Immune-Mediated and Allergic Conditions

5

Introduction

A wide variety of immune-mediated conditions can affect the orofacial region. Some present in a limited fashion related to a localized immune response, such as contact hypersensitivity, while others represent more widespread systemic disease with distinct oral manifestations, such as the group of autoimmune vesiculobullous disorders. The underlying pathobiological mechanisms are also quite varied and involve components of the innate and acquired immune systems. Some of these are very well characterized while others are not.

Determining the correct diagnosis is critical, as management strategies can vary considerably from one entity to the next. In some situations additional medical specialty consultation may be indicated, such as dermatology, ophthalmology, or otolaryngology. Oral lesions may precede the appearance of findings in other areas of the body or may represent the sole manifestation of the disease. This chapter is devoted to conditions in which oral findings are a primary feature. Systemic conditions that variably present with oral findings or complications are discussed in Chap. 11.

When evaluating a patient with a suspected immune-mediated or allergic oral disease that requires a tissue diagnosis, it is important to obtain a biopsy prior to initiating any topical or systemic immunosuppressive therapies, as these may mask characteristic or defining histopathological features. Since many of these conditions are chronic and require treatment with long-term topical and or systemic therapies, all patients should be followed on a regular basis. Detailed prescribing guidelines for the most commonly used medications are provided in Chap. 12.

Angioedema

This condition is characterized by rapid localized swelling of the skin or mucosa and underlying connective tissue. While angioedema can occur anywhere in the body, it most commonly presents in the head and neck region. The lips and tongue are most frequently affected; however, the floor of mouth and other areas of the face can also be involved. With involvement of the pharynx and larynx, patients may develop wheezing, voice change, and difficulty in breathing; in severe cases this can progress to potentially fatal airway obstruction. The lower gastrointestinal tract can also be affected, resulting in abdominal pain and diarrhea. Episodes typically develop within minutes to a few hours and resolve within 2–3 days, although changes can persist for as long as 1 week. Affected areas are characterized by painless, non-pitting edema with adjacent uninvolved tissues exhibiting a normal appearance (Fig. 5.1). Swollen tissues may be secondarily traumatized, but this is not a primary feature of the condition.

J.M. Bruch, N.S. Treister, *Clinical Oral Medicine and Pathology*,
DOI 10.1007/978-3-319-29767-5_5

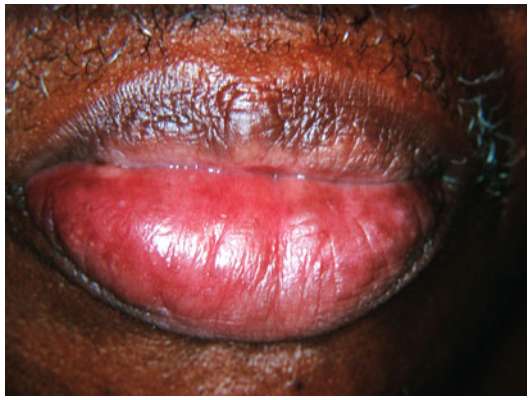


Fig. 5.1 Angioedema of the lower lip associated with ACE inhibitor use. The upper lip and facial skin are unaffected. Photograph courtesy of Andres Pinto, D.M.D., M.P.H., Philadelphia, PA

Angioedema occurs in hereditary and acquired forms. Hereditary cases typically present within the first or second decade of life and are caused by a deficiency in C1-esterase inhibitor, which is inherited in an autosomal dominant fashion. This results in uncontrolled activation of the complement cascade, causing tissue edema through mechanisms of vasodilation and increased vascular permeability. A rare form of acquired C1-esterase deficiency is believed to be autoimmune in nature and in some cases may be associated with an underlying lymphoproliferative disorder. Nonhereditary angioedema may be medication-induced, allergic, or idiopathic. The idiopathic variety is the most common of all types, affecting approximately 40 % of patients with angioedema. The majority of medication-induced cases are caused by ACE inhibitors and these typically present within the first few weeks of therapy, although some may occur years later. ACE inhibitors decrease the production of angiotensin II, a potent vasoconstrictor that is involved in the inactivation of bradykinin. Allergic cases are related to IgE-mediated mast cell degranulation with release of histamine, and symptoms typically develop within an hour of exposure. Common allergic triggers include nonsteroidal anti-inflammatory agents, opiates, other antihypertensive agents, contrast dyes, and foods (e.g., nuts, eggs, and shellfish). In some cases, stress and trauma have been implicated as triggers.

Oral lesions are usually self-limiting and resolve within 2–3 days. Patients with upper airway symptoms, including wheezing, gasping, or voice changes, should be evaluated emergently, as airway obstruction results in a significant risk of death in this condition. Patients with angioedema that is not obviously associated with an ACE inhibitor should be referred to an allergist or immunologist for comprehensive evaluation. Prophylactic therapies in patients with recurrent episodes include use of antihistamines (diphenhydramine, ranitidine); androgens (danazol, stanozolol), which directly increase levels of C1-esterase inhibitor; hemostatic agents (aminocaproic acid, tranexamic acid), which act through inhibition of plasmin; and glucocorticosteroids.

Angioedema

	**DIAGNOSTIC TESTS**	Referral to a specialist to further characterize the disorder and identify risk factors. Allergy and immunology work-up is generally indicated.
	**BIOPSY**	Not required in most cases.
	**TREATMENT**	Androgens, hemostatic agents, antihistamines, and glucocorticosteroids can be effective prophylactic therapies.
	**FOLLOW-UP**	Patients should be followed as needed to assess response to treatment.

Orofacial Granulomatosis

Orofacial granulomatosis (OFG) is a rare disorder characterized by chronic recurrent painless swelling of the oral mucosa, lips, and perioral tissues (Fig. 5.2). The etiology is poorly understood, but in some cases can be attributed to hypersensitivity to certain foods or additives. The condition typically presents during early adulthood, and while generally asymptomatic, the disfiguring changes can have significant psychosocial consequences. Lesions are characterized by diffuse swelling, oftentimes with associated erythema, folded or fissured mucosal changes ("cobblestoning"), and focal areas of ulceration (Fig. 5.3). While the lips and perioral region are most frequently affected, any part of the mouth or face can be involved. OFG presenting with both fissured tongue and facial nerve paralysis is referred to as *Melkersson-Rosenthal syndrome*.

The diagnosis of OFG is made based on biopsy of affected tissue. Histopathology demonstrates granulomatous inflammation and edema. A carefully recorded food diary may be helpful in identifying potential causative agents, but most cases are idiopathic. *Inflammatory bowel disease* (i.e., Crohn disease and ulcerative colitis) and sarcoidosis must also be considered, as each of these can present with similar clinical features (see Chap. 11).

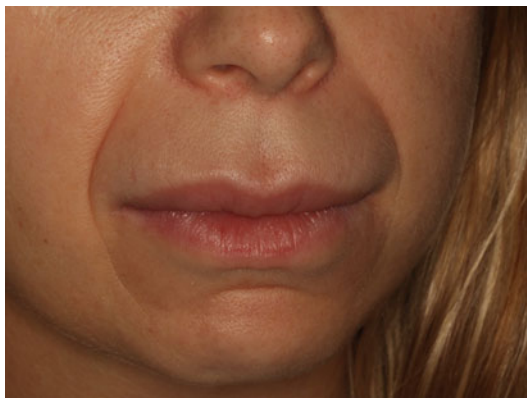


Fig. 5.2 Orofacial granulomatosis with prominent enlargement of the upper lip and characteristic vertical creases

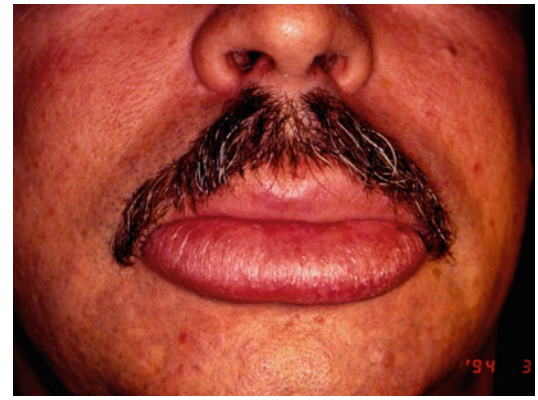


Fig. 5.3 Orofacial granulomatosis with painless swelling and fissuring of the lower lip. Photograph courtesy of Sook-Bin Woo, D.M.D., M.M.Sc., Boston, MA

Effective treatment of OFG can be challenging. Any suspected food triggers should be strictly eliminated from the diet. Episodes will generally respond to a short course of high-dose prednisone, which can be very effective in controlling lesions in the short-term; however, this is not an appropriate treatment strategy for long-term management. Other medications that can be used include dapsone, hydroxychloroquine, sulfasalazine, minocycline, azathioprine, thalidomide, and anti-tumor necrosis factor (TNF-alpha) biological agents. For cases refractory to systemic therapies, Intralesional corticosteroid therapy can be very effective with or without concurrent systemic therapy. Intralesional steroid therapy must be administered regularly over an extended time period, even weekly, to maintain clinical control.

Orofacial Granulomatosis

	**DIAGNOSTIC TESTS**	None specific for this condition. Evaluate for sarcoidosis and inflammatory bowel disease. Consider allergy patch testing.
	**BIOPSY**	Yes.
	**TREATMENT**	Initial therapy consists of systemic and/or intralesional corticosteroid therapy. Preventive therapies include dapsone, hydroxychloroquine, minocycline, sulfasalazine, azathioprine, thalidomide, and anti-TNF-a biological agents.
	**FOLLOW-UP**	Patients should be followed regularly because even those receiving prophylactic therapy frequently develop breakthrough lesions.

Traumatic Ulcerative Granuloma

Traumatic ulcerative granuloma (TUG), sometimes also referred to as *traumatic ulcerative granuloma with stromal eosinophilia* (TUGSE), is a painful intraoral inflammatory lesion that is initiated by some type of traumatic event, most frequently a bite injury.

