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Review

Oral mucosal manifestations of autoimmune skin diseases

Mayson B. Mustafa [a,b], Stephen R. Porter [c], Bruce R. Smoller [d], Cassian Sitaru [a,e,*]

[a] Department of Dermatology, University of Freiburg, Hauptstrasse 7, 79104 Freiburg, Germany
[b] Oral medicine section, Department of Oral and Maxillofacial Surgery, University of Khartoum, Faculty of Dentistry, Khartoum, Sudan
[c] UCL, Eastman Dental Institute, London,United Kingdom
[d] Department of Pathology, University of Rochester, School of Medicine and Dentistry, USA
[e] BIOSS Centre for Biological Signalling Studies, Signalhaus Freiburg, Schänzlestr. 18, 79104 Freiburg, Germany

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ABSTRACT

A group of autoimmune diseases is characterised by autoantibodies against epithelial adhesion structures and/or tissue-tropic lymphocytes driving inflammatory processes resulting in specific pathology at the mucosal surfaces and the skin. The most frequent site of mucosal involvement in autoimmune diseases is the oral cavity. Broadly, these diseases include conditions affecting the cell-cell adhesion causing intra-epithelial blistering and those where autoantibodies or infiltration lymphocytes cause a loss of cell-matrix adhesion or interface inflammation. Clinically, patients present with blistering, erosions and ulcers that may affect the skin as well as further mucosal surfaces of the eyes, nose and genitalia. While the autoimmune disease may be suspected based on clinical manifestations, demonstration of tissue-bound and circulating autoantibodies, or lymphocytic infiltrates, by various methods including histological examination, direct and indirect immunofluorescence microscopy, immunoblotting and quantitative immunoassay is a prerequisite for definitive diagnosis. Given the frequency of oral involvement and the fact that oral mucosa is the initially affected site in many cases, the informed practitioner should be well acquainted with diagnostic and therapeutic aspects of autoimmune dermatosis with oral involvement. This paper reviews the pathogenesis and clinical presentation of these conditions in the oral cavity with a specific emphasis on their differential diagnosis and current management approaches.

Contents

Abbreviations: BP, bullous pemphigoid; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; ELISA, enzyme-linked immunosorbent assay; IF, immunofluorescence; LAD, linear IgA disease; MMP, mucous membrane pemphigoid; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris.

* Corresponding author at: Department of Dermatology, University of Freiburg, Hauptstrasse 7 D-79104 Freiburg, Germany. Tel.: +49 761 27067690; fax: +49 761 27068290.
E-mail addresses: cassian@mail.sitaru.eu, cassian.sitaru@uniklinik-freiburg.de (C. Sitaru).

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1. Introduction

Oral mucosa and skin are composed of highly specialized stratified epithelium that functions as a first-line barrier against physical and chemical damage. The integrity of this epithelial barrier is essentially dependent on structures maintaining cell-cell and cell-matrix adhesion [1]. Autoimmune bullous diseases are associated with autoantibodies directed against structures that mediate cell-cell and cell-matrix adhesion in skin and mucous membranes [2]. In pemphigus diseases tissue injury is mediated by autoantibodies against the cell-cell junction causing intra-epithelial blistering, whereas in subepidermal autoimmune diseases autoantibodies are directed against the epithelial – connective tissue junction at the basement membrane zone (BMZ) [3]. Primary or extensive oral involvement is the hallmark of further inflammatory autoimmune conditions, including lichen planus (LP), erythema multiforme (EM), lupus erythematosus (LE) and chronic ulcerative stomatitis (CUS).

Skin and oral mucosa are stratified epithelia, in which the cell-cell adhesion is mainly mediated by desmosomes and adherens junctions, whereas the adhesion of basal epithelial cells on the underlying basement membrane essentially depends on hemidesmosomes and focal contacts (Fig. 1) [4]. Desmosomes are anchoring complexes that link epithelial cells to each other and attach the keratin filaments to the cell surface. Desmosomes consist of calcium-dependent adhesion molecules called cadherins, including desmogleins and desmocollins, which are transmembrane proteins that extend across the plasma membrane and mediate cell-cell adhesion by homo- or heterophilic interactions between their extracellular protein domains. An additional group of intracellular proteins resides on the cytoplasmic face of desmosomes and constitutes the desmosomal plaque. Desmosomal plaque is associated with different types of proteins including plakoglobin, the desmoplakins, the plakophilins, envoplakin, and periplakin. It provides adhesion by linking the desmosomal transmembrane cadherin proteins to the cytoplasmic keratin filaments [1,5].

Hemidesmosomes are specialized junctional complexes on the ventral surface of the basal keratinocytes that maintain the epithelial cell attachment to the underlying basement membrane. In the oral cavity they can also be found in the junctional epithelium in contact to the tooth surface [6]. The basement membrane zone comprises the basal cell plasma membrane, the lamina lucida, the lamina densa and the sublamina densa. Anchoring filaments traverse the lamina lucida perpendicularly from the basal cell membrane to the underlying lamina densa [3]. At molecular levels, the basement membrane zone contains a mixture of structural components and antigens including collagen VII, which is the major structural component of anchoring fibrils, and collagen IV, which is a major ubiquitous component of vertebrate basement membranes. Laminins, which exist in various molecular forms as abundant non-collagenous glycoproteins of basement membranes, are heterotrimers consisting of alpha, beta and gamma chains [3,6].

Hemidesmosomes, together with the anchoring filaments, form the hemidesmosomes anchoring filament complex, which plays an important role in cell-basement membrane adhesion. The molecular

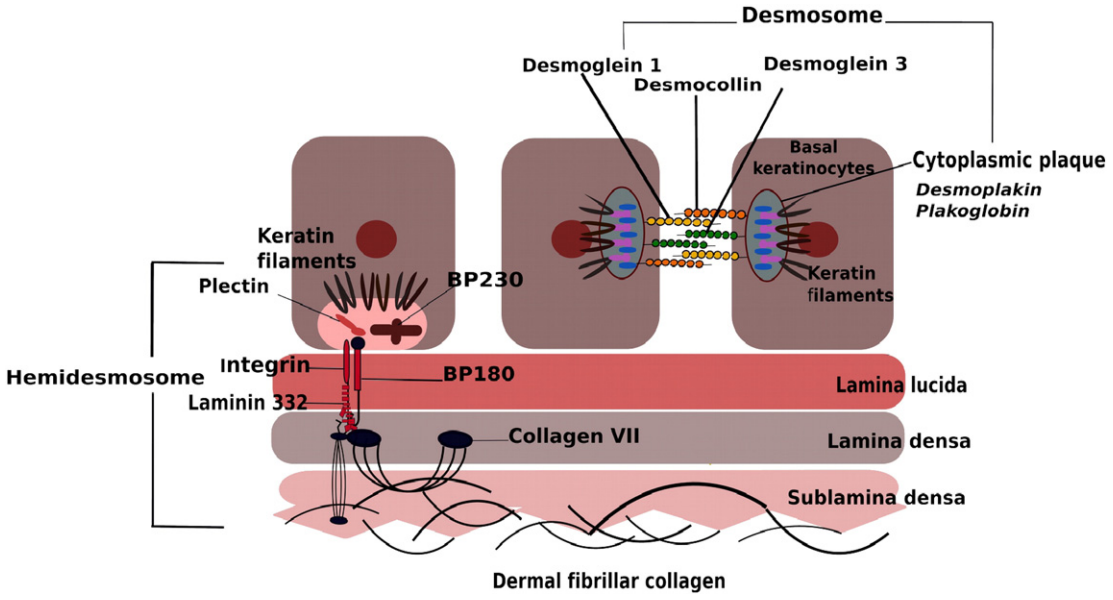

Fig. 1. Schematic representation of major autoantigens found in the skin and mucous membranes. Autoantigens are molecules that maintain cell-cell and cell-matrix adhesion. Desmosomes consist of cadherins, including desmogleins and desmocollins, which are transmembrane proteins that extend across the plasma membrane and confer adhesion by calcium-dependent interactions between their extracellular protein domains. On the cytoplasmic sides of desmosomes, resides the desmosomal plaque, through which the carboxy-terminal regions of cadherins are rooted and composed of different types of proteins such as plakoglobin and desmoplakin, which provide adhesion by linking the desmosomal transmembrane cadherin proteins to the cytoplasmic keratin filaments. Hemidesmosomes have an important role in cell-basement membrane adhesion and are organized in three classes of proteins. The first class is the cytoplasmic plaque proteins, which connect the intermediate filament cytoskeleton to the plasma membrane. These include bullous pemphigoid antigens BP230 (BPAG 1) and plectin. The second class includes α6β4 integrin and BP180 (also termed BPAG 2 or type XVII collagen), which are transmembrane proteins involved in the assembly of hemidesmosomes, connecting the cell interior to the extracellular matrix and serving as cell receptors. The final class of proteins consists of basement membrane associated proteins of the extracellular matrix, which include different laminin isoforms. Laminin (Ln) 332 is a major component of the lamina densa. Laminin γ1 chain, present in the vessel walls and also in the structure of laminin 511, may also function as autoantigen. Laminins interact with different subsets of integrins such as α6β1, α3β1 or α6β4 and regulate cellular adhesion and function . Collagen VII is the main constituent of the anchoring fibrils, which connect lamina densa to the collagen fibers of the upper dermis.

organization of hemidesmosomes is based on three classes of proteins. The first class is the cytoplasmic plaque proteins, which connect the intermediate keratin filament cytoskeleton to the plasma membrane. These include bullous pemphigoid antigens BP230 (BPAG 1) and plectin. BP230 was the first recognized targeted antigen in patients with bullous pemphigoid. The second class consists of transmembranous proteins, including α6β4 integrin and collagen XVII/BP180 (also termed BPAG2), which connect the hemidesmosomal plaque to the extracellular matrix and may serve as cell receptors [7]. The extracellular domain of α6β4 integrin is crucial for cell adhesion and acts as a receptor for various laminin types with particular high affinity to laminin 332. BP180 is a collagenous molecule that can interact with α6β4 integrin. A further main class of proteins of the epidermal basement membrane are components of the extracellular matrix and include different laminin isoforms and collagen IV. Laminins are large family of glycoproteins serving as major cell adhesion substrates at the basement membranes. They interact with different subsets of integrins such as α6β1, α3β1 or α6β4. Such an interaction at the cell surface regulates not only epithelial cell adhesion to the basement membrane zone but also further physiological cellular functions such as proliferation, migration polarity and differentiation [6,7].

Various autoimmune diseases may involve oral epithelium, including pemphigus vulgaris, mucous membrane pemphigoid, epidermolysis bullosa acquisita, lichen planus, erythema multiforme, lupus erythematosus and chronic ulcerative stomatitis. Affected individuals present with variable degrees of oral mucosal lesions associated with extraoral manifestations due to involvement of the skin and/or further mucosal surfaces, including nasal mucosa, pharyngeal mucosa or the conjunctiva [8,9]. The clinico-epidemiological features of autoimmune diseases have been studied in different populations worldwide. However, the majority of existing reports focus on the epidemiology of a single disease or a group of diseases and only a few describe the epidemiological features of the whole spectrum of autoimmune diseases in particular population. Studies from Eastern Europe show that pemphigus is the most common autoimmune blistering disease with an estimated incidence and prevalence of 4 and 24.8 per 100 000 inhabitants, respectively [10]. Similar results also emerged in studies conducted in Western Asia, East Asia and Africa, where pemphigus was also found to be the most prevalent autoimmune bullous dermatoses [11–13]. In contrast, in Western Europe and North America, bullous pemphigoid was found to be the most common autoimmune blistering disease with an incidence ranging from 0.6 to 4.3 cases per 100 000 inhabitants [14–16]. Several descriptive epidemiological studies on lupus erythematosus have been also conducted worldwide. The most extensive available data come from the European Union and the United States of America. The incidence rate of SLE in Europe is 3.3–4.8 cases per 100,000 population and year and in the USA 2.2–7.6 [17,18].

The prevalence of oral mucosal involvement in immune-mediated disorders varies according to the type of disease. Studies show that oral lichen planus is the most common immune-mediated disorder affecting the oral cavity, followed by pemphigus vulgaris and mucous membrane pemphigoid [19–23] (Table 1). Moreover, oral mucosa can be the first affected mucosal surface in many of these conditions, a fact that emphasizes the need for better understanding of clinical features and diagnostic tools for autoimmune diseases among practitioners. Precise and early diagnosis greatly facilitates timely, effective and specific treatment [19].

Table 1
Prevalence of oral mucosal involvement in immune-mediated disorders.

Disease	No. of cases	Reference
Lichen planus (65%) Pemphigus vulgaris (26.8%) Pemphigoid (7.3%)	82	Carvalho et al. 2011 [20]
Lichen planus (70.2%) Pemphigus vulgaris (24.9%) Pemphigoid (3.3%) Erythema multiforme (I.3%) Lupus erythematosus (0.33%)	309	Jaafari-Ashkavandi et al. 2011 [22]
Lichen planus (51%) Lupus erythematosus (20%) Erythema multiforme (20%) Pemphigus vulgaris (9%)	88	Goncalves et al. 2010 – [21]
Lichen planus (76.56%) Pemphigoid (9,37%) Erythema multiforme (7.82%) Pemphigus vulgaris (6.25%)	64	Arisawa et al. 2008 – [19]
Lichen planus (70.5%) Pemphigoid (14%) Pemphigus vulgaris (13%) Linear IgA disease (1.6%)	187	Leo et al. 2008 – [23]

2. Clinical phenotypes of oral involvement in autoimmune disorders

Autoimmune diseases may manifest on oral mucous membrane as erythema, blisters, erosions, and ulcerations. By far, oral blisters and ulcerations are the most common presenting features of immune-mediated disorders in the oral cavity. Oral blisters erode rapidly and leave behind ulcers associated with moderate to severe pain and discomfort that may interfere with speaking, eating and swallowing. A variety of local and systemic factors and conditions may trigger mucosal ulceration such as trauma, recurrent aphthous stomatitis, haematological diseases, gastrointestinal disorders and malignant conditions. Patients with immune-mediated disorders usually present with multiple ulcers or erosions, which may have an acute onset or develop slowly over a period of time. Erosions and ulcerations appear variable in size with irregular shape and are preceded by blisters as a result of intra-epithelial or sub-epithelial damage (Table 2). Further mucosal lesions, including white striae or plaques may also be identified upon clinical examination. Extra-oral examination is important and may reveal lesions of the skin and of other mucous membranes including the nose, eyes or genitalia. These lesions may appear concomitantly with oral lesions or may precede or arise later in the course of the disease.

