMG, geometric stomatitis, is rare.[33] It occurs on nonlingual sites, typically the buccal and palatal mucosa, with invariable tongue involvement.[34] The major clinical differential diagnosis includes psoriasis, reactive arthropathy, lichen planus (LP), lupus erythematosus, graft-versus-host disease, median rhomboid glossitis, leukoplakia, fissured tongue, and chronic herpes simplex virus infection.

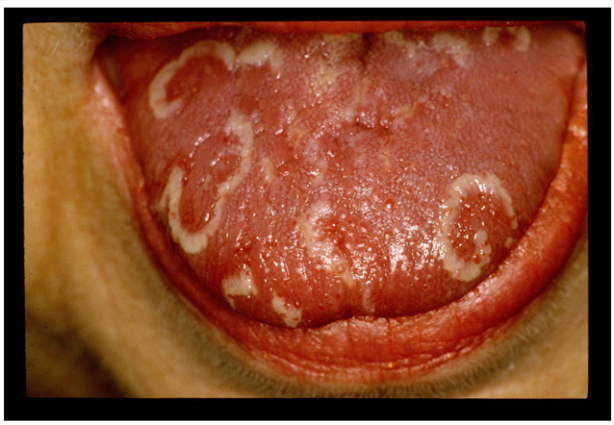

Fig. 5 Benign migratory glossitis is characterized by multiple, circinate, atrophic red plaques with a white, raised border.

BMG is often asymptomatic, with up to 1 in 4 individuals experiencing burning pain or sensitivity to foods.[31] The symptomatic areas tend to occur in the atrophic patches. Although there are no rigorous studies, the mainstay of treatment for symptomatic BMG is similar to that of plaque psoriasis with potent topical corticosteroids as well as topical calcineurin inhibitors.[35] The use of systemic immunosuppressants, such as cyclosporine, has also been reported.[36]

Fissured tongue

Fissured tongue (FT) is a normal variant seen in up to 20-30% of the population, characterized by an increased number of fissures and grooves at the central and lateral aspects of the tongue[16,37] (Figure 6). More severe fissuring is often referred to as "lingua plicata." This condition is idiopathic, more common in older individuals, and thought to be a reactive process.[24,26,37] FT is more common in individuals with geographic tongue, as well as those with psoriasis.[38] FT is the most common tongue finding, seen in up to one third of patients with psoriasis.[28,39] Other associations include Down syndrome, Melkersson-Rosenthal syndrome, pernicious anemia and macroglossia, pachyonychia congenita, and Cowden syndrome.[40–43]

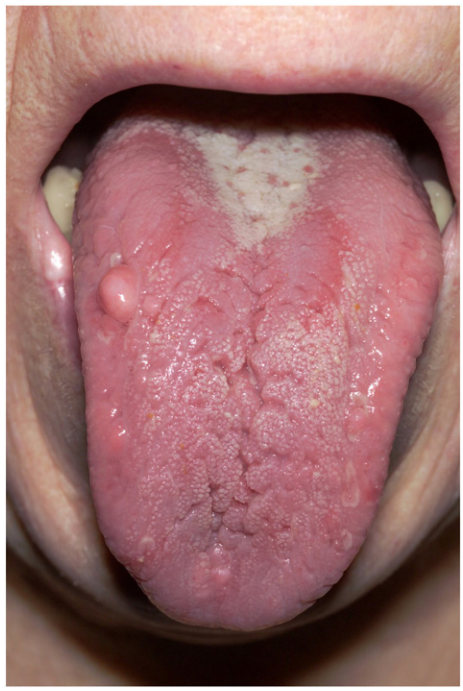

Fig. 6 Fissured tongue is characterized by a central groove with smaller radiating grooves. This patient has an incidental bite fibroma on the right lateral tongue.

Clinically, FT is characterized by multiple, asymptomatic 2- to 3-mm grooves and fissures on the dorsal surface of the tongue.[37] There is often a midline groove with smaller, symmetric radiating grooves.[37] The differential diagnosis also includes concomitant infections. Unless harbingers of underlying systemic disease are present, no workup is necessary.

