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

Ulcerated Lesions of the Oral Mucosa: Clinical and Histologic Review

Sarah G. Fitzpatrick[1] · Donald M. Cohen[1] · Ashley N. Clark[2]

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Abstract
Ulcerated lesions of the oral cavity have many underlying etiologic factors, most commonly infection, immune related, traumatic, or neoplastic. A detailed patient history is critical in assessing ulcerative oral lesions and should include a complete medical and medication history; whether an inciting or triggering trauma, condition, or medication can be identified; the length of time the lesion has been present; the frequency of episodes in recurrent cases; the presence or absence of pain; and the growth of the lesion over time. For multiple or recurrent lesions the presence or history of ulcers on the skin, genital areas, or eyes should be evaluated along with any accompanying systemic symptoms such as fever, arthritis, or other signs of underlying systemic disease. Biopsy may be indicated in many ulcerative lesions of the oral cavity although some are more suitable for clinical diagnosis. Neoplastic ulcerated lesions are notorious in the oral cavity for their ability to mimic benign ulcerative lesions, highlighting the essential nature of biopsy to establish a diagnosis in cases that are not clinically identifiable or do not respond as expected to treatment. Adjunctive tests may be required for final diagnosis of some ulcerated lesions especially autoimmune lesions. Laboratory tests or evaluation to rule out systemic disease may be also required for recurrent or severe ulcerations especially when accompanied by other symptoms. This discussion will describe the clinical and histopathologic characteristics of a variety of ulcerated lesions found in the oral cavity.

Keywords Oral ulcer · Herpetic gingivostomatitis · Aphthous stomatitis · Oral erythema multiforme · Oral medication related ulcer · Oral lichen planus · Oral vesiculobullous lesions · Traumatic oral ulcer · Oral squamous cell carcinoma · Oral lymphoma

Introduction

Ulceration is a commonly presenting sign of a wide spectrum of diseases of the oral cavity involving many etiologic factors. These lesions may pose a unique diagnostic challenge for clinicians due to overlap of clinical and histologic features between different types of ulcerated lesions. Most ulcerative lesions of the oral mucosa fall into one of four categories: infection, immune related, traumatic, or neoplastic.

✉ Sarah G. Fitzpatrick
sfitzpatrick@dental.ufl.edu

[1] Department of Oral and Maxillofacial Diagnostic Sciences, University of Florida College of Dentistry, Gainesville, FL, USA

[2] Department of Diagnostic and Biomedical Sciences, University of Texas at Houston Health Science Center School of Dentistry, Houston, TX, USA

Ulcerations of Infective Etiology

Oral ulcerations resulting from infections may present diagnostic difficulties due to a wide potential range of non-specific symptoms and a lack of familiarity amongst health care providers with the symptoms and presentations of these less common diseases.

Bacterial: Syphilis and Tuberculosis

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*; it can occur congenitally or as primary, secondary or tertiary disease (Fig. 1). Concerning syphilis the lesion of relevance to this manuscript is the chancre, a highly infectious, non-specific ulceration which occurs in primary syphilis. In the oral cavity, the chancre typically presents as a deep, solitary ulceration which can be painful. The most common location is the lips, and the tongue, palate, or tonsillar region are less common sites of involvement. The patient may demonstrate associated cervical

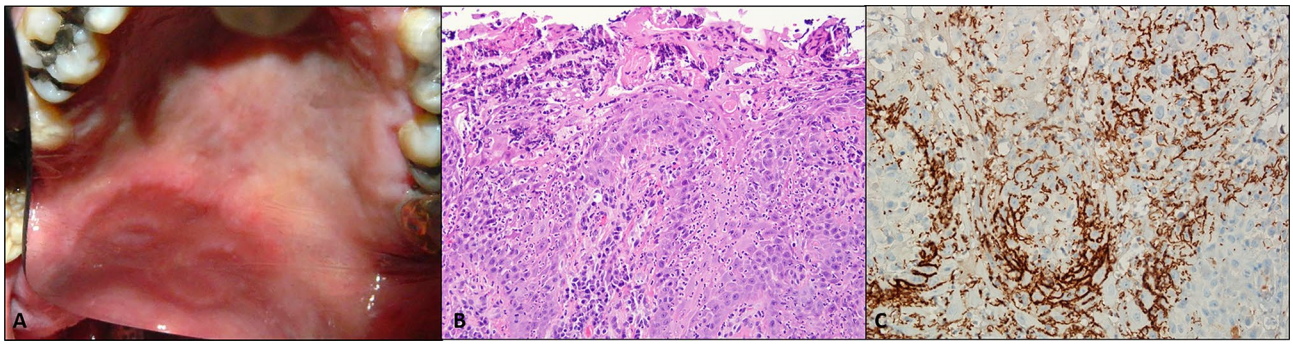

Fig. 1 Bacterial ulceration. **a** Syphilitic ulceration of the soft palate. **b** Hematoxylin and eosin (H&E) medium power magnification demonstrating ulceration with perivascular and diffuse inflammation consisting of plasma cells and neutrophils. **c** *Treponema pallidum* immunohistochemical staining exhibiting abundant organisms (high power). Clinical and histologic photos courtesy of Dr. Brenda Nelson

lymphadenopathy. Oral chancres typically involute in 3–8 weeks [1, 2]. Diagnosis can be challenging. Specific tests for IgM or IgG antibodies to *T. pallidum* should be administered if primary syphilis is suspected. Histopathology is nonspecific and special stains such as Warthin-Starry may not be positive [1]. Preferred treatment for syphilis of all stages is parenterally-delivered penicillin G, and most patients require only a single dose [3].