Several immune-mediated disorders share a common clinical feature in the oral cavity, the so-called “desquamative gingivitis”. This term was introduced to describe the presence of erythema, localized or generalized desquamation and /or erosion on the buccal aspect of attached gingiva mainly of the anterior teeth. In some cases, marginal gingiva may also be affected. Gingival desquamation has a subacute or chronic onset in the majority of cases, with variable degrees of extension and distribution [24]. Desquamative gingivitis thus may be a common clinical phenotype occurring in a variety of disorders such as chronic ulcerative stomatitis, lichen planus, mucous membrane

Table 2
Major autoantigens in immune-mediated disorders affecting the oral mucosa.

Disease	Autoantigen
Pemphigus Diseases	
Pemphigus vulgaris	Desmoglein 3, Desmoglein 1
Paraneoplastic pemphigus	Desmoglein 3, Desmoglein 1, Desmoplakin, Periplakin, Envoplakin, Plectin, Desmocollins 1-3, BP230, Alpha-2-macroglobuline-like -1
Pemphigus vegetans	Desmoglein 3, Desmoglein 1
Pemphigus foliaceus	Desmoglein 1
Pemphigoid Diseases	
Mucous membrane pemphigoid	Collagen XVII/BP180, BP230, Laminin 332, α6β4 integrin
Linear IgA disease	LAD-1 (120 kDa), LABD97(97 kDa), 285 kDa, 180 kDa
Epidermolysis bullosa acquisita	Collagen VII
Bullous pemphigoid	Collagen XVII/BP180, BP230
Dermatitis herpetiformis	Tissue/epidermal transglutaminase
Chronic ulcerative stomatitis	deltaNp63alpha
Lichen planus	Not known
Erythema multiforme	Not known, Desmoplakin I and II (?)
Systemic lupus erythematosus	Nuclear antigens

(cicatricial) pemphigoid, pemphigus vulgaris, erythema multiforme, plasma cell gingivitis and graft-versus-host disease [24]. Epidemiological data shows that desquamative gingivitis is associated with immune-mediated disorders in about 88% to 98% of the cases [25]. Mucous membrane pemphigoid has been reported in many published series to be the most common cause of desquamative gingivitis, responsible for 35% to 48% of the cases [24,26,27]. However, more recent data showed a predominance of oral lichen planus over mucous membrane pemphigoid as a cause for desquamative gingivitis (75% vs 9%) [25].

3. Diagnostic approach

The specificity of the clinical features as a diagnostic parameter tends to vary among different autoimmune disorders. A significant overlap exists in their clinical presenting features, which makes accurate diagnosis extremely difficult based on clinical features alone. Therefore, for initiating an adequate differential diagnosis, observation of the clinical features must be accompanied by histopathological examination of the skin or mucosal biopsy [28]. Biopsies that are taken from fresh vesicles/blisters are helpful in revealing the pathological pattern of tissue damage regarding the site of vesicles formation as well as the presence, intensity, and composition of the inflammatory cells infiltrate [29]. However, the definitive, accurate diagnosis of autoimmune diseases requires the detection of immunoreactant deposits in the tissues and the circulating autoantibodies by direct and indirect immunofluorescence (IF) microscopy, respectively. Direct IF microscopy helps to detect molecules such as immunoglobulins and complement within biopsy specimens. Selection of the site for the biopsy specimen is important. Direct IF microscopy is performed on non-bullous or non-eroded skin or mucosa (i.e. erythematous or normal appearing tissue adjacent to blisters or erosions), because immune deposits may be degraded in the area where the dermal-epidermal separation occurs, leading to false negative results. False negative results may also occur as a result of improper handling or faulty preservation of the biopsy, which must be frozen immediately and stored at temperatures below −70 °C or placed in a saline or a special Michel's medium for transport for no longer than 48 hours for subsequent immunofluorescence testing [29,30].

Indirect IF microscopy, is a test in which patient's serum is examined for the presence of circulating autoantibodies to a defined antigen. Substrates used in this technique include frozen sections of normal tissues such as human skin and monkey oesophagus. These sections are then incubated with serum samples and the binding of serum autoantibodies to their corresponding antigens in the tissues is detected by using fluorescent-labelled anti-immunoglobulin antiserum [31]. For further characterising the binding sites of autoantibodies against the basement membrane, the sensitivity of this technique may be increased by using salt-split skin as a substrate. This substrate is generated by incubating normal human skin in 1 M NaCl until splitting occurs within the lamina lucida of the basement membrane. This test allows the differentiation between serum autoantibodies that bind to the roof and those that stain the floor of the artificial split reflecting the molecular difference in autoantibody specificity [30].

A number of other immunoassays, including enzyme-linked immunosorbent assay (ELISA), immunoblot or immunoprecipitation are available to facilitate the characterization of the molecular specificity of autoantibodies. Of these techniques, the ELISA is most commonly used. With the identification of target antigens and advancement of molecular biology and recombinant technology, antigens have been produced in bacteria and eukaryotic cells. These recombinant, cell-derived forms of the target antigens have been utilized in the development of sensitive and specific ELISA kits for detection of circulating autoantibodies. ELISA using recombinant antigens has several advantages over indirect IF techniques on tissue sections. It provides information on the molecular specificity of autoantibodies, it is easy to perform and readily amenable to standardization, and, importantly gives quantitative results. Therefore, these are exquisite parameters for monitoring diseases, in which levels of serum autoantibodies have been shown to correlate with disease activity. Several commercially available ELISA kits are now used for the diagnosis and monitoring of immune-mediated diseases (Table 3) [32,33].

4. Pemphigus diseases

Pemphigus diseases represent a group of immune-mediated disorders characterized by widespread blistering and ulceration affecting the skin and mucous membranes. The term pemphigus is the latinised form of the Greek *Pemphix* (meaning bubble or blister). In 1964, it was Beuter and Jorden who found that patients with pemphigus diseases exhibit circulating autoantibodies against calcium-dependent adhesion molecules (desmosomes), which maintain keratinocytes adhesion [34]. Binding of autoantibodies to desmosomal components results in cell-cell detachment (acantholysis) and formation of intra-epithelial blisters [35].

Main diseases of the pemphigus group include pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, pemphigus erythematosus, paraneoplastic pemphigus and IgA pemphigus [36,37]. Oral mucosa can be involved to variable degrees in different pemphigus conditions, however, pemphigus vulgaris and paraneoplastic pemphigus are the most common variants of the pemphigus group that consistently show oral lesions during the course of disease.

Paraneoplastic pemphigus, sometimes also termed paraneoplastic autoimmune multi-organ syndrome (PAMS), is usually associated with malignant tumours such as lymphomas, leukaemia and malignant melanoma. The disease arises as a result of several autoantibodies directed against several keratinocyte proteins such as desmoglein 1, desmoglein 3, desmoplakin 1, envoplakin, periplakin and BP230 [38]. Patients develop intractable mucosal ulceration of the oropharynx and severe crusting of the lips along with the typical cutaneous eruptions of pemphigus diseases [39].

Pemphigus vegetans is a rare variant of pemphigus vulgaris, that constitutes only 1–2% of all pemphigus cases. The main antigenic targets of pemphigus vegetans are the same as for pemphigus vulgaris, namely desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1). Pemphigus vegetans usually affects intertriginous areas such as the axilla and the groin and gives rise to vegetating skin lesions and vesicles. Long-standing disease may produce hyperkeratotic and fissured vegetations [40]. More than 50% of the patients show oral manifestations preceding cutaneous lesions and those with cutaneous lesions eventually develop oral manifestations. Oral lesions appear as irregular ulceration that may have a vegetative appearance with occasional pustules formation. The tongue may acquire a cerebriform appearance with numerous sulci and gyri [38,41].

Pemphigus foliaceus is a rare type of pemphigus with both sporadic and endemic forms occurring mainly in children and young adults. Pemphigus foliaceus is characterized by the presence of IgG4 antibodies directed against Dsg1 that give rise to acantholysis in the upper spinous layer. Resulted vesicle and bulla are therefore very superficial and extremely fragile [42]. Pemphigus foliaceus can occur at almost any cutaneous surface, however, the skin of the chest, back and shoulders are most commonly affected. Presumably, because of the absence of

Table 3
Commercially available quantitative immunoassays for the detection of autoantibodies in patients with oral manifestations of autoimmune blistering diseases.

Disease	Autoantigen	Epitope(s)	References
Pemphigus	Desmoglein 1	Ectodomain	[215,216]
Pemphigus	Desmoglein 3	Ectodomain	[215,216]
Paraneoplastic pemphigus	Envoplakin	Full-length	[217]
Pemphigoid (IgG, IgE)	BP180	NC16A domain	[218,219]
Pemphigoid (IgG)		4xNC16A domain	[220]
Epidermolysis bullosa acquisita (IgG)	Collagen VII	NC1 domain	[221,222]
		NC1, NC2 domains	[223]

anti-Dsg1 antibodies, the oral mucosa and gingivae are rarely affected in patients with pemphigus foliaceus and when present are similar to those of pemphigus vulgaris [43].

Other rare forms of pemphigus foliaceus include pemphigus erythematosus (Senear-Usher type), pemphigus herpetiformis, and drug-induced pemphigus vulgaris [2].

4.1. Pemphigus vulgaris

Pemphigus vulgaris (PV) is a life-threatening organ-specific human autoimmune disease. This variant represents the most frequent form of the pemphigus group, corresponding to about 70% of the cases. Pemphigus vulgaris has a wide range of incidence across worldwide geographic locations and ethnic groups, ranging between 0.76 and 16 cases per million per year [44,45]. The disease is more common among Jewish populations, in particular of Ashkenazi origin and in Eastern countries such as India, Malaysia, China and Japan. It affects both males and females with a mean age between 40 and 60 years [46].

Pemphigus vulgaris is a potentially lethal disease. Before the advent of corticosteroid therapy, the mortality was about 90%. Detailed data on the real incidence of pemphigus vulgaris mortality is not available, however, recent studies show that patients with pemphigus has a 2.36-fold increase in mortality compared with the general population. Pemphigus vulgaris is still associated with high mortality rate ranging in the literature from 5 to 30% during various lengths of follow-up [44].

Tissue damage in pemphigus vulgaris results from binding of autoantibodies to the intercellular junctions within the epidermis. Tissue-bound antibodies are generally of IgG type, but IgA and complement deposits may also be detected by direct immunofluorescence of perilesional biopsy [47,48]. Pemphigus vulgaris may manifest clinically with mucosal or mucocutaneous involvement. The clinical features of each type roughly correlate with anti-Dsg autoantibody profile in the patient's serum as well as the difference in Dsg expression between the skin and mucous membranes. The so- called desmoglein compensation hypothesis has been advanced to explain this phenomenon and is reviewed in details elsewhere [46,49]. Dsg1 and Dsg3 are considered the main target antigens in pemphigus diseases. Several lines of clinical and experimental evidence support the pathogenic role of Dsg-specific autoantibodies [8]. Thus, titres of anti Dsg1 and anti Dsg3 antibodies correlate well with clinical severity of the disease and injection of these antibodies into neonatal mice leads to acantholytic blistering [50]. In addition, autoantibodies to several non-desmoglein antigens have been detected in patients with pemphigus vulgaris, including those against E-cadherin, desmoplakin and the alpha9 acetylcholine receptor [51–53]. As with other autoimmune diseases, pemphigus vulgaris may associate clinically or serologically with other autoimmune disorders, such as myasthenia gravis, ulcerative colitis, rheumatoid arthritis, lupus erythematosus or vitiligo [54–56].

The initiating stimulus for the production of pemphigus autoantibodies remains unclear, however, predisposing factors have been suggested. Genetic association between HLA class II genes and pemphigus vulgaris is well documented. Additional support for a genetic basis comes from the observation that pemphigus vulgaris is increased in certain ethnic groups and that only sporadic cases involve first-degree relatives [57,58]. However, genetic predisposition is not sufficient by itself to initiate the pathogenic autoimmune mechanism resulting in tissue damage. Exogenous factors in genetically predisposed individuals have been suggested such as drugs (e,g. penicillamine and angiotensin-converting enzyme inhibitors), diet and viral infections. Also, endogenous factors, including emotional stress and increased levels of oestrogen hormones have been implicated [46,53].

Clinically, pemphigus vulgaris usually begins with mucosal involvement with or without skin lesions. Mucosal lesions are usually located in the oral and pharyngeal mucosa, although conjunctiva, larynx, nasal mucosa and vagina may also be involved [59]. Oral mucosa is the most commonly affected mucosal surface in patients with pemphigus vulgaris. Oral lesions are hallmark of pemphigus vulgaris and occur in almost all the cases usually at the onset of the disease [10,19,20,60–63]. The prevalence of oral involvement as the initial site varies in different population studies, ranging between 37% and 77.5% [60,61,64–66]. Importantly, the high frequency of initial isolated oral mucosal involvement may result in delayed diagnosis despite the fact that patients seek medical help at an early stage due to pain and discomfort associated with mastication, swallowing and speech [67,36].

Oral lesions of pemphigus vulgaris may present as multiple chronic ulcers involving any part of the oral mucosa, with sites subjected to friction trauma. The buccal mucosa, palate, lips and gingiva, are particularly affected [68]. Oral lesions start initially as fluid-filled blisters which may be localized or diffuse with tendency to spread. Blisters are usually thin-walled and easily rupture, giving rise to painful, multiple ulcerations. New blisters keep developing as the older ones rupture and ulcerate. Ulcerations are initially superficial, irregular in shape, with a red base and ragged whitish margins, but as infection supervenes, a yellowish slough may develop (Fig. 2a). These ulcers heal slowly without scaring [36]. Gingival pemphigus lesions are less common and at onset appear as isolated blisters and erosions located on free gingiva. In longstanding disease, erosive or desquamative gingivitis may develop [69]. Oral lesions in pemphigus vulgaris may persist for months before progressing to the skin and other mucosal surfaces. Cutaneous involvement may be localized or generalized. Skin lesions have a predilection for the trunk, groins, axillae, scalp, face, and pressure points. Flaccid blisters develop on these sites and may coalesce; these blisters eventually rupture and result in painful erosions [59].

