Review

**Immune-mediated diseases: what can be found in the oral cavity?**

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**Abstract**

Immune-mediated diseases frequently affect oral mucosa, which may often be the first site of clinical manifestation. In this review, we describe the most important oral lesions related to inflammatory disorders and present their management and novel therapies. The review is based on an open PubMed literature search from 1980 to 2012 with relevant keywords. Pemphigus vulgaris, oral lichen planus, cicatricial pemphigoid, erythema multiforme, Stevens–Johnson syndrome, systemic lupus erythematosus, Sjögren’s syndrome, and linear IgA dermatosis are the immune-mediated diseases with oral manifestations discussed. Etiology is unknown in most of these diseases, but recently some of them have been found to share common genes. Modern treatment of these diseases is based on drugs that interfere along the pathogenic mechanisms instead of the still commonly used palliative measures. However, the immunomodulatory drugs may also cause oral side effects, complicating the clinical picture. Therefore, consulting dental or oral medicine specialists can be necessary in some cases with various immune-mediated diseases.

**Introduction**

Immune-mediated diseases frequently involve the oral mucosa, which is often the first site of manifestation.¹ A detailed clinical examination of oral mucosa of an asymptomatic patient can therefore be the best opportunity for early diagnosis and treatment allowing control over the spread of the disease to the skin and/or other organs.² Some lesions in the mouth may indeed represent oral manifestations of an inflammatory disease. Hence, the aim of this review was to explain the most important oral lesions related to immunity disturbances, to present the common management and some novel therapies. The review is based on an open PubMed literature search from 1980 to 2012 with the keywords autoimmunity, oral lesion, and treatment. Owing to the scarcity of controlled trials in the area, no meta-analysis with subsequent systematic review could be conducted on this topic.

**Oral manifestations of immune-mediated diseases**

The main oral manifestations of the immune-mediated diseases discussed in this review are given in Table 1 and will be mentioned here in detail.

**Pemphigus vulgaris**

Pemphigus vulgaris is a chronic, autoimmune bullous disease characterized by the formation of an intraepithelial bulla. It is the most common subtype of pemphigus and involves the skin and/or mucosa. The oral mucosa is the primary site of manifestation in about 50% of patients with pemphigus. Skin lesions appear later, reaching several regions of the body, including the trunk, scalp, and neck. The nasal, pharyngeal, esophageal, conjunctive, vaginal, penile, and anal mucosa can also be affected.¹⁻³

Most studies show higher prevalence of the disease in women, while others report no difference between genders. The disease is more frequent between the fifth and...
sixth decades of life. The liability of some ethnic groups to pemphigus suggests genetic predisposition of the disease, although reports of familiar cases are rare.

The oral lesions appear as small bullae that burst rapidly, leaving painful erosions with a burning sensation. They mainly affect the buccal mucosa, soft palate, and lips, and less frequently the gingiva, where desquamative gingivitis is seen (Fig. 1a,b). The etiology of pemphigus is uncertain, but triggering or aggravating factors of the disease include pesticide exposure, malignancies, certain drugs, infections, dietary factors, and stress. The autoimmune mechanism of pemphigus is related to the production of immunoglobulin G (IgG) autoantibodies that react with desmoglein-3, adhesion structure of keratinocytes critical for maintaining epithelial integrity, promoting acantholysis and the formation of intraepithelial clefts.

Clinical, histopathological, and immunohistochemical examinations are used in the differential diagnosis of pemphigus to separate it from other diseases with similar clinical manifestations such as aphthae, erosive lichen planus, oral candidiasis, and pemphigoid, among others. A biopsy of the perilesional mucosa is required where acantholysis and a scarce inflammatory infiltrate are the characteristic pathologic features. The formation of a cleft occurs in the upper suprabasal layer, while the basal cells remain adhered to the basal membrane, creating the appearance of a row of tombstones. Direct immunofluorescence reveals circulating autoantibodies in the patient serum that bind to the intercellular junction of the keratinocyte substrate.

Oral lichen planus

Lichen planus is an inflammatory chronic disease of the skin and mucosae and is one of the most frequent dermatological diseases of the oral cavity. Cutaneous lesions produce itching and are usually self-limiting, whereas oral lichen planus (OLP) lesions are chronic, potentially premalignant, causing frequent morbidity, and rarely remit spontaneously. The prevalence of OLP ranges between 0.2 and 2%. It is fourfold higher in women than men, and the 30 to 70-year-old age group is at the highest risk. The most frequent localization of OLP is the posterio-inferior part of the buccal mucosa, with bilateral and symmetric involvement in 90% of the cases.