While the majority of traumatic injuries heal uneventfully in the oral cavity, TUGs transform into chronic, deep, and penetrating ulcerations that can be extremely painful and disabling (Fig. 5.4). The borders of the lesion may appear thickened and indurated with hyperkeratosis and striations, representing an attempt by the surrounding tissue to heal (Fig. 5.5). This lesion can be easily mistaken for oral cancer clinically. There are no known risk factors, and these can be seen in any age group. The most common location for TUG is the posterior lateral tongue but lesions can also be seen on the buccal and labial mucosa and soft palate. Once established, TUGs rarely resolve without intervention.

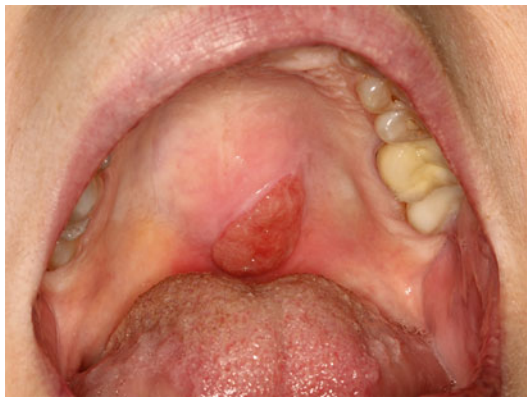


Fig. 5.4 Traumatic ulcerative granuloma of the hard palate

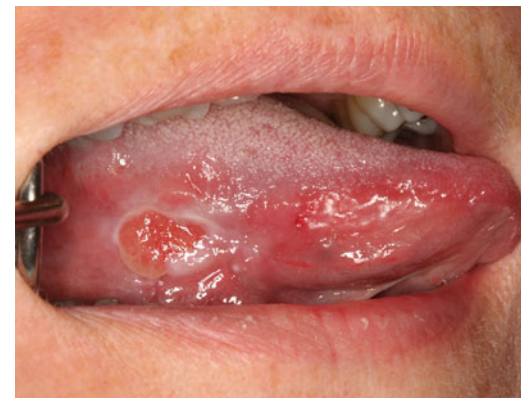


Fig. 5.5 Exophytic traumatic ulcerative granuloma of the right posterior lateral tongue with well-defined white borders

Diagnosis requires an incisional biopsy, which should be taken from the ulcer margin to avoid obtaining necrotic tissue from the center of the lesion. Histopathology demonstrates ulceration with a dense infiltrate of acute and chronic inflammatory cells, often including numerous eosinophils that penetrate into the underlying skeletal muscle.

TUGs rarely heal spontaneously, and are typically present for several weeks before patients seek evaluation. Any obvious parafunctional habits or other factors contributing to persistent irritation, such as a fractured dental restoration,

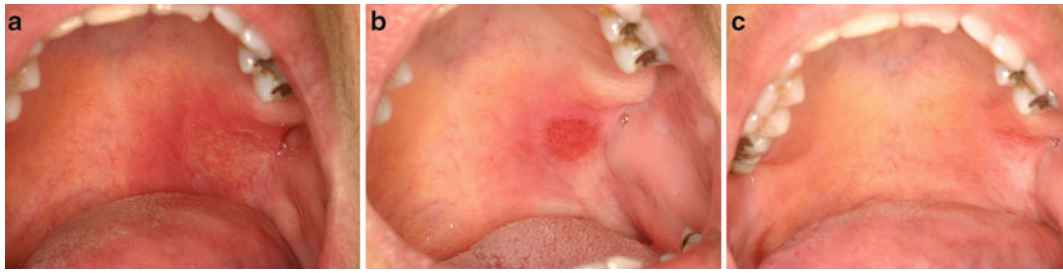


Fig. 5.6 Traumatic ulcerative granuloma of the left soft palate with extensive surrounding erythema. (**a**) This patient complained of severe odynophagia and referred pain to the ear. (**b**) Lesion 2 weeks, and (**c**) 4 weeks following combined intralesional and topical corticosteroid therapy

Traumatic Ulcerative Granuloma

	DIAGNOSTIC TESTS	None; consider viral culture to rule out herpes simplex virus (HSV).
	BIOPSY	Yes, specifically to rule out other pathology including squamous cell carcinoma.
	TREATMENT	Topical and intralesional corticosteroid therapy.
	FOLLOW-UP	None following healing.

should be addressed and corrected if possible. Once the diagnosis is made, the most effective first-line therapy is intralesional corticosteroid injection (Fig. 5.6). This often requires multiple sequential injections on a weekly basis; at least three to four treatments should be provided before determining the lesion to be nonresponsive. A high-potency topical corticosteroid gel, such as fluocinonide 0.05 % or clobetasol 0.05 % should also be prescribed and applied three to four times daily. Nonresponsive lesions can be treated with a 7–10-day course of high-dose prednisone. If still refractory, lesions should be considered for surgical excision; in some cases the inflammation is so deep and established that tissue debridement and primary wound closure is required.

Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS) is the most common painful oral mucosal disease, affecting approximately 20 % of the population. Also referred to as *aphthous ulcers*, or the more commonly used lay term *canker sores*, RAS presents with a wide spectrum of severity ranging from a minor nuisance to a disabling condition. Characteristic oral ulcerations initially present in the first or second decade of life, making this one of the few immune-mediated oral inflammatory conditions seen in both children and adults. While the frequency of episodes often diminishes sharply during the third decade, patients are always at risk for developing recurrent lesions. Rarely, for reasons that are not understood, the frequency and severity of RAS can increase later in life.

Lesions appear clinically as nonspecific shallow round or oval ulcerations covered by a grayish-white fibrin pseudomembrane that is surrounded by a sharply defined erythematous halo (Fig. 5.7). Aphthous ulcers most commonly present as solitary lesions limited to the *nonkeratinized mucosa*, although exceptions exist and are discussed below. Ulcers may be preceded within hours by a tingling or burning sensation, allowing most patients to sense when they will develop a lesion. Once

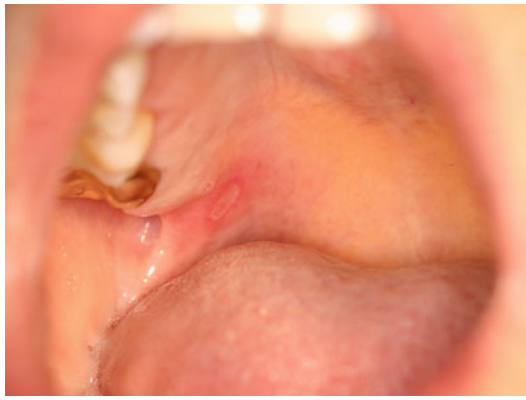


Fig. 5.7 Minor aphthous ulcer on the right soft palate with characteristic erythematous halo

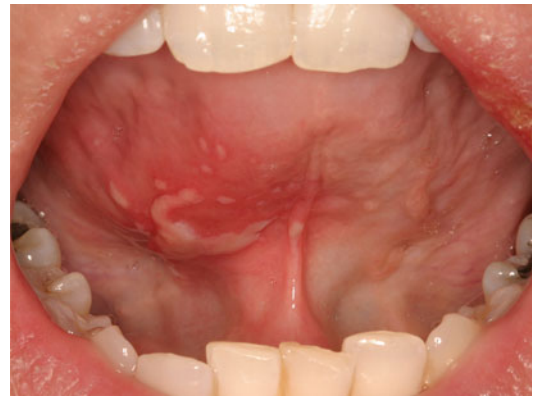


Fig. 5.8 Herpetiform aphthous ulcers of the ventral tongue. There is a central zone of coalescing ulceration with multiple crop-like smaller surrounding lesions

formed, ulcers typically last 7–10 days (with the first 3–4 days generally being the most symptomatic), and heal without complications.

The defining feature of RAS is pain. While lesions can be uncomfortable at rest, it is during function, such as speaking and eating, that symptoms are most intense. Like most painful oral inflammatory conditions, the location of lesions influences the severity of symptoms. Ulcers on the tongue can make speaking and chewing uncomfortable, while ulcers on the soft palate or in the esophagus can cause swallowing to be acutely painful. Ingestion of acidic foods and beverages can also be particularly uncomfortable.

There are four distinct clinical presentations: *minor, herpetiform, major and complex/severe aphthous ulcers*. By far the most common, *minor aphthous* ulcers are less than 0.5 cm in diameter and follow the classic clinical pattern described above. An uncommon variant, *herpetiform aphthous ulcers* present as multiple small ulcerations that erupt in crops and subsequently coalesce to form an irregularly shaped lesion that mimics (but is unrelated to) those caused by HSV (Fig. 5.8; see Chap. 7). Although individual herpetiform aphthous lesions are less well-defined and typically smaller in size than minor RAS lesions, the overall appearance is identical; these also typically heal within 7–10 days. *Major aphthous ulcers* are larger than 1.0 cm in diameter

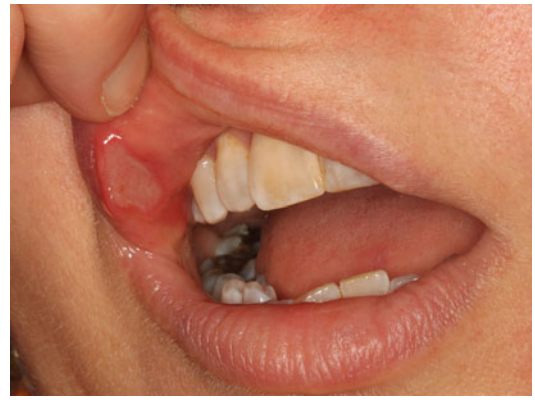


Fig. 5.9 Major aphthous ulcer of the right upper labial mucosa

and occur far less frequently than minor lesions. These are deeper, more penetrating ulcers that can be intensely painful even at rest (Figs. 5.9 and 5.10). Major ulcers can last for weeks or months and may result in scar formation with resolution. *Complex* or *severe aphthous stomatitis* is a clinical entity in which an affected individual is almost never without ulcers, resulting in debilitating chronic pain that can lead to weight loss, malnutrition, and considerable morbidity. Patients often suffer from multiple ulcers at any given time with new lesions developing as existing ones heal. The keratinized mucosa may also