Extra-oral mucosal sites may be also affected in patients with pemphigus vulgaris. In a recent study conducted in 38 patients, 87% of the patients with pemphigus vulgaris were found to have blisters and erosions involving the ear, nose and throat (ENT) mucosae upon endoscopic examination [70]. Involvement of the mucosae of the eye, nose and larynx are associated with pain or discomfort and may cause multiple dysfunctions affecting swallowing, phonation, respiration and olfaction. Endoscopic findings show greater frequency of clinically active pemphigus vulgaris lesions than the ENT symptoms reported by affected patients. These findings highlight the need for endoscopic assessment for patients with pemphigus vulgaris [68,70].

A number of scoring systems have been developed in recent years to provide objective and standardized values for disease severity and progression (Table 4). Presently, the pemphigus disease area index (PDAI) and autoimmune bullous skin disorder intensity score (ABSIS) are the most established tools to assess disease activity in pemphigus [71–73].

Pemphigus vulgaris must be differentiated from other blistering disorders such as lichen planus, mucous membrane pemphigoid, linear IgA disease and erythema multiforme (Table 5). It is crucial to establish an early diagnosis for patients with pemphigus vulgaris, so that adequate treatment can be commenced. The informed practitioner will suspect pemphigus vulgaris in a patient with non-scarring, fragile blisters and erosions involving the mucosa with varying degree of cutaneous involvement, especially when suprabasilar acantholytic cleavage is documented as the histopathological correlate in lesional skin. The diagnosis of pemphigus vulgaris is confirmed by the detection of tissue-bound and circulating autoantibodies against the intercellular junctions in the epidermis, by direct and indirect immunofluorescence microscopy, respectively. In addition, the molecular specificity of pemphigus autoantibodies may be characterized by quantitative immunoassays using recombinant Dsg 1 and 3, which may be used as monitoring tools for the follow-up.

Histopathological examination is typically characterized by suprabasal loss of adhesion (acantholysis), leaving a single layer of basal keratinocytes attached to the dermal-epidermal basement membrane (tombstone pattern) (Fig. 2b). This characteristic feature differentiates pemphigus vulgaris from pemphigus foliaceus, which is associated with a more superficial, subcorneal split formation [30,59].

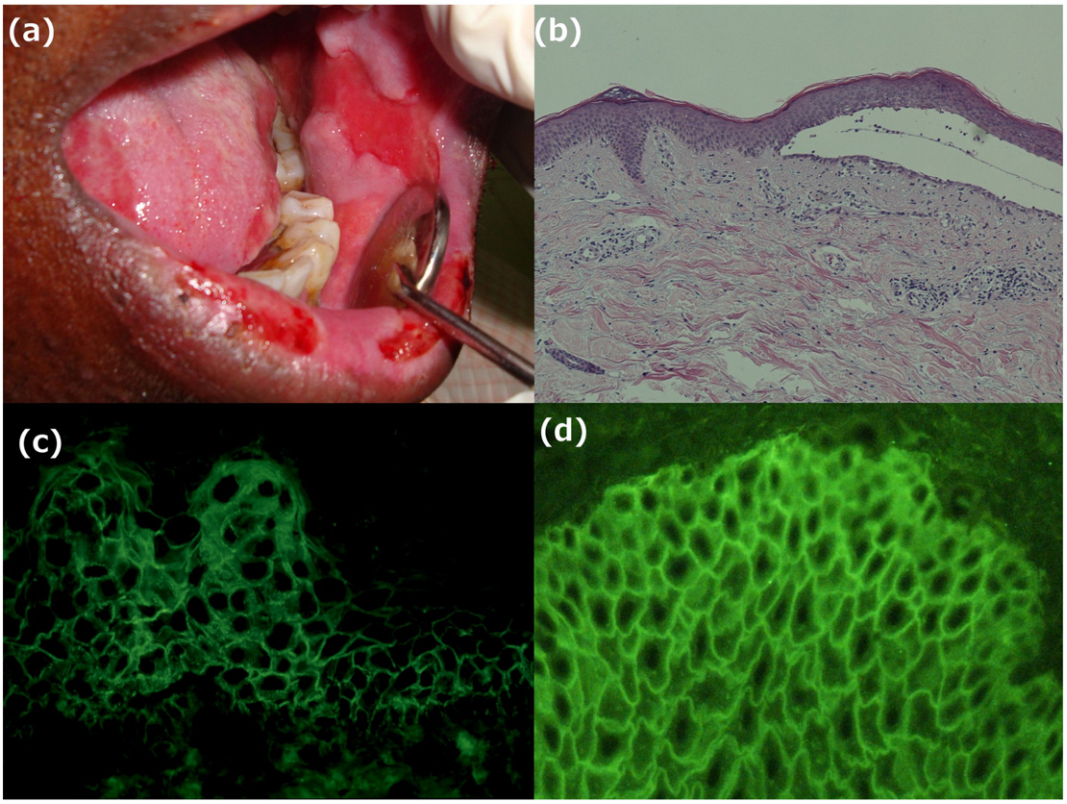

Fig 2. Pemphigus vulgaris (PV). (a) Oral lesions in a patient with pemphigus vulgaris showing generalized ulceration and erosions. (b) Histopathological examination shows typical intra-epithelial suprabasal acantholysis with moderate inflammatory infiltrate. A "row of tombstones" appears as a single layer of basal keratinocytes remains attached to the basement membrane. (c) Direct immunofluorescence microscopy of a perilesional biopsy shows intercelular deposition of IgG in epidermis. (d) Serum IgG autoantibodies binding with an intercellular pattern are detected by indirect immunofluorescence microscopy on monkey oesophagus.

By direct IF microscopy, IgG or C3 binding to the intercellular adhesion substance in the mid-lower or entire epidermis of perilesional skin or mucosa, is characteristic. Tissue-bound IgG, C3, IgM, or IgA will appear in a characteristic net-like intercellular pattern within the epidermis (Fig. 2c). Pemphigus autoantibodies predominantly belong to the IgG4 subclass, however autoantibodies belonging to the IgA and IgE isotypes have also been detected [74,75]. Indirect IF microscopy reveals the presence of serum autoantibodies binding with an intercellular fluorescence (net-like) pattern within the epithelia of suitable substrates such as monkey oesophagus (Fig. 2d) [30].

Enzyme-linked immunosorbent assay (ELISA) provides higher sensitivity and specificity in making the diagnosis of pemphigus subtypes. ELISA tests provide a quantitative method for measuring Dsg-specific autoantibody levels, and are currently used for the diagnosis of pemphigus [32,76]. The severity of skin and oral mucous membrane lesions in pemphigus was found to correlate well with the levels of autoantibodies to Dsg1 and Dsg3 , respectively [77,78].

5. Pemphigoid diseases

Pemphigoid diseases represent a family of chronic, subepithelial blistering disorders, characterized by autoantibodies against structural components of the dermo-epidermal junction. Pemphigoid diseases are heterogeneous with respect to the clinical presentation, degree of

Table 4
Scoring systems for pemphigus diseases involving oral mucosa.

Scoring System	Description (Advantages / Limitations)	References
Pemphigus Disease Activity Index (PDAI)	Integrates cutaneous with mucosal disease in a well- defined anatomical locations. Assesses number and size of the lesions. Scores post-inflammatory hyperpigmentation of resolving lesions	[71,224]
Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)	Is a quality and quantity based score for cutaneous and oral mucosal lesions Monitors clinical status of individual patients overtime. Oral involvement scores comprise both objective and subjective information	[73]
Pemphigus Area and Activity Score (PAAS)	Scores are based on the body surface area, number of new blisters, peripheral extension of lesions and Nikolsky's sign Severity description is subjective. Does not incorporate size of the lesions. Large changes in the body surface area are required to reflect change in severity score	[225]
Saraswat's oral pemphigus scoring	A scoring system for oral pemphigus Assesses both the extent of lesions on different oral sites and their severity. May be used for assessing MMP, herpetic gingivostomatitis and Steven -Johnson's Syndrome.	[226]
Pemphigus Activity Score	Introduces intensity of steroid and immunosuppressive therapy along with the extent of disease. Lacks the differential clinical involvement of mucosal and cutaneous lesions	[227]
Mahajan's Scoring System	Assesses severity of pemphigus by the degree of body surface area involved.	[228]
Harman's Pemphigus grading	Scores the severity of oral and skin lesions. Incorporates the antibody titer as assessed by ELISA	[78]

Table 5
Diagnostic criteria for pemphigus vulgaris.

Diagnostic criteria	Findings
Clinical features	
Oral lesions	First manifestation in (50–70%) of the patients Multiple ulcerations / erosions resulting from blisters Desquamative gingivitis
Skin lesions	Skin blistering, erosions
Laboratory investigations	
Histology	Intraepithelial suprabasal cleavage with acantholysis
Direct IF microscopy	Intraepidermal deposition of IgG/C3 with an intercellular pattern
Indirect IF microscopy	IgG autoantibodies binding to epithelial cells with an intercellular pattern
ELISA / Immunoblotting	IgG autoantibodies specific for desmoglein 3 (mucosal) +/- desmoglein 1 (mucocutaneous)

skin and / or mucosal involvement, target antigens and autoantibody isotypes. Diseases of the pemphigoid group include bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA-disease, anti-p200 pemphigoid and lichen planus pemphigoides [79,80]

5.1. Mucous membrane pemphigoid

Mucous membrane pemphigoid is an autoimmune subepithelial blistering disease that predominantly affects mucous membranes with varying degrees of severity, such as the oral mucosa, ocular mucosa, laryngeal mucosa and genital mucosa. Previously, different terms such as cicatricial pemphigoid and benign cicatricial pemphigoid were used as a reference for this condition [81]. This rare disease predominantly affects women with mean age of onset in the mid 60s [10,11,16]. Mortality associated with mucous membrane pemphigoid is usually secondary to aero-digestive tract stricture and has been estimated as 0.029 per 100 000 in the United States during 1992–2002 [82].

Mucous membrane pemphigoid is associated with autoantibodies directed against several components at the dermal-epidermal junction. Thus, in about 2/3 of patients, mucous membrane pemphigoid is associated with autoantibodies targeting collagen XVII/BP180 [83,84]. Approximately 25% of mucous membrane pemphigoid patients also show reactivity to BP230. A subgroup of about 20% of patients with mucous membrane pemphigoid, shows autoantibodies to laminin 332 (also known as epiligrin). Studies coming mainly from one laboratory also incriminated both subunits of $\alpha6\beta4$ integrin as autoantigens in mucous membrane pemphigoid [81,85]. The autoantibodies targeting these antigens are of IgG class, but IgA deposition along the epidermal basement membrane can also be detected [86,87]. Combined presence of circulating IgG and IgA in the serum of patients with mucous membrane pemphigoid is associated with more severe and persistent disease than IgG autoantibody alone [88].

The marked variability of targeted antigens has suggested the existence of several subsets of mucous membrane pemphigoid. Each has distinct features regarding tissues affected, the pattern of immnopathology and antigen specificity of autoantibodies. They include the *oral pemphigoid* that predominantly affects the oral mucosa with a significant autoantibody reactivity (46–75%) against BP180. An o*cular variant* is the second distinct subset of mucous membrane pemphigoid in which lesions are mainly affecting the conjunctiva. *Anti-BP180 mucosal pemphigoid* is a subset of mucous membrane pemphigoid characterized by a concomitant involvement of oral mucosal and skin lesions, with or without other mucosal lesions. Similarly, the *anti-epiligrin cicatricial pemphigoid* (*AECP*), is characterized by oral and ocular mucosal involvement and autoantibodies against laminin 332. Clinical evidence suggests that patients with AECP have increased risk of developing solid cancers early on during the course of disease, such as adenocarcinomas and non-Hodgkin's lymphoma [89,90].

Clinically, mucous membrane pemphigoid most commonly affects the oral mucosa, followed by the conjunctiva, nasal cavity, nasopharyngeal mucosa, anogenital area, skin, larynx and oesophagus in a descending order of frequency [81,91]. The disease has a relapsing and remitting course, with symptoms and signs that typically develop progressively over several weeks, and persist for many years with intermittent periods of activity and remission. Clinical severity is variable and ranges from mild oral and conjunctival lesions to severe and painful generalized mucosal involvement [80]. In all the affected mucosal surfaces, ulcers and erosions have a pronounced tendency to heal with scaring and hence compromise the function of the affected mucosa. Sequelae and complications such as strictures of the larynx or oesophagus may develop and could be fatal [92]. However, in the oral mucosa re-epithelialization of the affected sites without scaring may also occur.

Oral lesions may be the first and only manifestation of the disease. Patients present with complaints of pain and dysphagia associated with peeling of the mucosa. Lesions initially appear as tense vesicles, with serous and/or hematic contents, that progress quickly to irregularly shaped erosions, covered with yellowish pseudomembranes and surrounded by inflammatory halos (Fig. 3a) [93]. Oral lesions most commonly affect the gingivae, buccal mucosa, and palate; they may also occur on the alveolar ridge, tongue, and lower lip. Gingival lesions may represent the onset of the diseases in the oral cavity and appear clinically as a desquamative gingivitis. In a recently conducted large cohort study of patients with desquamative gingivitis, mucous membrane pemphigoid was found to be the second most common cause, following lichen planus, representing more than 25% of the patients [94]. Several studies have shown that mucous membrane pemphigoid affects the periodontal health status, especially with regard to the development of supragingival dental plaque as well as worsening of periodontal parameters, including periodontal depth, clinical attachment level, mobility scores and bleeding [95–97].

Ocular involvement is a serious aspect of mucous membrane pemphigoid. Patients complain of dryness and burning sensation of their eyes. Subsequent erosions may result in scaring and symblepharon formation (fusion of the bulbar and palpebral conjunctiva) ankyloblepharon (defined as full thickness fusion of the lid margins), entropion (inward rolling of the eyelid), trichiasis (eyelashes rubbing on the eyeball), corneal neovascularization and scarring with end result of blindness (Fig. 3b). Conjunctival lesions usually start in one eye but involve the other within few years [98,99]. While nasopharyngeal lesions are less common, nasal discharge, epistaxis or crusting may develop, resulting in hoarseness, dysphonia, shortness of breath and stenosis of the upper airways in severe cases [100]

Mucous membrane pemphigoid must be differentiated from other subepidermal blistering diseases, such as linear IgA disease and epidermolysis bullosa acquisita (Table 6). Histopathological examination reveals subepidermal bullae and an inflammatory infiltrate consisting mostly of lymphocytes, with the possible presence of eosinophils and neutrophils (Fig. 4a). Plasma cells are frequently found in mucosal lesions, but are site specific and not related specifically to this disease. Mild to moderate degrees of fibrosis can also be detected [101].