There is no effective treatment for FT; however, we recommend good oral hygiene with brushing deep into the fissures to remove debris, lessen the microbial burden, and reduce halitosis.[44] If pain is present, the possibility of a systemic disease or concomitant infection and therapy should be targeted at reducing inflammation or eradication of the infection.

Infectious conditions

Oral hairy leukoplakia

Oral hairy leukoplakia is characterized by hyperkeratotic white plaques and is often unilateral on the lateral aspect of the tongue. The plaques are asymptomatic and cannot be wiped off with gauze. The disease was originally described during the HIV epidemic in 1984, is still one of the most specific oral manifestations of HIV, and may herald more progressive disease.[45–47] Oral lesions are very common in HIV and are indicative of the degree of immunosuppression. OHL has been described in other immune-compromised states: solid organ transplant, corticosteroid usage, and malignancy.[48] OHL is an Epstein-Barr virus (EBV)–related disease that is driven by immunosuppression[49–52]; however, immunosuppression and EBV are necessary but not sufficient for disease, because OHL occurs in only 25% of HIV patients.[53] Other modulating factors include host response, age, local irritants, and concomitant infections.[53]

Clinically, OHL is characterized by adherent, corrugated white plaques on the lateral aspect of the tongue.[47,53] The disease course is often chronic and dependent on the immune status of the individual. The clinical differential diagnosis includes HT, hypertrophic candidiasis, LP, leukoplakia, and squamous cell carcinoma.[47]

Although OHL is often asymptomatic, has no malignant potential, and does not require treatment, the underlying HIV infection should be treated or the immunosuppressed states should be modified. First-line topical treatment of OHL includes topical retinoids, podophyllin, and acyclovir, as well as treatment for such exacerbating factors as *Candida* with gentian violet and other antifungal agents.[54,55] Systemic antivirals typically diminish OHL within 1 to 2 weeks, but the disease often flares on discontinuation due to persistent latent virus as well as viral resistance.[51,56–58]

Herpes simplex virus infections

Primary and recurrent herpes simplex virus (HSV) infections, secondary to human herpesvirus 1 (HHV-1) or HHV-2, can occur on any mucosal surface and is most common on the lips and gingiva.[59] The three major forms of intraoral HSV infections are acute herpetic gingivostomatitis, recurrent intraoral herpetic stomatitis, and herpetic geometric glossitis. The clinical differential diagnosis includes LP; graft-versus-host disease; fissured tongue; recurrent aphthous stomatitis; hand, foot, and mouth disease; erythroplakia; and herpangina.[60,61]

Clinically, acute herpetic gingivostomatitis is characterized by fever, sore throat, malaise, and tender adenopathy.[60] The lesions resemble aphthae with grouped, superficial vesicles that rupture and form shallow red ulcers[61] (Figure 7, a). Acute herpetic gingivostomatitis is often self-limited; however, treatment with oral antivirals will hasten the resolution.[59] A 10-day course of valacyclovir, famciclovir, or acyclovir is appropriate, with valacyclovir and famciclovir being preferred due to ease of administration, 2 to 3 times daily. Therapy should be initiated in the first 72 hours of onset.

Herpetic geometric glossitis, a unique form of recurrent HSV infection described in 1993,[62] is classically described as linear and symmetric striations and fissures of the dorsal aspect of the tongue in an immunocompromised individual, although there are rare reports of herpetic geometric glossitis in immunocompetent patients as well[63] (Figure 7, b). This condition is characterized by exquisite tenderness and pain within the atrophic and uniquely branched and fissured lesions.[62,64] The branched fissures of herpetic geometric glossitis are analogous to the dendritic ulcerations of corneal herpetic infections.[64] When examining the tongue in these cases, one should carefully examine for small foci of traditional vesicles of HSV infections. Confirmatory testing can be performed with polymerase chain reaction amplification of viral DNA.[65] Therapy with systemic antiviral drugs is essential and should be guided by cultures and clinical response.[59] In cases of recurrent and refractory disease in an immunocompromised host, one should test for resistance and consider a reduction in immunosuppression.