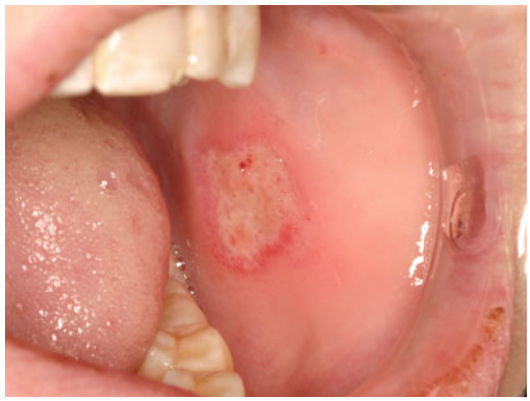


Fig. 5.10 Trauma-induced major aphthous ulcer of the left buccal mucosa. The patient accidentally bit both cheeks and subsequently developed bilateral major aphthae 2 days later. A focal area of petechiae shows where the bite injury initially occurred

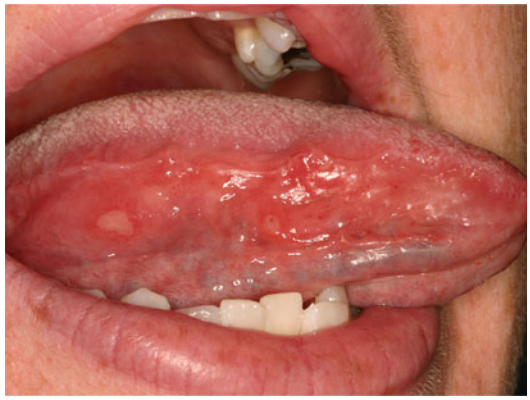


Fig. 5.11 Patient with severe recurrent aphthous ulcers with two minor ulcers of the right lateral tongue in addition to multiple other lesions throughout the oral cavity

be affected in these patients (Figs. 5.11, 5.12, 5.13, and 5.14).

The etiology of RAS is poorly understood. Histopathology demonstrates nonspecific ulceration with a dense infiltration of acute and chronic inflammatory cells. T-cells predominate and there are high local levels of the proinflammatory cytokine TNF-α. Lesions are not contagious and are not caused by HSV. Precipitating factors in some patients include stress, trauma, hormonal fluctuations, and certain foods and drinks. A number of conditions and diseases can present

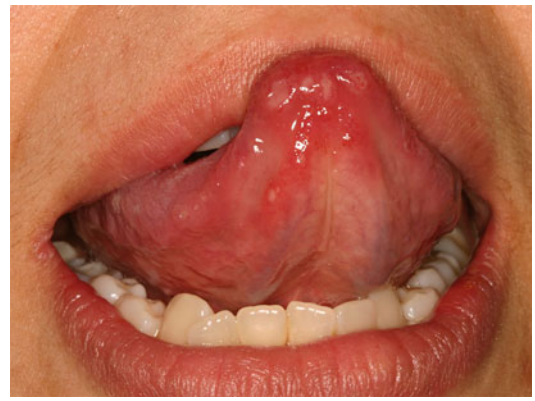


Fig. 5.12 Multiple minor aphthous ulcers of the tongue in a patient with severe recurrent aphthous stomatitis

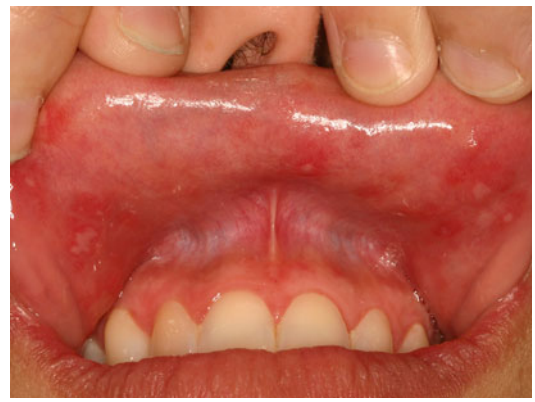


Fig. 5.13 Severe recurrent aphthous stomatitis with extensive ulcers of the upper labial mucosa

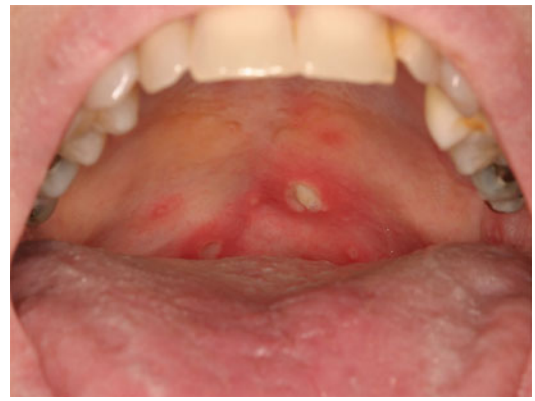


Fig. 5.14 Multiple soft palatal ulcers in a patient with severe recurrent aphthous stomatitis. Due to the location of the lesions, all oral activities were very painful

with RAS, including deficiencies in folic acid, vitamin B_{12}, and iron, inflammatory bowel disease (see Chap. 11), celiac disease, Behcet disease, and HIV disease. For reasons not well understood, patients with HIV disease can develop severe recurrent *major* ulcers that are often larger than 1.0 cm in diameter (Fig. 5.15; see Chap. 11).

Depending on the severity and frequency of outbreaks, management strategies range from simple palliative measures to systemic preventive therapies. The vast majority of patients with RAS never requires any specific therapy and simply lives with occasional oral discomfort. Isolated painful episodes can be treated with over-the-counter products such as mucoadhesive agents and topical anesthetics.

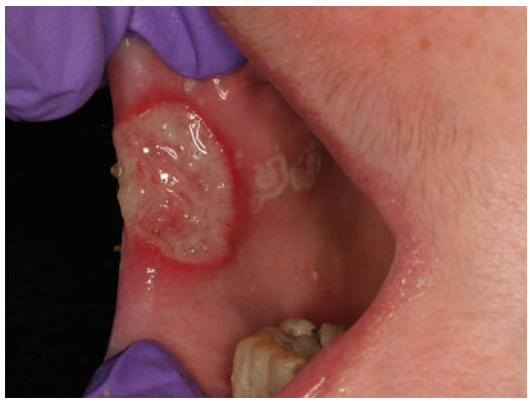


Fig. 5.15 Major aphthous ulcer of the anterior right buccal mucosa and commissure in a patient with advanced AIDS. Pseudomembranous candidiasis is also seen more posteriorly, although the two lesions are not specifically related (see Chap. 7)

Application of high-potency corticosteroid gels can significantly reduce sensitivity and may reduce healing time. *Major* lesions require intensive topical corticosteroid therapy (e.g., 3–4 times/day) and may benefit from intralesional corticosteroid injection (Fig. 5.16). For topical treatment of multiple or poorly accessible lesions, a corticosteroid rinse (e.g., dexamethasone 0.1 mg/mL) can be much easier to apply than a gel.

Patients with *severe* RAS often require management with systemic medications. Acute or persistent ulcers are highly responsive to short courses of corticosteroids. Several agents can be effective in long-term prevention, including pentoxyfylline, colchicine, thalidomide, and azathioprine. Topical corticosteroid rinses (at least daily) should also be included as part of any preventive approach. Patients responding favorably to treatment may cease developing ulcers altogether, or may experience lesions less frequently and of less severity. Even in patients with well-controlled disease, occasional short pulses of systemic corticosteroids may be necessary to control breakthrough episodes.

Aphthous Stomatitis

	DIAGNOSTIC TESTS	Consider evaluation of iron, B12, and folate levels.
	BIOPSY	No.
	TREATMENT	For occasional episodes: topical methylcellulose combined with benzocaine, viscous lidocaine, and high potency topical corticosteroids. For acute management of severe outbreaks: high-dose prednisone for 7–10 days. For prevention: pentoxyfilline, followed by addition of colchicine if adequate response is not achieved (must give up to 2-3 months to evaluate response). Other effective agents include azathioprine and thalidomide.
	FOLLOW-UP	All patients with *major* and *severe* RAS should be followed closely.

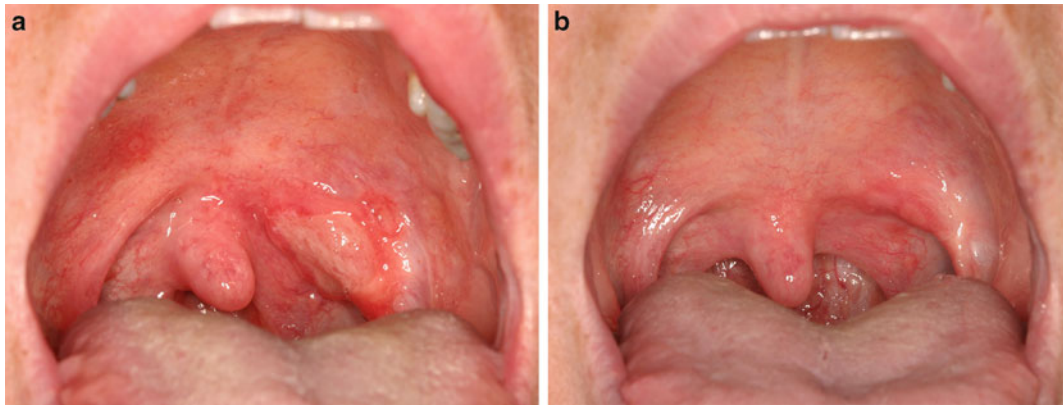


Fig. 5.16 Treatment of major aphthous ulcers with intralesional corticosteroid therapy. (**a**) Large, painful ulceration of the soft palate. (**b**) Same lesion 2 weeks following intralesional therapy

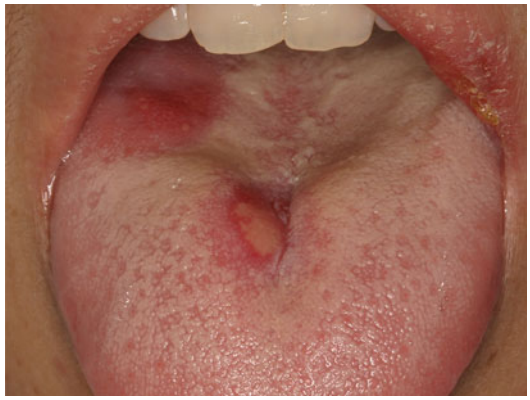


Fig. 5.17 Ulcerations of the tongue dorsum in a patient with Behcet disease. The patient also had painful genital ulcerations

Behcet Disease

Behcet disease is a systemic disease with RAS as one of its defining features (Fig. 5.17). These include aphthous ulcers of the oral and anogenital mucosae, uveitis, inflammatory skin lesions, and other systemic findings such as arthritis, vasculitis, and CNS symptoms. Behcet disease is genetically determined and seen more frequently in individuals from the Middle East and Far East. Systemic therapy is indicated in those with sufficiently severe clinical disease. In addition to the treatments for RAS discussed above, the use of anti-TNF-α biological agents, such as infliximab and etanercept, has demonstrated significant efficacy in patients with Behcet disease.