Direct IF microscopy of perilesional mucosa or skin, shows linear deposits of IgG and C3 at the dermal-epidermal junction (Fig. 4b). Autoantibodies of the IgG4 subtype predominate in patients with mucous membrane pemphigoid, especially in the anti-epiligrin (laminin 332) form [102]. Indirect IF microscopy in patients with mucous membrane pemphigoid is often negative due to low serum reactivity. The indirect IF microscopy on salt-split skin demonstrates binding of autoantibodies from mucous membrane pemphigoid patients to the epidermal (Fig. 4c) or dermal side of the artificial split largely reflecting their molecular specificity to hemidesmosomal antigens such as BP180 or to laminin 332, respectively [103,104].

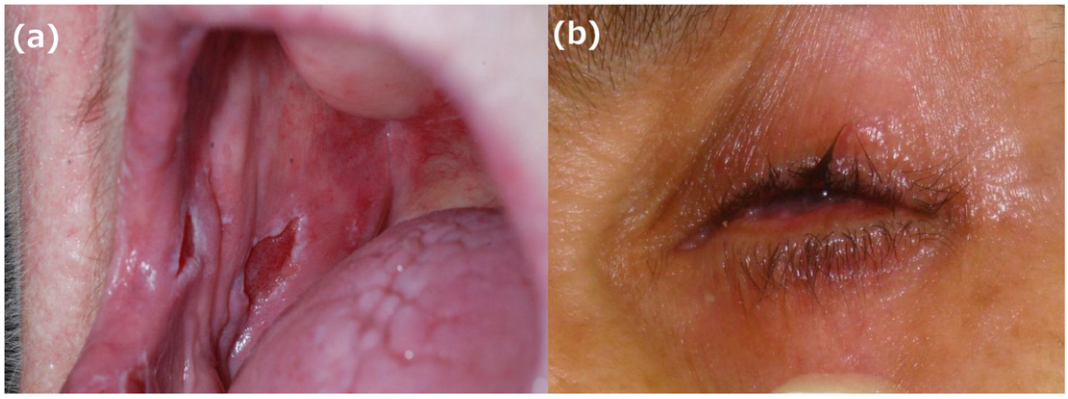

Fig. 3. Clinical features of mucous membrane pemphigoid (MMP). (a) Oral ulceration and erosions on the buccal and labial mucosa of a 65 year-old female patient with mucous membrane pemphigoid. (b) Ocular involvement in the same patient appears as conjunctival scarring with symblepharon.

5.2. Linear IgA disease

Linear IgA disease (LAD), also known as linear IgA bullous dermatosis, is an autoimmune subepidermal blistering disease characterized by linear deposition of IgA at the epidermal basement membrane. The features of this disease were first described in 1901 in children who were diagnosed as having dermatitis herpetiformis. However, it was not until 1979, when the term linear IgA disease was coined and the entity was formally separated from dermatitis herpetiformis [105].

Linear IgA disease is a rare disease, and only limited and heterogeneous data regarding its prevalence and incidence worldwide are available. Linear IgA disease is the most common autoimmune bullous disorder of childhood and usually appears in children under the age of 5, while the adult-onset linear IgA disease generally appears after the age of 60 [16,106,107].

Patients with linear IgA disease produce IgA autoantibodies directed against multiple autoantigens at the basement membrane zone. Most patients with linear IgA disease develop IgA antibodies against a 97 kDa protein (LABD97) and a 120 kDa (linear IgA disease-1) antigens, which were both found to be generated as proteolytic cleavage products of the BP180 ectodomain [2,108]. Therefore, a staining of the epidermal side of salt-split skin will appear upon examination using indirect IF microscopy. On the other hand, staining of the dermal side of the skin may also be detected in some patients where IgA autoantibodies react with collagen VII and other dermal proteins [2].

The triggering factors for IgA autoantibody production in patients with linear IgA disease are not clear. However, induction of patients IgA autoimmune response against the epidermal basement membrane by viral infections, drugs (e.g. vancomycin, diclofenac and captopril) and malignancies have been hypothesised [109].

Table 6
Diagnostic criteria for mucous membrane pemphigoid.

Diagnostic criteria	Findings
Clinical features	
Oral lesions	Multiple erosions/ulcerations resulting from blisters Desquamative gingivitis
Skin lesions	Not common Blisters, possible scarring
Laboratory investigations	
Histology	Subepithelial cleavage, mixed leukocytic infiltrate, mild-moderate fibrosis
Direct IF microscopy	Linear deposition of IgG and C3 at the dermo-epidermal junction
Indirect IF microscopy	Binding of the patient's IgG/IgA to epidermal or dermal side of human salt-split skin
ELISA / Immunoblotting	IgG/IgA autoantibodies specific to collagen XVII/BP180, laminin 332, α6β4 integrin

Linear IgA disease shows a heterogeneous clinical presentation involving the skin and mucous membrane. Characteristically, lesions tend to appear in a "cluster of jewels" pattern, where new lesions arise at the periphery of old ones [107]. In adults, lesions predominantly affect the trunk, extensor surfaces and face. Mucous membrane involvement can be seen in up to 80% of the patients. Oral lesions appear as multiple, painful ulcers that follow the rupture of blisters. They may sometimes exhibit in a form of erosive cheilitis or desquamative gingivitis [110,111].

Linear IgA disease may be difficult to differentiate on clinical grounds from other autoimmune bullous diseases, particularly, mucous membrane pemphigoid, bullous pemphigoid and dermatitis herpetiformis (Table 7). Histopathological examination shows subepithelial blistering with a predominant neutrophils infiltrate in the epidermis. Importantly, detection of tissue-bound and circulating IgA autoantibodies is mandatory for diagnosis [107]. Direct IF microscopy reveals linear IgA deposition along the basement membrane. Using indirect IF microscopy on salt-split skin, IgA antibodies from patients with linear IgA disease bind to the roof of the split. Furthermore, recombinant BP180 ectodomain or concentrated supernatant from cultured keratinocytes can be used in immunoblotting for the sensitive detection of IgA autoantibodies against the BP180 ectodomain. ELISA systems using recombinant BP180 have also been used for measurement of IgA levels in patients' sera [112,113].

6. Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is a chronic blistering disease of the skin and mucous membranes characterized by subepidermal blistering associated with tissue-bound and circulating autoantibodies against collagen VII. Epidermolysis bullosa acquisita is a rare disease with approximate prevalence of 0.2/million people and has no gender or racial predilection [16]. The disease has a variable age of onset, from early childhood to late adult life, however, most of the patients are between fourth and fifth decades of life.

Epidermolysis bullosa acquisita is characterized by autoantibodies directed against collagen VII, the major constituent of the anchoring fibrils located at the dermal-epidermal junction. These autoantibodies, most often of IgG type, bind mainly to epitopes within the NC1 domain of collagen VII. Subsequent complement activation and neutrophils recruitment by bounded IgG at the dermal-epidermal junction results in subepidermal blister formation [114].

Epidermolysis bullosa acquisita presents clinically with heterogeneous clinical features that are difficult to differentiate from other autoimmune diseases. However, patients may present with several clinical forms, including a non-inflammatory and inflammatory phenotype. The non-inflammatory form (also called the classic, mechanobullous variant of epidermolysis bullosa acquisita), occurs in about one-third of the patients and is characterized by skin fragility and tense blisters

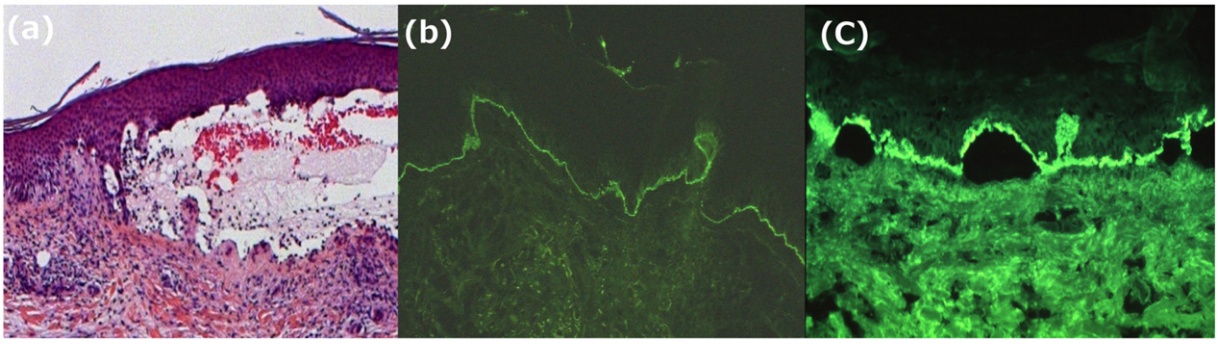

Fig. 4. Histopathological and immunological findings in mucous membrane pemphigoid (MMP). (a) Histopathological examination reveals sub-corneal epithelial acantholysis with adjacent neutrophils inflammatory infiltrate. (b) Direct immunofluorescence microscopy of perilesional mucosal biopsy shows a linear and continuous deposition of IgG and C3 at the basement membrane zone. (c) By indirect immunofluorescence microscopy using 1 M NaCl-split tissues, serum IgG autoantibodies appear to bind to the epidermal side of the split.

formation. Lesions predominantly appear at sites subjected to trauma, such as elbows, knees and dorsal surfaces of the hands and feet. Lesions usually heal with scaring and post-inflammatory hyper and hypo pigmentation (Fig. 5a) [115]. This clinical phenotype shares further features with the hereditary dystrophic epidermolysis bullosa, including loss of the hair and nails, oesophageal involvement and stenosis. Patients with inflammatory subtype of epidermolysis bullosa acquisita present clinically with widespread bullous lesions that resemble other pemphigoid diseases. Brunsting–Perry cicatricial pemphigoid is a chronic recurrent bullous eruption localized to the head and neck, characterized by residual scars, subepidermal bullae and modest mucosal involvement. IgG autoantibodies in this condition are heterogeneous with regard to their molecular specificity, but were often reported to recognize collagen VII [116,117]. In addition to bullous systemic lupus erythematosus, autoimmunity to collagen VII has been shown to associate with other systemic inflammatory diseases such as inflammatory bowel diseases. The oral mucosa shows multiple blisters and erosions and is most commonly described in patients with the non-inflammatory form (Fig. 5b) [118].

The inflammatory type of epidermolysis bullosa acquisita may be clinically and histologically indistinguishable from other subepidermal bullous diseases including bullous pemphigoid, mucous membrane pemphigoid and linear IgA disease. Histopathological examination of patients' lesional skin reveals subepidermal blisters typically infiltrated by various inflammatory cells including neutrophils, eosinophils, and lymphocytes (Fig. 6a). Diagnosis is achieved through detection of linear deposition of IgG autoantibodies at the basement membrane by direct IF microscopy (Fig. 6b) and the detection of serum autoantibodies by indirect IF microscopy (Table 8). Indirect IF using 1M NaCl-split normal human skin as a substrate demonstrates circulating IgG autoantibodies binding to the dermal side of the artificial split in serum of patients with epidermolysis bullosa acquisita (Fig. 6c). These autoantibodies recognize the immunodominant region of collagen VII, the NC1 domain, by immunoblotting with normal human dermal extract. Furthermore, for the detection of circulating anti-collagen VII IgG antibodies, different ELISA systems have been developed, of which two are commercially available [119] (Table 3).

Table 7
Diagnostic criteria for linear IgA disease.

Diagnostic criteria	Findings
Clinical features	
Oral lesions	Erosions/ulcerations resulting from blisters
Skin lesions	Erythema, blisters, erosions, crusts
Laboratory investigations	
Histology	Subepithelial cleavage with inflammatory infiltrates dominated by neutrophils
Direct IF microscopy	Linear IgA deposition at the dermo-epidermal junction
Indirect IF microscopy	Binding of IgA autoantibodies to the epidermal side of salt-split skin
ELISA/Immunoblotting	IgA against the shed ectodomain of BP 180 (LAD1)

7. Other autoimmune skin diseases with oral manifestations

Oral lesions may less commonly manifest other autoimmune skin diseases such as bullous pemphigoid and dermatitis herpetiformis. Bullous pemphigoid is a subepidermal blistering disease characterized by autoantibodies directed against the basement membrane zone and targeting a 230-kDa protein (BPAG1) and a 180-kDa transmembrane protein (BPAG2). Bullous pemphigoid is the most common autoimmune blistering disease in North America and Western Europe, with a recent reported incidence of 4.3 cases per 100,000 person-years in the United Kingdom [2,15]. The clinical picture of bullous pemphigoid is dominated by polymorphic skin eruptions consisting of large, tense blood and/or fluid filled blisters associated with eczematous papules and plaques. The lower trunk, thighs and flexor aspects of the arms are typical sites of involvement [43]. Atypical pruritic erythematous or eczematous lesions may also coexist with typical bullae and may sometimes resemble polycyclic, targetoid, nodular or lichenoid reactions [120]. The frequency of mucosal involvement in bullous pemphigoid appears to be low in comparison with other bullous diseases, such as pemphigus vulgaris and mucous membrane pemphigoid. Oral bullous lesions are usually asymptomatic and temporary in nature with consequent ulceration. Lesions are mostly located on the palate, buccal mucosa, lips, and tongue [121]. Histopathological examination reveals subepithelial blistering with inflammatory infiltrate comprising lymphocytes and eosinophils. Direct IF microscopy of the skin or perilesional mucosa shows linear IgG and C3 deposits at the basement membrane, whereas the indirect IF microscopy shows IgG circulating autoantibodies in approximately 80% of patients [2].

Dermatitis herpetiformis, is an autoimmune blistering disease that arises secondary to gluten hypersensitivity. The disease is characterized by an inflammatory cascade following exposure to gluten, which results in IgA autoantibodies formation directed against epidermal transglutaminase [122]. It is a relatively rare disease, being more prevalent in Scandinavian countries and in the UK [123]. Dermatitis herpetiformis manifests as papulovesicular eruptions of the extensor surfaces of the elbows and knees, back, scalp and buttocks. The disease rarely affects the oral cavity and when present, occurs especially in areas subject to trauma. All patients with dermatitis herpetiformis have intestinal sensitivity to gluten, but only a small proportion of them (10%) will present symptoms suggestive of celiac disease such as diarrhea, cramps, and malabsorption [122,124].