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and affects over 9000 Americans each year [4]. Up to 1.5% of these patients present with oral lesions and the most common are ulcerations. If ulceration occurs in primary TB, the lesion is non-painful and the patient may present with an accompanying lymphadenopathy. This presentation is most commonly found in children. If occurring in secondary TB, ulcerations are painful with variable lymphadenopathy and are seen more commonly in adults. TB ulcerations are usually solitary; however, multiple lesions have been reported. The irregular ulcers may be superficial or deep and can be surfaced by necrotic tissue centrally. The ulcers slowly increase in size and do not self-resolve [5]. Diagnosis of tuberculosis is made via various laboratory tests, including cultures, microscopic examination, and molecular testing. Treatment consists of a combination of the anti-microbial drugs rifampin, isoniazid, pyrazinamide, and ethambutol [6].

Viral: Human Herpesvirus: Herpes Simplex Virus, Varicella Zoster Virus, and Cytomegalovirus

Human simplex virus type 1 (HSV-1) and type 2 (HSV-2) belong to the family of human herpesvirus. Both viruses produce similar ulcerations, though HSV-1 occurs in the oral mucosa more frequently [7]. Though the primary infection is typically asymptomatic, patients who experience acute herpetic gingivostomatitis can develop oral ulcerations on the palate, gingiva, buccal mucosa, labial mucosa, and tongue. The ulcerations start as small vesicles which rupture and coalesce (Fig. 2) [7–9]. Symptoms of primary HSV infection may overlap with other acute oral ulcerative conditions primarily seen in childhood such as hand foot and mouth

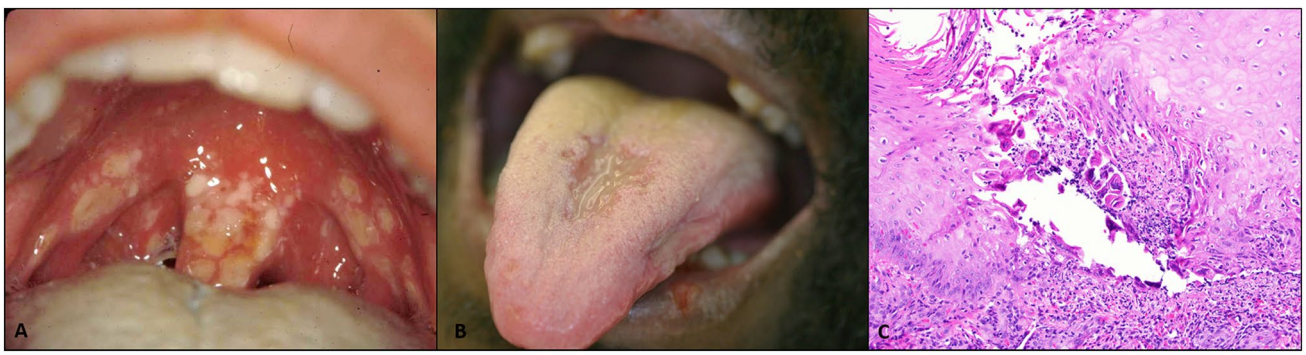

Fig. 2 Viral ulceration. **a** Primary hepetic infection involving the soft palate and oropharynx in a young adult (photo courtesy Dr. Donald Cohen). **b** Multiple coalescing ulcerations of the tongue and lips of secondary HSV related ulceration in an HIV positive patient (photo courtesy University of Florida Oral Pathology Biopsy Service Archives). **c** HSV related epithelial changes with prominent Tzanck cell formation (H&E medium power magnification)

disease or herpangina. Recurrent infection is experienced by 40% of patients and typically presents as herpes labialis on the vermilion border. Intraoral recurrences in healthy individuals consist of ulcerations limited to the attached gingiva and hard palate. These typically begin as multiple, small, painless ulcerations which may coalesce and heal within 10 days. In immunocompromised patients, recurrences may occur on non-keratinized mucosa [7, 10–12]. Diagnosis of HSV-1 is typically made clinically. Primary infection can be treated with acyclovir rinses, while recurrences are treated with over-the-counter topical 10% n-docosanol cream or systemic acyclovir, valacyclovir, or famciclovir [13–16].

Primary infection of varicella-zoster virus (VZV) results in varicella (chickenpox); recurrences occur in the form of herpes zoster (shingles) [17]. Though varicella classically affects the skin, oral ulcerations may also occur in severe disease. They manifest as small vesicles which rapidly rupture to form shallow ulcerations. They are most commonly found on the lips, buccal mucosa, and palate [18, 19]. Zoster occurs in older or immunosuppressed patients. A prodromal stage of pain usually precedes the visible lesions of the acute phase by a few days. Oral manifestations of the acute phase start as vesicles overlying erythematous macules which ulcerate and crust over a 10-day period. These lesions are unilateral in distribution and affect both keratinized and non-keratinized mucosa. Postherpetic neuralgia may follow leading to immense pain which may last a year or longer [20–23]. Diagnosis of VZV is usually made clinically. Palliative treatments are appropriate for varicella, while systemic antiviral therapy if given within 48 h is beneficial in patients with zoster [24–26].

Cytomegalovirus (CMV) is another member of the human herpesvirus family that uncommonly presents with oral ulcerations. These non-specific ulcerations occur in immunosuppressed patients, and most commonly affect the tongue, floor of mouth, and hard or soft palate [27, 28]. Histopathologic analysis of CMV-induced ulcerations can show enlarged endothelial cells or salivary duct epithelium. Grocott–Gomori methenamine silver (GMS) stain or periodic acid-Schiff (PAS) stain will highlight intranuclear inclusions. Prominent nucleoli are also present within the affected cells [29]. Ganciclovir has historically been used for treatment in immunocompromised patients [30].