Herpes zoster virus infections

Varicella-zoster virus, HHV-3, can produce two entities: varicella (chickenpox) and varicella-zoster (shingles). Chickenpox occurs in childhood with a 30% lifetime risk of shingles in affected individuals.[66] The lifetime risk of shingles, as well as age of onset, is dependent on immune status, with an increased lifetime risk in the immunosuppressed as well as an earlier onset.[66] There is often a prodrome of dysesthesias, followed by vesiculation. Shingles is characterized by a localized and unilateral eruption following the anatomic distribution of a single sensory nerve ganglion. Although shingles is uncommon in the mouth, involvement of the mandibular (V3) branch of the trigeminal nerve can result in blistering and ulceration of the tongue, floor of the mouth, mandibular gingiva, and buccal mucosa.[67–71] Oral vesiculation is often accompanied by facial involvement. Patients report having odontalgia, dysgeusia, and ageusia.[71]

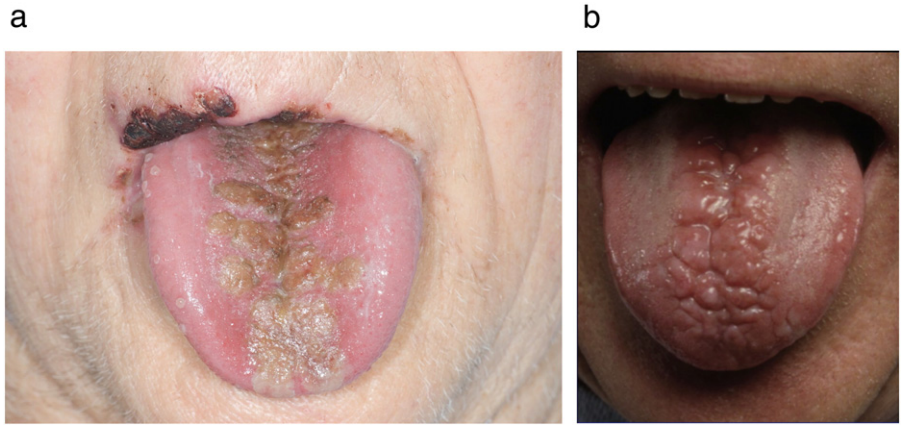

Fig. 7 Herpes simplex virus. a, Acute herpetic gingivostomatitis is characterized by a vesiculobullous eruption, which may be associated with adherent hyperkeratosis and hemorrhage. This severe case occurred in the setting of immunosuppression. b, Herpetic geometric glossitis is classically described as linear and symmetric striations and fissures of the dorsal aspect of the tongue.

Although classic eruptions can be diagnosed easily, atypical cases without vesiculation or with ulceration and necrosis bring in a broader differential diagnosis. The clinical differential diagnosis may include: secondary syphilis; herpetic geometric glossitis; burning mouth syndrome; cytomegalovirus ulcers; EBV-mucocutaneous ulcers; hand, foot, and mouth disease; eosinophilic ulcer of the oral mucosa (EUOM); pemphigus; mucous membrane pemphigoid; and even epithelial carcinoma.[72,73] Varicella-zoster virus polymerase chain reaction testing remains the most sensitive and specific method of diagnosis; however, culture should be considered in immune-compromised patients to evaluate for resistance.[74] In atypical cases, a biopsy should be performed to confirm the diagnosis and rule out other entities. In cases with an atypical presentation, one should consider testing for an immune-suppressed state such as HIV.