Histopathological examination of skin lesions reveals an inflammatory infiltrate in the upper dermis and at the dermo-epidermal junction dominated by collections of neutrophils and eosinophils. These granulocytes form typical papillary microabscesses that lead to blister formation in these areas [125]. Direct IF microscopy from biopsies of

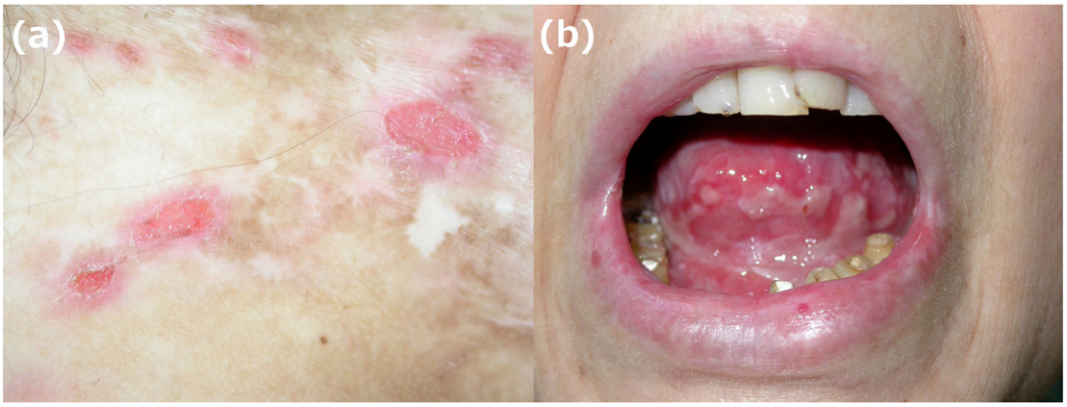

Fig. 5. Epidermolysis bullosa acquisita (EBA). (a) Multiple erosions and crusting affecting the skin. (b) Oral lesions present as diffuse, multiple ulcerations, blisters and erosions.

unaffected skin reveal granular deposits of IgA along the dermal-epidermal junction and on top of the dermal papillae. Indirect IF may be useful for the detection of IgA autoantibodies against endomysium, which specifically recognize the epidermal transglutaminase (TG3) and tissue transglutaminase (TG2) [2,122].

8. Chronic ulcerative stomatitis

Chronic ulcerative stomatitis (CUS) is a rare mucocutaneous disease, involving the mucosal surfaces, particularly the oral mucosa, and sometimes the skin, occurring particularly at fifth and sixth decades of life with an average age of 59 years. Females represent the majority of reported cases, of which 90% are white women [126].

The condition is characterized by ulcerative mucosal lesions that show a distinctively unique direct immunofluorescence pattern. Patients present with persistent or recurrent painful erosive, ulcerative, vesicular lesions, predominately affecting the tongue, buccal mucosa and the gingiva. Labial mucosa and hard palate are less frequently affected. Gingival soreness is a main source of patients' discomfort and many patients refer to periodontists regarding persistent areas of gingival desquamation that may display areas of white lichenoid striae that mimics lichen planus [127,128]. Furthermore, the bilateral presentation of the lesions on the buccal mucosa may also lead to a wrong diagnosis of lichen planus. Widespread lesions have been observed in 29% of the reported cases. In particular, oral lesions may present in conjunction with skin lesions in 5.1% of the cases [128].

Chronic ulcerative stomatitis is indistinguishable clinically from other immune-mediated disease, such as mucous membrane pemphigoid, linear IgA disease, pemphigus vulgaris, erythema multiforme and particularly lichen planus (Table 9). Diagnosis of chronic ulcerative stomatitis should be considered in patients with prolonged oral ulceration. Histopathological examination of mucosal lesions shows identical or very similar features to lichen planus exhibiting partially atrophic epithelium with saw-toothed rete ridges formation. Interface stomatitis (leukocytic exocytosis) and a dense band-like inflammatory infiltrate composed mainly of lymphocytes and a few plasma cells in the epithelium-connective tissue interface are also noted [126].

A goal standard in the diagnosis of chronic ulcerative stomatitis is the direct IF staining with IgG of lesional and perilesional oral mucosal tissues, which reveals a speckled, finely granular pattern of IgG deposition in the nuclei of keratinocytes. This stratified epithelial-specific antinuclear antibody (SES-ANA) signal is confined to the basal cells and the lower third of the spinous layers. This pattern is generated because patients with chronic ulcerative stomatitis have autoantibodies that bind to specific protein, deltaNp63alpha, an antigen of the nuclei of the oral epithelium keratinocytes [129]. Furthermore, patients have circulating autoantibodies that show the SES-ANA pattern on indirect IF. The pathogenic role of these autoantibodies has been investigated in a recent study using three-dimensional in vitro tissues with a fully differentiated epithelium resembling the human counterpart. Incubation of these tissues with serum from patients with chronic ulcerative stomatitis causes tissue detachment, confirming the role of these autoantibodies in the pathogenesis of the disease [130].

9. Lichen planus

Lichen planus is a chronic immune disease mediated by T lymphocytes that commonly involves the stratified squamous epithelium of the skin, genitalia and oral mucosa. Oral lichen planus (OLP) is a common condition that affects individuals mainly in their 4^{th}–5^{th} decade of life. The disease has variable reported prevalence, calculated in a recent meta-analysis of approximately 1.27%, with predilection for

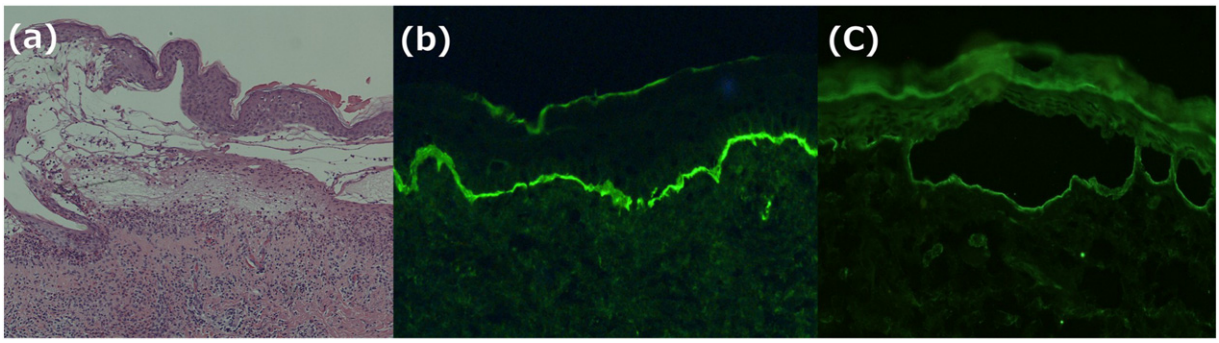

Fig. 6. Histopathological and immunological features of epidermolysis bullosa acquisita (EBA). (a) Histopathological examination reveals dermal-epidermal separation associated with inflammatory infiltrate. (b) Direct immunofluorescence microscopy shows IgG deposits at the basement membrane zone (c) By indirect immunofluorescence microscopy using 1 M NaCl-split tissues, serum IgG autoantibodies appear to bind to the dermal side of the split.

Table 8
Diagnostic criteria for epidermolysis bullosa acquisita.

Diagnostic criteria	Findings
Clinical features	
Oral lesions	Erosions/ulcerations resulting from blisters
Skin lesions	*Inflammatory form*: generalized eruption with tense blisters *Mechanobullouos form*: skin and mucosal fragility, trauma induced blistering
Investigations	
Histology	Subepithelial cleavage with neutrophilic inflammatory infiltrate
Direct IF microscopy	Linear IgG and C3 deposition at the dermo-epidermal junction
Indirect IF microscopy	Binding of IgG or IgA autoantibodies at the dermal side of salt-split skin
ELISA	Collagen VII-specific IgG or IgA

women in up to 67% of the cases [131,132]. In 1978, the World Health Organization classified oral lichen planus as a potentially malignant disorder due to its tendency to exhibit malignant changes over time [133].

The exact antigen triggering oral lichen planus lesions is unknown, however, it is likely that multiple factors or antigens, of extrinsic or intrinsic origin, could explain the disease process. The role of autoimmunity in oral lichen planus is undermined by the lack of specific inducing factors, however, supported on the other hand by many autoimmune features such as disease chronicity, adult onset, female predilection and its association with other autoimmune diseases [134].

Several reports have pointed out the role of viral and bacterial infections in the aetiology of oral lichen planus. In particular, a positive association between hepatitis C virus infection (HCV) and lichen planus has been reported in many studies across the world. [135–137]. A high prevalence of human papilloma virus (HPV) in oral lichen planus cases has also been found, ranging between 9.2% for HPV-16 and −18 up to 42.6% for non-specific types. These findings suggest that HPV may not only play a role in the aetiology of oral lichen planus, but also in the malignant progression of this disorder [138,139]. Psychological disturbances such as depression, anxiety and stress as well as autoimmune thyroid diseases have been also linked to the aetiology of lichen planus [140–143].

The clinical features of oral lichen planus vary widely, from mild to moderate or severe presentation. The disease is known for its chronic nature and its tendency to persist for several years with periods of remission and exacerbations. In many cases, oral lichen planus has a silent onset and progression where patients are not aware of their condition, and their lesions are often detected upon routine dental examination. Other patients may report roughness of the oral mucosa, sensitivity to hot or spicy food, or intense pain and discomfort due to mucosal ulceration. Clinical manifestations of oral lichen planus are heterogeneous with reticular, plaque-like, papular, atrophic, erosive and bullous presentations. The white forms of oral lichen planus are reported to be more prevalent (72.6%) than red forms (27.4%) [133]. Lesions are multiple and symmetrically distributed bilaterally, most commonly on the buccal mucosa (60–70% of the cases), followed by the dorsum and lateral borders of the tongue and the gingiva. The reticular appearance is the most common form and appears clinically as intertwined white striae, called "Wickham striae". These lesions are usually asymptomatic with a preference bilateral location on the posterior buccal mucosa. The plaque-like variant presents as a white homogeneous irregularity that mimics leukoplakia. Papular lichen planus is rarely observed and presents as small white papules with fine striae in its periphery [144]. Atrophic lichen planus is characterised by areas of erythema and atrophy with or without white striae (Fig. 7a). Erosive lichen planus is the most significant form of the disease, associated with great pain and discomfort. It appears clinically as irregular areas of ulceration that maybe covered with a yellowish fibrin pseudomembrane. Areas of surrounded "Wickham striae" can be seen. Finally, is the bullous variant, which is the most unusual form in the oral mucosa, appearing as blisters that rupture leaving painful and ulcerative surfaces [133,144,145]. Gingival lesions in oral lichen planus can occur in about 48% of the cases (Fig. 7b). Furthermore, exclusive gingival involvement is observed in up to 10% of the patients with oral lichen planus [146,147].

Oral lichen planus can occur with minimal skin involvement in about 15% of the cases. However, in 40–70% of the cases, patients may show skin lesions. Apart from the skin, the genital and anal mucous membranes, scalp, nails, larynx and conjunctiva can also be involved [148].

The term oral lichenoid lesions (OLL) is used to describe a group of oral lesions that have a similar clinical presentation to oral lichen planus, however, they are triggered by known aetiological factors. They can present in reticular, atrophic or erosive forms with very few distinguishing features from oral lichen planus [149]. Oral lichenoid lesions include several clinical types. (1) Oral lichenoid contact lesions (OLCL) are contact allergy of delayed hypersensitivity reactions due to direct relationship to dental restorative materials, most commonly amalgam. Lesions are typically localized to the area of amalgam contact, unilateral, with the lateral borders of tongue and buccal mucosa being the preference sites, due to their close contact to filling materials. (2) Oral lichenoid drug reactions (OLDR) arise in temporal association with the taking of certain medications, e.g. oral hypoglycemic agents, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory agents. Lesions can occur any time during the course of drug intake with localized and asymmetrical distribution in the oral mucosa. (3) Oral lichenoid lesions of graft-versus-host disease (OLL-GVHD) occur in patients with acute, or more commonly, chronic graft-versus-host disease (cGVHD). GVHD is a major complication that arises in recipients of allogeneic hematopoietic stem cell or bone marrow transplantation. It is believed to be a result of donor T lymphocyte reaction to major tissue antigens expressed by recipient cells. Several organs, such as the skin, liver, gastrointestinal tract and salivary glands can be involved. Keratotic oral lesions with areas of ulceration, predominantly arise at the chronic stage of the disease [150,149].

Oral lichen planus must be differentiated from other immune-mediated disease such as lupus erythematosus, leukoplakia and oral lichenoid lesions. Biopsy may not be required in patients who present with classic reticular lesions in a bilateral and symmetrical distribution,

Table 9
Diagnostic criteria for chronic ulcerative stomatitis.