Fungal: Deep Fungal Infections

Various fungal infections can cause oral ulcerations including *Aspergillus fumigatus* or *Aspergillus flavus* (aspergillosis), *Blastomyces dermatidis* (blastomycosis), *Histoplasma capsulatum* (histoplasmosis), *Cryptococcus neoformans* (cryptococcosis), *Coccidioides immitis* (coccidioidomycosis), and *Paracoccidiodes brasiliensis* (paracoccidiomycosis). Nearly all these infections occur in disseminated forms in immunocompromised individuals [31–36]. Ulcerations of aspergillosis appear as black or yellow necrotic lesions which most commonly affect the tongue or palate [31, 32]. Blastomycosis may present with oral ulcerations which mimic squamous cell carcinoma. These lesions are erythematous, irregular, have rolled borders, and may present anywhere in the oral cavity [33, 34]. Ulcerations seen in histoplasmosis are indurated with rolled borders and tend occur on the tongue, gingiva, or palate (Fig. 3) [31, 35]. Ulcerations occurring in cryptococcosis involve the palate, gingiva, or tonsillar pillars [31]. Though rare, coccidioidomycosis may present as an oral ulceration [36]. Finally, the mucocutaneous form of paracoccidiomycosis may begin as small vesicles which ulcerate and progress; they develop rolled borders and become painful over time [31]. Biopsy of the ulcerations with appropriate special stains lead to the proper diagnosis; intravenous amphotericin B is most commonly used for disseminated disease [31, 37, 38].

Ulcerations of Immune Related Etiology

Most immune mediated ulcerative diseases characteristically relapse, persist and frequently recur. Of particular importance is the identification of any possible triggering medications or concurrent symptoms that may indicate systematic disease.

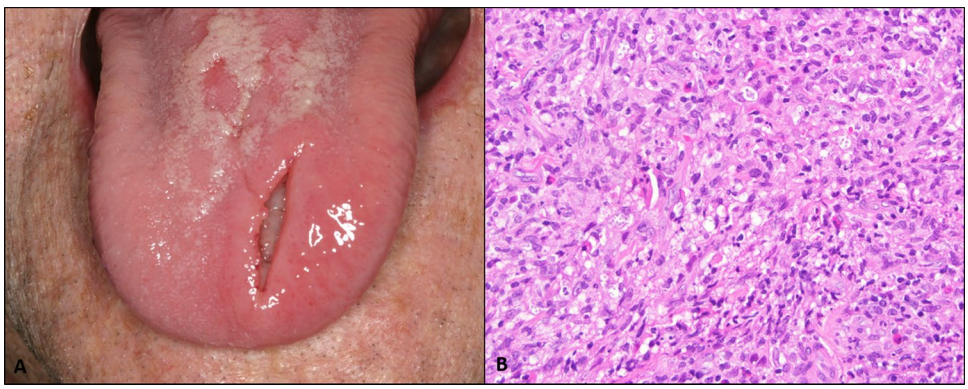

Fig. 3 Fungal ulceration. **a** Deep ulceration of the tongue secondary to histoplasmosis infection (photo courtesy Dr. Indraneel Bhattacharyya). **b** Fungal organisms consistent with histoplasmosis within inflamed tissue with numerous macrophages (H&E high power magnification)

Recurrent Aphthous Stomatitis and Associated Conditions

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal lesions in younger patients. The etiology is unknown and often multifactorial implicating underlying genetic susceptibility with possible contributing factors including viral or bacterial microbial agents, topical agents, foods, medications, hormones, stress, nutritional deficiencies, and systemic disease [39]. RAS occurs in three forms (minor, major, and herpetiform) which vary by number of lesions, duration and frequency of lesion recurrence, location involved, and severity. Complex RAS presents with frequent or constant oral lesions and possible genital lesions in the absence of systemic disease [39]. The individual ulcerations in all forms are painful and show a central yellow necrotic area surrounded by a distinctive red halo (Fig. 4a).

Patients with RAS should be evaluated for possible association with foods, topical agents or medications, nutritional deficiencies, and underlying systemic diseases. The toothpaste additive sodium lauryl sulfate is considered to be a potential RAS trigger [40]. Medications including nonsteroidal antiinflammatory drugs (NSAIDS), antibiotics, beta blockers, angiotensin-converting-enzyme inhibitors, and antianginal medications have all been implicated in causing RAS-like lesions [39]. Nutritional deficiencies in iron, B vitamins, vitamin C, or folate may be contributory [41]. Systemic immunosuppressing conditions such as HIV may cause RAS-type ulcers [42]. Inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis may have an association with RAS, and the oral lesions may present prior to the gastrointestinal symptoms, although Crohn's disease may also present with non-RAS ulceration related to chronic granulomatous inflammation [43, 44]. Celiac disease has been associated with RAS in up to half of patients [45, 46]. Children with RAS along with symmetric enamel defects should be evaluated for celiac disease [39, 45]. A history of skin, genital, or ocular ulcerative lesions with arthritis should prompt an evaluation for conditions such as Behçet's disease, MAGIC, and Reiter's syndromes [47–49]. Multiple conditions involve RAS along with recurring fever and infection including PFAPA syndrome, cyclic neutropenia, and Sweet's syndrome [50–52].

Diagnosis of RAS is generally made clinically and biopsy findings, if performed to rule out other pathology, generally show nonspecific ulceration. The first line of therapy for RAS is topical corticosteroids, though complex