Erythema Multiforme

Erythema multiforme (EM) is an acute, self-limiting mucocutaneous hypersensitivity reaction that presents with a wide range of clinical severity and appearance. Prodromal symptoms, including fever, malaise, and sore throat, are common and occur anywhere from days to 1–2 weeks prior to onset of lesions. EM can be divided into *minor* and *major* forms; *EM minor* is limited to skin, and *EM major* involves either the skin with at least one mucosal site or a single mucosal site with extensive involvement. *Stevens-Johnson syndrome* is a more severe manifestation of EM major in which there is extensive multisite involvement. Males are affected slightly more than females, with most patients presenting during their second or third decades of life. Recurrences are common.

Approximately 50 % of cases of EM are associated with either medications or recent infection. The most commonly implicated medications include sulfonamides, nonsteroidal anti-inflammatory agents, and anticonvulsants. A proportion of cases are associated with either HSV or *mycoplasma* infection. In the case of HSV, EM most commonly occurs following outbreak of oral or genital herpetic lesions (see Chap. 7), but activation during subclinical shedding can also occur. Approximately 50 % of cases are idiopathic with no obvious cause.

Behcet Disease

	DIAGNOSTIC TESTS	Skin pathergy test in which the skin is penetrated with a sterile 20 to 22-gauge needle and evaluated 48 h later for an erythematous papule >2 mm.
	BIOPSY	Not required in most cases.
	TREATMENT	Similar to treatment for RAS, including anti-TNF-α biological agents. Referral to an ophthalmologist for evaluation and management of ocular involvement.
	FOLLOW-UP	All patients should be followed regularly.

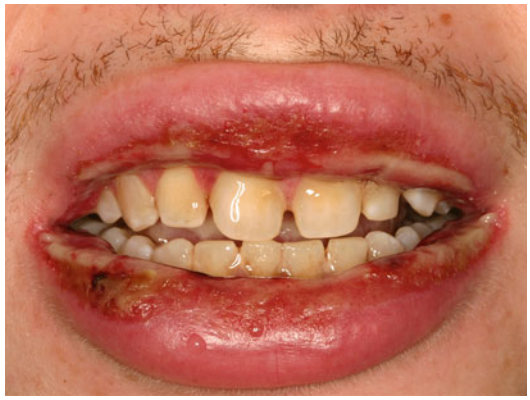


Fig. 5.18 Ulceration and crusting of the lips in a patient with erythema multiforme

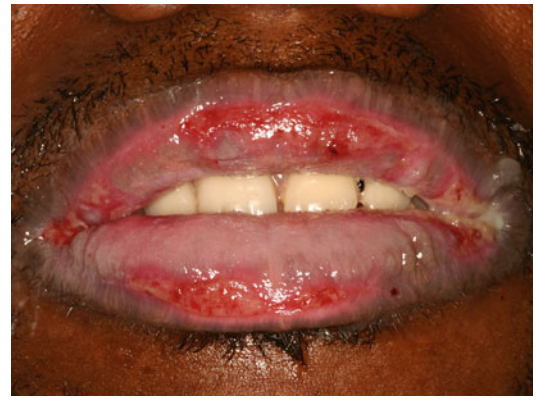


Fig. 5.19 Extensive ulceration of the lips in a patient with Stevens-Johnson syndrome. The patient had oral, ophthalmic, and genital ulcerations as well as skin lesions

Although not always present, the most consistent oral findings are crusting and ulceration of the lips (Figs. 5.18, 5.19, and 5.20). Intraorally, lesions are characterized by nonspecific irregular ulcerations ranging from millimeters to centimeters in diameter with prominent surrounding erythema (Figs. 5.21 and 5.22). The keratinized mucosa is generally spared, and lesions tend to occur toward the anterior aspect of the oral cavity. The genital and ophthalmic mucosa can also be affected. Skin lesions have a classic "target-oid" appearance (Fig. 5.23). Oral lesions develop over several days and can become intensely painful, resulting in inability to eat or speak (Fig. 5.24). The condition is self-limiting, lasting anywhere from 2 to 4 weeks, and ulcerations heal without scarring.

Diagnosis of oral EM is primarily clinical, although viral culture should be obtained and biopsy considered if the clinical presentation is atypical. A perilesional biopsy should be submitted for both histopathology and direct immunofluorescence (DIF). Characteristic findings include a high-density T-cell infiltrate with prominent necrosis of the basal cell layer, subepithelial or intraepithelial blistering, and eosinophils. DIF studies are nonspecific but are helpful in ruling out other conditions such as *pemphigus* and *pemphigoid* (see below). When present, characteristic lip crusting and sparing of the keratinized mucosa

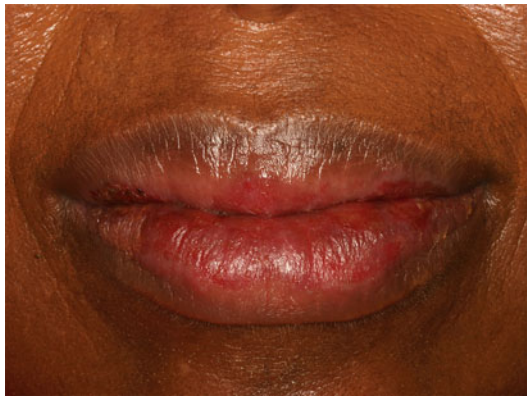


Fig. 5.20 Erythema and slight crusting of the lips in a patient with erythema multiforme. The patient had skin as well as oral lesions

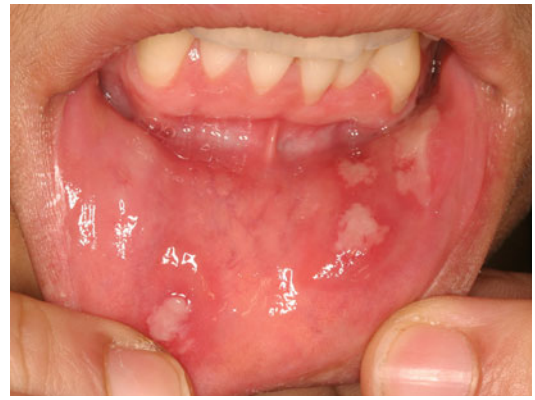


Fig. 5.22 Intraoral erythema multiforme in a patient with concurrent targetoid skin lesions. Although aphthous-like, the borders of the lesions are irregular and ragged in appearance

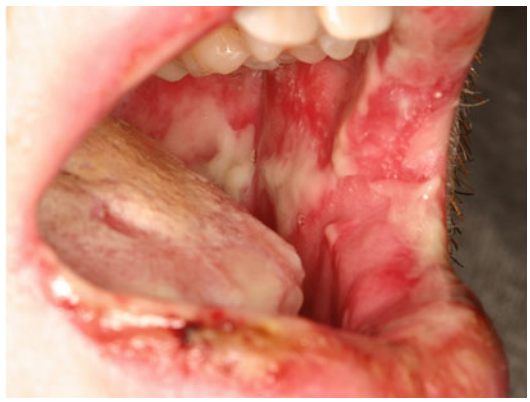


Fig. 5.21 Extensive intraoral lesions in a patient with erythema multiforme. The ulcers are irregular with extensive surrounding erythema. Given the severity of findings, this should be considered erythema multiforme *major* despite lesions being restricted to a single anatomic site