Findings	Diagnostic criteria
Clinical features	
Oral lesions	Chronic oral erosions/ulcerations
Laboratory investigations	
Histology	Atrophic parakeratinized stratified squamous epithelium Band-like interface of inflammatory cell infiltrate
Direct IF microscopy	Speckled, finely granular pattern of IgG deposition in the nuclei of keratinocytes (stratified epithelial-specific antinuclear antibody (SES-ANA))
Indirect IF microscopy	Circulating autoantibodies which exhibit the SES-ANA pattern using an oesophagus substrate
ELISA / immunoblotting	IgG antibodies against the N-terminal and DNA-binding domains of deltaNp63alpha

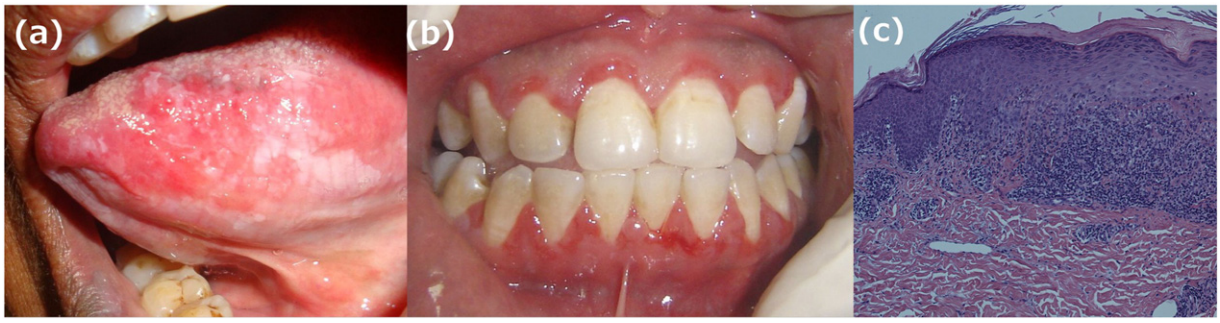

Fig. 7. Major clinical and histopathological features of oral lichen planus (OLP). (a) Clinical picture of a 32 year-old female patient with atrophic oral lichen planus, showing areas of mucosal atrophy and white plaques predominantly on the lateral borders of the tongue. (b) Desquamative gingivitis is seen on the same patient as diffuse atrophic and erosive areas involving both the marginal and attached gingiva. (c) Histopathological analysis of oral lichen planus, featuring the characteristic sub-epithelial band of lymphocytes associated with liquefaction degeneration of basal cells.

while patients with erosive or ulcerative lesions should undergo a biopsy for histopathological examination [151]. Furthermore, considerations should be made for repeating the biopsy during the follow-up periods whenever clinical presentation is changing or dysplastic changes are suspected.

Histopathological features of oral lichen planus are highly variable and depend partially on whether the biopsied lesion is reticular, atrophic, or erosive. A "sawtooth" pattern of the rete ridges, which is more commonly seen in cutaneous lichen planus, can also be observed in oral lichen planus. The epithelium may appear acanthotic or atrophic corresponding to the clinical presentation. Interface dermatitis is a hallmark of oral lichen planus. It is characterized by a superficial, dense, band-like, lymphocytic inflammatory infiltrate, predominately of T lymphocytes, which may obscure the junction of the epithelium and lamina propria. Liquefaction degeneration and necrosis of basal keratinocytes are also prominent. These degenerated keratinocytes form Civatte (colloid, hyaline, or cytoid) bodies that appear as homogenous eosinophilic globules in the lower epithelium and superficial lamina propria (Fig. 7c). Perivascular inflammation in not generally noted [151,152]. Biopsies of erosive oral lichen planus may lack many of these histological hallmarks and are not diagnostic. Furthermore, the histopathological aspects of various types of lichenoid reactions are often indistinguishable from oral lichen planus, which may cause a diagnostic dilemma for clinicians and pathologists. It has been suggested that in oral lichenoid drug reactions, a mixed subepithelial inflammatory infiltrate of eosinophils and lymphocytes is seen, in contrast to the lack of eosinophils infiltrate in oral lichen planus [153]. The inflammatory infiltrate is also more diffuse and extends deeper within the lamina propria and superficial submucosa than the band-like infiltrate seen in oral lichen planus. Amalgam associated oral lichenoid contact lesions are also characterized by a dense lymphocytic infiltrate forming tertiary lymphoid follicles [152].

For the differential diagnosis of oral lichen planus, it is important to include the clinical and histopathological findings together with other relevant factors such as the history of systemic diseases, history of drug intake and dental health. A widely used definition for the diagnosis of oral lichen planus was the criteria introduced by World Health Organization (WHO) in 1978. However, studies show that as many as 50% of oral lichen planus cases, lack the clinicopathological correlation in the diagnosis based on this criteria [154,155]. Therefore, in 2003 a set of revised criteria was proposed, based on the WHO definition, including clinical as well as histological aspects [154]. Substantial increase in clinicopathological correlation was observed when the modified WHO criteria were compared with the 1978 criteria [156].

Patients with oral lichen planus and oral lichenoid lesions should be followed regularly and closely, as they exhibit an increased risk for developing squamous cell carcinoma (SCC). Many series of cases have been published in relation to the malignant transformation of oral lichen planus and they reveal a highly variable rate of transformation ranging from 0.4–6.5% [157]. In a recently published systematic review, the overall rate of transformation was 1.09% for oral lichen planus and in a solitary study in which investigators evaluated oral lichenoid lesions, the rate of transformation was 3.2% [158]. One of the major problems for evaluating the risk of malignant transformation of oral lichen planus is that several studies have included cases with oral lichen planus and oral lichenoid lesions with no differentiation between the two processes. Therefore, data is insufficient to determine whether the rate of transformation of these two types of lichenoid diseases is different [159]. The systematic review has also found that patients' average age at onset of SCC was 60.8 years, with the tongue being the most common site for malignant transformation. Furthermore, the clinical presentation of the disease was found to be of relevance to the potential malignancy, with the atrophic, erosive and ulcerative forms having a higher risk of transformation than reticular, papular and plaque-like types [158].

10. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Erythema multiforme (EM) is an acute, reactive, immune-mediated disorder that affects the skin and mucosal surfaces. The disease is related to a hypersensitivity reaction to various agents including drugs and infections [160]. Erythema multiforme was considered to be a spectrum of clinical conditions with variable degrees of severity, including erythema multiforme minor, major, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (also known as Lyell's disease). However, it is now recognized as a distinct condition with clinical and epidemiological characteristics separate from those of Stevens-Johnson syndrome and toxic epidermal necrolysis [161]. The exact incidence of erythema multiforme is unknown, however, early reports show a possible incidence range between 0.01% and 1% [162]. The incidence of toxic epidermal necrolysis is estimated at 0.4–1.2 cases per million people per year, and of Stevens-Johnson syndrome, at 1–6 cases per million people per year [163]. Erythema multiforme affects healthy young adults with a peak age of onset between 20 and 40 years. Stevens-Johnson syndrome and toxic epidermal necrolysis occur in all age groups including children and infants, with 10–20% of reported cases involving children. The mortality rate of Stevens-Johnson syndrome is about 5% among affected adult patients and up to 30% in patients with toxic epidermal necrolysis [162].

Lesions of erythema multiforme occur as a result of body reactivity to different antigens, particularly following exposure to infections or drugs (Table 10) [164]. The most common causative infectious agent is herpes simplex virus (HSV), which is responsible for about 70% of the recurrent cases. Patients' medical history often reveals previous infection with HSV within 2 weeks before the onset of erythema multiforme [165]. Earlier studies using PCR for detection of HSV genome, identified HSV-1 in 66% and HSV-2 in 28% and both HSV1

Table 10
Trigger factors associated with erythema multiforme.

Drugs	Infections
Antibacterial	*Viral infections*
Sulfonamides (trimethoprim-sulfamethoxazole)	HSV-1, HSV-2, HIV
	Epstein Barr virus
Anticoagulants	Cytomegalo virus
Phenytoin, Carbamazepine, Valproic acid	Varicella Zoster virus
	Adenoviruses
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Enteroviruses: coxsackie B5
	Hepatitis virus
	Influenza
	Poliovirus
Further drugs	*Bacterial infections*
Allopurinol	Mycoplasma Pneumoniae
Barbiturates	Corynebacterium diptheriae
Chemotherapeutic agents	Neisseria Meningitidis
Cephalosporins	Mycobacterium
Herbal remedies	avium complex
Lamotrigine	Mycobacterium leprae
Penicillins	Mycobacterium tuberculosis
Progesterone	*Fungal infections*
Protease inhibitors	
Antifungals	Coccidiodomycosis
	Dermatophytes
	Histoplasmosis
	Sporotrichosis
	Trichimononas
	Toxoplasma gondii

and HSV-2 in 6% of the patients [166]. However, a recent retrospective study, conducted in Mayo clinic, found that only 23% of the cases could be confidently attributed to HSV infection [167]. Another well-documented infectious cause is *Mycoplasma pneumoniae*, which appears to have a particular importance in the development of erythema multiforme among children [168]. Several drugs have also been implicated as offending agents triggering attacks of variable severity of erythema multiforme such as non-steroidal anti-inflammatory drugs, sulfonamides, anti-epileptics and antibiotics [162].

The pathogenic mechanism by which these aetiological factors induce lesions of erythema multiforme is not clear. Genetic susceptibility as a predisposing factor, has been suggested in patients with severe Stevens-Johnson syndrome and toxic epidermal necrolysis following drugs use [169]. Furthermore, a diversity in pathogenesis is suggested among different subsets of erythema multiforme, all of which commonly involving cell-mediated immunity. Most of the studies that investigate the pathogenesis of HSV-induced erythema multiforme, found that HSV fragments in the skin induce a delayed-type hypersensitivity reaction driven by interferon gamma (INFγ). By contrast, interferon gamma is lacking in drug-induced erythema multiforme, in which tumour necrosis factor alpha is predominant [170]. An autoimmune pathogenesis in erythema multiforme has also been advanced, but is matter of controversy. Circulating autoantibodies to desmoplakin I and II were described in 6 reported cases with erythema multiforme and their level correlating with disease activity was found in another case report [171,172]. However, in a more recent study no significant association of erythema multiforme with autoantibodies against structural proteins of the skin was found [173].

The clinical manifestations of erythema multiforme vary from one patient to another and furthermore, lesions may change in their morphological appearance over the course of illness. Erythema multiforme has been classified into minor and a major types depending on the severity of the condition and the number of mucosal surfaces involved [160] (Table 11). *Erythema multiforme minor* is an acute, self-limiting disease that may be recurrent with frequent episodes over years. It is characterized by the skin "target lesions", that appear on cutaneous surfaces of the palms, soles and extensor surfaces of extremities with less involvement of the face and neck. Lesions are symmetrically distributed affecting less than 10% of the body surface area (BSA) [174]. Typical

Table 11
Diagnostic features of erythema multiforme (EM) minor, major, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Differential entity	EM minor	EM major	SJS	TEN
Cutaneous lesions	Affects >10% of the BSA	Affects >10% of BSA	Affects >10% of the BSA but more severe than EM major	Exfoliation of >30% of BSA
	Typical target lesions	Typical/atypical raised target lesions		Dusky atypical target lesions
	Symmetrically distributed on extremities	Symmetrically distributed on extremities	Confluent purpuric macules or atypical flat target lesions with blisters and erosion.	Starts on the trunk and spread distally
	Less involvement of skin of the face and trunk	Face and trunk are sometimes involved	Asymmetrically distributed	Flaccid bullae with epidermal sloughing and necrosis
Mucosal lesions	Uncommon	Common, in 25–60% of the patients.	Common, in 90–100% of the patients.	Common, in 100% of the patients.
	Only one site is involved, most commonly the oral mucosa	Multiple mucosal sites are affected	Multiple mucosal sites involved	Multiple internal and external mucosal surfaces involved
	Mild, superficial, irregular ulcers,affecting mainly the non-keratinized mucosa, labial ulceration and crusting.	Multiple, large oral ulcers involving all oral mucosal sites in more than 50% of the patients.	Severe, widespread oral ulcers with mucosal sloughing	Oral involvement in 71–100% of the patients
				Severe widespread oral ulceration with mucosal sloughing
Systemic symptoms	No systemic symptoms	Uncommon	30% of the patients develop prodromal symptoms of fever, anorexia, myalgia.	Usually begins with prodromal symptoms of fever, anorexia and pharyngitis
Clinical course and prognosis	Lesions can be, persistent (continuous), cyclical (acute and self-limiting) or recurrent.	Lesions can be, persistent (continuous), cyclical (acute and self-limiting), recurrent	Lesions are mostly persistent and may continue to erupt in crops as long as 1–3 weeks.	Lesions are persistent
	Lesions usually resolve in 2 weeks without sequel	Lesions usually revolve over 1–6 weeks with scarring	Almost 10% mortality rate	Poor prognosis
			Risks of mucosal scarring	30–40% mortality rate

target lesions begin as erythematous papules, expanding for 2–3 cm in diameter to form 3 distinct zones, a dusky purple centre, a pale middle zone and an erythematous border. Central blistering or crusting may occur. Lesions typically appear over 3–5 days and resolve over 1–2 weeks [160,174]. Mucosal involvement in patients with erythema multiforme minor is uncommon or mild in severity, usually affecting single mucosal site, that is most commonly the oral mucosa, in 25–50% of the patients. Oral lesions initially manifest as erythematous macules that develop rapidly into multiple vesicles with subsequent ulceration and pseudomembrane formation [175]. Predominantly, the lips and intra-oral non-keratinized mucosal surfaces are affected. Patients present with swollen blood-stained, crusted and erosive upper and lower lips with impairment in feeding and speaking. Intra-oral lesions are located mainly in the anterior parts of the oral mucosa, with the tongue and buccal mucosa being the most affected sites (Fig. 8). The hard palate and gingiva are usually preserved in patients with erythema multiforme minor [174]. Although lesions most frequently affect the oral mucosa, involvement of the ocular, genital, upper respiratory, or pharyngeal mucosa may also occur (165).

Erythema multiforme major shows a wider spectrum of clinical presentation, with tendency for recurrence or persistence in some patients. Skin lesions usually involve less than 10% of the body surface but are generally more severe than erythema multiforme minor. In addition to typical target lesions, atypical raised targets, characterized by two central zones and ill-defined borders, may also be seen. Multiple involvement of at least 2 mucosal surfaces, which typically involve the oral mucosa, is a hallmark feature for the diagnosis of erythema multiforme major [176]. Oral lesions are more extensive than erythema multiforme minor and in more than 50% of the cases, all the oral mucosal surfaces are involved. The presence of typical skin target lesions is necessary to consider the diagnosis of erythema multiforme minor or major [177]. However, a less recognized variant of erythema multiforme is termed *oral erythema multiforme* and characterized by oral lesions with the typical clinical features and aetiology of erythema multiforme, but without skin involvement. Oral erythema multiforme is also a chronically recurrent condition, with frequency of episodes varying from every 3 weeks to once yearly [177,178].

Stevens-Johnson syndrome and toxic epidermal necrolysis are considered clinically different disorders from erythema multiforme [179,180]. Stevens-Johnson syndrome and toxic epidermal necrolysis are characterized by diffuse, atypical flat target lesions, with bullous central areas, severe mucosal erosions; and, commonly, a prodrome of flu-like symptoms. The two conditions differ in the extent of epidermal detachment, with Stevens-Johnson syndrome limited to less than 10% of BSA, 10% to 30% of BSA for Stevens-Johnson syndrome/ toxic epidermal necrolysis overlap and 30–100% of BSA for toxic epidermal necrolysis. Involvement of the oral, ocular and genital mucosa occurs in 90–100% of the patients and associated with severe morbidity. Stevens-Johnson syndrome and toxic epidermal necrolysis are most often caused by a hypersensitivity reaction to medications such as sulfonamides, lamotrigine, and carbamazepine [180].