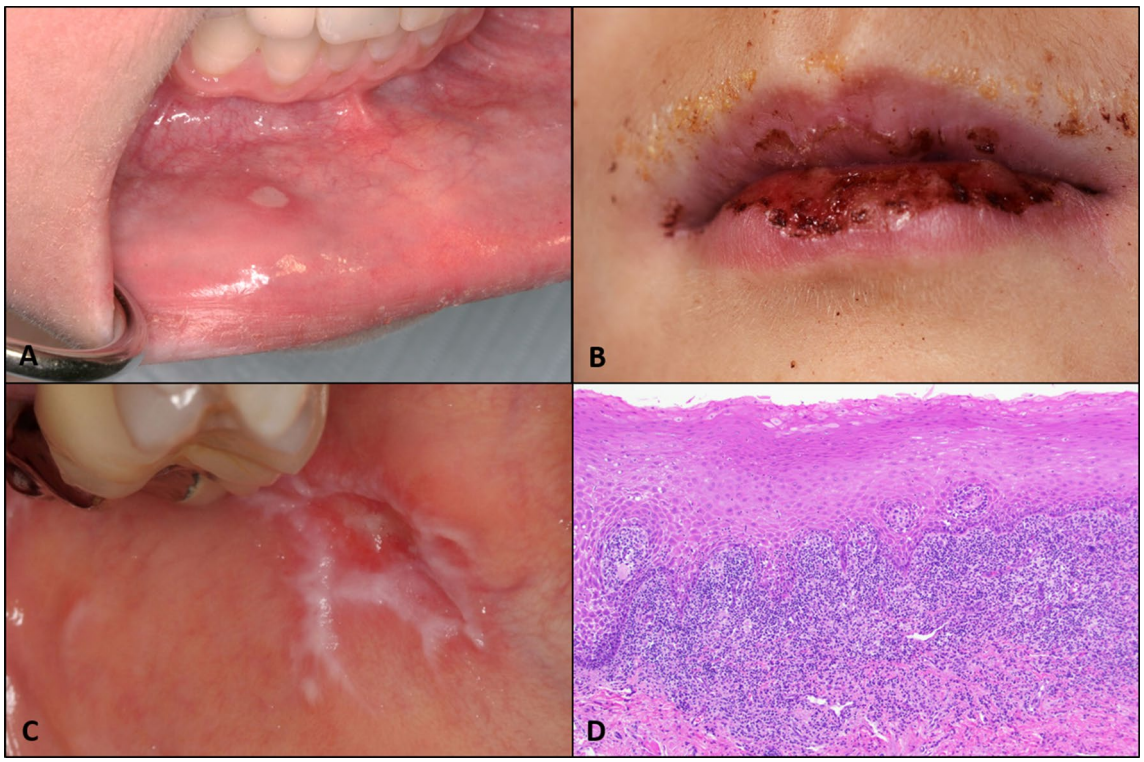

Fig. 4 Immune related ulcerations. **a** Aphthous stomatitis (photo courtesy Dr. Indraneel Bhattacharyya). **b** Erythema multiforme (photo courtesy Dr. Ashley Clark). **c** Ulcerated oral lichen planus (photo courtesy Dr. Mary Hartigan and Dr. Alan Fetner). **d** Histologic appearance of oral lichen planus demonstrating band-like lymphocytic infiltration in the superficial lamina propria and degeneration of the basal cell layer (H&E low power magnification)

or severe cases may require systemic steroids or alternate immunosuppressant medications [53].

Erythema Multiforme and Medication Related Ulcerations

Erythema multiforme (EM) is an immune mediated abnormal T-cell response with a wide range of clinical severity. EM is most commonly associated with infective agents, especially in recurrent cases [54, 55]. Herpes simplex virus (HSV) has been implicated in 61–100% of recurrent EM cases in adults and 35% in children [56, 57]. *Mycoplasma pneumoniae* and Epstein-Barr virus (EBV) have also been implicated in some cases [57]. EM in adults has been linked to medications in 10–50% of cases, particularly NSAIDS, antibiotics, antifungals, and antivirals [56]. Other possible etiologic factors include malignancy, radiation, immunization, foods and hormones [56]. EM is predominantly seen in a young to middle aged population, and there is often a male predominance particularly in children [56, 57]. Patients may have self limiting or recurrent episodes of skin and/or oral lesions, and ocular and genital lesions may also occur [57]. Oral involvement is symptomatic and often shows a characteristic crusting ulceration of the lips and ulcerations often involving buccal mucosa or other mucosal surfaces (Fig. 4b) [56, 57].

Biopsy results are generally nonspecific and may show ulceration, edema, acanthosis and subepithelial separation with perivascular inflammation. Treatment centers on identifying the etiologic agent associated with the condition. Recurrent EM associated with HSV is often treated with preventative antiviral medication. The use of corticosteroids for treatment of EM is controversial [57].

Fixed-drug eruptions in the oral cavity, while outside the spectrum of EM, generally present with recurrent or persistent ulceration that occur on the same site with the oral cavity following usage of the offending medication. The skin and genital mucosa may also be affected [55]. Medications implicated include antihistamines, NSAIDS, acetaminophen, azole antifungals, and antibiotics [55]. The antianginal medication nicorandil has also been associated with oral ulceration [58]. Similar to EM, biopsy results are nonspecific and treatment centers around identifying and eliminating the etiologic medication.

Lichenoid Lesions and Related Conditions

Oral lichen planus (OLP) is a T-cell mediated immune condition which may affect skin and oral, vaginal, or ocular mucosa. OLP classically presents as a symmetric and multifocal oral condition most commonly affecting middle aged women and frequently presenting in trauma prone areas such as the buccal mucosa and lateral tongue [59, 60]. OLP and related conditions may present with a wide variety of clinical appearances ranging from white, reticular or lacy asymptomatic lesions to ulcerated painful multifocal lesions (Fig. 4c). Up to two-thirds of patients with OLP will report symptoms, usually in the ulcerated or atrophic forms [61]. Over time, asymptomatic patients may develop ulcerations and become symptomatic.

Systemic disease may mimic OLP, particularly graft-versus-host disease (GVHD) and lupus erythematosus (LE). GVHD may present clinically and histologically similar to OLP in patients with history of bone marrow transplant, and both discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE) may also present with oral lichenoid appearing lesions [60, 61]. Hepatitis C has been associated with OLP in many populations [62]. Local irritants such as amalgam, food additives, or dental materials may be associated with oral lichenoid lesions (OLLs) and should be investigated as possible triggers especially in localized lesions [59]. Oral lichenoid drug reactions (OLDRs) have been long described anecdotally but a lack of reliable studies limit the full understanding of this phenomenon. Medications most classically implicated in OLDRs include NSAIDS, antihypertensives, antimalarials, and antiretroviral medications; however, the list of associated medications is extensive [59]. A recent systematic review of OLDRs found resolution or improvement of the OLDR upon cessation of suspected medication in less than a third of cases [63]. OLDRs are typically erosive and unilateral in contrast with classic OLP. OLDRs may present with a significant latency period of weeks to months after the onset of medication use and may take several months to resolve after cessation of the medication, complicating diagnosis and treatment [59, 63]. Finally, premalignant lesions such as epithelial dysplasia and proliferative verrucous leukoplakia (PVL) have been associated with lichenoid features clinically, histologically, and even upon DIF testing and must be carefully differentiated from OLP [60, 64, 65].

