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REVIEW ARTICLE

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Oral autoimmune vesicobullous diseases: Classification, clinical presentations, molecular mechanisms, diagnostic algorithms, and management

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1 | INTRODUCTION

Vesicobullous diseases are a large group of disorders with different etiologies, pathogenesis, and prognoses that affect the skin, the mucosal surfaces, or both. The clinical sign that marks all vesicobullous diseases is the onset of vesicles or bullae, defined as skin/mucosal lesions with a subcorneal or suprabasal intraepithelial detachment within the epithelium (acantholysis) or with a subepithelial detachment between the epithelium and the lamina propria. Clinical and histologic findings vary markedly among vesicobullous diseases, depending on the heterogenity of the etiology (Table 1). Many of these diseases can be extremely debilitating with serious sequelae, and are possibly fatal, so early treatment is necessary to reduce morbidity and mortality.

In this review we discuss autoimmune blistering disorders, and among them, those that more frequently affect the oral mucosa. Autoimmune blistering disorders are a rare subgroup of diseases that are characterized by the presence of serum autoantibodies (IgG, IgM, IgA) directed against antigens within the epithelium or the basal membrane zone. The different topography of the numerous antigens in the context of the epithelium and basal membrane zone explains the presence of intraepithelial or subepithelial bullous lesions, and identifies different diseases with totally different treatment strategies and prognoses. The application of immuno-molecular biology to the study of autoimmune blistering disorders has led to a more detailed understanding of the pathogenesis of the disorders. The oral mucosa often represents the first site of onset of autoimmune blistering disorders from which the disease may spread to the skin and/or other mucosal sites (conjunctiva, nose, pharynx, larynx, esophagus, genital area). Oral mucosal involvement is the sole presentation in some cases. For this reason, early diagnosis of autoimmune blistering disorders in oral mucosa is imperative for clinicians to maximize treatment response, minimize serious side effects and, above all, to achieve a good prognosis and better quality of life for the patient.

2 | PEMPHIGUS VULGARIS

Pemphigus is a group of potentially life-threatening autoimmune blistering diseases characterized by cutaneous and/or mucosal blistering caused by the presence of circulating IgGs directed against desmogleins 1 and 3, calcium-dependent adhesion molecules (cadherins) that are involved in cell-cell adhesion[1] (Figure 1). The interaction between desmoglein IgGs and their target antigens is responsible for acantholysis and the formation of intraepithelial blisters of the skin and mucous membranes. Differences in the location of particular desmogleins (only skin, only mucosal surfaces, skin and mucosal surfaces together) result in different phenotype of the disease.[3] The mean age of onset of pemphigus vulgaris is usually 40-60 years. The disease susceptibility is strongly associated with some class II HLA antigens.

The worldwide epidemiology of pemphigus has shown an incidence of 0.1-3.2/100 000 population.[4] The incidence of pemphigus in Central Europe is 1-2 cases per million persons per year, and 80% of patients have pemphigus vulgaris.[5] The incidence of pemphigus in Ashkenazi Jews can be as high as 16-32 cases per million persons per year. The prevalence of pemphigus is higher in Jewish populations, in particular of Ashkenazi origin, and in Japanese and Indian populations, than in North American or European populations.[6] In patients with pemphigus vulgaris, the mortality rate is between 5% and

TABLE 1 Classification of vesicobullous disease according to etiology

Autoimmune diseases	**Pemphigus vulgaris**
	Pemphigus foliaceus
	IgA pemphigus
	Paraneoplastic pemphigus
	Bullous pemphigoid
	Mucous membrane pemphigoid
	Linear IgA disease
	Pemphigoid gestationis
	Herpetiform dermatitis
Inherited diseases	Epidermolysis bullosa (with all variants)
	Hailey-Hailey disease
Infectious diseases	Herpes simplex and herpes zoster viruses
	Staphylococcal scalded skin syndrome
	Hand, foot, and mouth disease
	Herpangina
	Impetigo
Metabolic diseases	Bullous amyloidosis
	Porphyria
	Glucagonoma syndrome
	Diabetes
Iatrogenic/injury	Multiform erythema
	Toxic epidermal necrolysis
	Stevens-Johnson syndrome
	Radiation
	Allergic contact dermatitis
	Friction
	Thermal/chemical burns
Other	Lichen planus
	Lichen planus pemphigoid
	Graft-versus-host disease
	Eczema
	Grover's disease
	Lupus erythematosus
	Subcorneal pustular dermatosis (Sneddon-Wilkinson disease)

The diseases shown in bold are described in this review.

25%.[7] The pemphigus group of conditions encompasses diseases characterized by different clinical patterns, histologic features, immunologic pathways, and clinical behaviors, which are classified as follows: (a) pemphigus vulgaris and its variant pemphigus vegetans; (b) pemphigus foliaceus and its 3 variants pemphigus erythematosus (Senear-Usher syndrome), pemphigus herpetiform, and Brazilian pemphigus (fogo selvagem or Brazilian wildfire); (c) drug-induced pemphigus; (d) IgA pemphigus; (e) familial benign chronic pemphigus (Hailey-Hailey disease); and (f) paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan system).[8] Of those, the most common type is pemphigus vulgaris. Oral lesions are the first manifestations of the disease in 50%-90% of patients. Blisters can present in any part of the oral mucosa but frequently develop in areas subjected to frictional forces, such as the soft palate, buccal mucosa, ventral tongue, gingiva and lower lip (Figures 2-4). Blisters often readily rupture, leading to chronic, painful ulcers and erosions that take a long time to heal. This early mucosal involvement can probably be explained by the following compensation theory: desmoglein 1, mostly expressed in the skin, may compensate for the absence of desmoglein 3, primarily localized in the oral and pharyngeal mucosae.[9] So, through the phenomenon called "epitope spreading", from early mucosal involvement the disease progresses to the skin[10] over a varying period of time, of 3 months or longer.[11] On the skin, pemphigus vulgaris lesions are characterized by flaccid blisters that rapidly progress into erosions and crust formation and occasionally develop opportunistic infections.