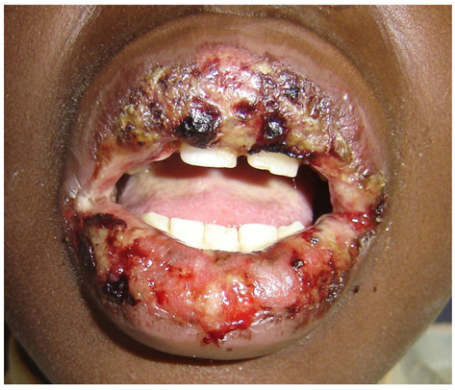

Fig. 8. Clinical feature of erythema multiforme. Clinical picture of a 9 year-old male patient with multiple, severe ulcerations and haemorrhagic crusting involving the labial and buccal mucosa.

Erythema multiforme must be differentiated from other immune-mediated diseases such as mucous membrane pemphigoid and pemphigus vulgaris and from toxic epidermal necrolysis and Stevens-Johnson syndrome. The abrupt clinical presentation, the associated aetiological factors and histological features are the main diagnostic measures [165]. Histopathological findings include liquefaction degeneration of the basal epidermal cells, necrotic keratinocytes, exocytosis of lymphocytes and intense lymphocytic infiltration at the basement membrane zone [164]. Biopsies from early stage papules or peripheral portions of the lesions show dermal changes such papillary oedema, vascular dilatation and perivascular mononuclear infiltrates, while those taken from central portions of the target lesions show more epidermal changes such as necrosis. The findings by direct and indirect immunofluorescence microscopy in erythema multiforme are non-specific, but may be occasionally relevant for differential diagnosis [164].

11. Lupus erythematosus

Lupus erythematosus (LE) is a chronic, autoimmune multisystem disorder that features a broad spectrum of symptoms and is associated with significant morbidity and mortality. The disease basically affects the body's connective tissues and blood vessels, hence accordingly, it has been classified into two forms, systemic lupus erythematosus (SLE), which is a multiorgan disease with variable prognosis and cutaneous lupus erythematosus (CLE) which is a more benign condition, limited to the skin and mucosal surfaces. However, the clinical differentiation between the 2 forms is not always clear and significant overlap may occur between CLE and SLE at clinical, histological and immunopathological levels [181]. Lupus erythematosus may affect both sexes at any age, however, it is more prevalent among women of childbearing age. Incidence rates of SLE range from approximately 1 to 10 per 100,000 persons per year and the prevalence rates generally range from 20 to 70 cases per 100,000 persons [182].

The pathomechanisms of lupus erythematosus involve a complex interaction of multiple genetic and environmental factors. The hallmark pathological features of the disease are inflammation and blood vessels abnormalities in a form of occlusive vasculopathy and vasculitis [183]. Antinuclear antibodies are the most characteristic feature in the pathogenesis of lupus erythematosus and present in more than 95% of the patients. Anti-double stranded DNA (ds-DNA) and anti-Sm antibodies are specific findings in patients with SLE and their presence is included in the classification criteria of SLE [183,184].

Initiation of the disease results from a number of environmental triggers and exogenous factors such infections, vaccines, smoking, drugs and dietary factors [183]. Exposure to ultra-violet light is an important trigger in many patients with SLE as it has been recently found to induce apoptosis of human keratinocytes that results in the exposure of nuclear and cytoplasmic antigens. Ultra-violet light also induces and modulates immune and inflammatory mediators by increasing levels of both IL-10 and IL-12 [185]. Genetic inheritance is strongly reflected by the concordance of lupus erythematosus in identical twins and its increased frequency among first-degree relatives and siblings. Furthermore, the higher incidence of lupus erythematosus among females at childbearing age suggests a role for endogenous sex hormones in disease predisposition [182].

Lupus erythematosus is a systemic autoimmune disorder that manifests with a wide range of clinical features, ranging from mild cutaneous lesions to life threatening visceral manifestations. Although many organs can be affected in patients with lupus, cutaneous lesions are seen in almost all the patients (Fig. 9a). Patients with SLE have a wide profile of autoantibodies and present with a complex range of clinical manifestations involving the mucocutaneous surfaces,

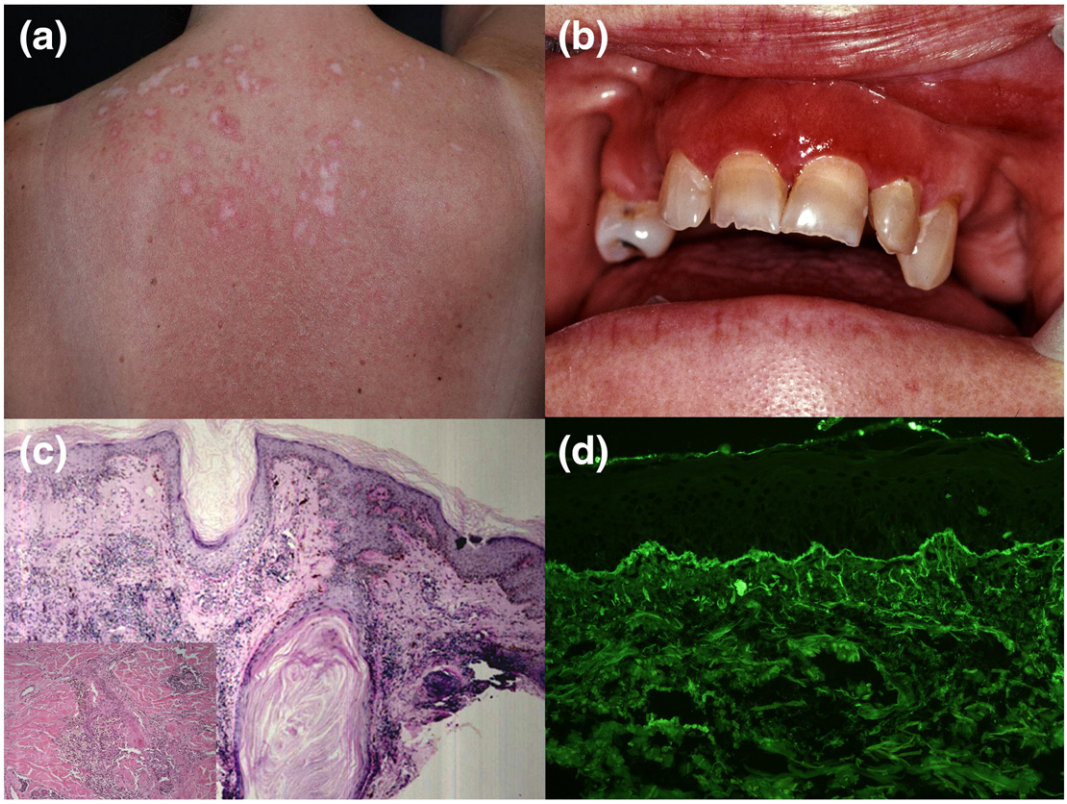

Fig. 9. Clinical and histopathological features of lupus erythematosus (LE)(a) A patient with skin lesions of lupus erythematosus (b) Erythematous gingival appearance in a patient with lupus erythematosus (c) Histopathological examination reveals hyperkeratosis, basal layer degeneration and sub-epithelial lymphocytic infiltrate (d) Direct immunofluorescence microscopy shows band-like deposition of IgG at the basement membrane zone.

musculoskeletal, hematological and renal systems [182]. Bullous systemic lupus erythematosus (BSLE) is a rare cutaneous manifestation of SLE, characterized by autoantibodies against collagen VII [186]. CLE includes a variety of lupus-specific skin lesions (lupus dermatitis) and has been subdivided into 3 categories, acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE) and chronic discoid lupus erythematosus (CDLE). In addition to the specific skin lesions, patients with SLE and CLE can also demonstrate less specific skin lesions such as periungual telangiectasias, Raynaud syndrome, leukocytoclastic vasculitis and urticarial vasculitis [187].

Oral manifestations of lupus erythematosus are frequent with a higher prevalence of oral lesions reported in patients with SLE (9–54%) compared to CLE (3–20%) [181,188]. Oral mucosal lesions are frequently chronic with a reported mean duration of 4.2 years in one study [189]. Also, lesions can be asymptomatic in up to 50% of the patients. It has been suggested that oral lesions represent the mucosal counterpart to the cutaneous lesions and should be similarly classified (Table 12). Oral lesions are usually multiple, asymmetrically distributed and most commonly affect the buccal mucosa, hard palate, lips and the gingiva (Fig. 9b). Different morphological presentations have been reported, ranging from the classic plaques with central erythema surrounded by a white rim with radiating keratotic striae and occasional telangiectasia to varicose or bullous forms [190]. Ulcerations are usually associated with SLE and are included in the American College of Rheumatology (ACR) criteria for the diagnosis of SLE. Ulcers are asymptomatic in 50–80% of the patients. They occur at the onset of the disease in 11% of patients and in some patients they can be the early manifestation of the disease. Due to the multisystem involvement, patients with SLE

Table 12
Clinical manifestations of cutaneous lupus erythematosus.

Cutaneous lupus erythematosus (CLE)	Skin lesions	Oral lesions
Acute Cutaneous Lupus Erythematosus (ACLE)	Localized: Classic butterfly rash in the centre of the face Generalized : maculopapular rash	Circumscribed red macules Diffuse palatal erythema Purpuric macules Symmetrically/ asymmetrically distributed ulcers and erosions
Subacute Cutaneous Lupus Erythematosus (SCLE)	Localized lesions on sun-exposed areas	Intra-oral lesions are rare well-demarcated round red patches Diffuse erythematous labial plaques
Chronic Cutaneous Lupus Erythematosus (CCLE)	Classic discoid lesions (well-demarcated scaly macules), develop into painful indurated plaques. Verrucous lupus erythematosus, intensely keratotic discoid lesions.	Oral discoid lesions: well-demarcated, round, irregular atrophic or ulcerated areas, with radiating keratotic striae Honeycomb plaques: intensely keratotic white lesions and linear fissured ulcerated lesions.

may present with a number of orofacial manifestations, such as the malar (butterfly) rash and the well-circumscribed white lacy plaques with hyperkeratosis and erythema, on the palatal mucosa. Xerostomia, due to minor salivary gland involvement, can also occur in patients with SLE associated with symptoms of hematological disturbances such as mucosal pallor, angular cheilitis and oral candidosis [191].

Lupus erythematosus with predominantly oral lesions should be differentiated clinically and histologically from oral lichen planus (Table 13). The main histopathological features of cutaneous and mucosal lupus erythematosus are interface mucositis with superficial and deep perivascular lymphocytic inflammation. Additionally, epithelial hyperkeratosis, atrophy of the rete pegs, oedema in the lamina propria and liquefaction degeneration of the basal epithelial cells, are prominent features (Fig. 9c) [190].

Direct IF microscopy is important for confirming the diagnosis of lupus erythematosus. Direct IF microscopy in oral lupus erythematosus is frequently positive. IgA, IgG, IgM as well as different complement components maybe found at the basement membrane in a linear or granular deposition pattern [192]. However, IgM is the most commonly identified immunoreactant in oral lupus erythematosus (Fig. 9d) [181].

12. Therapeutic approaches in autoimmune diseases with oral involvement

12.1. Principles of therapy

Management of oral lesions in patients with immune-mediated disorders can be challenging and requires a multidisciplinary approach. Early diagnosis is of extreme importance in order for proper management at early stages of disease. The aim of treatment is usually directed towards diminution of pain and discomfort, control of disease progression and prevention of related complications [193]. Several therapeutic guidelines exist in the literature for the management of immune-mediated disorders. However, the lack of large randomized clinical trials makes treatment optimization difficult [194–197].

Treatment regimens are usually tailored according to clinical findings such as the age of the patient, the medical history, severity of the disease, and the rate of disease progression (Table 14). Triggering factors such as antimicrobials and non-steroidal anti-inflammatory drugs should be identified and discontinued in collaboration with the patient's physician. Involvement of the oral mucosa in patients with immune-mediated disorders necessitates great attention to maintain oral hygiene, perhaps by regular visits to periodontists for oral hygiene instructions and periodic full mouth scaling [95,198]. Efforts must also be directed towards prevention of local irritation by avoiding spicy and hard food with cessation of smoking. Tooth brushing with soft brushes should be encouraged and antiseptic mouthwashes such as chlorhexidine gluconate 0.2% can be used. Topical analgesics such as benzydamine hydrochloride 0.15% (rinse or spray) are useful to relieve pain and discomfort particularly prior to eating or tooth brushing [193].

12.2. Topical therapy

Topical corticosteroids unfold locally their anti-inflammatory and immunosuppressive effects thereby significantly reducing disease activity and clinical morbidity, especially in patients with chronic or mild diseases such as atrophic lichen planus, mucous membrane pemphigoid and erythema multiforme [199].

Topical corticosteroids are generally used in a number of ways. First, they are used in a short course of therapy in order to accelerate remission in diseases that have natural tendency to remit spontaneously, such as erythema multiforme minor. Second, they can be used in prolonged courses and for unpredictable durations to lessen discomfort in diseases that tend to be chronic or with a marked tendency to recur such as atrophic lichen planus, mucous membrane pemphigoid and erythema multiforme major. Third, topical corticosteroids may be used as a maintenance regimen in patients with mild to moderate autoimmune diseases following a short course of systemic corticosteroids [200]. However, topical corticosteroids alone will not sufficiently control disease activity in patients with severe, multiple disseminated lesions and high levels of antibodies titers such as pemphigus vulgaris, Stevens-Johnson syndrome and toxic epidermal necrolysis [201,200].