Regarding etiopathogenesis, OLP develops at the basal stratum level on a susceptible area. The exogenous or endogenous agents that induce basal cells to express given antigenic determinants on their membrane surface remain unknown. CD4+ and CD8+ lymphocytes fail to recognize basal cells as normal cells and trigger a cytotoxic reaction against them, producing apoptosis. It is known that a series of precipitating factors such as the Koebner phe-

Table 1 Immune-mediated diseases with known oral manifestations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Oral mucosa findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>Small intraepithelial bulla and secondary erosion</td>
</tr>
<tr>
<td>Oral lichen planus</td>
<td>Variable lesion (from a dot-shaped area to epithelial atrophy)</td>
</tr>
<tr>
<td>Cicatricial pemphigoid</td>
<td>Desquamative gingivitis, shallow ulcer</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Polymorphic erosive, bullous and erythematous lesions</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>Severe mucosal erosions</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Red area with white radiating keratotic striae and telangiectasias</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Dry mouth sensation or xerostomia</td>
</tr>
<tr>
<td>Linear IgA dermatosis</td>
<td>Annular vesiculobullous lesions</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Multiple blisters affecting the oral mucosa</td>
</tr>
<tr>
<td>Paraneoplastic pemphigus</td>
<td>Severe, hemorrhagic, painful oral erosions</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Subepidermal blister in cheek and tongue</td>
</tr>
<tr>
<td>Epidermolysis bullosa acquisita</td>
<td>Erosions/blisters, tooth loss, and mandibular contraction</td>
</tr>
<tr>
<td>Fixed drug eruption</td>
<td>Rash with residual hyperpigmentation</td>
</tr>
<tr>
<td>Recurrent aphthous stomatitis</td>
<td>Recurrent, self-limiting ulcers in nonkeratinized oral mucosa</td>
</tr>
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![Figure 1](image-url) Bilateral involvement in a patient with pemphigus vulgaris. (a) Right buccal mucosa; (b) left buccal mucosa
nomenon and the accumulation of bacterial plaque modify the course of OLP, the recovery of affected mucosa, and the effectiveness of drug therapies, respectively. Under direct immunofluorescence microscopy, OLP shows the presence of IgM and eventually IgG, IgA, C3, and fibrin in the colloid bodies. However, this pattern is not specific due to immunoglobulins and complement fixation on necrotic keratinocytes of the basal layer. This can also be observed in other diseases, including lupus erythematosus and erythema multiforme.

Various authors recognize OLP as a chronic disease with successive waves of destructive activity at the epithelium–corium interface, which produce the different clinical expressions of the disease. Three progressive phases can be distinguished clinically and microscopically: The initial stage (6–12 months or more) that is clinically characterized by white dots on the mucosa, followed by a second phase where white Wickham striae on oral mucosa can be seen. Histologically this phase shows normal epithelial thickness with mostly lymphocytic infiltrate located mainly around the tip of the rete ridges. In the intermediate stage (<10 to more than 20–30 years duration), the course of the disease may include alternate periods of variable activity and quiescence, and the most prevalent OLP types of this stage are erythematous and erosive OLP. Histologically, there is parakeratosis or orthokeratosis, and interpapillary rete pegs that initially acquire a saw-tooth appearance may later become atrophic showing a flat epithelium/corium interface and more diffuse (band-like) inflammatory infiltrate. Finally, the late stage (many years or even decades after the onset of the disease) presents with an atrophic or hyperkeratotic oral mucosa and still shows white plaques or Wickham striae. It often ends in a clinically less known, inactive cicatricial post-lichen stage, in which the epithelium thickness often is reduced, with destroyed rete pegs and a rectilinear epithelium/corium interface. A variable degree of collagen fibrosis can appear in the corium, and keratosis may become irregularly thick or verrucous. The cicatricial post-lichen stage is permanent and does not respond to medical treatment. Its importance lies in the possibility of progressive malignant transformation during the preceding stages of OLP, which persists in the atrophic and fibrous mucosa. At this point, it is important to mention that there exists controversy regarding OLP malignant transformation probably due to variations in the diagnostic criteria and knowledge of the post-lichen stage. There may also be confusion with other atrophic or hyperkeratotic lesions and in accepting the possibility of dysplastic changes in OLP. The presence of areas highly susceptible to the development of carcinomas, regardless of previous disease, may also confuse the clinician. There also are different opinions regarding the follow-up periods needed for OLP patients. However, a short follow-up time may underestimate the incidence of malignant transformation and the presence of risk factors associated with malignant transformation. Recently, it has been described that the amplification of c-Myc may be a helpful tool for identifying those cases of OLP that have higher risk for developing squamous cell carcinoma (Fig. 2a,b).

Cicatricial pemphigoid
Cicatricial pemphigoid is an autoimmune, chronic, bullous, subcutaneous disease characterized by the formation of painful bullae, predominantly on the mucosa, with or without skin involvement, and there is a tendency to form scars. Women are twice as frequently affected as men, most commonly between the fifth and sixth decades of life.

