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SPECIAL ISSUE: COLORS AND TEXTURES, A REVIEW OF ORAL MUCOSAL ENTITIES

Erythematous and Vascular Oral Mucosal Lesions: A Clinicopathologic Review of Red Entities

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Abstract
Erythematous lesions of the oral mucosa are common and can reflect a variety of conditions, ranging from benign reactive or immunologically-mediated disorders to malignant disease. Together with vascular abnormalities, which can vary from reddish to bluish-purple in color, the differential diagnosis for erythematous oral mucosal change is quite diverse. This review focuses on salient clinical features and histopathologic findings of selected conditions which clinically present as red or vascular-like oral mucosal alterations, including oral vascular malformations and neoplasms, pyogenic granuloma, localized juvenile spongiotic gingival hyperplasia, denture stomatitis, benign migratory glossitis (geographic tongue), orofacial granulomatosis, granulomatosis with polyangiitis (Wegener granulomatosis), megaloblastic anemia, and erythroplakia. Recognition of the characteristic clinical features of these conditions, in conjunction with thorough patient history, will allow clinicians to narrow the differential diagnosis and guide appropriate clinical decision making, including the need for tissue biopsy, in order to complete the diagnostic process and initiate optimal patient care.

Keywords Erythematous · Erythema · Red · Vascular · Oral mucosa · Diagnosis

Introduction

Erythematous lesions of the oral mucosa are common and may result from a variety of tissue alterations, including inflammation, erythrocyte extravasation, and atrophy or reduced keratinization of the surface epithelium. Together with vascular processes, which can vary from reddish to bluish-purple in color, the differential diagnosis for erythematous mucosal change is quite diverse and includes both benign and malignant vascular anomalies, reactive processes, immune-mediated diseases, hematologic disorders as well as potentially malignant (precancerous) and malignant epithelial lesions.

This review focuses on salient clinical features and histopathologic findings of select conditions that clinically present as erythematous or vascular-appearing oral mucosal alterations (Table 1). Differential diagnosis and diagnostic pitfalls are discussed to aid both clinicians and pathologists as integral members of the multidisciplinary care team.

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Vascular Anomalies

Vascular anomalies consist of a diverse collection of congenital and acquired lesions composed of vascular structures. Significant progress has been made in our understanding and distinction between anomalies, aided by the work of Mulliken and Glowacki [1] and expanded by the International Society for the Study of Vascular Anomalies (ISSVA) [2]. According to their classification scheme, vascular anomalies can be categorized as *vascular malformations* or *vascular tumors*.

Vascular Malformations

Vascular malformations (VMs) are structural abnormalities of vascular channels that exhibit normal endothelial cell turnover and arise from formational errors during fetal development. The majority are sporadic, but they can be associated with a number of inherited genetic mutations [3]. VMs are usually congenital and tend to grow proportionately with the patient; however, they may not be recognized until adolescence or adult life. Spontaneous involution is rarely reported and some VMs may exhibit episodes of rapid enlargement secondary to traumatic injury, infection,

Table 1 Differential diagnosis of erythematous and vascular oral mucosal lesions

Vascular anomalies
Vascular malformations
Vascular tumors
Reactive processes
Pyogenic granuloma
Peripheral giant cell granuloma
Localized spongiotic gingival hyperplasia
Denture stomatitis
Erythematous candidiasis
Infammatory papillary hyperplasia
Immune-mediated diseases
Benign migratory glossitis
Desquamative gingivits
Orofacial granulomatosis
Granulomatosis with polyangiitis
Hematologic disorders
Megaloblastic anemia
Lymphoproliferative disease
Epithelial neoplasia
Erythroplakia
Squamous cell carcinoma

attempted intervention or hormonal fluctuation [1, 4]. VMs can be subclassified by endothelial cell origin and rheostatic (high- vs. low-flow) characteristic. High-flow lesions contain an arterial component and include arterial malformations, arteriovenous malformations, capillary arteriovenous malformations and arteriovenous fistulae. Low-flow VMs are devoid of an arterial component and are classified by their predominant endothelial cell type, namely capillary, venous, lymphatic or combined lesions [3, 5].

Vascular Tumors

Vascular tumors (VTs) consist of benign and malignant neoplasms of endothelial cell origin. The majority are *hemangiomas*, a term restricted to benign neoplasms composed of vessels that exhibit disproportionate growth relative to the patient. The ISSVA classification recognizes more than a dozen subclassifications of hemangioma [2], details of which are beyond the scope of this manuscript. While pyogenic granuloma (lobular capillary hemangioma) is a subtype commonly seen intraorally, most oral pyogenic granulomas are considered reactive rather than neoplastic proliferations [6, 7]. Locally aggressive/borderline and malignant vascular neoplasms, including hemangioendothelioma, Kaposi sarcoma and angiosarcoma, rarely present intraorally [8–12].

Clinical Features

Vascular anomalies have a predilection for the head and neck and can involve any intraoral location. The majority of oral mucosal lesions are small and superficial, but they can present as large, bulky tumors involving deep submucosal structures. Deeply situated lesions may appear normal in color, while superficial presentations appear erythematous to blue or purplish depending upon the mix of arterial-capillary-venous vascular channels. In the absence of thrombosis, VAs are usually soft and compressible. Characteristically, the application of gentle pressure results in a loss of color or tissue blanching, indicating that the reddish color is due to blood contained within a lesional vessel (Fig. 1). This clinical procedure, termed *diascopy*, can provide evidence to support the clinical impression of a benign vascular proliferation. In contrast, an area of recent hemorrhage will not blanch. Since malignant vascularity is often poorly formed with extensive erythrocyte extravasation, the absence of blanching must be correlated with the complete clinical presentation.

Lymphatic malformations (LMs), sometimes referred to as lymphangioma or cystic hygroma, can occur at any oral mucosal location and exhibit unique clinical features. They show a propensity for the anterior two-thirds of the tongue and are generally superficial with a distinct pebbly

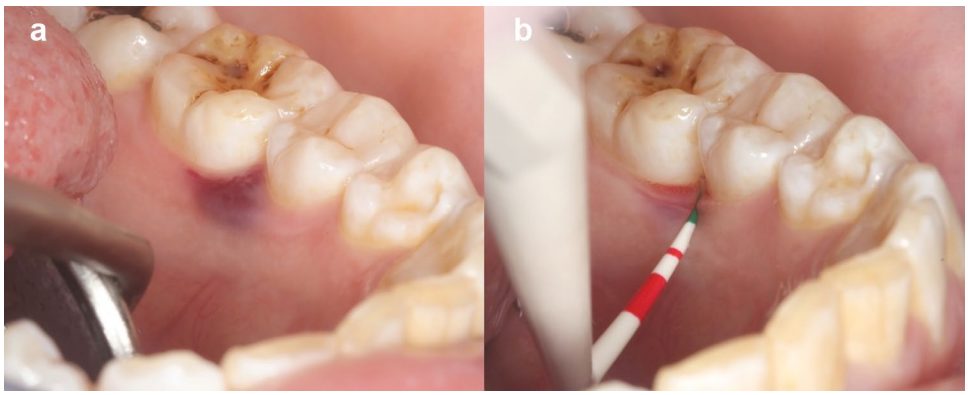

Fig. 1 **a** Reddish purple *vascular anomaly* of the gingiva. **b** Loss of color (blanching) is observed upon application of pressure (diascopy)

surface exhibiting erythematous, pink and translucent vesicles that have been described as resembling frog eggs or tapioca pudding (Fig. 2).