Topical corticosteroids are available in different strengths and preparations. They can be classified according to their potency into high, mid and low potency [199]. Many factors affect the choice of a particular topical corticosteroid for the management of oral lesions in immune-mediated disorders. A successful choice depends on choosing the adequate potency for the severity of the disease, using the appropriate vehicle for drug administration, prescribing the right number of drug applications per day, and tapering timely so that the maximum therapeutic effect with minimum side-effects are achieved [199,202]. Therefore, topical corticosteroids are mostly used in a form of adhesive ointments or aqueous solutions for the management of oral ulcers. Adhesive ointments are suitable for treatment of small isolated lesions or when few, easily accessible lesions exist or when the lesions are located on the palate or the gingiva, so that customized trays can be used to hold drugs in contact to lesions for longer durations. On the other-hand, aqueous solutions are used for the management of large and deep lesions. However, they have a wider contact with the mucosal surfaces, a fact that increases drug systemic absorption and hence complications may arise [199].

Triamcinolone acetonide is a moderate-potency topical corticosteroid that comes in a range concentration between 0.05% and 0.5%. It has been found to be effective for the management of mild cases of oral lichen planus. The drug should be applied several times per day (3–10 times) and for a period of 3 to 5 minutes each time in order to achieve therapeutic effect. This is inconvenient and thus, it maybe

Table 13
Diagnostic features of oral involvement in systemic lupus erythematosus.

Diagnostic features	Findings
Clinical features	
Oral lesions	Painless oropharyngeal ulceration (discrete with red/grey base and hyperkeratotic borders) Honeycomb white plaques on palatal mucosa
Skin lesions	Malar (butterfly) rash on the face (fixed erythema, over the malar area sparing the nasolabial folds), discoid lesions, photosensitivity
Other organs/systems	Non-erosive arthritis, serositis (pleuritis or pericarditis) neurologic disorder (seizures, psychosis)
Investigations	
Clinical chemistry	Nephritis (persistent proteinuria, red blood cell casts), anemia, leuko- and thrombocytopenia, low complement factors, increased complement turnover, positive Coombs test
Histology	Interface mucositis with superficial and deep perivascular lymphocytic inflammation
Direct IF microscopy	Deposits of immunoglobulin IgG, IgA, IgM and C3 at the dermal-epidermal junction (lupus band)
Indirect IF microscopy	Antinuclear antibodies (ANA)
Immunoassays	IgG autoantibodies against ds-DNA, Sm, cardiolipin, beta2-glycoprotein I, Ro-60/TROVE2, La/SS-B, ribosomal Protein P, U1 ribonucleoprotein (RNP) complex

Table 14
Therapeutic options for oral lesions associated with autoimmune skin diseases.

Therapy (Indications/Properties)	Drugs	Pre-therapeutic investigations	Adverse effect	Monitoring
Topical corticosteroids *First-line therapy for localized mild / chronic disease* *Maintenance therapy after short course of systemic corticosteroids*	E.g., mometasone furoate, triamcinolone acetonide, clobetasol propionate		Oral candidosis, mucosal atrophy	
Calcineurin-inhibitors *Second-line therapy, in patients who do not respond to topical corticosteroids*	Tacrolimus, Pimecrolimus		Irritation, pruritus and erythema on application	
Systemic corticosteroids *Cornerstone therapy, effective, has rapid onset*	Prednisolone	Weight, Blood pressure, FBC, Glucose (FPG, OGTT), BMD, Lipids profile	Diabetes; osteoporosis; adrenal suppression; peptic ulceration; weight gain; increased susceptibility to infection; Cushing's syndrome; cataracts Oral candidosis, mucosal atrophy	Weight, blood pressure, FBC, Glucose (FPG, OGTT), BMD, Lipids profile
Immunosuppressant drugs *Slower in onset than corticosteroids, so rarely used alone to induce remission.* *Used in conjunction with corticosteroids for their steroid-sparing actions;* *Can be used alone to maintain remission after corticosteroids withdrawal*	Azathioprine	Thiopurine methyltransferase (TPMT) assay (determines risk of bone marrow aplasia) FBC, LFTs, UA	Myelosuppression and nausea (related to TPMT activity); Gastrointestinal toxicity, hepatotoxicity, alopecia, pancreatitis, lymphoproliferative diseases, increased infection rates	FBC weekly for first 8 weeks; thereafter monthly LFTs every two weeks,
	Mycophenolate mofetil	FBC, blood pressure, LFTs, UA, HIV, HBV, HCV	Gastrointestinal distress, anaemia, leukopenia, thrombocytopenia, increased risk of infections	FB and LFTs monthly
	Cyclophosphamide	FBC, blood pressure, LFTs, UE, HIV, HBV, HCV	Acute myelosuppression, mucosal ulceration, gastrointestinal distress, nephrotoxicity, cardiotoxicity, increased risk of cancer, infertility	RFP, FBC , UE
	Cyclosporine	FBC, blood pressure, LFTs, UE, HIV, HBV, HCV	Electrolyte abnormalities, renal toxicity, tremors, hirsutism, hyperlipidemia, hypertension, gingival hyperplasia	REF, LFTs, FBC,UE, lipids profile, blood pressure

FPG: Fasting peripheral glucose, OGTT: Oral glucose tolerance test, FBC: Full blood count, BMD: Body mineral density, LFTs: Liver function tests, UE: Urea and electrolytes, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus.

difficult for many patients to comply with treatment. Fluocinonide is a moderate to high potency corticosteroid that is used at concentration ranging between 0.025% and 0.05%. The drug has better effect on lesional resolution, however, it is still used for the management of mild to moderate oral lesions [203].

Clobetasol propionate is a high-potency topical corticosteroid that is used in concentrations of 0.025% and 0.05%. Both in the aqueous solution and adhesive orabase forms, clobetasol propionate has superior therapeutic effects in comparison to other topical corticosteroids. The drug is effective in rapidly controlling oral lesions following a few daily applications. Clobetasol propionate can be used for management of more severe localized oral lesions in patients with oral lichen planus, mucous membrane pemphigoid and erythema multiforme. It can also be used as a supplement to systemic therapy in patients with pemphigus vulgaris [203,199].

Other topical corticosteroids preparations, such as betamethasone sodium phosphate tablets dissolved in water and used as mouthwash, can be also used in patients with more diffuse and multiple oral lesions. Hydrocortisone in a form of lozenges or sprayed directly to the oral lesions with an asthma inhaler can also be effective [204].

The use of topical corticosteroids in the management of oral lesions can often be complicated with a number of topical or systemic side effects. Oral candidosis is a common side effect of topical corticosteroids that appears in 25–55% of the patients, particularly following the use of high potent topical corticosteroids for long duration. Furthermore, the use aqueous mouthwash appears to be a greater risk factor for the development of oral candidosis, in comparison with adhesive pastes. Oral candidosis can be prevented or treated successfully with topical antifungals. Mucosal atrophy, burning sensation, nausea and refractory responses may also occur [202]. The presence of large erosive and atrophied areas treated with topical corticosteroids may increase the risk of drug's systemic absorption and hence complications such as, adrenal suppression, Cushingoid appearance (moon face), hypertension and hyperglycemia. Therefore, patients on topical corticosteroids should be closely monitored especially when high-potency corticosteroids in aqueous solutions are applied three or more times a day for the management of extensive oral lesions [202,205].

Topical calcineurin inhibitors, such as tacrolimus, pimecrolimus and ciclosporin, are microbially derived immunosuppressive agents that have been used in transplant medicine and for the management of immune-mediated diseases. Calcineurin inhibitors bind to different cytoplasmic proteins of the T lymphocytes (cyclosporine to cyclophilin; tacrolimus and pimecrolimus to mFK506-binding protein) to form complexes that in turn inhibit the phosphorylase enzyme calcineurin, leading to suppression of transcription and production of many inflammatory cytokines. Tacrolimus also inhibits histamine release and the synthesis of prostaglandin D2 from mast cells activated by IgE, whereas pimecrolimus can inhibit mast cell cytokines and serotonin [206].

Topical calcineurin inhibitors are important treatment options for patients where the use of topical corticosteroid has failed to control the symptoms or where painful refractory lesions occur following initial healing. The most frequently reported adverse side effects associated with the use of these drugs include, transient burning or stinging sensation associated with application. Some patients also report a degree of skin rashes, local swelling dyspepsia and gastrointestinal upset [206]. A recently conducted double-blind controlled trial, comparing the efficacy of topically applied pimecrolimus and tacrolimus in the treatment of atrophic-erosive lichen planus refractory to topical steroids, was undertaken. The study shows that both drugs are equally effective at inducing clinical improvement among those patients with limited side effects. However, pimecrolimus showed a significantly better stability of therapeutic effectiveness throughout the study duration with a longer-term resolution of signs and symptoms, in comparison with tacrolimus [207].

Comparative studies of the efficacy of topical corticosteroids and topical calcineurin inhibitors in the management of oral lichen planus,

found no significant superiority of either of the treatment modalities in controlling the patient's symptoms. Therefore, for the reason of the higher cost of the calcineurin inhibitors, their use is recommended as a second-line treatment for symptomatic oral lichen planus that fails to respond to topical corticosteroids [208]. In contrast to topical corticosteroids, tacrolimus does not affect collagen synthesis and hence does not cause thinning of the skin or mucous membrane. Few reports have recently shown that topical tacrolimus 0.1% is a safe and effective agent in inducing full remission of lesions in patients with oral mucous membrane pemphigoid [209].

12.3. Systemic therapy

Systemic corticosteroids are the first line treatment for patients with severe and progressive mucosal lesions associated with immune-mediated diseases. Systemic corticosteroids exhibit an anti-inflammatory and immunosuppressive effects due to inhibition of pro-inflammatory cytokines production. They reduce the number of circulating T-cell lymphocytes and hence diminish their response to antigens. In addition, systemic corticosteroids decrease antibodies production and therefore, the reaction with self-antigens is also decreased [210].

Oral prednisolone is the most commonly used systemic corticosteroid that successfully suppresses disease activity in patients with severe oral ulceration. Its effectiveness has been proved by a number of randomized controlled trials, however, its optimal dosing and formulation remains unclear. In general, oral prednisolone is used at high doses first to arrest blisters formation and achieve disease control. Once this objective has been reached, a careful tapering of prednisolone according to the patient's clinical and serological response is recommended [211]. The use of systemic corticosteroids is often associated with severe side effects such as hypertension, diabetes, glaucoma and systemic infections, especially among elderly people. Therefore, it is important to minimize the total dose and duration of therapy with systemic corticosteroids [210].

Systemic corticosteroids are usually combined with other immunosuppressive agents to allow for rapid reduction of the corticosteroid dose. Most commonly used immunosuppressive agents include azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate and calcineurin inhibitors. These drugs are slower in onset than corticosteroids, so rarely used alone to induce remission. They are commonly used in conjunction with corticosteroids for their steroid-sparing action and may also be used alone to maintain remission after corticosteroids withdrawal [195].

Azathioprine is a pro-drug that is converted to 6-mercaptopurine in the body. 6-mercaptopurine is subsequently converted by several enzymatic metabolites into 6-tioguanine nucleotides that function as nucleotide analogs and lead to eventual lymphocyte impairment [211]. Azathioprine is the first choice adjuvant drug for the management of severe immune-mediated diseases such as pemphigus vulgaris. Myelosuppression, with marked reduction of white blood cells, is the most significant side effect following the use of azathioprine. The risk of myelosuppression is related to the level of thiopurine methyltransferase (TPMT), an enzyme that converts 6-mercaptopurine into inactive metabolites. Patients with low levels of TPMT have increased susceptibility to develop myelosuppression. Patients on azathioprine treatment should also be monitored for other side effects such as cytopenia, hepatitis, pancreatitis and increase risk of infections [210,211].

Mycophenolate mofetil is another adjuvant immunosuppressive therapy that impairs purine synthesis and alters the function of proliferating T and B lymphocytes. Mycophenolate mofetil has a selective inhibitory immunosuppressive action, therefore, a more favourable safety profile than other less selective adjuvant immunosuppressants such as azathioprine. Mycophenolate mofetil, as a monotherapy, was found to be successful in controlling disease activity, although it is typically used in combination with corticosteroids for potential steroid- sparing effect [212]. Mycophenolate mofetil is generally well tolerated. The drug's most common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhoea and abdominal pain. Patients who receive mycophenolate mofetil are also at risk of developing systemic infections, leukopenia and anaemia [210].

Cyclophosphamide is a nitrogen mustard alkylating agent that is metabolized in the liver to active forms. These active metabolites are known to cross-link DNA, inhibiting its replication and leading to cell death. Cyclophosphamide used as intravenous pulse therapy may be considered in patients with severe pemphigus vulgaris or mucous membrane pemphigoid that fail to be controlled with combination of corticosteroids and azathioprine or mycophenolate mofetil or those with clinically significant side effects from these therapies. Side effects can be severe and include infections, nausea, vomiting, leukopenia, thrombocytopenia, cystitis and increased risk of lymphomas [213].

Calcineurin inhibitors are drugs which inhibit the action of calcineurin, a protein phosphatase involved in activating the T-cells of the immune system. Calcineurin inhibitors such as cyclosporine, tacrolimus or pimecrolimus are occasionally used for topical and systemic therapy in autoimmune diseases, including pemphigus vulgaris. Their effects are mediated by inhibition of calcineurin resulting in a blockade of interleukin 2 production and T cell activation. The main adverse reactions of ciclosporin are renal dysfunction, hypertension, tremor and gingival hyperplasia [214].

Concluding remarks

Oral lesions may be the first and occasionally the only manifestation for a number of immune-mediated diseases that affect the skin and mucosal surfaces. Autoantibodies directed against structural compounds of the skin and oral mucosa and/or inflammatory infiltrates cause tissue damage. An accurate diagnosis can be reached by utilizing a number of diagnostic tools such as direct immunofluorescence microscopy of a perilesional biopsy and serological testing for circulating autoantibodies in conjunction with histopathological analysis. An early and precise diagnosis of autoimmune and inflammatory diseases with oral involvement is a prerequisite for their effective treatment.

Take-home messages

- Autoantibodies against adhesion structures result in a wide range of autoimmune diseases affecting the skin and mucosal surfaces.
- Oral mucosal lesions occur in several of these conditions and often can be the first clinical sign of the autoimmune disease.
- General practitioners and dental care professionals play an important role in early diagnosis of autoimmune skin diseases which may significantly influence disease progression and outcome.
- An in-depth knowledge of the clinical presentation, diagnostic tools and management regimens should arm clinicians, not only for early diagnosis of the autoimmune dermatosis, but also for providing the appropriate, timely management and follow up for the associated oral lesions in a multidisciplinary team.

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