The oral mucosa is involved in 90% of the cases as either the only affected mucosa or associated with the involvement of other sites such as ocular, nasopharyngeal, esophageal, laryngeal, genital, rectal mucosa, and/or the skin. The conjunctiva is affected in 65% of the cases, and a large proportion of patients with oral lesions show asymptomatic conjunctiva involvement. Skin lesions are rare and appear after the mucosal lesions. These are most frequently seen in the head, neck, and upper part of the

Figure 2 Oral lichen planus (OLP). (a) Desquamative gingivitis in a patient with OLP; (b) OLP on dorsal tongue. Desquamative gingivitis is a common sign for OLP, cicatricial pemphigoid, and pemphigus vulgaris.
Patients with restricted oral mucosal lesions have an excellent prognosis (Fig. 3).

The most common clinical manifestation of cicatricial pemphigoid in the mouth is desquamative gingivitis, varying from an irregular erythema with slight discomfort to an intense general erythema with highly painful bullae. In other affected areas, such as buccal mucosa, alveola, palate, tongue, soft palate, and lower lip, cicatricial pemphigoid appears typically as a blister that readily bursts, leaving shallow ulcers with rough and bleeding bases that are very painful and remit only slowly. Gingival involvement might entail the loss of gum and bone tissue with subsequent tooth loss.

The pathogenesis of cicatricial pemphigoid has not been clarified. These patients have autoantibodies directed against specific adhesion molecules located in the hemidesmosomes at the basal epidermal keratinocytes and in the lamina lucida of the basal membrane, which induce the formation of a subepidermal cleft. The diagnosis of the disease is difficult, and clinical, histological, and immunopathological examinations are required for differential diagnosis from other autoimmune bullous diseases. This includes pemphigus vulgaris, paraneoplastic pemphigus, and Stevens-Johnson syndrome.

The histopathological examination is not distinctive, however, as it only reveals the presence of a subcutaneous bulla with inflammatory infiltrate. Direct and indirect immunofluorescence techniques are sensitive indicators but not specific for cicatricial pemphigoid as the findings are undistinguishable from other subcutaneous bullous diseases. Immunohistochemical techniques such as immunoblotting, enzyme-linked immunosorbent assay, and immunoprecipitation have simplified the diagnostic process by identifying new target proteins recognized by antibodies in different cicatricial pemphigoid subgroups.

**Erythema multiforme**

Erythema multiforme is an acute, immune-mediated, self-limiting mucocutaneous condition characterized by distinctive lesions with a pointed appearance. It is considered a hypersensitivity reaction to certain medications and infections. Erythema multiforme was previously thought to be a spectrum of clinical conditions, but today it is recognized as a distinct entity with different clinical and epidemiological characteristics. It is manifested by skin lesions that are generally characteristic by palpation or raised atypical lesions, with epidermal detachment in less than 10% of the body surface area and with minimal mucous membrane involvement. The oral lesions manifest as polymorphic erosive, ampullar, and erythematous lesions and blood-stained crusts, commonly located in areas of non-keratinized mucosa.

The etiology of erythema multiforme is unclear, although a type IV cytotoxic immune reaction has been implicated. This is mediated by T lymphocytes that react to antigens (viral, bacterial, pharmacological, or chemical). Cytotoxic immune complexes are formed that in turn affect keratinocytes, causing important intra- and subepithelial damage. The keratinocytes show intra- and extracellular edema, necrosis, and apoptosis-mediated cell death. It is now believed that these cytotoxic phenomena may result from the presence of autoantibodies targeted to desmoplakin I and II.

Infections are the primary etiological factor for erythema multiforme, with herpes simplex virus accounting for more than 50% of the cases. Specific herpes simplex virus antigens have been detected within keratinocytes by immunofluorescence, and herpes simplex virus genomic DNA has been detected by polymerase chain reaction in skin biopsies of erythema multiforme. Other common etiologies include *Mycoplasma pneumoniae*, fungal infections, and medications such as barbiturates, hydantoins, nonsteroidal anti-inflammatory drugs, penicillins, phenothiazines, and sulfonamides.

The acute and relapsing nature of the disease in addition to the typical target-like lesions leads to the clinical diagnosis. Necrotic keratinocytes in histopathological examination support the diagnosis. Finally, other autoimmune mucocutaneous blistering disorders can be ruled out by direct immunofluorescent examination. Special attention should be given to the sudden and intense onset of these lesions.
of the lesions, history of similar episodes, pleomorphic nature of the oral and skin lesions, and typical presence of blood-stained crusts on the lips.19

Stevens–Johnson syndrome
Stevens–Johnson syndrome has long been considered to resemble erythema multiforme with mucosal involvement but is now thought to be a single disease entity with toxic epidermal necrolysis. Although Stevens–Johnson syndrome is less severe, the etiology, genetic susceptibility, and mechanism are the same as for toxic epidermal necrolysis. They are both characterized by severe mucosal erosions, diffuse, non-palpable, flat atypical findings and, commonly, by preceding fever and flu-like symptoms. The condition is mainly caused by drugs but also by infections and probably by other risk factors not yet identified.