Histopathology

A detailed discussion of the histopathologic features of vascular anomalies is beyond the scope of this manuscript. In general, helpful immunohistochemical markers include CD31, a sensitive and relatively specific endothelial marker. Differentiation between endothelial cell types can be achieved with ETS-related gene (ERG) and D2-40 (podoplanin), which are selectively and strongly expressed in vascular and lymphatic endothelia respectively [13].

Differential Diagnosis

A *varix (varicosities, varices)* should be included in the differential diagnosis for a lesion exhibiting a vascular appearance. This lesion represents a dilated and tortuous vein, thought to result from age-related degeneration of elastic support for the vessel wall, and usually presents as a solitary, reddish to bluish-purple nodule. While they may appear on any oral mucosal surface, the lips, buccal mucosa and tongue are favored locations [14]. Numerous non-vascular entities may also appear bluish in color, clinically mimicking a vascular process. Differential considerations could include salivary gland lesions (mucocele, salivary duct cyst, benign and malignant salivary tumors), gingival cyst, amalgam tattoo and blue nevus. While histopathologic assessment is often required for diagnosis, diascopy (as described above) can also be helpful in discriminating vascular processes from non-vascular counterparts.

Reactive Processes

Pyogenic Granuloma (Lobular Capillary Hemangioma)

Pyogenic granuloma (PG) is a common, reactive soft tissue and vascular proliferation associated with chronic, low-grade irritation. While it may occur at any cutaneous or mucosal site, oral presentations show a striking predilection for the gingiva, particularly the anterior maxillary region, followed by extragingival locations such as the lips, tongue and buccal mucosa [15, 16]. PG occurs across a broad age range, with mean age in second to third decades of life [7, 16, 17]. A female predilection is thought to be secondary to hormonal influences.

Clinical Features

PG presents as an exophytic, smooth or lobulated nodule that frequently exhibits a pedunculated base and ranges in color from pinkish-red to purplish (Fig. 3a). While generally asymptomatic, the surface is often ulcerated and hemorrhagic. Lesions typically range in size from a few millimeters to 2 cm, although larger lesions have been reported together with rapid enlargement, features concerning for malignancy [15, 17].

Histopathology

PG may present as a cellular, highly vascular proliferation that resembles granulation tissue or as a lobular collection of blood vessels, also termed *lobular capillary hemangioma* [15]. The mucosal surface is frequently ulcerated with variable edema, vascular dilation and mixed inflammation (including neutrophils, plasma cells and lymphocytes) together with the endothelial cell and capillary proliferation. As lesions mature, sclerotic changes may develop

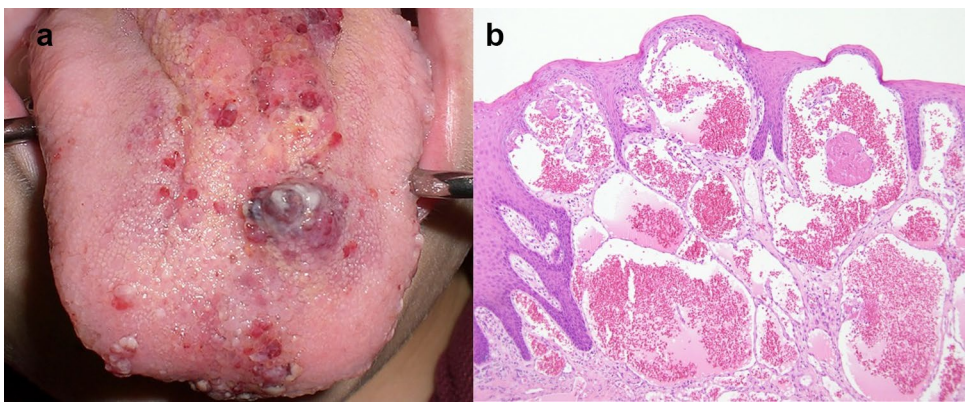

Fig. 2 **a** *Lymphatic malformation* presenting as pink to reddish pebbly appearance of dorsal tongue. **b** Histopathologic features show dilated lymphatic and vascular channels partially replacing connective tissue papillae

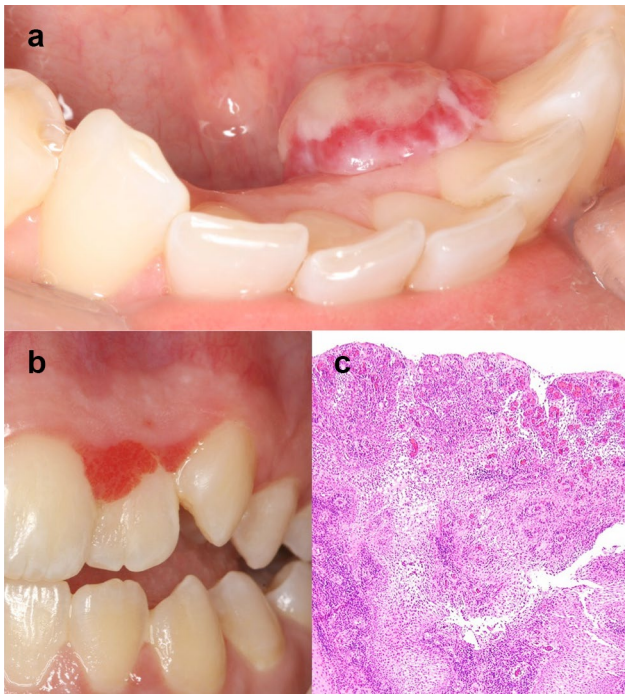

Fig. 3 **a** Ulcerated erythematous nodule of the mandibular gingiva diagnosed as *pyogenic granuloma* on biopsy. **b** Velvety erythematous lesion of the marginal attached gingiva of a 14-year-old female diagnosed as *localized juvenile spongiotic gingival hyperplasia* (LJSGH) on biopsy. **c** LGSGH histopathologically exhibits a nonkeratinized epithelial proliferation exhibiting prominent spongiosis and leukocytic exocytosis

with persistence of ectatic vascular channels, aggregates of inflammatory cells and intervening areas of fibrosis.

Differential Diagnosis

For presentations on the gingiva or alveolar ridge, the clinical differential diagnosis for PG will include other reactive gingival epulides, such as peripheral giant cell granuloma, peripheral ossifying fibroma and inflammatory fibrous hyperplasia (fibroma). Malignant processes, such as metastatic disease, sarcoma and lymphoma, may enter the clinical differential, particularly when lesions arise from an extraction socket, exhibit rapid enlargement and/or attain significant size. Biopsy and histopathologic diagnosis of suspected PG lesions is required. Brierley et al. provide a detailed review of gingival lesions [18].