Definitive diagnosis needs 3 major criteria: clinical features; histopathology; and immunologic data. Together, these criteria represent the gold standard for autoimmune blistering disorders.[12] The Nikolsky's sign is a definitive and useful tool for recognizing bullae; on oral mucosa, the specificity of Nikolsky's sign was found to be much higher than the sensitivity, thus it represents a viable test in the preliminary detection of a bullous disease.[13] Oral blistering lesions are very common in patients with pemphigus vulgaris, and are often the first sign of the disease. Oral involvement is found in 50%-90% of patients with pemphigus vulgaris, of whom 50% will have only oral symptoms.[14-16] Histolopathologic analyses of fresh blister specimens can be used to detect the suprabasal acantholysis in the stratiform spinous layer with residual basal keratinocytes on the dermo-epidermal junction zone known as "tombstone effect" (Figure 5). Direct immunofluorescence to identify tissue-bound autoantibodies is an essential supplement for accurately diagnosing immune-mediated dermatological disorders and helps to classify various autoimmune bullous disorders. In pemphigus vulgaris specimens, direct immunofluorescence reveals intercellular space deposition ("fishnet pattern") of IgG, IgA, IgM, and C3 in the epithelium[17] (Figure 6). Indirect immunofluorescence on human skin or monkey esophagus, as substrates, and ELISA aid in detecting anti-desmoglein-1 and -3 in serum. Usually, elevated titers of autoantibodies for pemphigus vulgaris, reported with ELISA, correlate with earlier stages of disease and provide useful information in assessing disease activity.[18,19]

Despite the development of new knowledge in medicine, establishing the optimal therapeutic strategy for pemphigus vulgaris is still a challenge.[20] In the majority of cases, the use of glucocorticoids, either alone or in combination with immunosuppressive/immunomodulant drugs, can control disease activity.[21] Some adjuvant agents (azathioprine, methotrexate, mycophenolate mofetil, cytosine arabinoside, cyclophosphamide, ciclosporine, dapsone, gold,

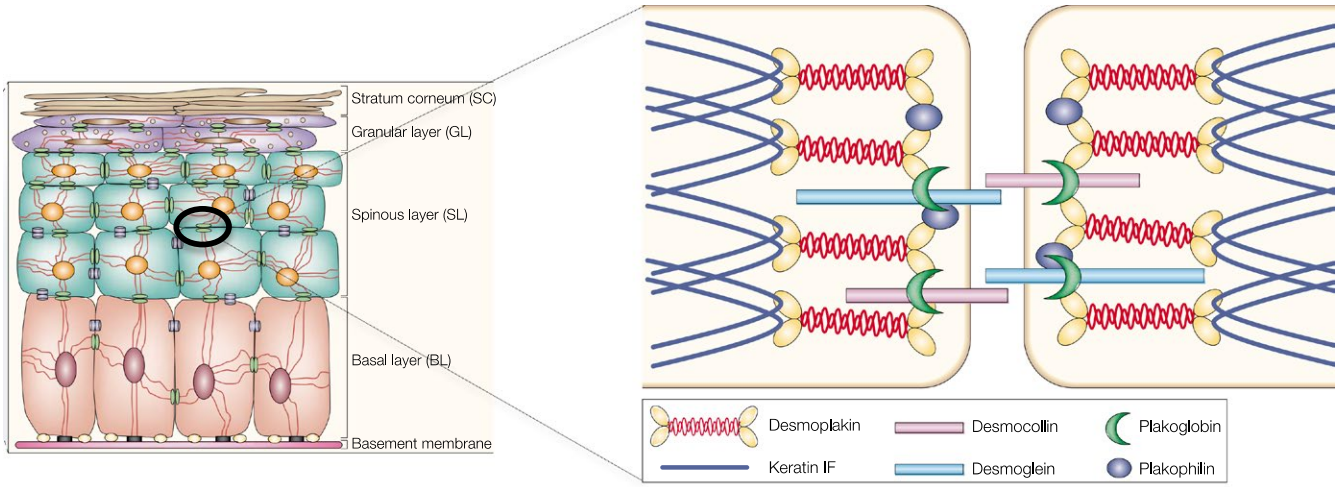

FIGURE 1 A, Structure of stratified squamous epithelium. The oral epithelium consists mainly of keratinocytes, which adhere to each other via desmosomes and to the underlying lamina propria/dermis via hemidesmosomes, constituting the basement membrane zone. B, Desmosomes are cell-cell adhesion proteins and represent the site of attachment of keratin intermediate filaments of the cytoskeleton [from ref. 2]

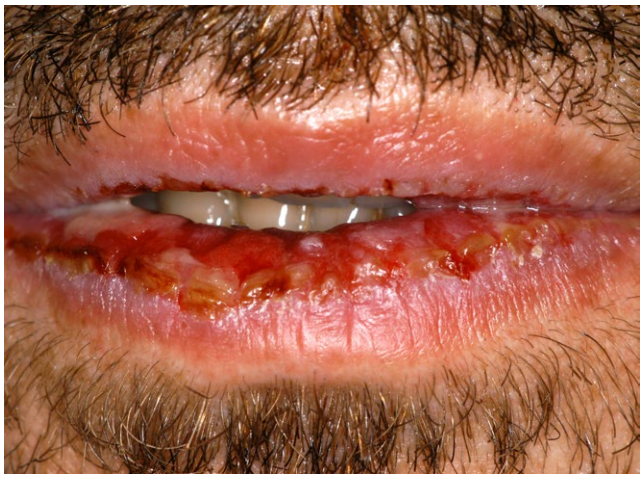

FIGURE 2 Infected blisters and erosions of the lower lip in a 42-y-old Caucasian man with pemphigus vulgaris. Disease onset had been reported 2 mo previously with lesions of the soft palate, uvula, floor of the mouth, and lips. The patient was given conventional treatment; in addition, prophylactic lamivudine was administered to control preexisting hepatitis B virus positivity