Finding out the cause in an individual patient is important. Thus, patients with drug-induced disease can be treated by withdrawal of the drug(s), and patients with a suspected infectious cause can be given the appropriate anti-infective treatment. Supportive therapy is crucial in improving the condition of these patients and may be more important than specific immunomodulatory treatments. Despite all therapeutic efforts, the mortality rate is high and increases with the severity of the disease, age of the patient, and with any underlying medical condition. Survivors may have long-term after-effects in mucous membranes, including severe eye problems.20–24

Systemic lupus erythematosus
Systemic lupus erythematosus (SLE) is a prototype systemic autoimmune disease characterized by loss of tolerance to nuclear antigens and various immunological abnormalities. These include the deregulated activation of T and B lymphocytes and the subsequent polyclonal activation of circulating B lymphocytes, producing a large quantity of autoreactive antibodies, and forming immune complexes with subsequent tissue and organ damage.25

The most frequent mucosal presentation of chronic SLE is an oral discoid lesion. The typical clinical picture is a well-demarcated, round, or irregular red area that can be atrophic or ulcerated, with white radiating keratotic striae and telangiectases, i.e., the same appearance as that of classic cutaneous discoid lupus. Morphologic variants of chronic oral lupus include the so-called honeycomb plaques with clinical appearance of mucosal scarring, intense keratotic white lesions, and linear fissured, ulcerative, and keratotic lesions that may arise in the buccal mucosa.26 Most of these patients have simultaneous cutaneous lesions, but mucosal manifestations alone are not rare. Isolated palatal lesions have also been reported. Pain is variable. Lesions are usually asymmetriically distributed in the mouth (palate, buccal mucosa, tongue), and this asymmetry is important in the differential diagnosis, because the lesions of clinically similar diseases such as OLP are usually symmetrical. Lip involvement is frequent in SLE, and clinical manifestations include well-demarcated discoid lesions or a diffuse cheilitis.27 Lesions typically tend to spread from the vermillion to the surrounding perioral skin, obscuring the limits of the vermillion. This feature is useful in differentiating discoid lupus from lip OLP and other types of cheilitis, because OLP lesions are characteristically limited to the vermillion area. The designation lupus cheilitis is used at times,28–30 but this may suggest a different or special manifestation instead of a typical discoid lupus lesion at that site.

Oral ulcerations or ulcers in the setting of SLE have long been considered predictors of systemic vasculitis and a worse prognosis.31 However, Jorizzo et al.32 demonstrated that these lesions are clinically and histopathologically specific lupus lesions (interface mucositis) with no prognostic implications.

The differential diagnosis for keratotic discoid lesions includes OLP, lichenoid reactions to dental fillings, traumatic or smoker’s keratitis, and verrucous carcinoma. Ulcerated discoid lesions must be differentiated from aphthous, erosive OLP, traumatic ulcers, deep mycoses, and Langerhans cell histiocytosis. Lip lesions may simulate contact cheilitis, factitious cheilitis, actinic cheilitis, OLP, psoriasis, erythema multiforme, and pemphigus vulgaris. The differential diagnosis for erythematous or purpuric macules includes OLP, erythema multiforme, mucous syphilis patches, petechiae of viral exanthema, and negative pressure purpura. Finally, the differential diagnosis for oral bullous SLE includes pemphigus vulgaris, mucous membrane pemphigoid, herpes simplex, varicella, and erythema multiforme with its variants, Stevens–Johnson disease and toxic epidermal necrolysis.27

Characteristic features of cutaneous and mucosal SLE are perivascular and interface dermatitis/mucositis. The histopathological distinction among acute, subacute, and chronic cutaneous SLE cases is based on the intensity of epithelial involvement, severity of follicular damage, and the nature and level of inflammatory infiltrate in the dermis.33 Thickening of epithelial and vascular basement membranes is visible with hematoxylin–eosin and periodic acid-Schiff (PAS) staining.34–35 The presence of epithelial atypia is not rare, probably attributable to a hyperproliferative state of the mucosa.33,36

Karjalainen and Tornich13 compared histopathological features of oral SLE with those of OLP and concluded that the most important differences included a thicker basement membrane in SLE (as assessed by hematoxylin–eosin and PAS staining), more pronounced edema in lamina propria in SLE, PAS-positive thickening of blood vessel walls in SLE, deeper perivascular infiltrates in SLE.
and, finally, greater epithelial atrophy in OLP. The presence of mucin in the lamina propria is an important clue for differentiating SLE from OLP.33

**Sjögren’s syndrome**

Sjögren’s syndrome is a systemic autoimmune disorder characterized by lymphocytic infiltration of the lacrimal and salivary glands, leading to dryness of the eyes and mouth. Patients with Sjögren’s syndrome have a typical pattern of lymphocytic infiltrates in the glands, characteristic autoantibodies, and extraglandular manifestations. These patients also have an increased frequency of lymphoproliferative disorders, ranging from enlarged glands to non-Hodgkin’s lymphoma. This syndrome may occur alone, defined as primary Sjögren’s syndrome, or in association with another defined autoimmune disease, such as rheumatoid arthritis, SLE, or scleroderma, and is then defined as secondary Sjögren’s syndrome.37,38