Localized Juvenile Spongiotic Gingival Hyperplasia

Localized juvenile spongiotic gingival hyperplasia (LJSGH) is a unique gingival alteration that was initially described in 2007 as *juvenile spongiotic gingivitis* [19]. While the etiopathogenesis is unknown, some evidence suggests that LJSGH may result from exteriorized junctional or sulcular epithelium which is minimally keratinized and, therefore, susceptible to local irritants, such as mouth breathing or minor local trauma [19, 20]. This process does not appear to be bacterial plaque-related as conventional periodontal treatment fails to improve the problem [19, 21].

LJSGH shows a female predilection and primarily affects young patients, with up to 96% of cases diagnosed before the age of 15 [19, 21]. The *juvenile* designation, however, is not entirely appropriate, as this process has occasionally been observed in adults [19, 21].

Clinical Features

LJSGH consistently presents as an elevated, bright red gingival alteration that exhibits a papillary, granular or velvety surface architecture (Fig. 3b). It shows a strong predilection for the maxillary anterior facial attached gingiva and typically develops along the marginal gingiva. Lesions range in size between 2 and 10 mm in diameter and are generally solitary; however, multifocal gingival involvement has been reported [22, 23].

Histopathology

The histopathologic features of LJSGH include an exophytic, epithelial hyperplasia exhibiting variable papillomatosis, elongated and interconnecting rete ridges, and prominent intercellular edema with inflammatory cell exocytosis composed primarily of neutrophils [19, 21] (Fig. 3c). The epithelial proliferation is generally nonkeratinized, reminiscent of junctional epithelium of the gingival sulcus [20]. Dilation and congestion of the superficially capillary network is frequently seen within connective tissue papillae, in association with mixed inflammation.

Differential Diagnosis

The distinct clinical presentation of LJSGH significantly limits the clinical differential. Some clinicians may consider puberty gingivitis or foreign body gingivitis, although the localized presentation, exophytic nature, and lack of response to oral hygiene measures may be more suggestive of early pyogenic granuloma or, if a prominent papillary surface architecture is observed, squamous papilloma. Histopathologic findings of LGSGH are characteristic and should exclude other clinical considerations. While overlapping features of inflamed squamous papilloma may be observed, papillomas generally exhibit variable parakeratosis.

Denture Stomatitis

Denture stomatitis (DS) is an inflammatory condition limited to denture-bearing mucosa underlying a removable prosthesis. This is a common pathosis affecting up to 70% of denture wearers, particularly their palatal and maxillary alveolar mucosal surfaces, that clinically presents as smooth, atrophic mucosa exhibiting variable erythema and petechial hemorrhage [24]. The zone of erythema may be localized or diffuse with a well-delineated border following the contour of the denture base (Fig. 4a). The etiology of DS is poorly understood and likely multifactorial, with increased risk associated with suboptimal denture fit, poor denture hygiene, colonization by *C. albicans*, nocturnal denture wear and smoking [24, 25]. While DS is often categorized as a form of *erythematous candidiasis*, this association is controversial. Some authorities view DS as a mucosal inflammatory reaction to bacterial and fungal microorganisms colonizing the denture base as opposed to a true host tissue infection [25–27]. Increased suspicion for candidal infection may arise in clinical settings suggestive of *chronic multifocal candidiasis*. Such patients may exhibit, in addition to palatal erythema, redness and cracking at the oral commissures, termed *angular cheilitis*, as well as well-delineated erythema with atrophy of filiform papillae at the midline of the posterior dorsal tongue, termed *central papillary atrophy* or *median rhomboid glossitis*. Detailed discussion of oral candidiasis is provided by Hellstein [28].

A reactive tissue overgrowth, *inflammatory papillary hyperplasia (IPH)*, may also develop on palatal denture-bearing mucosa in association with chronic denture irritation. Provided the overlapping risk factors and clinical setting, some investigators classify this process within the spectrum of denture stomatitis [29, 30]. The asymptomatic erythematous to pink palatal alterations associated with IPH, however, typically exhibit an exophytic, cobblestone-like surface architecture (Fig. 4b). This process may rarely be observed on palatal mucosa of dentate patients (non-denture wearers), particularly in the clinical setting of a high palatal vault and mouth-breathing habit [31, 32]. IPH is often diagnosed on clinical features, however histopathologic assessment shows epithelial hyperplasia with bulbous, papillary surface projections in association with chronically inflamed, well-vascularized, edematous to densely collagenous fibrous connective tissue cores.

Immune-Mediated Diseases

Benign Migratory Glossitis (Geographic Tongue; Erythema Migrans)

Benign migratory glossitis (BMG) is a chronic, inflammatory condition of the tongue estimated to occur in 1.0–2.5% of the population across a broad age range, but most commonly affecting children and young adults [33, 34]. While the etiopathogenesis is poorly understood, BMG is believed to be an immunologically-mediated process and frequently occurs in conjunction with fissured tongue [34]. Possible association with psoriasis of the skin has long been debated, most recently fueled by identification of a common genetic marker, the human leukocyte antigen (HLA) HLA-Cw6; however, the existence of disease-related oral lesions of psoriasis remains controversial [35–37].

Clinical Features

BMG most frequently presents as multiple, well-demarcated zones of erythema and atrophy of the filiform papillae of the anterior two-thirds of the dorsal and lateral surfaces of the tongue. These zones are at least partially surrounded by thin, circinate or serpentine yellowish-white borders (Fig. 5a). The size and shape of lesions tend to morph or "migrate" over days or weeks, hence the designation of *wandering rash of the tongue or benign migratory glossitis*. The atrophic or depapillated areas of the tongue have also been described as reminiscent of continents on a globe, leading to the popular term *geographic tongue*. Characteristic lesions occasionally

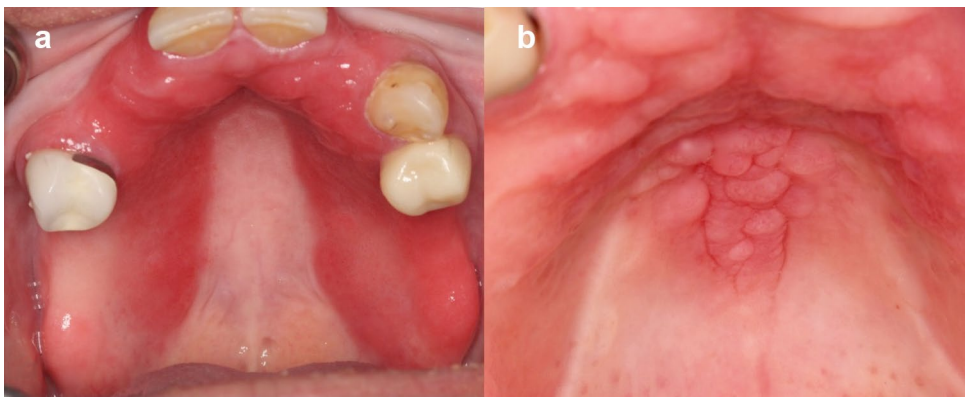

Fig. 4 **a** Diffuse erythema of alveolar and palatal mucosa that follows contour of denture base consistent with *denture stomatitis* (Courtesy of Dr. Vimi Mutalik). **b** Erythematous, cobblestone surface of *inflammatory papillary hyperplasia* involving the anterior hard palate associated with an ill-fitting removable prosthesis