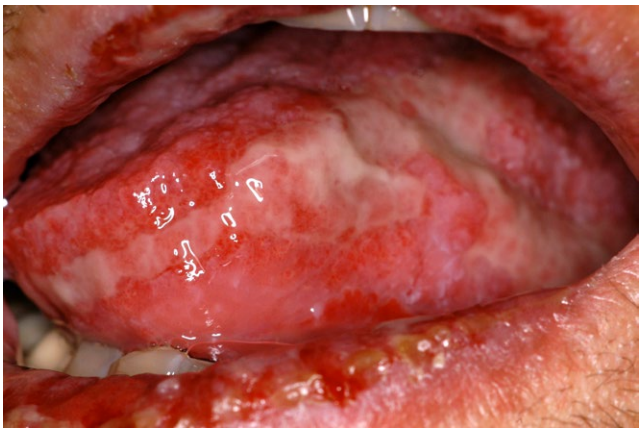

FIGURE 3 Extensive bullous and erosive involvement of the oral mucosa in pemphigus vulgaris. The patient is a 48-y-old Caucasian man with an 11 mo history of mucosal pemphigus vulgaris; he presented with skin lesions on the scalp and in the ear canal

tetracyclines, tumor necrosis factor-α inhibitors) were considered to increase the efficacy of steroids and reduce steroid-related side effects.

This so-called "conventional" treatment is used worldwide with different dosing schedules and with no standardization, and currently represents the first line of therapy. Even though it is well known that the different adjuvant drugs used with oral steroids have a "sparing effect", there is no solid evidence that this combination improves the clinical response over that achieved with glucocorticoids alone.[22]

However, for patients with severe pemphigus vulgaris, those with significant side effects related to conventional treatment, or in patients for whom conventional treatment is contraindicated, different therapeutic approaches should be considered for controlling oral and cutaneous lesions. There is increasing evidence for the use of immunoadsorption[23] and plasmapheresis,[24] high-dose human intravenous immunoglobulins,[25-27] and rituximab.[28,29] According to the most recent international literature, rituximab seems to be the optimal off-label therapeutic agent for treating recalcitrant pemphigus vulgaris because of its ability to produce a sustained clinical remission through B-lymphocyte depletion and as a consequence depleting pathogenic or antigen-presenting B cells.[30] To date, it is not possible to indicate rituximab as the first-line therapy in pemphigus vulgaris and there is no universally accepted protocol. However, case reports and an increasing number of case-series analyses show that it is effective and well-tolerated and could be used in the future as a single agent.

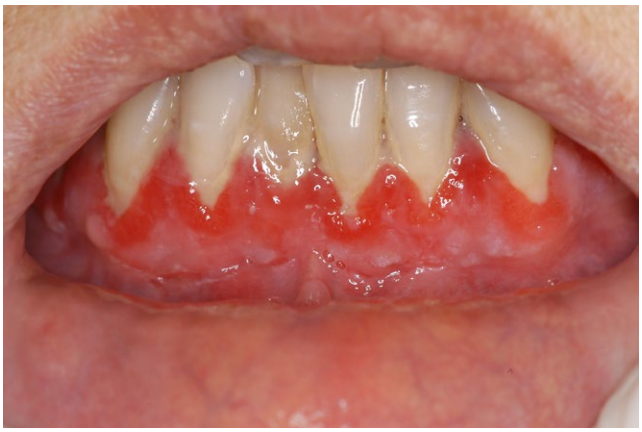

FIGURE 4 Pemphigus vulgaris in a 22-y-old Caucasian woman with extensive mucocutaneous disease. The image shows the affected gingiva with mixed desquamative, vesicular, and hypertrophic/hyperplastic features. After 11 y of several relapses and different treatments the patient died from a human papillomavirus-related squamous cell carcinoma of the vulva

In line with the recent evidence carefully described in the systematic review from McMillan et al,[28] among 32 empirical treatments of pemphigus vulgaris identified following the methodology of the Cochrane Collaboration, only 10 were randomized controlled trials or controlled clinical trials. The protocols described among these 10 papers concern corticosteroids (intravenous and topical), azathioprine, mycophenolate mofetil, cyclophosphamide, immunoadsorption, intravenous immunoglobulin, tacrolimus, etanercept, dapsone, and pentoxyphylline/sulfasazine. Despite the huge number of heterogeneous studies (mostly case series and case reports) in the published literature, there is still inadequate evidence of sufficient quality to demonstrate a clear strategy of treatment in patients with pemphigus vulgaris.

Considering the evidence available to date, the optimal management of a patient with pemphigus vulgaris includes 3 crucial steps: (a) an accurate diagnosis; (b) correct evaluation of the spread and severity of the disease; and (c) comprehensive analysis of the systemic conditions of the patient (age, comorbidities) and, if present, the side effects of previous therapies.

As pemphigus vulgaris is a chronic disease, the high incidence of iatrogenic comorbidities associated with conventional therapies plays a key role when comparing the quality of life in patients with pemphigus vulgaris with subjects from the general population. Despite the lack of a standardized methodology, research conducted by different groups in the last 10 years has shown a great alteration in the quality of life of patients with pemphigus vulgaris;[31] anxiety and depression are the most common psychiatric comorbidities that affect patients who are either receiving treatment for, or are in clinical remission of, blistering diseases.[32] Generic and easy questionnaires for measuring health-related quality of life (ie, SF-36), in association with questionnaires exploring the impact of pemphigus vulgaris on self-perception, social relationships, and behavior, are useful for clinicians to evaluate the more subjective dimensions of the disease and its treatment.