The syndrome affects 0.5–3% of the population and clearly predominates in women (9:1 vs. men). The disease is usually diagnosed at about 50 years of age, though there are two peak incidences, one following menarche, and another during menopause.40

Epidemiologic studies have indicated that genetic and environmental factors both play a role in the pathogenesis of Sjögren’s syndrome. Exogenous agents such as different viruses may trigger the disease in genetically predisposed individuals. However, the etiology is unknown. Disturbance in glandular cell apoptosis may be one possible explanation for the sicca symptoms in Sjögren’s syndrome. However, discrepancies have been described between glandular pathology and salivary flow. Recent reports suggested autoantibodies inhibiting innervation of acinar cells and defective water transport to be implicated in salivary secretion deficiency observed in Sjögren’s syndrome.38 Lymphoproliferative sialadenitis in Sjögren’s syndrome is associated with lymphocyte infiltration, epithelial cell proliferation, and apoptosis.41 A hallmark of the syndrome is B-cell hyperactivity manifested by autoantibody production, hypergammaglobulinemia, and the formation of ectopic lymphoid structures within the inflamed tissues, and it is associated with risk of B-cell lymphoma. The development of overt lymphoma likely results from sustained immune stimulation, which would promote the expansion of scarce B-cell clones and produce the outgrowth of monoclonal aggregates of B cells.42

In relation to the oral cavity, patients typically present difficulties with speech, chewing, and swallowing, and report dry mouth sensation or xerostomia, taste alterations including metallic, salty, or bitter taste, burning sensation in oral mucosa, and pain in the salivary glands at eating.43 Chronic erythematous candidiasis due to *Candida albicans* is seen in 70–80% of all patients, affecting the tongue, palate, and lip commissures, respectively.44 The most widely used complementary diagnostic techniques for Sjögren’s syndrome include lower lip minor salivary gland biopsy and sialometry.37

**Linear IgA dermatosis**

Linear IgA dermatosis is a rare autoimmune blistering disease characterized by subepidermal blisters and linear deposition of IgA autoantibodies at the dermoepidermal junction.47 Anular vesiculobullous lesions all over the body are typical presentations of the lesions.48 In childhood, the disease manifests with specific clinical characteristics distinct from the adult form designated as chronic bullous dermatosis. Most cases occur during the sixth decade of life, whereas the infantile form usually begins at about 4–5 years of age.49

In the pathogenic mechanisms of linear IgA dermatosis, the antigen is the carboxy terminus portion of the BPAG2 or BP180. The lesion formation is related to the disruption of the hemidesmosomes by the aggression of IgA autoantibodies against their molecular components. Some drugs can act as inducers of the disease, although the underlying mechanisms remain unknown. Spontaneous remission of the condition with removal of the drug suspected to be the trigger confirms its role in some cases. Drug-induced dermatosis is most commonly reported after treatment with intravenous vancomycin, although no cases have been reported after its oral administration because vancomycin is not absorbed when it is orally administered.50,51

**Bullous pemphigoid**

Bullous pemphigoid is a blistering disease affecting predominantly older individuals.52 It is clinically characterized by generalized, pruritic tense blisters, and crusts, usually in erythematous or apparently normal skin, together with infiltrated and urticarial plaques, papules, or eczematous lesions. The symptoms are most often symmetric and are located predominantly on the trunk and proximal extremities. Involvement of the oral cavity has been described in 10–30% of the cases, with the presence of multiple erosions affecting the marginal gingiva.53

The disease can be classified into two main groups: typical and atypical pemphigoid. In the typical type, generalized, localized, seborrhelic, mucous membrane, and paraneoplastic variants can be distinguished. Generalized pemphigoid is the most common form of the disease, with dozens to hundreds of blisters, usually affecting the elderly. The localized form is characterized by some solitary eruptions on the head or on the extensor surface of the extremities, without causing complaints.54 The histological features of bullous pemphigoid include subepidermal...
blisters with inflammatory infiltrates that often are rich in eosinophils but also contain lymphocytes, histiocytes, or neutrophils. These can also be observed in several other related conditions, and therefore further diagnostic testing is essential.\textsuperscript{52} Biochemical characterization of the bullous pemphigoid antigen has shown the existence of two bullous pemphigoid antigens, BP\textsubscript{230} for the 230 kDa protein and BP\textsubscript{180} for the 180 kDa protein, both located next to the hemidesmosomes.\textsuperscript{53–56}