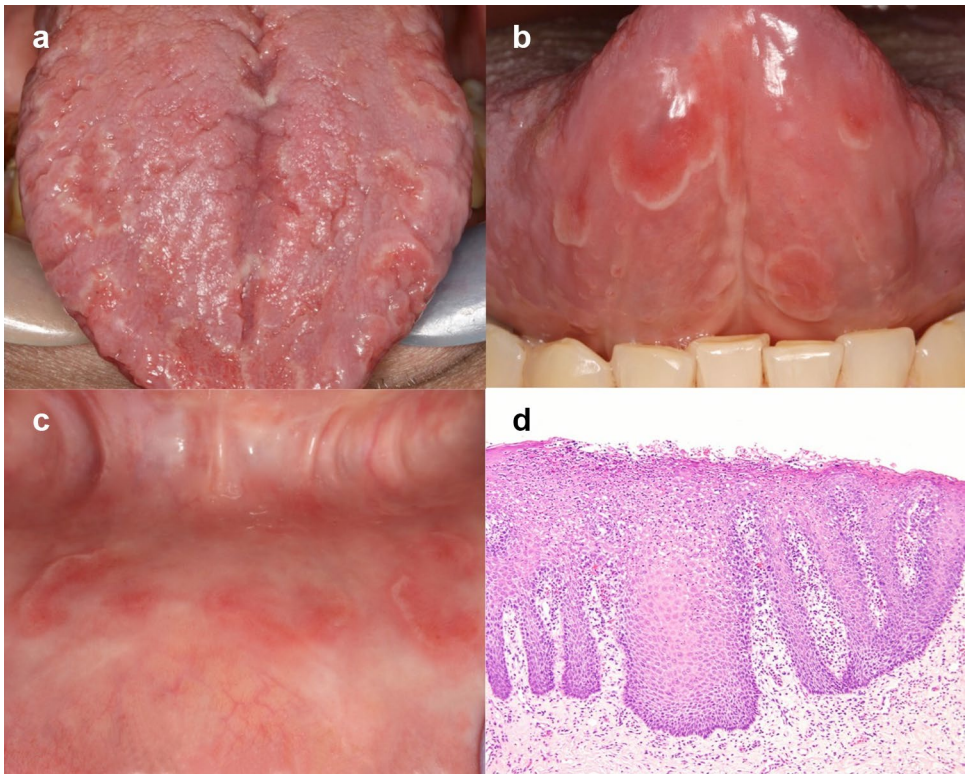

Fig. 5 **a** *Benign migratory glossitis (BMG)* of the dorsal tongue presenting as multiple zones of erythema and atrophy encircled by thin yellowish borders. **b** BMG involving the ventral tongue. **c** *Ectopic geographic tongue* exhibiting characteristic yellowish circinate borders partially surrounding erythema. **d** The classic histopathologic features of BMG include psoriasiform mucositis with prominent neutrophilic microabscess formation

involve the ventral tongue (Fig. 5b). Less commonly, lesions may develop at extraglossal sites, such as buccal mucosa, labial mucosa, soft palate and floor of mouth, where they have been termed *ectopic geographic tongue* or *erythema migrans* (Fig. 5c). Most cases of BMG are asymptomatic and identified on routine head and neck examination, however mild tenderness may be reported and prompt patients to seek medical evaluation.

Histopathology

BMG is often diagnosed on clinical examination alone; however, incisional biopsy may be performed in some cases. Characteristic histopathologic features include parakeratosis, variable spongiosis with elongation of epithelial rete ridges and atrophy of suprapapillary plates (Fig. 5d). Collections of neutrophils (*Munro microabscesses*) are frequently noted within the parakeratin with occasional involvement of the superficial stratum spinosum [37]. These microabscesses are most apparent at the periphery of lesions and correspond clinically to the observed yellowish-white circinate borders. In samples obtained from the dorsal tongue, atrophy or absence of the normal papillary architecture is characteristic. The lamina propria typically supports a mild influx of lymphocytes and neutrophils. These histopathologic features are reminiscent of psoriasis, and thus referred to as *psoriasiform mucositis*.

Differential Diagnosis

From a clinical perspective, the yellowish-white borders that surround zones of erythema should prevent confusion with entities such as erythroplakia, atrophic glossitis of anemia, or erythematous candidiasis. However, prominence of the yellowish borders is variable and may only partially (or focally) encircle the erythema. Thus, careful clinical inspection may be necessary. Additional distinguishing features of

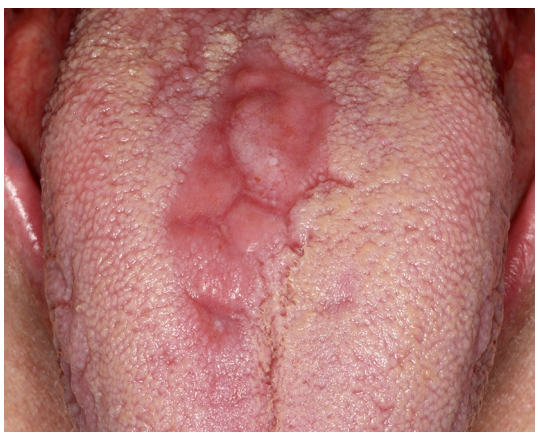

Fig. 6 Well-defined erythema and atrophy of the posterior dorsal tongue consistent with *central papillary atrophy (Erythematous candidiasis)*; note absence of the yellowish border seen in benign migratory glossitis

erythematous candidiasis include location centered at the midline of the posterior dorsal tongue (termed *central papillary atrophy* or *median rhomboid glossitis*) and absence of migratory pattern (Fig. 6).

The histopathologic finding of superficial microabscess formation may suggest the possibility of candidiasis. Candidal organisms are rarely superimposed on BMG, thus the identification of candidal hyphae by Periodic acid-Schiff (PAS) or Gomori-methenamine silver (GMS) staining would most likely correlate with erythematous candidiasis. With appropriate antifungal treatment, the zones of erythema and atrophy would be expected to resolve.