Oral antivirals remain the standard of care. Early intervention within 72 hours of onset decreases the disease severity, but the benefit in preventing postherpetic neuralgia is unclear.[75] Although most studies suggest treating with antivirals in the first 72 hours, treatment after this window of time is also appropriate, especially in patients at high risk for complications. For a more detailed review on dosing and duration for varicella-zoster virus infections, please see *Comprehensive Dermatologic Drug Therapy*, Chapter 10, Systemic Antiviral Agents.[76]

Human papillomavirus infections

Human papillomavirus (HPV) is responsible for a large number of epithelial diseases occurring on cutaneous and mucosal sites. Most commonly, HPV causes cutaneous verrucae. Oral HPV is present in approximately 7% of the adolescent and adult population in the United States, and 1% of the population harbors the high-risk strain HPV type 16.[77] HPV types 16, 18, 31, 33, and 52 are associated with an increased risk of head and neck malignancy.[78] The four major low-risk oral HPV diseases are oral verruca vulgaris, condyloma acuminata, squamous papilloma, and focal epithelial hyperplasia. The clinical differential diagnosis of HPV-induced epithelial changes includes squamous papilloma, condyloma acuminata, exophytic squamous cell carcinoma, keratoacanthoma, exophytic verrucous carcinoma, focal epithelial hyperplasia, and verruciform xanthoma.[78]

Oral verrucae are rare, relative to cutaneous disease, and are caused by HPV types 1, 2, 4, 26, 27, and 57.[78] The verrucous papules most commonly occur on the lips, tongue, and gingivae. Clinically, oral verrucae are characterized by exophytic, sessile, or pedunculated lesions. Although treatment is not necessary, local destruction with cryosurgery, electrosurgery, and carbon dioxide lasers is often effective. For refractory or atypical lesions, surgical excision is preferred.

Condyloma acuminata may be caused by HPV types 6 and 11 and high-risk strains.[79] They are most commonly found in the genital region of young adults; however, oral lesions, on the lips and tongue in particular, can occur in individuals engaging in oral sex. Clinically, these lesions are indistinguishable from other forms of HPV verrucae. Similar treatment modalities to oral verruca may be used. High-risk phenotypes, as well as high degrees of dysplasia, require more aggressive treatment.[80–82] Prevention and risk reduction of condyloma and HPV-related cancers can be achieved with safe sex practices, as well as HPV immunization. The new Gardasil 9 vaccine protects against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 and, in the United States, is recommended for everyone 9 to 26 years of age.[83]

Candidiasis

Oral candidiasis is most commonly caused by *Candida albicans*.[84] Median rhomboid glossitis is a unique form of candidiasis that is characterized by large rhomboidal, atrophic plaques on the posterior-central tongue anterior[84] (Figure 8). Median rhomboid glossitis is likely a reactive process to *Candida* and occurs more commonly in adults. The surface of the tongue may be lobulated or smooth, and the lesions

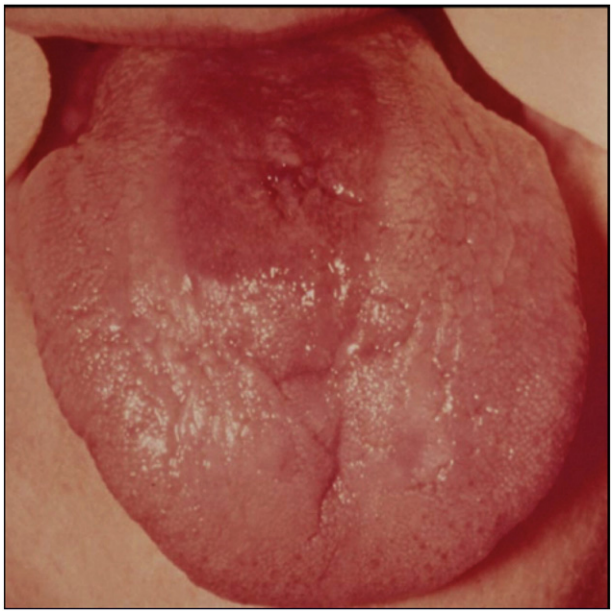

Fig. 8 Median rhomboid glossitis is characterized by large rhomboidal, atrophic plaques on the posterior-central tongue.