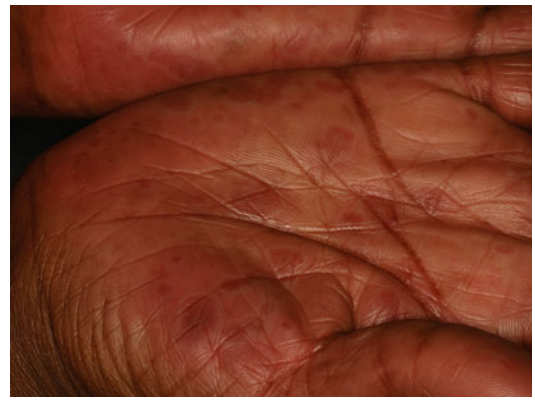
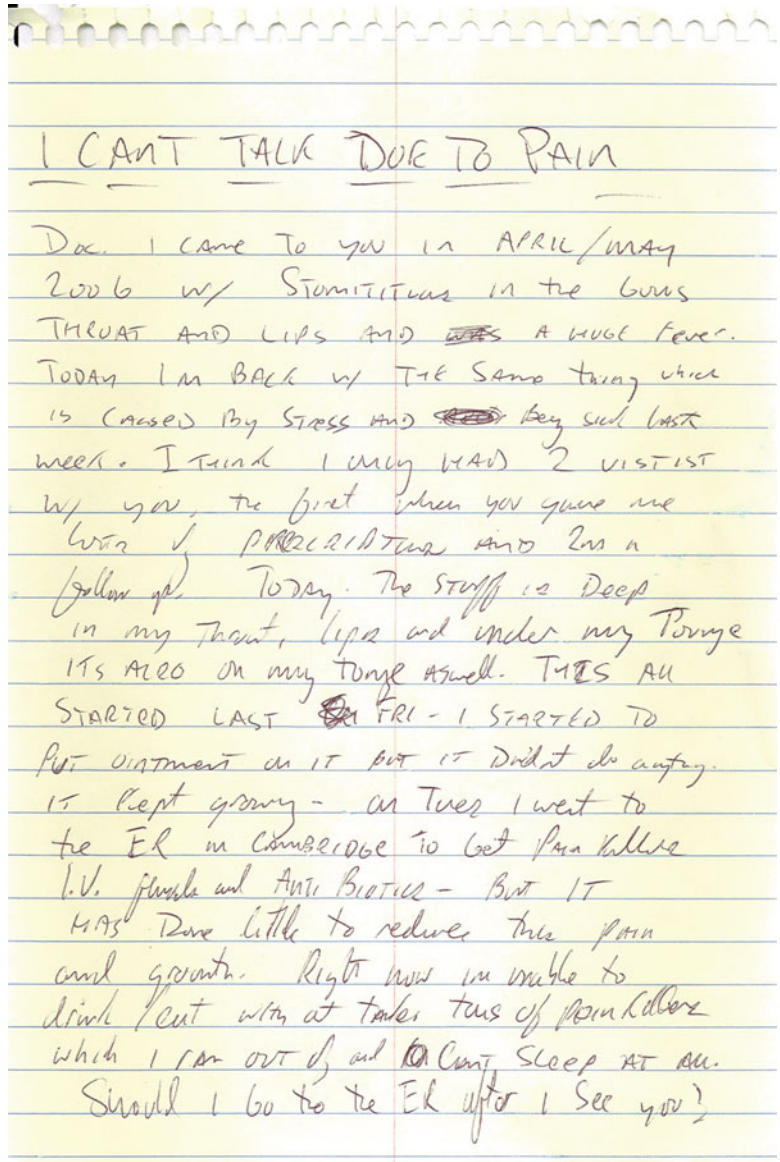


Fig. 5.23 Target lesions on the palms of the patient depicted in Fig. 5.20

easily distinguishes EM from primary HSV. When target lesions are also present, the diagnosis is very straightforward.

Treatment should be initiated as early as possible. The use of systemic corticosteroids in EM is controversial but is generally prescribed for patients with extensive oral involvement, and is given for 7–10 days without taper. Topical steroid rinses, three to four times daily, are also useful. Topical anesthetics (e.g., magic mouthwash) can help control symptoms, but many patients require opioid analgesics. Patients must be instructed to maintain adequate hydration and nutrition. For patients with a history of recurrent herpes labialis, acyclovir therapy may prevent future recurrences.


I CANT TALK DUE TO PAIN

Dr. I came To you in APRIL/MAY 2006 w/ STOMITITUS in the Gums THROAT AND LIPS AND ~~WAS~~ A HUGE Fever. TODAY I'm BACK w/ THE SAME thing which is CAUSED By STRESS AND ~~BEING~~ Being sick LAST week. I THINK I only HAD 2 VISTIST w/ you, the first when you gave me both A PRESCRIPTION AND 2ND a follow up. TODAY. The STUFF is Deep in my Throat, Lips and under my Tongue ITS ALSO on my Tongue Aswell. THIS ALL STARTED LAST ~~SUN~~ FRI - I STARTED TO PUT OINTMENT on IT BUT IT Didn't do anything. IT Kept growing - on Tues I went to the ER in CAMBRIDGE To Get Pain killers I.V. fluids and ANTI BIOTICS - BUT IT HAS Done Little to reduce this pain and growth. Right now im unable to drink/eat with at times tons of pain killers which I ran OUT of and ~~can~~ Can't Sleep AT all. Should I Go to the ER after I See you?

Fig. 5.24 The patient in Fig. 5.21 was in so much pain that he was not able to speak or eat

Erythema Multiforme

	**DIAGNOSTIC TESTS**	Viral culture to rule out HSV.
	**BIOPSY**	Only if the clinical picture is not consistent with EM. Specimens should be perilesional and submitted for both routine histopathology and DIF to rule out autoimmune vesiculobullous disorders.
	**TREATMENT**	Systemic and topical corticosteroids for severe cases; topical corticosteroids alone for milder cases. Pain management and nutritional support.
	**FOLLOW-UP**	Patients should be reevaluated 1 week after initiating therapy. For patients with a history of recurrent HSV and recurrent EM, long-term prophylaxis with acyclovir or valacyclovir should be initiated.

Oral Lichen Planus

Lichen planus is a chronic mucocutaneous T-cell mediated inflammatory condition that affects nearly 1 % of the adult population. Oral lesions are common and in many cases present as the only site of involvement. Although the extent and severity of lesions may fluctuate over time, the condition tends to be persistent once established. Women are affected slightly more than men, with most patients diagnosed during their fourth through seventh decades of life. Since lichen planus can affect the skin as well as other mucosal sites including the larynx and genitalia, patients should be specifically questioned regarding extraoral symptoms.

Oral lichen planus (OLP) most likely represents a heterogeneous group of hypersensitivity reactions exhibiting indistinguishable clinical and histopathological features. If a specific causative agent, typically a medication, is identified, the condition may be referred to as a *lichenoid hypersensitivity reaction*. Numerous medications have been associated with OLP including antihypertensive and nonsteroidal anti-inflammatory agents. Discontinuation of the suspected trigger may be effective, although cross-sensitivity with other medications is common and lesions may persist. Amalgam dental restorations (silver fillings) and cinnamon-flavored products have been associated with localized *contact lichenoid hypersensitivity reactions*. These lesions appear clinically identical to OLP, occur at the site of contact with the offending agent, and generally resolve following removal of the causative agent (Fig. 5.25). The majority of cases of OLP are idiopathic with no obvious cause.

Patients may complain of symptoms, which are highly variable, but often consist of oral sensitivity to toothpaste, acidic substances, alcohol, carbonated beverages, spicy or salty foods, and abrasive foods. Many patients with OLP may be unaware of their condition due to complete lack of symptoms.

There are three distinct clinical presentations of OLP, any of which may be observed in an affected individual at a given time: *reticular, erythematous*, and *erosive*. *Reticular* lesions, also known as *Wickham striae*, appear as lacey white mucosal changes due to a distinct pattern of hyperkeratosis. This is a classic defining feature of OLP that is also seen in skin lesions (Figs. 5.26, 5.27, and 5.28). A less common variation of the reticular form includes *plaque-like* changes (Fig. 5.29), which may be difficult to differentiate from true leukoplakia (see Chap. 9). *Erythematous* lesions, which are often intimately associated with reticular changes, are due to thinning or atrophy of the epithelium with inflammation of the underlying connective tissue (Fig. 5.30). *Erosive/Ulcerative OLP* is the most severe form, and is almost always associated with

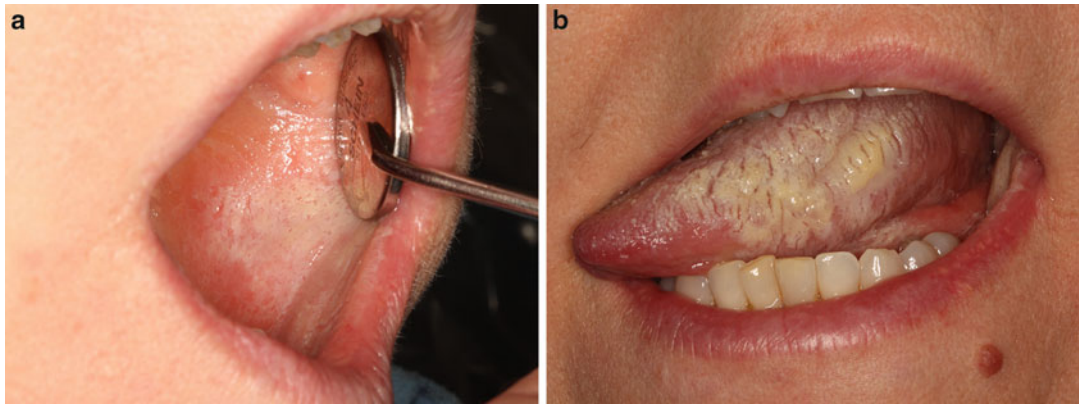


Fig. 5.25 Contact lichenoid hypersensitivity reaction to cinnamon-containing chewing gum, primarily affecting the buccal (**a**) and lingual (**b**) mucosae due to direct, repeated contacts. There was complete resolution of lesions after the patient changed to a different flavor gum

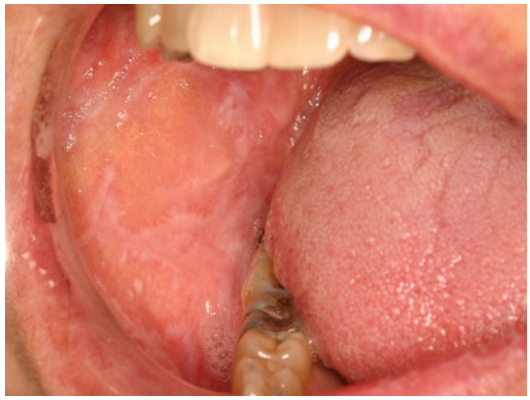


Fig. 5.26 Oral lichen planus of the right buccal mucosa exhibiting a fine reticular pattern and minimal erythema

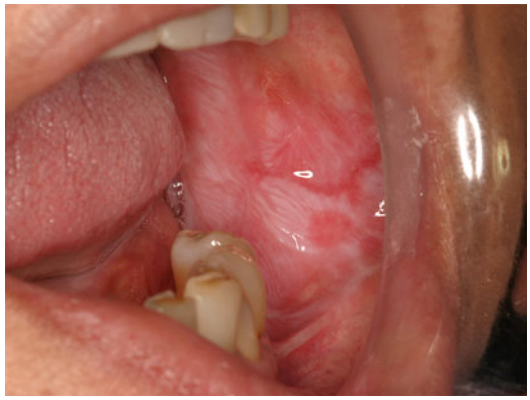


Fig. 5.27 Oral lichen planus of the left buccal mucosa with prominent linear reticulation and erythema