Desquamative Gingivitis

Desquamative gingivitis (DG) is a clinical term used to describe gingival erythema resulting from peeling or desquamation of the epithelial surface. It is generally limited to the attached gingiva and can present in a localized or generalized distribution (Fig. 7). DG is not specific for any one condition; this clinical presentation can be seen with a number of vesiculobullous (vesiculoerosive) disease processes, such as erosive lichen planus, lichenoid reactions (lichenoid drug reaction, foreign body gingivitis or contact stomatitis), mucous membrane pemphigoid and pemphigus vulgaris. Less likely considerations could include chronic ulcerative stomatitis, systemic lupus erythematosus, linear IgA disease, epidermolysis bullosa acquisita and paraneoplastic pemphigus [38, 39]. Definitive diagnosis rests on incisional biopsy with a tissue portion submitted in 10% neutral-buffered formalin for standard light microscopic examination and a portion submitted in Michel's solution for direct immunofluorescent studies. Fitzpatrick et al. review oral manifestations of select vesiculobullous diseases [40].

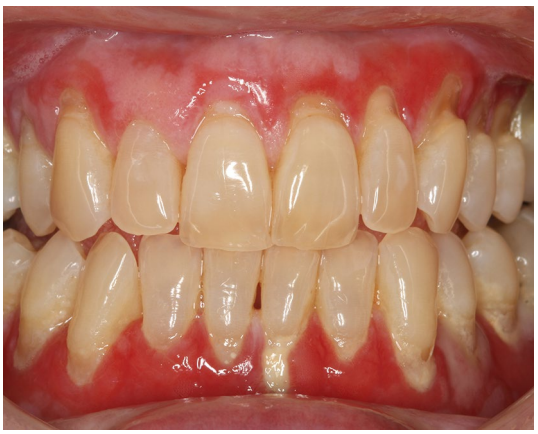

Fig. 7 *Desquamative gingivitis* presenting as patchy erythema and erosions diffusely involving the maxillary and mandibular facial attached gingiva

Orofacial Granulomatosis

Orofacial granulomatosis (OFG) is a term used to describe a variety of clinical presentations resulting from granulomatous inflammation of the oral and perioral soft tissues. Medical evaluation to rule out known causes of granulomatous inflammation, such as Crohn disease, sarcoidosis, chronic granulomatous disease, and mycobacterial or deep fungal infection, should precede the designation of OFG.

While the precise etiopathogenesis remains unknown, OFG is speculated to be an abnormal immune reaction to various inciting agents, including a variety of foods and food additives (such as cinnamon and benzoate compounds), dental restorative materials and microbial infections [41–43]. Given the uncommon nature of this process, reliable epidemiologic data is lacking; however, it seems to occur across a broad age range, most often arising in young adults [41, 43].

Clinical Features

The clinical presentation of OFG is highly variable. Non-tender, persistent lip swelling, termed *cheilitis granulomatosa (of Miescher)*, is the most frequent clinical finding and may be accompanied by vertical lip fissuring, exfoliation, and angular cheilitis. Intraorally, however, erythematous oral mucosal alterations predominate. The labial mucosa may develop a granular pink to reddish appearance, with formation of translucent mucosal "blebs" corresponding to ectatic superficial lymphovascular channels. Generalized erythema and swelling of the buccal mucosa may impart a "cobblestone" architecture, which may be seen in association with gingivitis, granular gingival overgrowth, and chronic oral ulceration with linear hyperplastic tissue folds of the mucobuccal sulcus (Fig. 8a).

Histopathology

Histopathologic features of OFG include edema of the superficial connective tissue with dilation of lymphatic channels, perivascular lymphocytic infiltration and variable noncaseating granulomatous inflammation. Granulomas are often sparse and poorly formed, consisting of vague collections of lymphocytes and epithelioid histiocytes with or without associated multinucleated giant cells. As a result, their absence may simply represent sampling error and does not preclude a diagnosis of OFG [43]. When granuloma formation is identified, special stains to exclude microorganisms should be performed. Polarized light microscopy and careful inspection for foreign material may also be indicated to rule out a foreign body reaction.

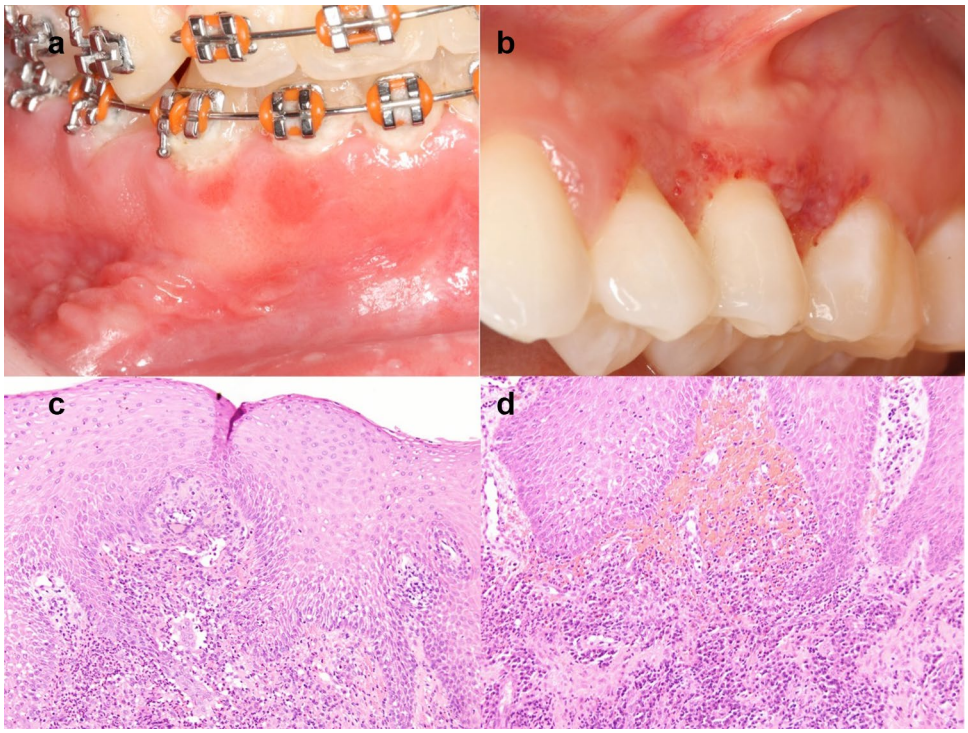

Fig. 8 **a** Granular gingival erythema and linear tissue folds of the buccal sulcus diagnosed as *orofacial granulomatosis* on biopsy. **b** Papillary gingival hyperplasia with petechial hemorrhage consistent with early "*strawberry gingivitis*", suggestive of *granulomatosis with polyangiitis (Wegener granulomatosis)*. **c** Gingival biopsy from lesion depicted in **b** shows epithelial hyperplasia and dense inflammation with microabscess formation and occasional giant cells. **d** In other areas, the inflammatory infiltrate supports lymphocytes, plasma cells and scattered eosinophils in association with prominent hemorrhage

Differential Diagnosis

OFG is often a diagnosis of exclusion, as similar clinical features and histopathologic evidence of granulomatous inflammation can be seen with a number of local and systemic conditions. Patient work-up can include detailed medical history, serologic studies, radiologic imaging, and/or endoscopic investigation to rule out Crohn disease, sarcoidosis, chronic granulomatous disease, mycobacterial or deep fungal infection. If systemic granulomatous disease is identified, orofacial lesions would presumably be associated with that process. Even when the initial assessment is negative, however, it has been estimated that approximately 20% of OFG patients will subsequently develop manifestations of systemic granulomatous disease, and several investigators have reported that childhood onset of OFG carries significant risk for future development of Crohn disease [44, 45].