Establishing reliable clinical and histopathologic diagnostic criteria for OLP has been a longstanding challenge. Recently proposed updated criteria for histologic diagnosis of OLP includes variable surface thickness, "band-like" infiltration of predominantly lymphocytes in the superficial lamina propria, basal layer degeneration, lymphocytic exocytosis, and the strict absence of epithelial dysplasia or verrucous surface change such as is common in PVL (Fig. 4d) [61]. OLDRs and LE often show deeper and mixed inflammatory infiltrate with plasma cells and eosinophils accompanying lymphocytes along with a perivascular pattern of inflammation, though these are nonspecific features [60, 63]. Direct immunofluorescence testing (DIF) testing may show fibrinogen or complement deposition at the basal layer but is nonspecific and best utilized to distinguish OLP from clinical mimics such as vesiculobullous disease and chronic

ulcerative stomatitis [60, 61, 66]. Indirect immunofluorescence testing (IIF) is not useful in OLP diagnosis [61]. Treatment of OLP depends on severity of disease, and topical corticosteroids remain the first line of treatment for most symptomatic cases [61]. Other alternatives include topical retinoids, topical calcineurin inhibitors, and low level laser therapy [67, 68]. Long term monitoring of OLP is essential due to a controversial association with possible malignant transformation, estimated to be between 1–3% [69].

Vesiculobullous Lesions

Multiple immune-modulated vesiculobullous (VB) diseases may affect the oral cavity including mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA), pemphigus vulgaris (PV), and paraneoplastic pemphigus (PNP). In addition, multiple medications have been reported to cause VB appearing oral lesions as well including NSAIDS, penicillamine, antipsychotics, spironolactones, and sulfonamides [55].

Patients with oral VB disease usually present with recurrent transient bullous formation and ulceration involving the oral cavity along with other mucosal locations such as the oropharynx, larynx, nasopharynx, and conjunctiva (Fig. 5a, c) [70, 71]. The skin is variably affected depending on diagnosis and severity of disease. In PV, cutaneous lesions are widespread but mucosal lesions may occur first [72]. MMP may involve ocular mucosa and lead to scarring [73]. Most MMP patients are middle aged women whereas a roughly equal gender distribution is seen in PV [72, 74]. Oral cavity involvement is variable, with MMP most frequently presenting with gingival involvement, often as the only oral site [74]. Oral PV most often involves the buccal mucosa and gingiva [71]. PNP generally has an abrupt onset and may show extensive oral ulcers and crusting of the lips similar to EM [75].

Biopsy for suspected VB disease shows subepithelial separation in MMP (Fig. 5b) and EBA [70, 75]. Intraepithelial separation is noted in PV (Fig. 5d), and PNP may show both intraepithelial and subepithelial separation [75]. DIF is often necessary to distinguish between these entities

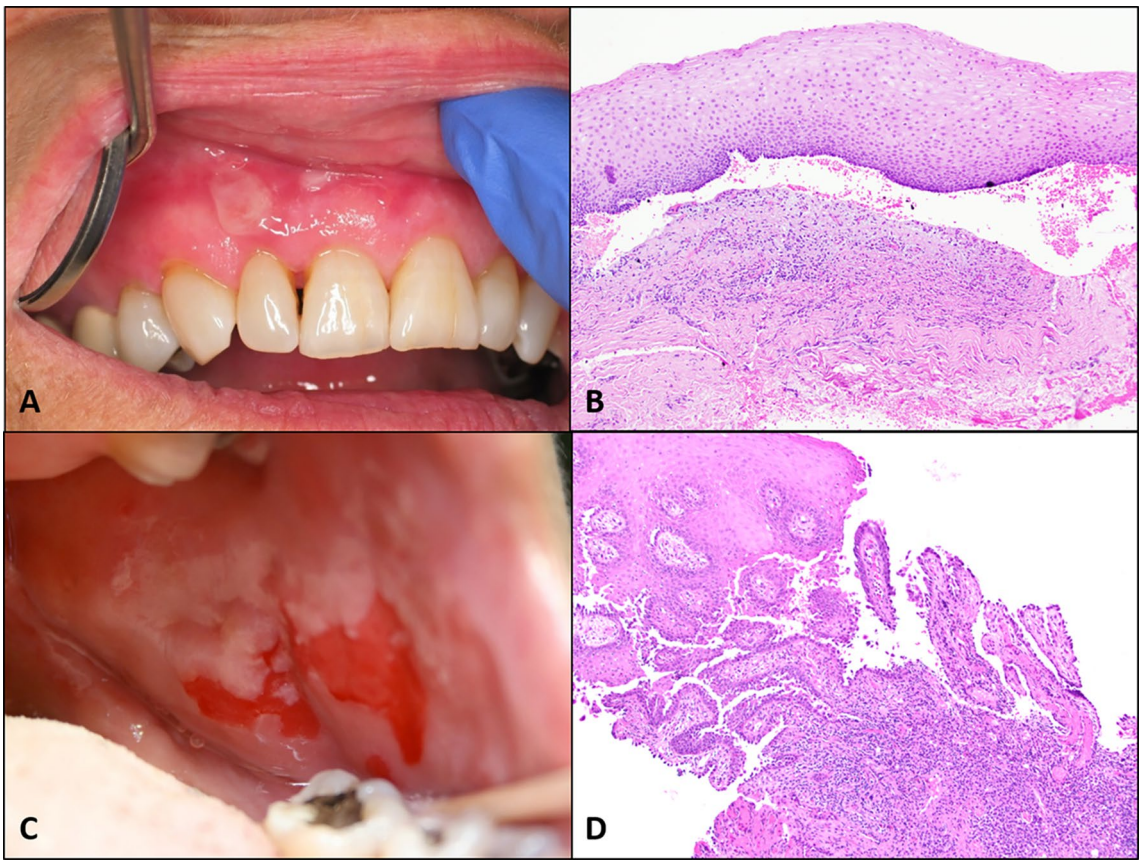

Fig. 5 Vesiculobullous immune related ulcerations. **a** Mucous membrane pemphigoid affecting the gingiva (photo courtesy Dr. Angela Wilson). **b** MMP exhibiting subepithelial separation and chronic inflammation (H&E low power magnification). **c** Pemphigus vulgaris affecting the buccal mucosa (photo courtesy Dr. Christopher Lee). **d** PV exhibiting intraepithelial separation (H&E low power magnification)