**Paraneoplastic pemphigus**

Paraneoplastic pemphigus, or paraneoplastic autoimmune multiorgan syndrome, is a rare autoimmune vesiculobullous disease first described by Anhalt \textit{et al.}\textsuperscript{57} in 1990 in patients with occult malignancies. In paraneoplastic pemphigus, there are polymorphic cutaneous lesions ranging from blisters to erosions and even denudation on the trunk and extremities but also on the palms and soles. Severe, hemorrhagic, painful oral erosions are typical. This form tends to be associated with hematologic neoplasms.\textsuperscript{52} It has been observed that there are immunological effects of the tumor on the resident immune system rather than by direct tumor infiltration or tissue damage caused by metastasis. The affected individuals in most instances are between 45 and 70 years of age and are males.\textsuperscript{58} The simplified and most referred diagnostic criteria are proposed by Camisa \textit{et al.} and include three major criteria: (1) polymorphic mucocutaneous eruptions; (2) concurrent internal neoplasia; and (3) serum antibodies with specific immunoprecipitation-2 pattern, and three minor criteria: (1) histologic evidence of acantholysis; (2) direct immunofluorescence showing intercellular and basement membrane staining; and (3) indirect immunofluorescence staining with rat bladder epithelium for circulating autoantibodies. The presence of three major or two major and two minor of these criteria is considered diagnostic.\textsuperscript{59} Response to treatment is generally poor with significant morbidity and mortality.\textsuperscript{58}

**Dermatitis herpetiformis**

Dermatitis herpetiformis is a distinctive bullous skin eruption characterized by its chronic nature and by the grouping of the skin lesions, especially on knees, elbows, buttocks, and shoulders. The pathology shows a subepidermal blister, neutrophilic microabscesses in the papillary dermis, and IgA deposits in the dermal papillae and along the basement membrane. Mucosal involvement is distinctly unusual but has been seen on the tongue, cheeks, and even the larynx. The rash is caused by a gluten enteropathy, and even though most patients do not have specific gastrointestinal symptoms, a biopsy from the small intestine will show celiac disease in all patients.\textsuperscript{60}

**Epidermolysis bullosa acquista**

Epidermolysis bullosa acquista is an acquired, subepidermal bullous disease with clinical features similar to the genetic forms of dystrophic epidermolysis bullosa.\textsuperscript{61} It is a chronic disease with an incidence ranging from 0.2 to 0.5 new cases per million and per year. Patients can be classified into two major clinical subtypes: non-inflammatory (classical or mechanobullous) and inflammatory epidermolysis bullosa acquista, which is characterized by cutaneous inflammation resembling bullous pemphigoid, linear IgA disease, mucous membrane pemphigoid, or Brunsting-Perry pemphigoid.\textsuperscript{62} Widespread vesiculobullous eruptions are observed, typically involving the trunk, central body, extremities, and skin folds. Extracutaneous manifestations include ocular, oral mucosa, esophagus, anal, vaginal, tracheal, and laryngeal lesion. Oral lesions range between erosions, blisters, tooth loss, and mandibular contraction resulting in impaired ability to open the mouth and alveolar bone loss. The diagnosis is based on the clinical presentation, the detection of tissue-bound antibodies by direct immunofluorescence microscopy, and the detection of circulating antibodies directed against COL7 and/or a u-serrated pattern in direct immunofluorescence microscopy.\textsuperscript{62,63}

**Fixed drug eruption**

Fixed drug eruption is an interesting type of drug rash that is always caused by medication and is composed of one or more lesions that recur at the same site every time a specific drug is administered. When the drug in question is stopped, the lesions usually resolve with residual hyperpigmentation, which makes it easy to determine the affected area. It is mediated by CD8\textsuperscript{+} T cells with an effector memory phenotype, and these cells are limited to the site of the lesion.\textsuperscript{64,65} When a fixed drug eruption is limited to a single lesion, it is usually mild, but when it is extensive, it can be more serious with systemic symptoms such as fever and arthralgias, and it can even mimic Stevens–Johnson syndrome.\textsuperscript{64}

**Recurrent aphthous stomatitis**

Recurrent aphthous stomatitis is the most common type of ulcerative disease of the oral mucosa, and it affects approximately 20% of the general population. Minor, major, and herpetiform variants have been described for clinical presentation; the minor variant is the most common. The classic presentation of recurrent aphthous stomatitis is recurrent, self-limiting ulcers that mainly affect non-keratinized oral mucosa.\textsuperscript{66,67} Many different factors such as genetic, immunological, microbiological, nutritional, hormonal, emotional, traumatic, and others are involved in the etiology of recurrent aphthous stomatitis. Unfortunately, there is still no clear and definitive
explanation of how all these factors are really implied in the pathogenesis of RAS.\textsuperscript{64,67} Tumor necrosis factor alpha is one of the most important cytokines implied in the development of new aphthous ulcers in patients. There is no definitive curative treatment for RAS, and the most frequent treatment is with antimicrobials, steroids, immunomodulators, and others.\textsuperscript{65}

Management of oral manifestations of autoimmune diseases

The increase in life expectancy is followed by an increase in the number of patients with chronic health problems and subsequent increased use of drugs. A detailed medical history is mandatory to avoid the possibility of drug interactions and adverse effects, which are often in the underlying pathology of the oral manifestations of immune-mediated diseases discussed here.