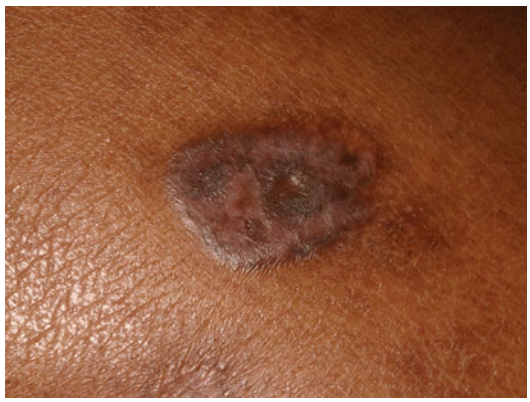


Fig. 5.28 Lichen planus of the skin in an African-American patient with concurrent oral lesions. The same characteristic reticulation seen in the mouth can be seen on the skin

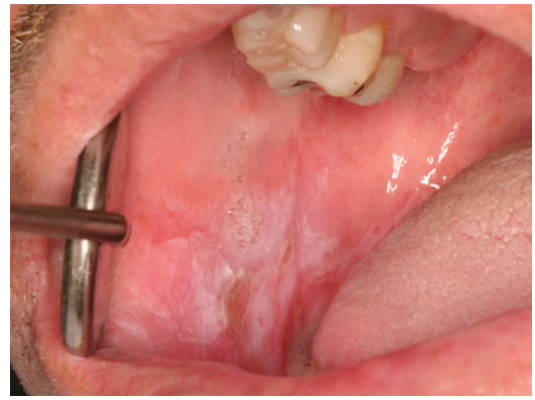


Fig. 5.29 Plaque-like oral lichen planus of the right buccal mucosa. While some areas of reticulation can be seen, these lesions are characterized by white plaques that can easily be mistaken for leukoplakia. There are also focal areas of ulceration

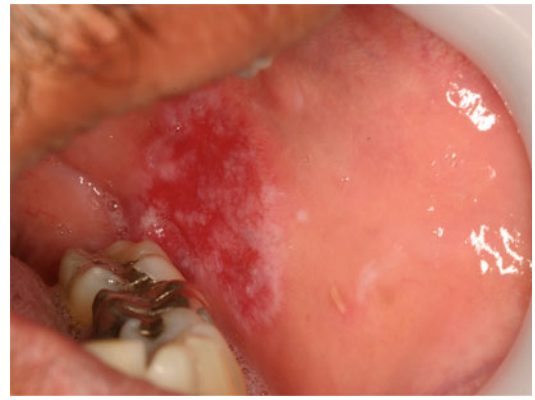


Fig. 5.30 Oral lichen planus of the left buccal mucosa with reticulation and severe erythema

reticular and erythematous changes (Figs. 5.31, 5.32, and 5.33). Patients with extensive ulcerative lesions tend to have more severe symptoms than those with purely reticular changes, although even patients with apparently "mild" clinical disease may experience significant morbidity.

Any intraoral site can be affected, with the most common being the buccal mucosa and lateral tongue; these lesions are almost always present bilaterally. The gingiva and alveolar mucosa are also frequently affected (Figs. 5.34, 5.35, and 5.36); if this represents the only site of involvement, and erythema and/or ulceration are present, the clinical condition is called *desqua-*

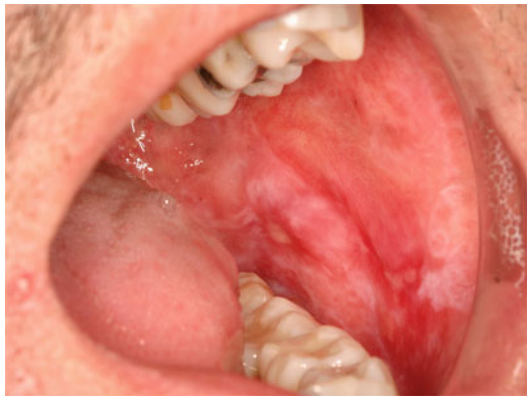


Fig. 5.31 Oral lichen planus of the left buccal mucosa with reticulation, erythema, and focal ulcerations

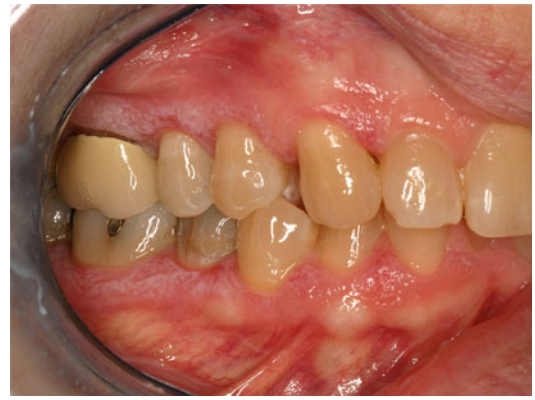


Fig. 5.34 Oral lichen planus with prominent reticulation restricted to the gingiva

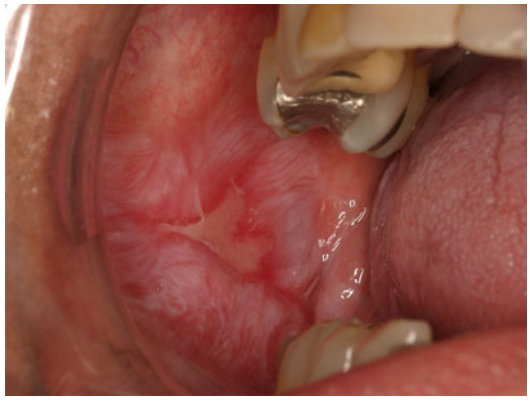


Fig. 5.32 Oral lichen planus of the right buccal mucosa with prominent reticulation, erythema, and central ulceration

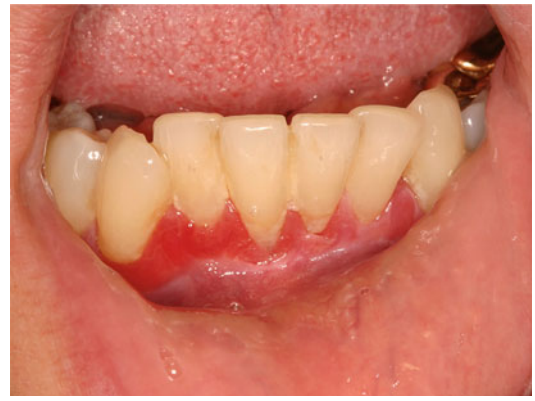


Fig. 5.35 Oral lichen planus presenting with only desquamative gingivitis. Without classic reticulation, biopsy is needed for diagnosis

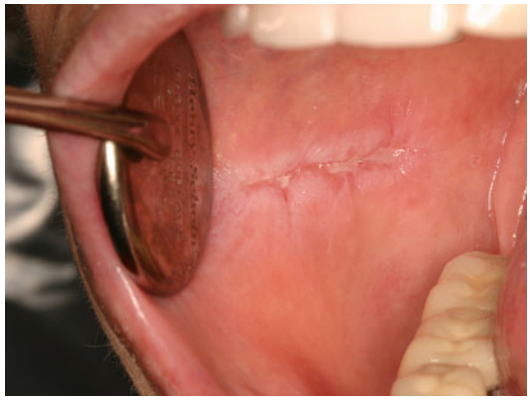


Fig. 5.33 Oral lichen planus of the right buccal mucosa with focal linear ulceration

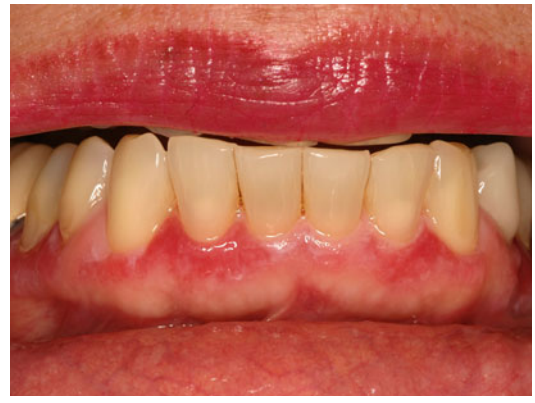


Fig. 5.36 Oral lichen planus with erythema and reticulation of the anterior mandibular gingiva

mative gingivitis. Fifty percent of cases of desquamative gingivitis ultimately prove to be *mucous membrane pemphigoid (MMP)*, 25 % are OLP, and the remaining 25 % are composed of other vesiculobullous disorders including *pemphigus vulgaris* and *linear IgA disease* (see below). The extent and severity of lesions can fluctuate over time and are often exacerbated during periods of illness and stress.

In patients presenting with classic appearing reticulated lesions, the diagnosis can typically be made by clinical examination alone. In cases when the diagnosis is not evident, a biopsy should be obtained avoiding ulcerative areas due to lack of intact epithelium. In the case of desquamative gingivitis, the specimen should be submitted for both routine histopathology as well as DIF. Histopathological features of reticulated lesions include hyperkeratosis, a "saw-toothed" appearance of the epithelial rete ridges, and the presence of band-like lymphocytic (primarily T-cell) infiltrate in the connective tissue just below the basement membrane with associated basal cell degeneration. There are no blood tests that help with the diagnosis of OLP.

Treatment should be dictated by the severity of symptoms rather than clinical appearance. Patients with asymptomatic OLP do not require treatment. In symptomatic cases the mainstay of therapy is high-potency topical corticosteroids. Limited lesions can be treated with a topical gel, while more extensive or difficult-to-reach areas are most effectively treated with a rinse. Patients with desquamative gingivitis can benefit from custom fabricated trays to apply the medication.

In refractory cases, topical tacrolimus can be applied in addition to corticosteroids. This is commercially available as an ointment, but can be formulated as a solution by a compounding pharmacy.