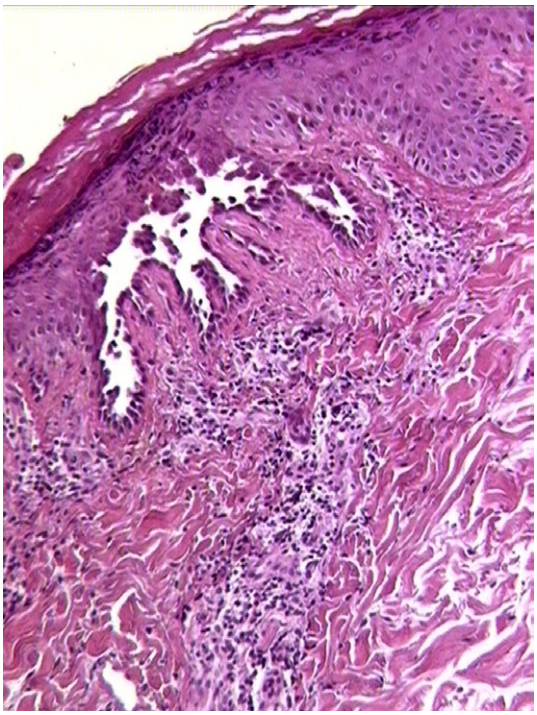

FIGURE 5 Intraepithelial suprabasal cleft of the oral mucosa with scattered acantholitic cells inside the bulla. Isto-morphology was suggestive for pemphigus vulgaris (hemotoxylin-eosin staining, 40×)

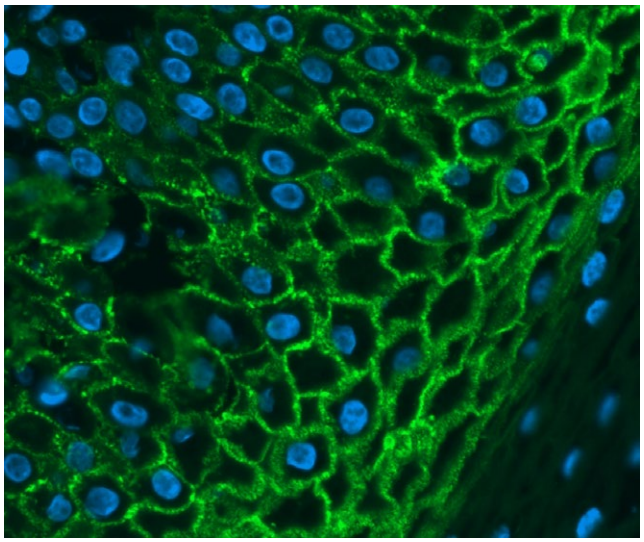

FIGURE 6 Direct immunofluorescence with an intercellular net-like pattern of fluorescence inside the epithelium. The localization of the signal confirms the diagnosis of pemphigus vulgaris

3 | PARANEOPLASTIC PEMPHIGUS

Paraneoplastic pemphigus is a distinct entity in the field of autoimmune blistering disorders; it presents with extensive and painful mucositis and polymorphic lesions of the skin, which are similiar to pemphigus vulgaris, erythema multiforme, and lichenoid lesions. There is no gender predominance, and two-thirds of patients have

a recognized neoplasia at the onset of paraneoplastic pemphigus.[33] Paraneoplastic pemphigus occurs in association with malignancy, among which lymphoproliferative diseases are the most commonly associated.[34] Malignancy is probably caused by an aberrant immunologic response to the neoplasm by the resident immune system; antigenic components produced by malignancies stimulate humoral pathways with the consequent production of autoantibodies directed against a heterogeneous spectrum of antigens of the epithelial cell membrane that clinically simulate a "pure" autoimmune blistering disorder.[35] Another hypothesis shows that an initial cytotoxic host response induced by the neoplasm can stimulate epitope spreading of hidden antigens of the epithelial cell membrane, leading to production of autoantibodies.[36] In addition, cytokine dysregulation was found: in particular, interleukin-6 seems to play a fundamental role in the pathogenesis of clinical manifestations of paraneoplastic pemphigus.[37]

In 2001, Nguyen et al[38] proposed the term paraneoplastic autoimmune multi-organ syndrome in place of paraneoplastic pemphigus, in which pemphigus vulgaris represents one of a complex spectrum of different clinical signs and immunopathological variants in different organs. Paraneoplastic autoimmune multi-organ syndrome can manifest with several (at least 5) clinical phenotypes: pemphigus-like; bullous pemphigoid-like; erythema multiforme-like; graft-vs-host disease-like; and lichen planus-like. Oral lesions have been described in the majority of cases of paraneoplastic pemphigus and may be the sole manifestation[39]; severe conjunctival involvment is usually present (Figures 7-10). The antigens described in patients with paraneoplastic pemphigus are primarily desmoplakins I and II, envoplakin, periplakin, desmogleins 1 and 3, bullous pemphigoid major antigen, and (the most recently identified) alpha 2 macroglobulin like 1.[41]

Paraneoplastic pemphigus is recalcitrant to all conventional therapies because it is strictly related to underlying malignancy. An early diagnosis is of crucial importance for a good prognosis in order to identify the neoplasm and consequently to introduce an appropriate therapeutic strategy.