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

Granulomatosis with polyangiitis (GPA), formerly known as *Wegener granulomatosis*, is an uncommon systemic vasculitis that is highly associated with anti-neutrophil cytoplasmic antibodies (ANCA). While the precise etiopathogenesis is unknown, this process seems to represent an abnormal immune reaction to environmental or infectious agents in genetically predisposed individuals. Mean age at diagnosis is between 45 and 60 years in a primarily Caucasian population [46].

This process is classically associated with a triad of (1) necrotizing granulomatous inflammation of the upper and lower respiratory tract, (2) glomerulonephritis and (3) systemic small vessel vasculitis. Almost any organ system can be involved and reported prevalence of oral lesions varies widely, affecting between 10–62% of patients [47]. Oral lesions may represent the initial sign of disease and can persist as a localized or limited form of GPA for long periods of time prior to multi-organ involvement. The diagnosis of GPA can be challenging and recognition of its unique oral mucosal alterations may be pivotal for timely diagnosis. In the absence of appropriate medical management, significant morbidity and mortality may be seen [48].

Clinical Features

The most characteristic oral manifestation of GPA is a hyperplastic gingivitis termed "*strawberry gingivitis*", which can be an early and pathognomonic finding [47, 49]. Affected gingiva is enlarged and friable with numerous short projections exhibiting red to purple petechial hemorrhage, resulting in an appearance reminiscent of the surface of a strawberry (Fig. 8b). These alterations generally originate at the interdental papillae with gradual lateral progression to diffusely involve the entire attached gingiva. Additional oral manifestations of GPA may include persistent oral

ulceration, destruction of bone, tooth mobility and oral-antral fistulae [47].

Histopathology

The characteristic leukocytoclastic vasculitis and necrotizing granulomatous inflammation seen in lung biopsies of GPA are rarely observed in oral specimens due to the paucity of large vessels in most oral mucosal biopsies. In contrast, the histopathologic features of oral lesions may include vague collections of histiocytes together with lymphocytes, neutrophils, eosinophils, and multinucleated giant cells[47]. Samples obtained from areas of strawberry gingivitis will typically demonstrate pseudoepitheliomatous hyperplasia with extensive subepithelial hemorrhage, intense mixed inflammation and microabscess formation (Fig. 8c, d).

Differential Diagnosis

Characteristic histopathologic findings, in conjunction with a classic clinical presentation of strawberry gingivitis, are highly suggestive of GPA. However, the clinical presentation of early or localized cases may not be considered pathognomonic and the differential could include conditions such as reactive gingival hyperplasia, granulomatous disease, foreign body reaction, specific infection, benign or malignant vascular proliferation, lymphoproliferative disease and papillary squamous cell carcinoma. A combination of clinical and histopathologic features, often in conjunction with laboratory finding of cytoplasmic-staining ANCA (PR3-ANCA), are employed to establish a diagnosis of GPA [48].

Hematologic Disorders

Megaloblastic Anemia

Megaloblastic anemia (MA) generally occurs in older adults and can result from any condition that interferes with nucleic acid synthesis. Vitamin B12 deficiency is the most common basis for MA and may arise in the clinical setting of insufficient dietary intake or malabsorption, often associated with autoimmune destruction of intrinsic factor (pernicious anemia) or gastric bypass surgery [50]. Clinical symptoms of MA, including fatigue, headache and dyspnea, are often insidious and oral mucosal alterations may represent the first sign of disease [51].

Clinical Features

Oral manifestations of MA include patchy areas of diffuse mucosal erythema and atrophy involving any oral mucosal surface, which may be accompanied by hyperesthesia or a burning sensation [51, 52]. Involvement of the dorsal tongue typically exhibits patchy erythema with atrophy of the filiform papillae.

Histopathology

Histopathologic evaluation of oral mucosal erythema associated with MA shows mild chronic mucositis with marked epithelial atrophy and abbreviated or absent rete ridges. Keratinocytes may exhibit increased nuclear-to-cytoplasmic ratio, however the nuclei are generally pale staining with clumped peripheral chromatin [51, 52]. The observed cytologic atypia may erroneously suggest the possibility of early preneoplastic change.

Differential Diagnosis

The clinical diagnosis of MA is often challenging due to non-specific clinical and histopathologic features. The differential for multifocal, diffuse oral erythema and atrophy could include erythematous candidiasis, immune-mediated processes such as contact mucositis or physical irritation. It is important for clinicians to consider the possibility of MA when nonspecific chronic mucositis, epithelial atrophy and/or epithelial atypia are histopathologically observed in an appropriate clinical setting. Once suspected, serologic studies are warranted to confirm the diagnosis of MA.

Lymphoproliferative Disease

Lymphoproliferative processes that affect the oral mucosa are diverse. The clinicopathologic spectrum includes reactive lymphoid hyperplasia, histiocytic disorders such as Langerhans cell histiocytosis, plasma cell dyscrasias such as plasmacytoma and multiple myeloma, and various forms of leukemia and extranodal lymphoma. Though not frequently encountered, lymphoid malignancies represent the third most common oral malignancy following squamous cell carcinoma and malignant salivary gland tumors [53].

Detailed discussion of lymphoproliferative disorders is beyond the scope of this manuscript; however, this category of disease should not be overlooked in the differential diagnosis of exophytic, erythematous to purplish lesions, particular those presenting as gingival or palatal swellings (Fig. 9a) or diffuse hemorrhagic gingival enlargement [54, 55].

Epithelial Neoplasia

Oral squamous cell carcinoma (OSCC) is the most common malignancy affecting the oral cavity, with an estimated 33,950 new cases diagnosed in the United States in 2018,

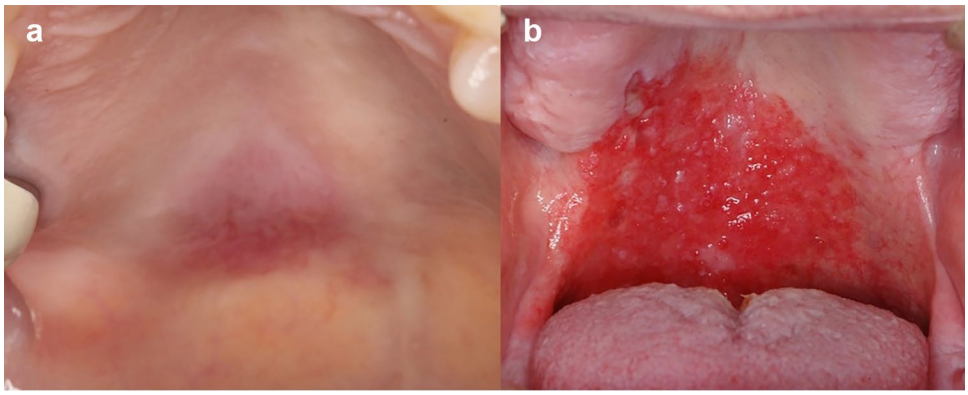

Fig. 9 **a** *Non-hodgkin lymphoma* presenting as an erythematous palatal swelling in a 73-year-old male (Courtesy of Dr. Christine Harrington). **b** *Erythroplakia* presenting as a well-defined red patch diffusely involving the soft palate and diagnosed as squamous cell carcinoma on biopsy (Courtesy of Dr. Phillip Cary)

resulting in 6800 deaths [56]. Risk factors include male gender, increasing age, smoking, excessive alcohol use, immunosuppression and poor diet. Human papillomavirus (HPV) infection is a well-recognized risk factor for oropharyngeal cancer; however, this infection appears to have minimal role in the development of OSCC, with less than 5% of oral mucosal cases being HPV-related [57, 58].