and establish a diagnosis. IIF and ELISA testing may also be useful to distinguish PV, EBA and PNP from MMP [72]. Treatment of oral VB diseases is highly dependent on extent of involvement and diagnosis. MMP may often be controlled with topical corticosteroids, although severe or widespread cases will require systemic therapy [74, 76]. PV typically requires treatment with systemic corticosteroids or steroid sparing immunosuppressants [72].

Ulcerations of Traumatic Etiology

Ulceration of the oral cavity may result from chemical, thermal, electrical, or mechanical trauma, either acute or chronic. A careful history of when the lesion began and potential inciting events along with careful physical inspection of the lesion in relation to dental restorations and appliances is important in properly classifying these lesions. Ulcers resulting from acute trauma are generally self-resolving without complication within 14 days, but chronic ulcerations may not present with a clear and obvious source of trauma and may require biopsy to rule out neoplasia or other conditions.

Ulcerations Due to Chemical Trauma

Oral ulcerations have been reported in conjunction with dental materials such as restorative materials, local anesthetics, sodium hypochlorite, formocresol, topical aspirin; topical oral care products such as hydrogen peroxide, denture cleaners, and mouthwashes; and illicit drug use including cocaine, amphetamines, and methylenedioxymethamphetamine (MDMA) (Fig. 6) [77].

Ulcerations Due to Thermal or Electrical Trauma

Thermal trauma to oral tissues results most frequently from contact with high temperature substances, but may also result from extreme cold temperatures as well (cryogenic burns) such as from contact with frozen metal, dry ice, or liquid nitrogen [78]. Thermal burns due to high heat most commonly result from hot food or drinks, particularly microwaved food items, and most commonly affect the anterior one-third of the tongue and the palate [79]. More recent reports have surfaced of oral burns caused by exploding electronic cigarettes [80]. Electric burns are rare but may be severe and cause debilitation, especially in children [78, 81].

Ulcerations Due to Mechanical Trauma

Ulcerations due to mechanical trauma may be either acute or chronic in nature. In a recent study of denture wearers with oral lesions, traumatic denture related ulcerations were present in nearly 20% [82]. Necrotizing sialometaplasia is a distinct entity which may result from trauma causing deep ulcerations of the hard palate and may mimic malignancy [83]. One distinct form of chronic traumatic ulcer in the oral cavity is traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), which presents as a distinctive and worrisome non-resolving chronic ulceration with elevated margins. TUGSE most commonly affect middle aged patients although a similar lesion is observed in infants in tissues approximating natal teeth (Riga-Fede disease) (Fig. 7a–c) [84]. TUGSE most commonly affects the tongue, followed by the buccal mucosa and rarely other locations such as retromolar area, floor of the mouth, or lip [84–86].

Though most traumatic lesions have nonspecific histologic findings, TUGSE is characteristically a distinct deep seated ulceration with a mixed inflammatory infiltrate consisting of lymphocytes, macrophages, and numerous eosinophils and proliferating blood vessels (Fig. 7d) [86]. Large CD30+ cells may be present, but do not signal malignancy as TUGSE is a benign entity though at least partial surgical excision may be necessary for resolution in some cases [86, 87]. Treatment of trauma related ulcerations focuses on removal of the etiologic source of the trauma though supportive care may be necessary.

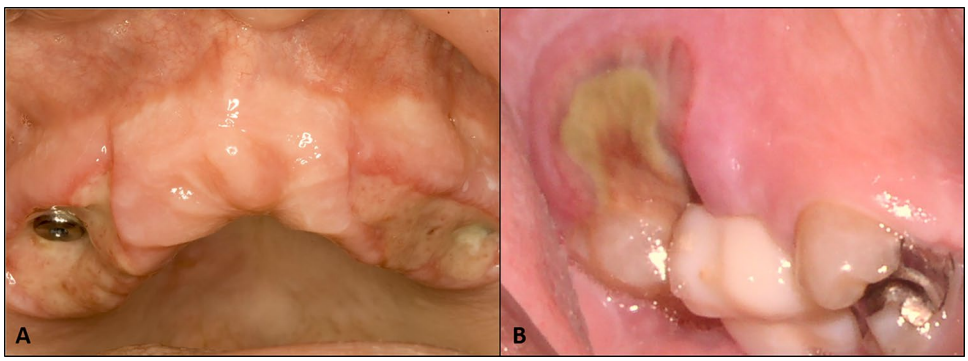

Fig. 6 Acute traumatic ulcerations. **a** Chemical burn due to topical aspirin placement over implant sites (photo courtesy Dr. Shawn Lottier). **b** Post-anesthetic ulceration reaction (photo courtesy University of Florida Oral Pathology Biopsy Service Archives)