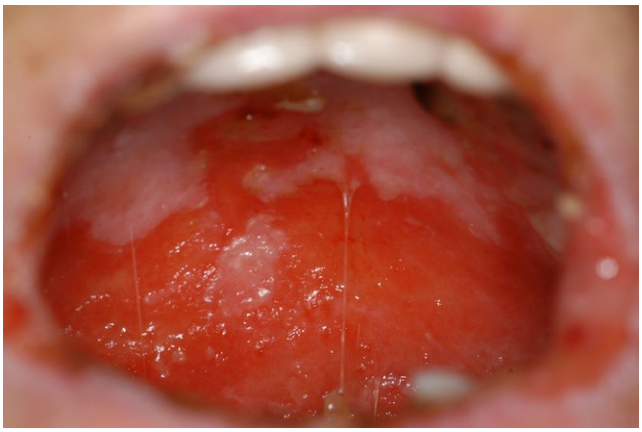

FIGURE 7 Oropharyngeal involvement in a 70-y-old woman affected by paraneoplastic pemphigus. The underlying disease is a myelodysplastic syndrome (refractory cytopenic myelodysplasia; [from ref. 40])

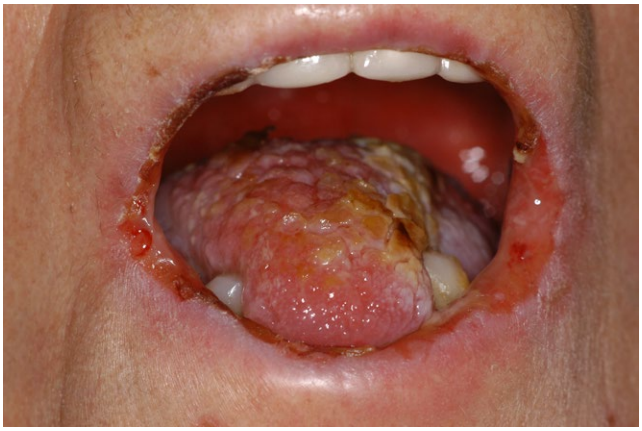

FIGURE 8 Oral involvement in the same patient shown in Figure 7, with extensive lesions on the lips, oral mucosa, and oropharynx

4 | MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid is a heterogeneous group of rare, systemic, autoimmune subepidermal inflammatory diseases that affect mucous membranes containing stratified squamous epithelium and occasionally the skin;[42] these diseases can have major morbidities and but are rarely fatal.[43] The oral (in 85% of cases) and ocular (in 64% of cases) mucosae are frequently involved.[25,44] Epidemiologic data report an estimated incidence of 1 in 20 000 to 1 in 46 000 ophthalmic cases.[45] It is primarily a disease of the elderly (mean age = 64 years) and affects more women than men (ratio of 6:1).[46] Several studies have demonstrated an increased incidence of the major histocompatibility complex, class II, DQ beta 1 (HLA-DBQ1), 0301 allele in patients with mucous membrane pemphigoid (relative risk [RR] = 3.24).[47-49]

In mucous membrane pemphigoid, autoantibodies (IgG or IgA) bind to basement membrane antigens, thereby activating complement-mediated inflammation in the subepithelial tissue.[50] Presentation of mucous membrane pemphigoid in different clinical subsets is determined by target antigens in the basement membrane

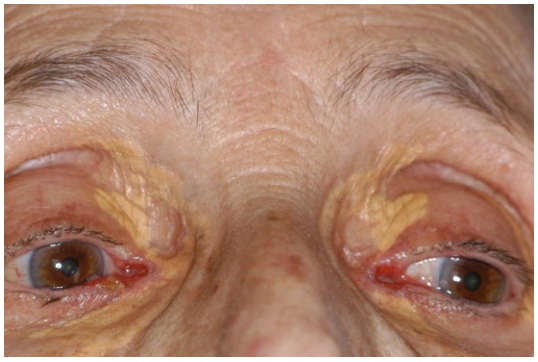

FIGURE 9 Bilateral ocular involvement in the same patient shown in Figure 7, with severe conjuctival inflammation and erosions of the eyelids

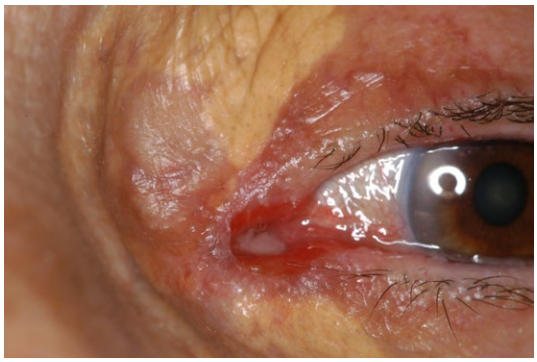

FIGURE 10 A detail of the patient in Figure 7, showing deep loss of substance of the medial canthus of the left eye

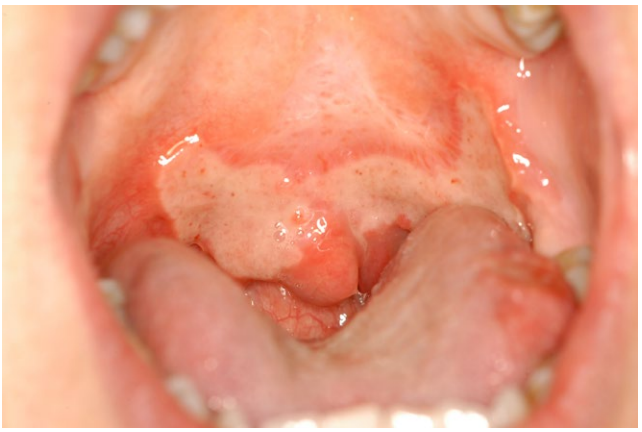

FIGURE 12 Wide and deep ulceration of the soft palate in a 65-y-old woman with mucous membrane pemphigoid. The onset of disease occurred on the soft palate, and after a few weeks had spread widely to the bilateral conjuctiva and vagina

zone, such as collagen alpha-1(XVII) chain (antigen 180/BP180),[1,51] dystonin (antigen 230/BP230),[52] antigens 205 kDa, 160 kDa, and 85 kDa,[53] laminin subunit alpha 5 (epilegrin,[54,55] integrin beta 4,[52,56] and antigen 168 kDa[57] (Figure 11). Although distinct subgroups of mucous membrane pemphigoid have been identified by the use of advanced immunopathologic and immunochemical techniques, diagnosis should still be made on the clinical presentation combined with the results of pathologic, immunohistologic, and serum antibody analyses.