OSCC generally arises from surface precursor lesions called *potentially malignant disorders (PMDs)*, which harbor increased risk for malignant transformation. While the majority of oral PMDs present as *leukoplakia* (well-defined white plaques or patches), some lesions may have an erythematous presentation, termed *erythroplakia* (well-defined red plaques or patches) (Fig. 9b) or *erythroleukoplakia* (mixed red and white lesions). The erythematous alterations hold the greatest malignant potential; up to 90% of true erythroplakic lesions demonstrate histopathologic evidence of high-grade dysplasia or superficially invasive squamous cell carcinoma at the time of initial biopsy [59, 60]. Distinguishing clinical characteristics of erythroplakia include well-defined margins and a velvety, micropapillary or granular surface texture. Clinicians should also hold a heightened level of suspicion for lesions arising in high-risk sites, including the ventrolateral tongue, floor of mouth, retromolar area, soft palate, and anterior tonsillar pillars. These anatomic locations comprise roughly 20% of the total oral cavity surface area yet give rise to approximately 75% of OSCC [61]. In the absence of clinical features allowing for diagnosis of any other condition, histopathologic assessment is required to distinguish true erythroplakia from the vast number of conditions (such as those discussed in this manuscript) that may also present with a similar erythematous clinical appearance.

Summary

Despite vast differences in etiology and pathogenesis, many disease processes may present with erythematous or vascular-appearing alterations of the oral mucosa. Recognition of characteristic clinical features, in conjunction with thorough patient history, will allow clinicians to narrow the differential diagnosis and guide appropriate clinical decision making, including the need for tissue biopsy. Since proper management and, in some cases, patient prognosis are reliant upon a timely and accurate diagnosis, practitioners should be aware that both clinical and microscopic features may be needed to complete the diagnostic process and initiate optimal patient care.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69(3):412–22.
2. ISSVA Classification of Vascular Anomalies. ©2018 International Society for the Study of Vascular Anomalies Available at "issva.org/classification" Accessed 12 Oct 2018.
3. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: Part I. J Am Acad Dermatol. 2007;56(3):353. quiz 371–4.
4. Fowell C, Verea Linares C, Jones R, Nishikawa H, Monaghan A. Venous malformations of the head and neck: current concepts in management. Br J Oral Maxillofac Surg. 2017;55(1):3–9.
5. Love Z, Hsu DP. Low-flow vascular malformations of the head and neck: clinicopathology and image guided therapy. J Neurointerv Surg. 2012;4(6):414–25.
6. Saravana GH. Oral pyogenic granuloma: a review of 137 cases. Br J Oral Maxillofac Surg. 2009;47(4):318–9.
7. Al-Khateeb T, Ababneh K. Oral pyogenic granuloma in Jordanians: a retrospective analysis of 108 cases. J Oral Maxillofac Surg. 2003;61(11):1285–8.
8. Chi AC, Weathers DR, Folpe AL, Dunlap DT, Rasenberger K, Neville BW. Epithelioid hemangioendothelioma of the oral