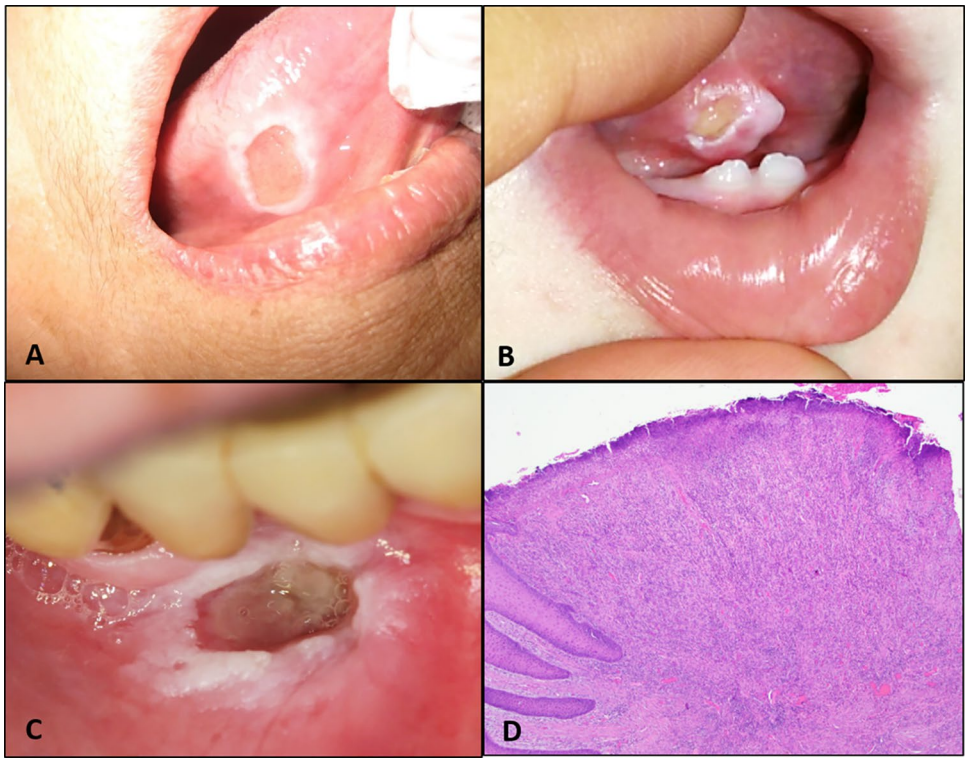

Fig. 7 Chronic traumatic ulcerations. **a** Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) on lateral tongue (photo courtesy Dr. Prashant Pandya). **b** Riga-Fede disease on ventral tongue adjacent to natal teeth in an infant (photo courtesy Dr. Naveen Allin). **c** Factitious traumatic injury to the labial vestibule secondary to picking habit (photo courtesy Dr. Donald Cohen). **d** Deep TUGSE ulceration extending into skeletal muscle (H&E low power magnification)

Ulcerations of Neoplastic Etiology

A significant concern regarding oral ulcers is the accurate diagnosis of ulcerated malignant lesions mimicking benign ulcerations. Though a full discussion of all oral neoplasms is out of the scope of this manuscript, this section will focus on those malignant neoplasms that may present primarily as an ulcerated lesion.

Ulcerated Oral Dysplasia and Squamous Cell Carcinoma

The standard model of progression of oral malignant change begins with normal appearing epithelium which progresses from a thin to a thick white lesion and develops an erythematous component and often a surface ulceration. However, it is accepted that this transformation may not be linear and steadily progressive in nature, and OSCC may arise without clinically obvious precursors [88]. Tobacco and alcohol use have long been noted as risk factors for OSCC, but the full role of high risk human papilloma virus infection, though strongly linked to oropharyngeal SCC, is still not definitively established for OSCC [89]. Much research has been devoted to developing predictive tests or adjunct devices to identify lesions at high risk of transformation, but clinical utility of these is limited at this time and biopsy remains the gold standard [88, 90, 91]. Non-healing ulcerated lesions, particularly asymmetric or unilateral ones, therefore require biopsy to rule out dysplasia or invasive OSCC (Fig. 8a, b). Dysplastic lesions on the lateral and ventral surfaces of the tongue and floor of the mouth are at higher risk for malignant transformation [92]. Biopsy results are dependent on the stage of progression and may range from mild to severe dysplasia, carcinoma-in-situ, or frankly invasive carcinoma [93]. There have been multiple treatment protocols proposed for oral premalignant lesions but the most commonly accepted treatment remains surgical removal of moderate or higher levels of dysplasia with or without laser therapy along with long term monitoring for recurrence or progression to malignancy [92]. Treatment protocol for OSCC is well established and beyond of the scope of this manuscript.

Ulcerations Mediated by Underlying Hematologic Abnormalities

A wide variety of hematologic abnormalities may manifest in the oral cavity including both malignant and non-malignant lesions of B or T-cell origin. Though most extranodal oral lymphomas present as diffuse submucosal swellings, some hematologic disorders may often present with surface ulceration. Leukemia in particular commonly causes oral ulceration secondary to neutropenia and may be accompanied by other oral symptoms such as gingival bleeding and/or inflamed boggy gingiva [94].

Cutaneous T-cell lymphomas (CTCL) are rare in the oral cavity but often present as multiple ulcerations, and oral