Clinically, the reported sites of involvement were oral mucosa (85%) (Figures 12-14), conjunctiva (64%), skin (24%), pharynx (19%), genitals (17%), nasal mucosa (15%), larynx (8%), anus (4%), and esophagus (4%).[42] A subset of patients with mucous membrane

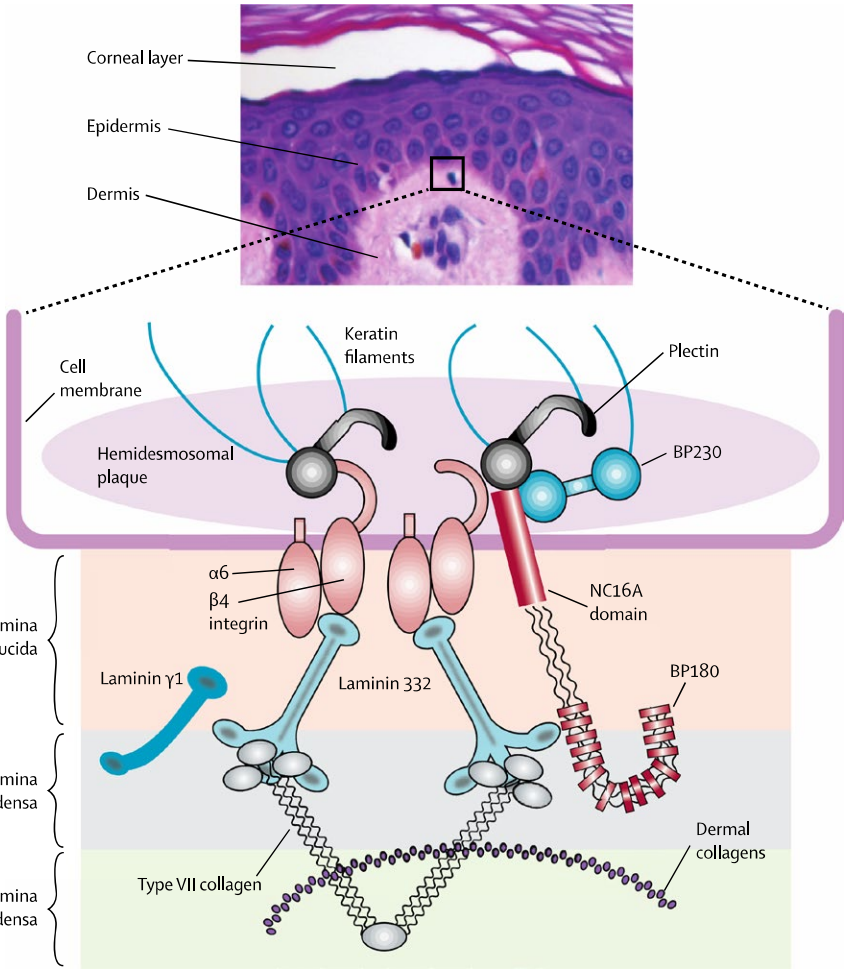

FIGURE 11 Structure of the basement membrane zone (from Schmidt et al[65]). BP180, collagen alpha-1(XVII) chain; BP230, dystonin

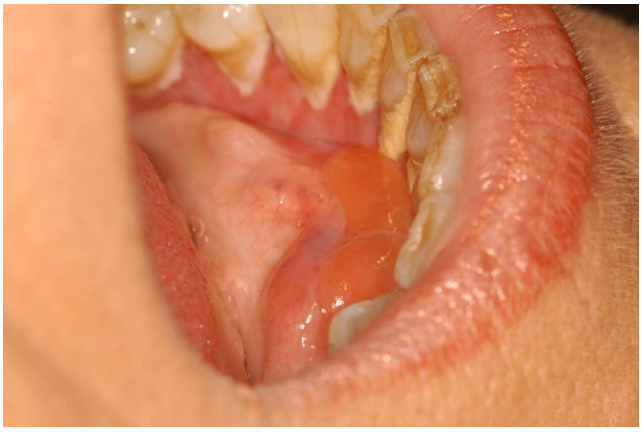

FIGURE 13 Intact blisters on the floor of the mouth were the sole manifestation of mucous membrane pemphigoid in a 51-y-old woman

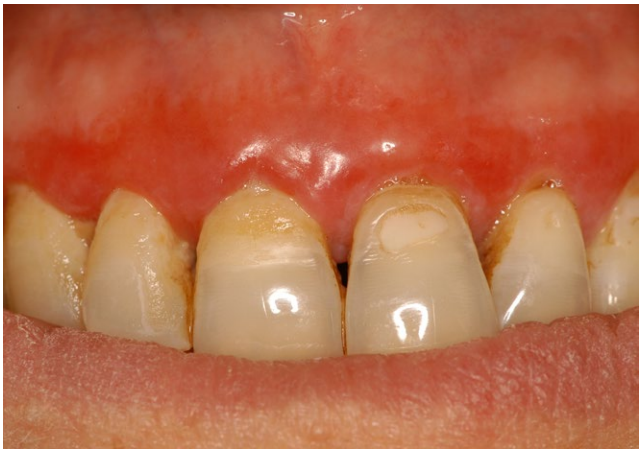

FIGURE 14 Mucous membrane pemphigoid of the gingiva with clinical features of desquamative gingivitis. This 76-y-old female patient presented few skin lesions on the face, which is rare in mucous membrane pemphigoid

pemphigoid primarily have ocular involvement, known as ocular cicatricial pemphigoid[50] (Figure 15). Severe and recurrent laryngotracheal involvement can result in scarring and death from asphyxiation. Similar stenosis can also occur with pharyngeal, esophageal, and ano-genital involvement. In ocular involvement, neovascularization and corneal scarring may lead to blindness;[43] accordingly, monitoring for eye changes, with referral to ophthalmology, is essential in the management of patients with oral lesions.