are always anterior to the circumvallate papillae. The plaques are often asymptomatic. Median rhomboid glossitis may be confused with BMG; however, the plaques of median rhomboid glossitis are not dynamic. Treatment with topical or oral antifungals is effective.[85–87]

Premalignant lesions

Leukoplakia

Leukoplakia is a misused term that refers to a phenotype, a white patch or plaque, that cannot be classified as any other disease[87–92] (Figure 9). *Leukoplakia* is therefore a clinically descriptive term and, in itself, does not denote malignant potential. Other entities have white plaques on clinical

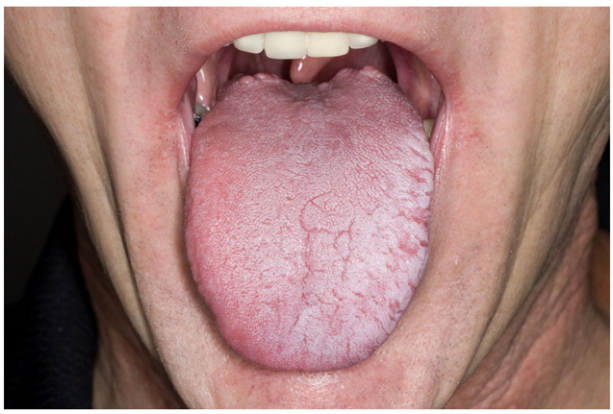

Fig. 9 Leukoplakia is characterized by a slightly elevated, white plaque. This patient had extensive benign leukoplakia.

examination, including candidiasis, LP, lupus erythematosus, graft-versus-host disease, BMG, white sponge nevus, frictional hyperkeratosis, nicotinic stomatitis, and squamous cell carcinoma (SCC).[87,93,94] When an entity has white plaques and cannot be identified further clinically, the term *leukoplakia* is often used pending a histopathologic analysis.[90] For the purpose of this section, we will use leukoplakia as a clinical pathologic correlation representing a white plaque clinically, with the absence of pathologic findings of other diseases and which may or may not have dysplasia.

Leukoplakia is the most common chronic disease in the mouth and represents 85% of all keratotic lesions.[92] Leukoplakia increases in frequency with age, is associated with smoking, and commonly occurs on the tongue.[92,95–97] Infectious risk factors include HPV, *Candida*, HIV, and syphilis. Squamous atypia may be found when a *Candida* infection is present. Although leukoplakia may be premalignant, dysplasia is not required for diagnosis. Up to 7% of cases of leukoplakia will show severe dysplasia on initial biopsy.[92] Clinically, leukoplakia is characterized by adherent, white plaques.[90,92] These plaques should be palpated because tenderness and induration are signs of malignancy. The floor of the mouth, as well as the ventral surface of the tongue, are commonly involved. A complete oral examination should be performed because leukoplakia can be associated with multifocal disease. The overall risk of malignant transformation varies between 2-3% per year, with long-term risk as high as 18%.[89,96] Risk factors for malignant transformation include old age, location on the tongue, speckled leukoplakia, a history of smoking or betel nut chewing, and high-grade dysplasia on initial biopsy.[89,95,97]

Treatment of leukoplakia may be difficult. A recent Cochrane review found no clear evidence for any treatment regime preventing malignant transformation of leukoplakia.[98] Close monitoring, best with serial photography, and frequent biopsies for malignant transformation are necessary. Treatment options are dependent on the degree of dysplasia. Highly atypical lesions often require surgical removal or other destructive methods: electrocautery, cryosurgery, or laser ablation. These methods will reduce the tumor burden, but recurrences are common and the rate of overall progression to malignancy is unaffected.[98,99] Adjuvant field therapy with imiquimod, fluorouracil, and photodynamic therapy may be appropriate to reduce the disease burden. Long-term follow-up, every 3 to 6 months for 2 to 3 years, is necessary to detect malignant transformation.[89]

Erythroplakia

Erythroplakia is a rare and poorly defined premalignant condition with a higher rate of progression to invasive SCC than leukoplakia.[100] Erythroplakia is a provisional diagnosis that refers to a clinical phenotype that cannot be classified as a specific clinical entity (Figure 10). For the purpose of this section, *erythroplakia* will only refer to purely red lesions