Some of the described oral lesions such as OLP are treated with palliative measures, and topical corticosteroids are the treatment of choice in many cases.\textsuperscript{68} To the best of our knowledge, there is only one randomized clinical trial that compared treatments with topical tacrolimus 0.1% ointment and topical clobetasol propionate 0.05% ointment in 40 patients with histologically proven symptomatic OLP. The group treated with tacrolimus had better results in terms of complete response rates.\textsuperscript{69}

Regarding other entities with scarring and/or fibrotic processes of oral mucosa, i.e., cicatricial pemphigoid, there currently is no medication or other treatment available for reversing that development. Both local and systemic measures may be used for ameliorating symptoms and delaying disease progression; however, because the etiology is mostly unknown, treatment is neither specific nor curative.\textsuperscript{18,19} Continuous antiviral therapy has been successfully used to suppress the disease in patients with recurrent erythema multiforme. Immunosuppressant drugs are typically used in patients who do not respond to antiviral treatment, and azathioprine has been shown to be particularly effective in those with severe disease refractory to other therapies.\textsuperscript{20}

Currently the aim regarding the treatment of immune-mediated diseases is to use drugs that interfere along the pathogenic mechanisms. Interest in B-cell–targeted therapies has increased worldwide following recent convincing evidence that innate immunity, most notably mediated by interferon signaling, plays a role in the initial B-cell activation. Numerous drugs under current evaluation, including epratuzumab, a monoclonal antibody directed at the CD22 B-cell surface antigen, target the B-lymphocyte pathogenic axis. Baminercept, a lymphocytotoxin-beta receptor fusion protein, which along with B-cell activating factor supports the formation of germinal centers within salivary glands, is another molecule of interest for autoimmune diseases.\textsuperscript{70,71}

Particular promise has been shown by belimumab, a monoclonal antibody that specifically targets the B-cell activating factor receptor and may disrupt the cycle of B-cell activation and antibody production. Belimumab appears to be effective in SLE and is undergoing early stage development for the treatment of Sjögren’s syndrome.\textsuperscript{72}

Potential new cytokine therapeutic targets were recently suggested by data implicating the role of proinflammatory T-helper 17 cells in Sjögren’s syndrome. Interleukin (IL)-17 and IL-23, as well as related proinflammatory cytokines IL-12 and IL-6, are prominently expressed in salivary gland tissue in Sjögren’s syndrome.\textsuperscript{73}

Rituximab was the first B-cell targeting drug evaluated in Sjögren’s syndrome. Rituximab is a mouse–human (chimeric) antibody directed against the CD20 cell surface antigen present on B cells. It was introduced as treatment for primary lymphoma and results in a depletion of circulating B cells. The usefulness of rituximab to treat lymphoma and knowledge of the role played by B-cell hyperactivity in the systemic manifestations of Sjögren’s syndrome led to its proposal for therapeutic application in that syndrome some years ago. The use of B-cell–depleting therapies in Sjögren’s syndrome is supported by evidence that rituximab treatment depletes B cells in parotid gland tissue and in peripheral blood, as well as restores normal T-cell regulatory function, reducing glandular inflammation and improving function and regression of lymphoepithelial lesions that predispose to the development of lymphoma.\textsuperscript{74} Rituximab was found to improve subjective sicca symptoms, fatigue, and quality of life,\textsuperscript{75,76} and two small, randomized double-blind controlled studies demonstrated its efficacy and safety in Sjögren’s syndrome. The evidence suggests that rituximab is also effective for the extraglandular manifestations of this syndrome and that it has also been successfully administered in patients with oral pemphigus vulgaris since 2000 with favorable results, especially in patients that do not respond to classic or conventional treatments.\textsuperscript{77} Rituximab has shown efficacy in uncontrolled trials of recalcitrant pemphigoid with complete responses in 50–68% of the cases. As severe infections may occur as an unwanted adverse effect, close monitoring of the patients is a necessity.\textsuperscript{78–81} However, data in literature are scarce regarding the use of rituximab in this condition and regarding the other conditions later described in this paper.

In the case of paraneoplastic pemphigus, for the autoimmune phenomenon, treatment with systemic corticosteroids in high doses is needed. Intravenous
immunoglobulin, rituximab, alemtuzumab, plasmapheresis, and photopheresis are some other modalities of promising efficacy. The skin lesions respond better than mucosal (oral/bronchial) lesions, which are highly refractory to treatment. Additionally, treatment of the underlying neoplasia is of paramount importance.58

Dermatitis herpetiformis usually responds very well to dapsone with patients showing clear improvement in itch within 48 hours. This contrasts with no relief from oral corticosteroids. A strict gluten-free diet will also keep the rash under control after a few months.60