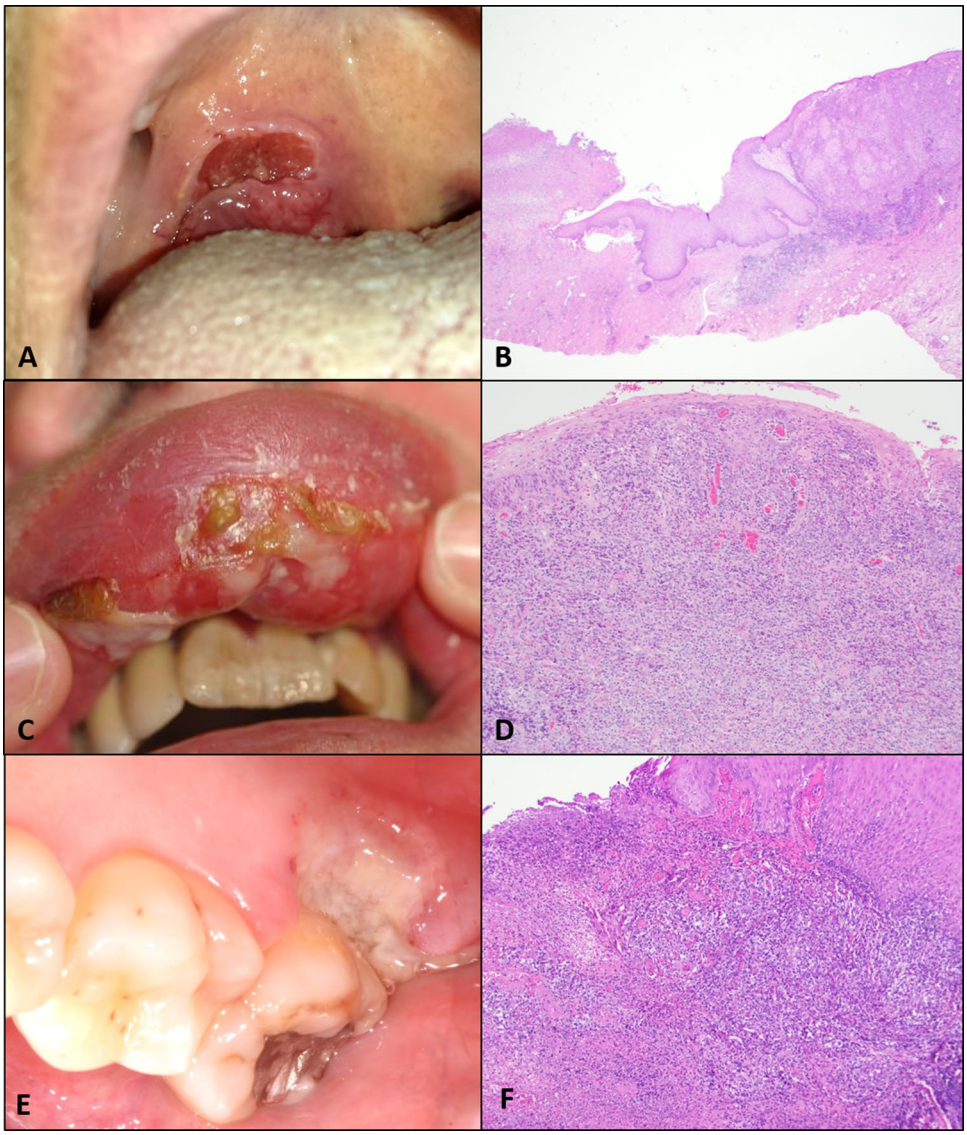

Fig. 8 Neoplastic ulcerations. **a** Squamous cell carcinoma of the soft palate (photo courtesy Dr. Hardeep Chehal). **b** Invasive squamous cell carcinoma (right) and adjacent ulceration (left) (H&E low power magnification × 2). **c** T-cell lymphoma of the upper lip (photo courtesy Dr. Donald Cohen). **d** Atypical lymphocytic proliferation in T-cell lymphoma (H&E medium power magnification). **e** EBVMCU of the maxillary hard palate (photo courtesy Dr. Leah Strange). **f** EBVMCU demonstrating ulceration overlying atypical lymphocytic proliferation with Reed Sternberg like CD30 + cells (H&E medium power magnification)

lesions may precede skin lesions (Fig. 8c, d) [95]. Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma. Oral manifestations include ulcers, erythematous plaques, or masses and most commonly involve the tongue followed by the palate and gingiva [95]. The histologic appearance of MF may mimic inflammatory conditions and lead to misdiagnosis and includes a diffuse infiltrate of atypical lymphocytes with an epidermotropic pattern and irregular cerebriform nuclei [95, 96]. Immunohistochemical (IHC) tests are generally positive for CD3, CD4, and CD45 [95, 96]. Oral involvement in MF may indicate a poor prognosis due to advanced stage [95]. Other subtypes of CTCL have rarely been reported in the oral cavity.

Extranodal NK/T-Cell Lymphoma (ENKTCL) is a distinctive and aggressive malignancy with a proclivity for involvement of the nasal cavity which often causes destructive ulceration of the hard and soft palate, uvula, maxillary gingiva and posterior third of the tongue [97, 98]. The lesion is strongly linked to EBV and is most prevalent in Southeast Asia and Central and South American populations [97]. Biopsy of the lesions shows extensive necrosis which may obscure the features of malignancy and a heavy inflammatory infiltrate mixed with atypical lymphocytes which characteristically appear in an angiocentric pattern [97]. Positivity for CD56, CD2 and cytoplasmic CD3 is characteristic [97]. ENKTCL is generally treated with radiation and/or chemotherapy but the outcome is poor.

EBV is also implicated in a recently described lymphoproliferative disorder, the EBV + mucocutaneous ulcer (EBVMCU) [96]. EBVMCU is a self-limiting indolent ulcerative lesion mediated by B-cells that is most commonly seen in immunocompromised patients secondary to medications or advanced age (Fig. 8e, f) [99]. EBVMCU has also been described in transplant patients within the

spectrum of post-transplant lymphoproliferative disorder (PTLD). EBVMCU often presents in a localized manner associated with lymphoid hyperplasia but may have the potential to become more destructive and even develop a lymphoid malignancy with continued immunosuppression [100]. The ulceration most commonly involves the oral cavity but may affect the skin or in the gastrointestinal tract [101]. Oral lesions often involve the buccal mucosa, tongue, tonsillar area, and palate [99]. Biopsy of EBVMCU shows a necrotic ulcerated lesion with a mixed infiltrate of small T-cells and large atypical B-cells with Reed-Sternberg like CD30+ cells [100]. IHC demonstrates positivity for CD20 and CD30 with positivity for EBV testing [100]. Lesions often spontaneously resolve and most are responsive to conservative therapy and reduction in immunosuppression [99].

Conclusion

Oral cavity ulcerations are caused by any of a spectrum of etiologic factors including infection, immune disregulation, trauma, and neoplasms. Though careful clinical and medical history and clinical evaluation may lead to a strong presumptive clinical diagnosis in many cases, biopsy and/or additional adjunctive testing may be necessary to confirm the diagnosis or rule out a neoplastic sources.

Compliance with Ethical Standards

Conflict of interest All authors declare no conflicts of interests.

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

Informed Consent Not applicable for this article.

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