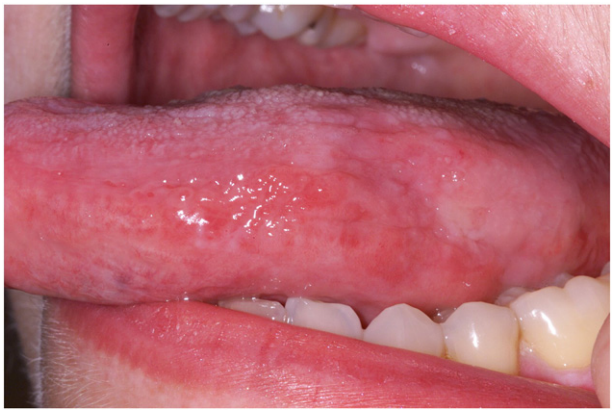

Fig. 10 Erythroplakia is characterized clinically by a poorly marginated red plaque. In this case, a biopsy revealed this to be an invasive squamous cell carcinoma.

and will exclude lesions of speckled leukoplakia, often classified as high-risk leukoplakia. It is unclear if erythroplakia develops from leukoplakia or if it arises *de novo*. Erythroplakia is most common in older individuals, and risk factors include chewing tobacco and alcohol.[101] Clinically, erythroplakia is described as a red, velvety patch. Oral mucosal erythroplakia commonly occurs on the floor of the mouth and rarely on the tongue and buccal mucosa.[102] The lesions may be atrophic and in some cases erosive. As with leukoplakia, a complete oral examination should be performed. The rate of malignant transformation may be as high as 50%.[103]

All erythroplakic lesions should be biopsied because SCC or SCC *in situ* are the most common diagnoses. Erythroplakia is a diagnosis of exclusion; in addition to malignancy, the most important differential diagnosis are lupus erythematosus, LP, and erythematous candidiasis. When erythroplakia is present in LP, it considered a high-risk feature for malignant degeneration.[104,105] Treatment options include surgical removal as well as other destructive methods: electrocautery, cryosurgery, or laser ablation. Recurrence is common, and long-term follow-up is necessary.

Malignant neoplasms

Squamous cell carcinoma

SCC is the most common oral malignancy and is a significant worldwide health issue.[88,106] Oral SCC is more common in men and in those older than age 40. Extrinsic risk factors include tobacco, alcohol, and sun exposure (if on the lip). Intrinsic risk factors include immunosuppression, longstanding inflammation, LP, HPV infection, HIV infection, and nutritional deficiencies.[88] The overall prognosis of SCC of the oral cavity is worse than SCC of the skin.

The clinical presentation of oral SCCs is highly variable; therefore, one should maintain a high index of suspicion, perform a biopsy early in the disease course, and perform repeat biopsies in refractory oral inflammatory diseases. SCCs can appear as exophytic masses or endophytic and indurated ulcers. Clues to the diagnosis include longstanding lesions, irregular and ulcerated papules, nodules, and plaques that extend above the normal epithelium. The lesions often have an indurated quality. The most common sites are the posterior lateral and ventral surface of the tongue.[107] The floor of the mouth is the second most common location, whereas SCC of the dorsal surface of the tongue is rare.

Multimodal therapy with surgical excision, chemotherapy, or radiation remains the standard of care.[108] Recurrence is high in oral SCC; therefore, long-term monitoring is required. In cases of multiply recurrent disease or field cancerization, chemoprevention with retinoids, topical chemotherapy, and photodynamic therapy should be considered.