Histopathologic features encompass subepithelial clefting with hyperplastic or atrophic epithelium and polymorphic infiltrate in the lamina propria (Figure 16). Direct immunofluorescence shows linear IgG, C3, and/or IgA at the basal membrane zone, while indirect immunofluorescence microscopy on salt-split skin reveals epidermal or dermal staining of the artificial split, depending on the target antigen (Figure 17). Mucous membrane pemphigoid staining positive for laminin-332 has been reported to be associated with a high incidence of malignancy (RR = 6.8, 95% confidence interval: 3.3-12.5); longitudinal studies found

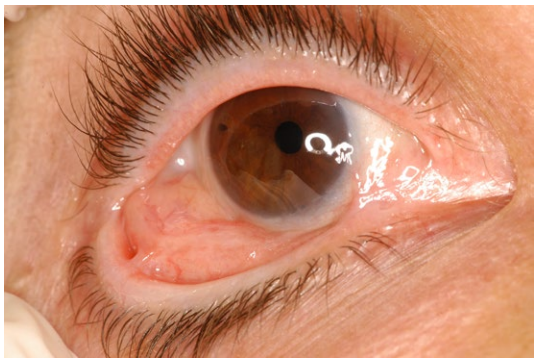

FIGURE 15 Symblepharon of the lateral portion of the conjunctival fornix in cicatricial mucous membrane pemphigoid in a 73-y-old female patient who underwent treatment with rituximab (a monoclonal antibody to CD20, which is primarily found on the surface of immune system B cells) as second-line therapy

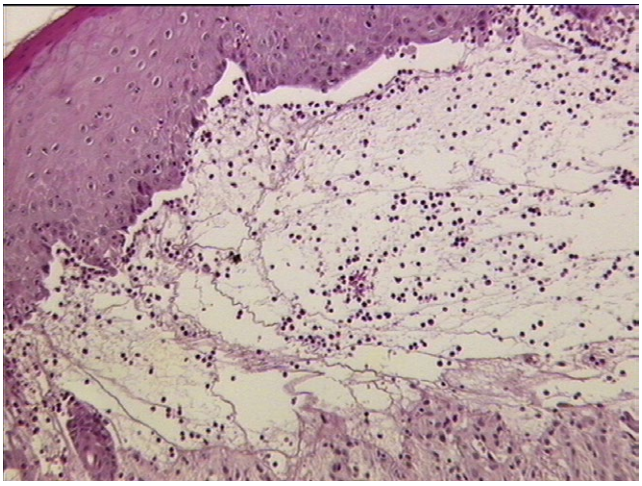

FIGURE 16 Subepithelial cleft with complete separation of the epithelium from the chorion in a patient with mucous membrane pemphigoid

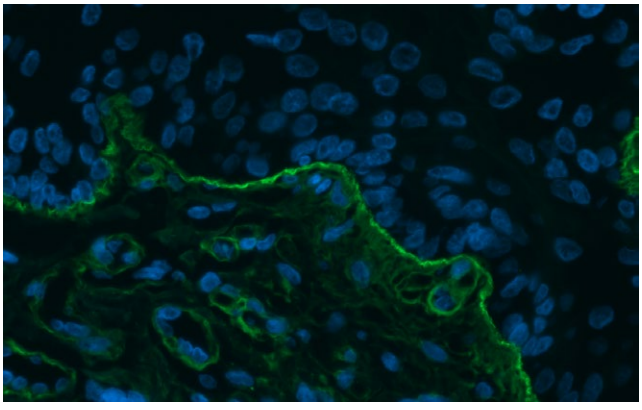

FIGURE 17 Direct immunofluorescence with linear subepithelial pattern fluorescence. The localization of the signal confirmed a diagnosis of mucous membrane pemphigoid

that this disorder is associated with solid cancers in different sites of the body and rarely with diffuse, large B-cell non-Hodgkins lymphoma.[58,59]

Systemic corticosteroids, used either alone or in conjunction with other immunosuppressive drugs, are the mainstay of treatment for severe mucous membrane pemphigoid. Indications for systemic therapy include ocular, laryngeal, and/or esophageal involvement, or the presence of oral or cutaneous disease unresponsive to less-aggressive topical measures, such as topical steroids. However, the high doses of corticosteroids and long duration of therapy that are often needed to control the disease can lead to many adverse, serious, and even life-threatening sequelae.[44] Hence, it is imperative to minimize steroid dosage whenever feasible. Adjuvant therapies for patients who do not respond to, or who experience complications from, corticosteroids include immunosuppressants such as cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, dapsone, daclizumab, and mitomycin-C.[44,60] Nevertheless, some patients do not respond to these agents or present with serious adverse effects. In these cases high dose of intravenous immunoglobulins and monoclonal anti-lymphocyte B-cell antibodies (rituximab) have been recommended.[61,62]

A key aspect influencing prognosis is the early diagnosis and early initiation of therapy. When mucous membrane pemphigoid appears as chronic conjunctivitis ("red eye"), specialists have difficulty in making an accurate diagnosis in the early stages of the disease. Indeed, in many cases mucous membrane pemphigoid is not considered until the disease process results in progressive scar formation and tissue contraction (symblepharon). The inferior fornix becomes shortened and symblepharon formation increases to the point that the eyelids become firmly attached to the globe, inhibiting its movement. At advanced stages, the eyelids grow together and the conjunctival sac is obliterated (ankyloblepharon); progressive ocular disease can lead to blindness. In the oral cavity, blisters quickly turn into ulcers that are frequently sites of secondary infection and are painful, and this may lead to compromised nutrition. Healing results in adhesions and scar formation. However, with exclusively oral involvement, the patient is considered of "low risk" in comparison with individuals with ocular, nasopharyngeal, esophageal, and laryngeal mucosa involvement.[44] Therefore, differentiation of patients as being high- or low risk is essential for management decisions. Management of patients with mucous membrane pemphigoid requires very careful clinical and laboratory assessment and treatment, and monitoring by a multidisciplinarity team of specialists.