cavity: report of two cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100(6):717–24.
9. Heera R, Cherian LM, Lav R, Ravikumar V. Hemangioendothelioma of palate: A case report with review of literature. J Oral Maxillofac Pathol. 2017;21(3):415–20.
10. Agaimy A, Mueller SK, Harrer T, Bauer S, Thompson LDR. Head and neck kaposi sarcoma: clinicopathological analysis of 11 cases. Head Neck Pathol. 2018;5:1–6
11. Fanburg-Smith JC, Furlong MA, Childers EL. Oral and salivary gland angiosarcoma: a clinicopathologic study of 29 cases. Mod Pathol. 2003;16(3):263–71.
12. Nagata M, Yoshitake Y, Nakayama H, Yoshida R, Kawahara K, Nakagawa Y, et al. Angiosarcoma of the oral cavity: a clinicopathological study and a review of the literature. Int J Oral Maxillofac Surg. 2014;43(8):917–23.
13. Ordonez NG. Immunohistochemical endothelial markers: a review. Adv Anat Pathol. 2012;19(5):281–95.
14. Lazos JP, Piemonte ED, Panico RL. Oral varix: a review. Gerodontology. 2015;32(2):82–9.
15. Epivatianos A, Antoniades D, Zaraboukas T, Zairi E, Poulopoulos A, Kiziridou A, et al. Pyogenic granuloma of the oral cavity: comparative study of its clinicopathological and immunohistochemical features. Pathol Int. 2005;55(7):391–7.
16. Gordon-Nunez MA, de Vasconcelos Carvalho M, Benevenuto TG, Lopes MF, Silva LM, Galvao HC. Oral pyogenic granuloma: a retrospective analysis of 293 cases in a Brazilian population. J Oral Maxillofac Surg. 2010;68(9):2185–8.
17. Toida M, Hasegawa T, Watanabe F, Kato K, Makita H, Fujitsuka H, et al. Lobular capillary hemangioma of the oral mucosa: clinicopathological study of 43 cases with a special reference to immunohistochemical characterization of the vascular elements. Pathol Int. 2003;53(1):1–7.
18. Brieley DJ, Crane H, Hunter KD. Lumps and bumps of the gingiva: a pathological miscellany. Head Neck Pathol. (pending).
19. Darling MR, Daley TD, Wilson A, Wysocki GP. Juvenile spongiotic gingivitis. J Periodontol. 2007;78(7):1235–40.
20. Allon I, Lammert KM, Iwase R, Spears R, Wright JM, Naidu A. Localized juvenile spongiotic gingival hyperplasia possibly originates from the junctional gingival epithelium-an immunohistochemical study. Histopathology. 2016;68(4):549–55.
21. Chang JY, Kessler HP, Wright JM. Localized juvenile spongiotic gingival hyperplasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(3):411–8.
22. Siamantas I, Kalogirou EM, Tosios KI, Fourmousis I, Sklavounou A. Spongiotic gingival hyperplasia synchronously involving multiple sites: case report and review of the literature. Head Neck Pathol. 2018;6:1–5
23. de Freitas Silva BS, Silva Sant'Ana SS, Watanabe S, Vencio EF, Roriz VM, Yamamoto-Silva FP. Multifocal red bands of the marginal gingiva. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(1):3–7.
24. Gendreau L, Loewy ZG. Epidemiology and etiology of denture stomatitis. J Prosthodont. 2011;20(4):251–60.
25. Barbeau J, Seguin J, Goulet JP, de Koninck L, Avon SL, Lalonde B, et al. Reassessing the presence of *Candida albicans* in denture-related stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95(1):51–9.
26. Aoun G, Cassia A. Evaluation of denture-related factors predisposing to denture stomatitis in a lebanese population. Mater Sociomed. 2016;28(5):392–6.
27. Nanetti A, Stancari F, Ferri M, Mazzoni A. Relationship between Candida albicans and denture stomatitis: a clinical and microbiological study. New Microbiol. 1993;16(3):287–91.
28. Hellstein JW. Candidiasis: diagnosis and management. Head Neck Pathol. (pending).
29. Bergendal T, Isacsson G. A combined clinical, mycological and histological study of denture stomatitis. Acta Odontol Scand. 1983;41(1):33–44.
30. Gual-Vaques P, Jane-Salas E, Egido-Moreno S, Ayuso-Montero R, Mari-Roig A, Lopez-Lopez J. Inflammatory papillary hyperplasia: A systematic review. Med Oral Patol Oral Cir Bucal. 2017;22(1):e36–42.
31. Thwaites MS, Jeter TE, Ajagbe O. Inflammatory papillary hyperplasia: review of literature and case report involving a 10-year-old child. Quintessence Int. 1990;21(2):133–8.
32. Gual-Vaques P, Jane-Salas E, Mari-Roig A, Lopez-Lopez J. Inflammatory Papillary Hyperplasia in a Non-Denture-Wearing Patient: A Case History Report. Int J Prosthodont. 2017;30(1):80–2.
33. Miloglu O, Goregen M, Akgul HM, Acemoglu H. The prevalence and risk factors associated with benign migratory glossitis lesions in 7619 Turkish dental outpatients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107(2):e29-33.
34. Shulman JD, Carpenter WM. Prevalence and risk factors associated with geographic tongue among US adults. Oral Dis. 2006;12(4):381–6.
35. Yesudian PD, Chalmers RJ, Warren RB, Griffiths CE. In search of oral psoriasis. Arch Dermatol Res. 2012;304(1):1–5.
36. Fatahzadeh M, Schwartz RA. Oral psoriasis: an overlooked enigma. Dermatology. 2016;232(3):319–25.
37. Picciani BL, Domingos TA, Teixeira-Souza T, Santos Vde C, Gonzaga HF, Cardoso-Oliveira J, et al. Geographic tongue and psoriasis: clinical, histopathological, immunohistochemical and genetic correlation—a literature review. An Bras Dermatol. 2016;91(4):410–21.
38. Lo Russo L, Fierro G, Guiglia R, Compilato D, Testa NF, Lo Muzio L, et al. Epidemiology of desquamative gingivitis: evaluation of 125 patients and review of the literature. Int J Dermatol. 2009;48(10):1049–52.
39. Suresh L, Neiders ME. Definitive and differential diagnosis of desquamative gingivitis through direct immunofluorescence studies. J Periodontol. 2012;83(10):1270–8.
40. Fitzpatrick SG, Cohen D, Clark A. Ulcerated lesions of the oral mucosa: clinical and histologic review. Head Neck Pathol. (pending).
41. Al-Hamad A, Porter S, Fedele S. Orofacial granulomatosis. Dermatol Clin. 2015;33(3):433–46.
42. Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis—a 20-year review. Oral Dis. 2009;15(1):46–51.
43. Miest R, Bruce A, Rogers RS. Orofacial granulomatosis. Clin Dermatol. 2016;34(4):505–13.
44. Saalman R, Mattsson U, Jontell M. Orofacial granulomatosis in childhood—a clinical entity that may indicate Crohn's disease as well as food allergy. Acta Paediatr. 2009;98(7):1162–7.
45. Campbell H, Escudier M, Patel P, Nunes C, Elliott TR, Barnard K, et al. Distinguishing orofacial granulomatosis from crohn's disease: two separate disease entities? Inflamm Bowel Dis. 2011;17(10):2109–15.
46. Lutalo PM, D'Cruz DP. Diagnosis and classification of granulomatosis with polyangiitis (aka Wegener's granulomatosis). J Autoimmun. 2014;48–49:94–98.
47. Stewart C, Cohen D, Bhattacharyya I, Scheitler L, Riley S, Calamia K, et al. Oral manifestations of Wegener's granulomatosis: a report of three cases and a literature review. J Am Dent Assoc. 2007;138(3):338.
48. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev. 2014;13(11):1121–5.
49. Ruokonen H, Helve T, Arola J, Hietanen J, Lindqvist C, Hagstrom J. "Strawberry like" gingivitis being the first sign of Wegener's granulomatosis. Eur J Intern Med. 2009;20(6):651–3.

50. Nagao T, Hirokawa M. Diagnosis and treatment of macrocytic anemias in adults. J Gen Fam Med. 2017;18(5):200–4.
51. Drummond JF, White DK, Damm DD. Megaloblastic anemia with oral lesions: a consequence of gastric bypass surgery. Oral Surg Oral Med Oral Pathol. 1985;59(2):149–53.
52. Greenberg MS. Clinical and histologic changes of the oral mucosa in pernicious anemia. Oral Surg Oral Med Oral Pathol. 1981;52(1):38–42.
53. Triantafillidou K, Dimitrakopoulos J, Iordanidis F, Gkagkalis A. Extranodal non-hodgkin lymphomas of the oral cavity and maxillofacial region: a clinical study of 58 cases and review of the literature. J Oral Maxillofac Surg. 2012;70(12):2776–85.
54. Epstein JB, Epstein JD, Le ND, Gorsky M. Characteristics of oral and paraoral malignant lymphoma: a population-based review of 361 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92(5):519–25.
55. Chowdhri K, Tandon S, Lamba AK, Faraz F. Leukemic gingival enlargement: A case report and review of literature. J Oral Maxillofac Pathol. 2018;22(Suppl 1):77–81.
56. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2018;68(1):7–30.
57. Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, Kreinbrink P, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol. 2013;49(1):1–8.
58. Poling JS, Ma XJ, Bui S, Luo Y, Li R, Koch WM, et al. Human papillomavirus (HPV) status of non-tobacco related squamous cell carcinomas of the lateral tongue. Oral Oncol. 2014;50(4):306–10.
59. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. Cancer. 1975;36(3):1021–8.
60. Reichart PA, Philipsen HP. Oral erythroplakia—a review. Oral Oncol. 2005;41(6):551–61.
61. Moore C, Catlin D. Anatomic origins and locations of oral cancer. Am J Surg. 1967;114(4):510–3.