In general, by acting on the immune system, all immunomodulatory drugs may increase the risk of infection. Although usually mild and risk-free, the infections can also be severe, including those caused by opportunistic agents.81-84 Secondary adverse effects have been described with drugs that affect the oral cavity; for example, the cyclosporine-caused manifestation of gingival hyperplasia, which is probably due to an effect on fibroblast proliferation.85,86 Intake of tacrolimus has been associated with a burning sensation in the mouth and altered taste perception.87 Development of periodontal disease might also be possible in patients on immunomodulatory drugs, although it has not been fully described in the literature.88

Regarding mucosal treatment, including dental care of these patients, we need to consider the CYP3A4 substrates such as the local anesthetic lidocaine and the popular anxiolytics midazolam and diazepam. CYP3A4 inhibitors such as erythromycin and clarithromycin and macrolide antibiotics in general and azole antifungal drugs in particular also demand attention. Apart from the increased drug concentrations observed with simultaneous use of certain antifungal agents and immunomodulating drugs, however, there is no evidence for interactions with the drugs commonly used in the dental practice and the novel biologic agents.84,89,90

Table 2 General principles for the treatment of immune-mediated associated lesions of oral mucosa

| Basic oral healthcare and treatment of xerostomia | Maintaining good oral hygiene is a necessity |
| Diagnosing and treating eventual Candida infection is important |
| Dry mouth should be treated by ensuring enough daily intake of water, stimulating saliva secretion by chewing non-sugar-containing lozenges or chewing gums, moisturizing dry mucosa by vegetable oil (e.g., olive oil), by using commercial dry mouth products, or in extreme xerostomia cases administering pilocarpine 5 mg tablets 5 times daily or cevimeline capsules 30 mg 3 times daily |
| Maintaining good oral hygiene is a necessity |
| Diagnosing and treating eventual Candida infection is important |
| Specific medication |
| Topical application of corticosteroids (ointments, mouthwash solutions, nasal sprays) |
| Systemic administration of corticosteroids (mild cases benefit from decreasing dosage corticosteroid therapy while severe cases may need titration of the dosage until symptoms ameliorate) |
| Topical application of immunomodulatory drugs such as tacrolimus in lichen planus |
| Systemic administration of immunomodulatory drugs, such as rituximab, in severe cases where corticosteroid therapy does not help |

Conclusion

Many immune-mediated diseases present with oral manifestations that often can be the first clinical symptoms and signs of the pathology. Oral health personnel must therefore be alerted, and a careful examination of mucosa is necessary often by consultation of dental and/or oral medicine specialists. Data are nevertheless scarce of the true prevalence of the respective oral lesions that are mostly nonspecific. In addition, immunosuppressant drug treatment as such may cause oral side effects needing attention. As long as randomized controlled trials are lacking, the treatment of choice of autoimmune diseases and their treatment-associated oral lesions needs to be based on clinical experience. Table 2 gives outlines of some general treatment principles in this regard. Dermatologists must not forget the thorough examination of the mouth as these diseases present mostly with mucosal and sometimes with dental problems, in addition to skin lesions. The oral health specialists may have special means to help the symptoms of an individual patient.

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Questions (answers found after references)

1 How often is oral mucosa involved in pemphigus vulgaris?
   a 20% of the cases
   b 50% of the cases
   c 75% of the cases
   d Not very often
2. Which are the different stages in oral lichen planus?
   a. Bullous, atrophic, verrucous
   b. There is only one stage
   c. Initial, intermediate, late
   d. Initial, quiescent, late

3. Are women more prone than men to autoimmune diseases?
   a. No
   b. Yes
   c. Both the same
   d. None are prone

4. How often is oral mucosa involved in cicatricial pemphigoid?
   a. 90% of the cases
   b. 25% of the cases
   c. Never is involved
   d. Not very often

5. Which is the association between Stevens–Johnson syndrome and toxic epidermal necrolysis?
   a. They both share etiology
   b. They both share genetic susceptibility
   c. They both share mechanism
   d. a, b, and c are correct

6. Describe the clinical appearance of an oral discoid lesion:
   a. A well-demarcated, round, or irregular red area
   b. An atrophic or ulcerated area
   c. An area with white radiating keratotic striae and telangiectases
   d. a, b, and c are correct

7. Are infections the primary etiological factor for erythema multiforme?
   a. Yes, with herpes simplex virus accounting for more than 50% of the cases
   b. Yes, with bacterial predominance
   c. Yes, with fungal predominance
   d. No

8. Which organ is most affected in Sjögren’s syndrome?
   a. Nose
   b. Eyes and mouth
   c. Heart
   d. None

9. Which is the antigen of linear IgA dermatosis?
   a. It is not known
   b. BPAg2
   c. BP180
   d. b and c are correct

10. Is there an effective therapy to treat immune-mediated diseases?
    a. There are promising results with some drugs
    b. There is not an adequate treatment
    c. Randomized controlled trials are lacking
    d. a and c are correct

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Answers to questions
1 b
2 c
3 b
4 b
5 d
6 d
7 a
8 b
9 d
10 d
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