Kaposi sarcoma

Kaposi sarcoma (KS) is a rare vascular malignancy in an endemic population; however, the epidemic form of KS became a more common finding with the HIV/AIDS epidemic.[109] KS is the most common malignancy associated with HIV. KS is a virus-associated malignancy with invariable infection with HHV-8.[110,111] Four patterns of KS are seen: classic, African/endemic, immunosuppressive, and HIV/AIDS related. Oral KS most often affects the hard and soft palate, gingiva, and dorsal tongue with plaques or tumors of coloration ranging from nonpigmented to brown-red or violet.[109] Oral KS is most common in HIV-related KS and may be the only area of involvement in 25% of cases.[109] Oral KS may be the first sign of an occult HIV infection. The differential diagnosis for oral KS includes pyogenic granuloma, benign vascular malformations, bacillary angiomatosis, and drug-associated hyperplasia (most commonly on the gingiva).[109] For focal lesions, locally destructive methods, including cryotherapy, topical alitretinoin, intralesional chemotherapy, and excision, are effective. For later-stage disease, chemotherapy or radiation is reasonable.[112–114]

Lymphoproliferative diseases

Eosinophilic ulcers of the oral mucosa can occur in adults, as well as in infants (Riga-Fede disease). The pathogenesis is unknown but is thought to be trauma related, with the tongue as the most common location.[115] Clinically, the lesion starts as a single nodule, enlarges, ulcerates centrally, and develops rolled borders.[115] In children, EUOM is often trauma associated and resolves with the cessation of trauma. Histologically, EUOM are characterized by a polymorphous inflammatory infiltrate with eosinophils and, more recently noted, a clonal population of CD30-positive cells.[116–118] This has led some to speculate that EUOM represent a variant of CD30-positive lymphoproliferative disease. No treatment is necessary because the lesions tend to spontaneously resolve within a few

months. A biopsy is often performed to rule out malignancy. If the lesion is nonresolving or increasing in size, one should consider anaplastic large cell lymphoma as an alternative diagnosis.

EBV-mucocutaneous ulcers, as well as EBV-associated lymphoproliferative diseases, occur in transplant patients.[119] Histologically, the ulcerations are characterized by a polymorphous inflammatory infiltrate with immunoblasts, Hodgkin-like cells, and apoptotic bodies.[72] Like EUOM, EBV-mucocutaneous ulcers are CD30 positive; however, EBV-mucocutaneous ulcers may not resolve spontaneously and may require a decrease in immunosuppression.

Signs of systemic disease

Nutritional deficiency

Oral changes are often the first clinical sign of a nutritional deficiency.[1] The clinical changes may not correlate with the disease severity and may be nonspecific. In some cases, there may be no clinical findings other than symptoms of a burning or sore mouth.[120] Additionally, problems with malabsorption, such as occur in patients with celiac disease, can result in nutritional deficiencies.[121] A detailed dietary history of gastrointestinal symptoms is required when a patient is suspected of having a nutritional deficiency. In early disease, the tongue papillae initially redden and may enlarge. In late disease, the tongue takes on an atrophic and smooth, beefy red appearance[122,124] (Figure 11). Other cutaneous and neurologic clues can be used to narrow the differential diagnosis.[122] Panel testing for nutrients is often required.[123] Treatment consists of replacement of the deficient vitamins and improved nutritional status. The two major entities discussed here are atrophic glossitis in association with iron deficiency and B-complex deficiency.

Changes to the tongue and oral mucosa are common in red blood cell disorders. Iron deficiency anemia is common and often has early manifestations with atrophy of the filiform and fungiform papillae.[124,125] The atrophy may begin on the tip and lateral aspect of the tongue and eventually spread to involve the entire tongue surface. Iron supplements will often reverse these changes. Plummer-Vinson syndrome is associated with the triad of dysphagia, iron deficiency anemia, and esophageal webs.[126] The major clinical findings are atrophic glossitis, angular cheilitis, and koilonychia. Patients with Plummer-Vinson syndrome are at increased risk of oropharyngeal SCC and require long-term follow-up.