In cases where topical therapy is inadequate, a short course of high-dose prednisone can be effective for severe flares. Some cases of OLP may require long-term use of systemic steroid-sparing agents to maintain adequate disease control. Nonsteroidal systemic therapies include hydroxychloroquine, azathioprine, cyclosporine, tacrolimus, and thalidomide, and in severe refractory cases, extracorporeal photopheresis can be considered. Due to the lack of adequate controlled trials of systemic agents for OLP, there is little evidence to recommend the use of one therapy over another. Once the disease is under good control, attempts should be made to taper any systemic agents to the lowest effective dose possible while maximizing the effects of topical treatment.

The most serious complication of OLP is malignant transformation to squamous cell carcinoma (see Chap. 9). It is estimated that approximately 1 % of cases of OLP ultimately develop oral squamous cell carcinoma. The epidemiology and risk factors are poorly characterized, but it is generally thought that the more severe or refractory cases represent the highest risk. For this reason, any suspicious changes should be biopsied and all patients with OLP should be examined at least annually.

Oral Lichen Planus

	**DIAGNOSTIC TESTS**	None.
	**BIOPSY**	Only when clinical presentation is not classic (reticular) in appearance.
	**TREATMENT**	Topical corticosteroids and topical tacrolimus are the mainstay of therapy. When necessary, systemic agents should be considered. For severe refractory cases consider extracorporeal photopheresis or anti-TNF-α biological therapy.
	**FOLLOW-UP**	Patients should be followed carefully to evaluate response to therapy. Stable or asymptomatic cases should be followed annually; assess carefully for signs of malignancy.

Mucous Membrane Pemphigoid

While there are several variants of pemphigoid, MMP most commonly affects the oral mucosa. MMP is an autoimmune vesiculobullous blistering disease characterized by autoreactive antibodies that target the hemidesmosomal complex of the epithelial basement membrane, resulting in subepithelial tissue separation. This disease most frequently presents during the fifth to seventh decades of life and affects women at nearly twice the rate of men. Aside from pain, one of the greatest complications of MMP is scarring, which can lead to blindness in the setting of ocular lesions. When disease manifestations are limited to the oral mucosa, scarring is relatively rare. All patients should be questioned about extraoral symptoms including involvement of the throat, nose, eyes, and genitals, as these may be sites of undiagnosed disease.

Any oral mucosal site can be affected. Intact blisters may be observed, however, these generally rupture quickly and leave irregularly shaped ulcerations (Fig. 5.37). Many patients present only with desquamative gingivitis (Fig. 5.38). Diagnosis of MMP relies on perilesional biopsy submitted for both histopathology and DIF studies. Histopathology demonstrates clear subepithelial clefting (Fig. 5.39). DIF shows distinct deposition of IgG and complement at the basement membrane (Fig. 5.40). Indirect immunofluorescence results are variable.

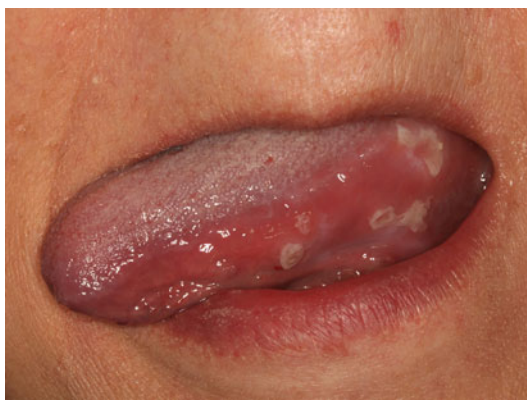


Fig. 5.37 Mucous membrane pemphigoid with nonspecific ulceration of the ventrolateral tongue

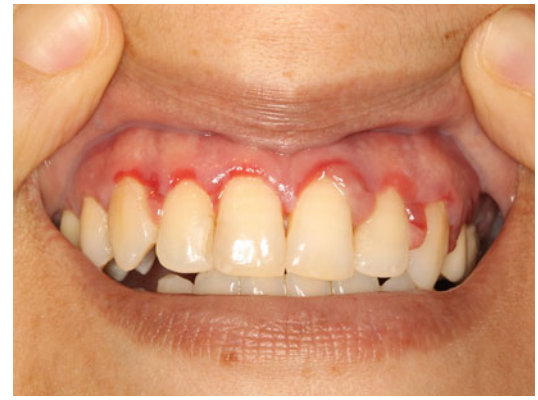


Fig. 5.38 Mucous membrane pemphigoid presenting as desquamative gingivitis. The gingiva is erythematous with focal areas of ulceration

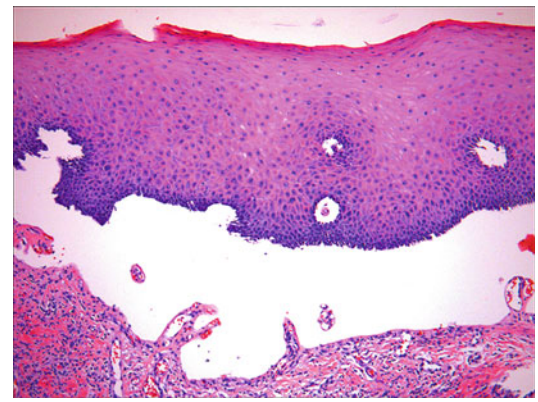


Fig. 5.39 Mucous membrane pemphigoid histopathology (H&E stain) demonstrating a clear subepithelial separation at the basement membrane. Photomicrograph courtesy of Mark Lerman, D.M.D., Boston, MA

If lesions are not limited to the oral mucosa, systemic therapy with corticosteroids and steroid-sparing agents is generally indicated. Purely oral cases of MMP should be treated based on symptoms and generally respond well to topical corticosteroids or tacrolimus. Desquamative gingivitis is most effectively treated with custom trays containing high-potency corticosteroid gels (Fig. 5.41).

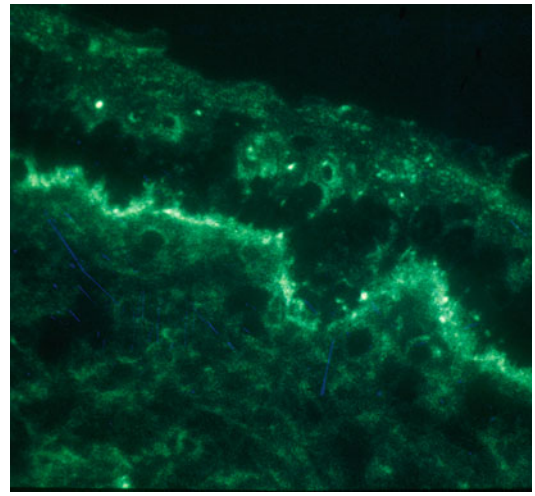


Fig. 5.40 Mucous membrane pemphigoid (direct immunofluorescence) showing a prominent band of reactivity along the basement membrane. Photomicrograph courtesy of Stephen Sonis, D.M.D., D.M.Sc., Boston, MA

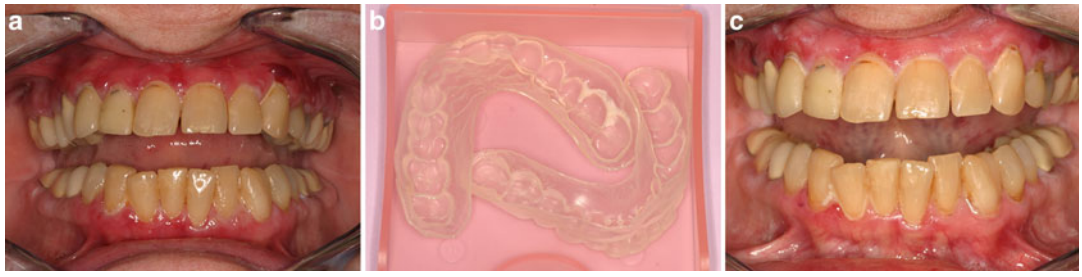


Fig. 5.41 Soft trays for localized intensive application of topical therapy for desquamative gingivitis. (**a**) Patient with extensive desquamative gingivitis due to mucous membrane pemphigoid. (**b**) Soft trays were made and the patient was instructed to treat with fluocinonide gel 0.05 % daily. (**c**) After 1 month of therapy with almost complete resolution of all signs and symptoms

Mucous Membrane Pemphigoid

	DIAGNOSTIC TESTS	None.
	BIOPSY	Yes; the specimen should be obtained from a perilesional area and submitted for both routine histopathology and DIF.
	TREATMENT	Topical corticosteroids (first-line) or tacrolimus (second-line) as the mainstay of therapy. Systemic agents if refractory: prednisone, mycophenolate mofetil, azathioprine, dapsone, cyclosporine, and tacrolimus. For severe refractory cases consider rituximab, intravenous immunoglobulin (IVIG), and extracorporeal photopheresis.
	FOLLOW-UP	Patients should be followed carefully while evaluating response to therapy. Patients with stable disease should be followed at least annually.

Pemphigus Vulgaris

The term "pemphigus" encompasses a group of autoimmune vesiculobullous blistering diseases, the most common of which is *pemphigus vulgaris*. This is a potentially severe disease, but it is no longer the life-threatening condition it was prior to the introduction of corticosteroids. Circulating IgG autoantibodies target the desmosomal complex, specifically binding the surface glycoproteins desmoglein 1 and 3, resulting in intraepithelial splitting. Females are affected slightly more frequently than males, with most patients presenting during the fourth to sixth decades of life. Patients of Mediterranean and Ashkenazi Jewish descent are affected at a higher rate. The skin is almost always involved; however, the appearance of oral lesions usually precedes cutaneous manifestations. Other mucosal sites, such as the nasal and anogenital regions, may be affected.

Oral lesions appear as well-demarcated, irregular erythematous erosions, and ulcerations that can become quite large and very painful (Figs. 5.42 and 5.43). Commonly affected oral sites are the buccal mucosa, palate, and gingiva. Intact bullae are rarely observed. A *positive Nikolsky sign* is a nonspecific feature in which a blister may be induced by rubbing unaffected skin or mucosa; this may be seen in pemphigus vulgaris but also in MMP or various other conditions. As any other mucosal site can be affected, patients should be questioned regarding extraoral symptoms and referred to an appropriate specialist as necessary. Without intervention, lesions tend to persist for weeks to months, often continuing to grow in size.

Diagnosis requires a perilesional tissue biopsy submitted for both histopathology and DIF studies. Histopathological findings include intraepithelial separation, typically just above the basal cell layer, and *acantholysis*, or separation of the epithelial cells from each other (Fig. 5.44). DIF demonstrates a classic intercellular binding pattern of IgG (Fig. 5.45). Indirect immunofluorescence (IIF) studies are typically positive for antibodies against desmosomal glycoproteins.

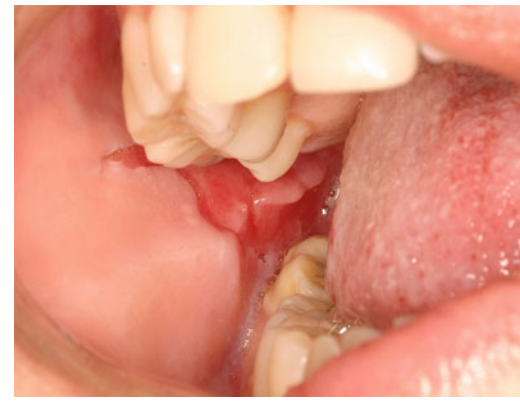


Fig. 5.42 Pemphigus vulgaris with well-defined ulceration and normal appearing surrounding tissues

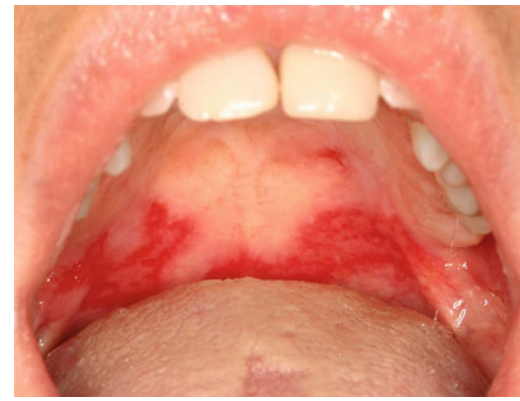


Fig. 5.43 Palatal lesions in a patient with pemphigus vulgaris

Management of pemphigus vulgaris invariably requires systemic therapy. Corticosteroids and steroid-sparing immunomodulatory agents (azathioprine, cyclosporine, tacrolimus, and mycophenolate mofetil) are the mainstays of treatment. Breakthrough lesions are common, in which case topical corticosteroids play an important role. Refractory cases of pemphigus vulgaris may be controlled with intravenous immunoglobulin therapy, rituximab, and extracorporeal photopheresis.

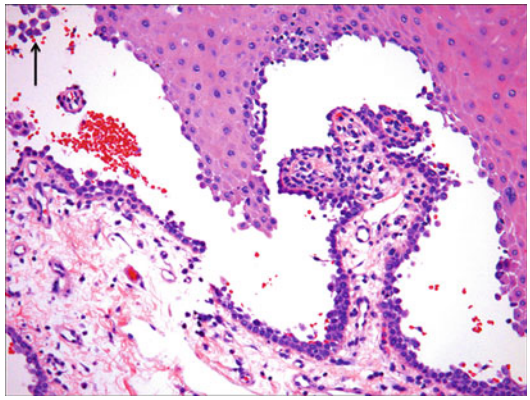


Fig. 5.44 Pemphigus vulgaris histopathology (H&E stain) demonstrating suprabasilar separation of cells and individual acantholytic (Tzanck) cells within the cleft (*black arrow*). Photomicrograph courtesy of Mark Lerman, D.M.D., Boston, MA

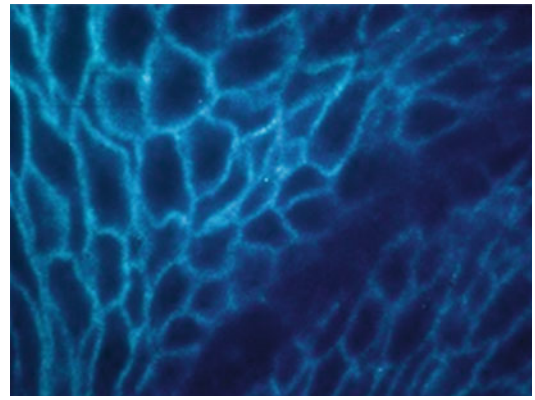


Fig. 5.45 Pemphigus vulgaris (direct immunofluorescence) showing prominent reactivity between keratinocytes throughout the epithelium. Photomicrograph courtesy of Stephen Sonis, D.M.D., D.M.Sc., Boston, MA

Pemphigus Vulgaris

	DIAGNOSTIC TESTS	IIF is generally positive.
	BIOPSY	Yes; the specimen should be obtained from a perilesional area and submitted for both routine histopathology and DIF.
	TREATMENT	Topical corticosteroids, or if ineffective, topical tacrolimus for oral lesions. Systemic agents include prednisone, mycophenolate mofetil, azathioprine, dapsone, cyclosporine, and tacrolimus. For severe refractory cases consider rituximab, IVIG, and extracorporeal photopheresis.
	FOLLOW-UP	Patients should be followed carefully while evaluating response to therapy. Patients with stable disease should be followed at least annually.

Other Autoimmune Vesiculobullous Diseases

Paraneoplastic Pemphigus

A very rare but important variant of pemphigus vulgaris seen exclusively in patients with underlying neoplasia is termed *paraneoplastic pemphigus*, also referred to as *paraneoplastic autoimmune multiorgan syndrome*. This condition has been associated with non-Hodgkin lymphoma, chronic lymphocytic leukemia, sarcomas, thymomas, and Castleman disease. Circulating autoantibodies are produced that target desmosomes and hemidesmosomes, resulting in potentially severe skin and mucosal lesions. Diagnosis and management of the underlying neoplasm are essential and generally results in resolution of the mucocutaneous disease.

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa is a rare chronic autoimmune subepidermal vesiculobullous disorder that affects the skin and mucosa. Onset is very early in life, however, severity varies greatly such that milder forms of the disease are often not identified for many years. Autoantibodies target mul-

tiple hemidesmosomal antigens, in particular components of type VII collagen, resulting in blister formation secondary to minor amounts of trauma. Diagnosis requires histopathology as well as direct and indirect immunofluorescence studies. Management includes corticosteroids, dapsone, azathioprine, mycophenolate mofetil, rituximab, and intravenous immunoglobulin. Oral lesions may be responsive to intensive topical corticosteroid therapy.

Linear IgA Disease

Linear IgA disease, also known as *Linear IgA bullous dermatosis*, is an autoimmune subepidermal vesiculobullous disorder characterized by deposition of IgA at the basement membrane zone. Numerous autoantibodies and target antigens have been identified. Linear IgA disease affects both children and adults; in children the course is often self-limiting while drug-related cases are more common in older adults. Oral lesions are common and clinically identical to those seen in MMP. Diagnosis requires perilesional biopsy for both histopathology and immunofluorescence studies. Management includes prednisone, dapsone, sulfapyridine, and colchicine. Intensive intraoral topical therapy as described above can be very effective.

Sources

Ayangco L, Rogers RS. Oral manifestations of erythema multi-forme. Dermatol Clin. 2003;21:195–205.

Challacombe SJ, Setterfield J, Shirlaw P, et al. Immunodiagnosis of pemphigus and mucous membrane pemphigoid. Acta Odontol Scand. 2001;59:226–34.

Dagistan S, Goregen M, Miloglu O, et al. Oral pemphigus vulgaris: a case report with review of the literature. J Oral Sci. 2008;50:359–62.

Eguia del Valle A, Aguirre Urizar JM, Martinez Sahuquillo A. Oral manifestations caused by the linear IgA disease. Med Oral. 2004;9:39–44.

Escudier M, Bagan J, Number SC, VII. Behçet's disease (Adamantiades syndrome). Oral Dis. 2006;12:78–84.

Grave B, McCullough M, Wiesenfeld D. Orofacial granulomatosis: a 20-year review. Oral Dis. 2009;15: 46–51.

Hirshberg A, Amariglio N, Akrish S, et al. Traumatic ulcerative granuloma with stromal eosinophilia: a reactive lesion of the oral mucosa. Am J Clin Pathol. 2006;126:522–9.

Kanerva M, Moilanen K, Virolainen S, et al. Melkersson-Rosenthal syndrome. Otolaryngol Head Neck Surg. 2008;138:246–51.

Mignogna MD, Fortuna G, Leuci S, et al. Nikolsky's sign on the gingival mucosa: a clinical tool for oral health practitioners. J Periodontol. 2008;79:2241–6.

Radfar L, Wild RC, Suresh L. A comparative treatment study of topical tacrolimus and clobetasol in oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105:187–93.

Scully C. Aphthous ulceration. N Engl J Med. 2006;355:165–72.

Scully C, Carrozzo M. Oral mucosal disease: lichen planus. Br J Oral Maxillofac Surg. 2008;46:15–21.

Scully C, Lo ML. Oral mucosal diseases: mucous membrane pemphigoid. Br J Oral Maxillofac Surg. 2008;46:358–66.

Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg. 2008;46:198–206.

Termino VM, Peebles RS. The spectrum and treatment of angioedema. Am J Med. 2008;12:282–6.

Tilakaratne WM, Freysdottir J, Fortune F. Orofacial granulomatosis: review on aetiology and pathogenesis. J Oral Pathol Med. 2008;37:191–5.

Woodley DT, Remington J, Chen M. Autoimmunity to type VII collagen: epidermolysis bullosa acquisita. Clin Rev Allergy Immunol. 2007;33:78–84.

Yancey KB, Egan CA. Pemphigoid: clinical, histological, immunopathologic, and therapeutic considerations. JAMA. 2000;19:350–6.

Zhu X, Zhang B. Paraneoplastic pemphigus. J Dermatol. 2007;34:503–11.