B-complex deficiencies (B_1, B_2, B_3, B_6, and B_{12}) can result in tongue changes with eventual atrophy and even ulceration. These changes are indistinguishable from diseases of malabsorption and iron deficiency. Niacin (B_3) deficiency, pellagra, is associated with distinctive clinical features, including diarrhea, photo-distributed dermatitis, and dementia. Cyanocobalamin (B_{12}) deficiency also has unique hematologic and neurologic findings. The recognition and treatment of B_{12} deficiency is critical because it is a reversible cause of bone marrow failure and neurologic disease.[122] Pernicious anemia is the most common cause of B_{12} deficiency and is secondary to antibodies against intrinsic factor with destruction of gastric parietal cells.[122] Other populations with B_{12} deficiency include the elderly, vegetarians, and chronically ill individuals. Clinically, burning pain on the tongue is often present before physical changes to the tongue, which may be mistaken for burning mouth syndrome.[127] As the disease worsens, there is a progressive, beefy red change to the tongue. Late-stage disease is characterized by atrophy of the filiform and fungiform papilla and a smooth, glistening appearance.[123] Taste and smell alteration occurs in late disease. Measurement of B_{12}, methylmalonic acid (elevated and the most sensitive test of B_{12} deficiency), and homocysteine is used to confirm vitamin B_{12} deficiency.[122] Oral or subcutaneous B_{12} replacement is necessary.

Systemic amyloidosis

Systemic amyloidosis is a heterogeneous disease characterized by the deposition of amyloid in various organs. Amyloid

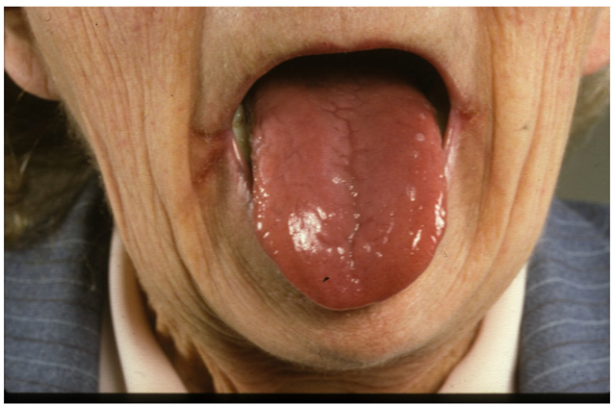

Fig. 11 Atrophic glossitis occurs in the setting of nutritional deficiency. In this case, the patient had pernicious anemia as well as angular cheilitis.

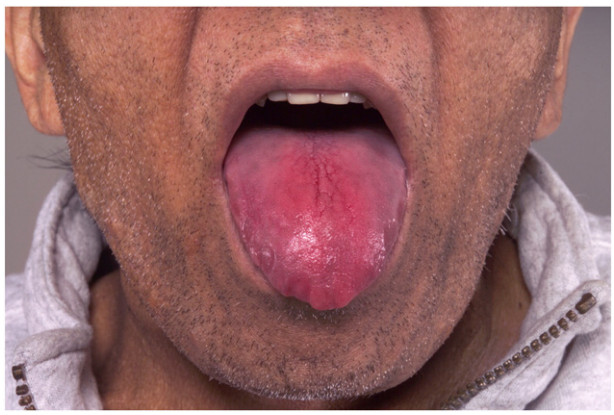

Fig. 12 Macroglossia can be diagnosed clinically with scalloped impressions on the lateral border of the tongue secondary to the compression of the tongue on the teeth. This case was secondary to systemic amyloidosis.

light chain is the most common form of systemic amyloidosis and most often occurs in individuals older than age 65.[128] Most patients have an underlying plasma cell dyscrasia. Areas commonly involved are the kidney, heart, peripheral nerves, skin, gastrointestinal tract, and oral cavity. Oral lesions predominantly affect the tongue, causing macroglossia in 15% of patients, along with purpura and bullae[128] (Figure 12). In systemic amyloidosis, the tongue has a woody quality on palpation and may cause airway obstruction. The major prognostic indicator of systemic amyloidosis is the degree of cardiac involvement.[128] The treatment of systemic amyloidosis is centered on treating the underlying plasma cell dyscrasia. Refractory and obstructive macroglossia can be managed surgically.[129]

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