In patients with severe laryngeal, tracheal, ocular, oral, and esophageal involvement, mucous membrane pemphigoid can be a serious and potentially devastating systemic disease. Timely diagnosis and recognition of potential complications should reduce the morbidity and mortality associated with mucous membrane pemphigoid.

5 | BULLOUS PEMPHIGOID

Bullous pemphigoid is a chronic subepidermal blistering disease of the skin that mainly affects the elderly with an annual incidence ranging from 2.6 cases per million population in the Arabian Gulf to 14 cases per million population in North-East Scotland.[63-65] Advanced age, medical comorbidities, disease severity, and treatment regimen influence prognosis.[66] The pathogenesis is characterized by an autoimmune process in which autoantibodies (IgG/IgE) target 2 different proteins - collagen alpha-1(XVII) chain (previously known as BP180 or BPAG2) and dystonin (previously known as BP230 or BPAG1) - at the basal membrane zone (Figure 11). Of these, degradation of collagen alpha-1(XVII) chain, followed by activation of complement and subsequent inflammatory cascades is thought to be essential for blister formation.[67] The NC16 domain seems to be the target epitope in the majority of patients affected by bullous pemphigoid. Histologically, the lesional/perilesional skin of patients with bullous pemphigoid exhibits detachment, of basal keratinocytes of the epidermis, from the dermis–this occurs at the level of the lamina lucida. Direct immunofluorescence shows linear staining of IgG and/or C3 at the basal membrane zone as in mucous membrane pemphigoid; however, in salt-split direct immunofluorescence, the IgG/C3 deposits are seen at the blister roof, in contrast to mucous membrane pemphigoid, in which these deposits are seen in either the blister roof or blister floor, depending on the location of the targeting antigen.

Clinically, bullous pemphigoid is characterized by large, tense bullae that may begin as erythematous macules, urticarial papules, or plaques.[68] Mucosal involvement is not common, but 10%-20% of patients have oral lesions (usually in the form of erosions; more rarely as blisters).[67] Chuah et al[69] state that oral mucosal involvement in patients with newly diagnosed bullous pemphigoid is associated with a slower response to conventional therapies and therefore recommend prudence in the management of therapy, in terms of adjuvant addition. Bullous pemphigoid has often been associated with malignancies such as solid and hematological tumors,[70] but the relationship is controversial.

Serum levels of antibodies to collagen alpha-1(XVII) chain (NC16A domain) can be detected using ELISA, and Schmidt et al[71] first demonstrated the presence of a positive correlation between clinical disease activity and antibodies to collagen alpha-1(XVII) chain. However, the cumulative data in the literature is insufficient to demonstrate a correlation between severity of the disease and the levels of antibodies to proteins in the basal membrane zone.[72] Patients with limited disease involvement may well respond to topical steroid therapy, particularly when only the oral mucosa is affected. Patients with mild-to-moderate forms of bullous pemphigoid are often treated with systemic antibiotics plus nicotinamide.[73] However, those with more extensive forms of the disease often require systemic corticosteroids and immunosuppressive agents. New therapeutic approaches in patients with refractory bullous pemphigoid are rituximab, interferon-gamma, and drugs that target the interleukin-17/T-helper 17 cell pathway (secukinumab, ixekizumab).[74]

6 | LINEAR IGA DISEASE

Linear IgA disease is a rare, chronic, autoimmune, subepidermal blistering disorder with 2 main variants that affect children and adults after their fifth decade. Epidemiologic data are not uniform across

the globe. The prevalence of linear IgA disease has been estimated as 0.5 per 1 000 000 adults in Europe,[75] with a 2:1 predilection for women; the disease has a lower prevalence among children. However, compared with the data from Europe, a higher incidence of linear IgA disease was reported in South Africa, North Africa, and Asia.[68] The etiology of linear IgA disease is not fully understood. However, some association with the use of drugs, such as vancomycin,[76] and malignancy, such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and bladder cancer,[77] have been identified in addition to the cases which are idiopathic.[78]

Histologic features encompass a subepithelial bulla with an inflammatory infiltrate along the basal membrane zone, in which neutrophils predominate. Direct immunofluorescence typically shows continous linear deposition of IgA along the basement membrane zone, and sometimes deposition of both IgA and IgG, while IgM and C3 are rarely seen.[77] This immunologic element is essential for distinguishing linear IgA disease from dermatitis herpetiformis in which the deposition of IgA is granular along the basal membrane zone.[79] Circulating IgAs directed against certain antigens in the basal membrane zone, such as 97 kDa linear IgA disease antigen (also known as LABD97), 120 kDa linear IgA disease antigen (also known as LAD 1), LAD 285, dystonin, collagen alpha-1(XVII) chain, laminin-γ1 chain, collagen 7, and others, have been described.[80]

Clinically the morphology and distribution of the bullae, ulcerations, and plaques are very polymorphic and heterogeneous, and cannot be distinguished from other bullous autoimmune dermatosis such as bullous pemphigoid. There are no major differences between the adult and the childhood forms of linear IgA disease. In the childhood form the lesions can be seen more frequently as annular lesions with characteristic bullae around the central urticarial plaque ("string of pearls"). Lesions in children are typically localized to the lower abdomen and anogenital areas. In adult-onset disease the trunk and the limbs are the areas most commonly involved. In up to 50% of patients, mucous membranes, including the oral mucosa, are involved,[81] with the appearance being similar to those of other autoimmune blistering diseases. Desquamative gingivitis is the most common presentation of linear IgA disease in the oral mucosa.[82] Although scarring is not a usual complication in oral mucosal involvement, it is a major cause of morbidity in other mucosal sites, such as conjunctiva, pharynx, esophagus, and larynx, where it can even be fatal.[83]

Compared with other autoimmune blistering disorders, linear IgA disease shows high responsiveness to dapsone or sulfapyridine, which represent the first line of therapy. Oral glucocorticoids can also be added to dapsone later when it needs to treat oral mucosal lesions usually more resistent to treatments compared to skin lesions (control

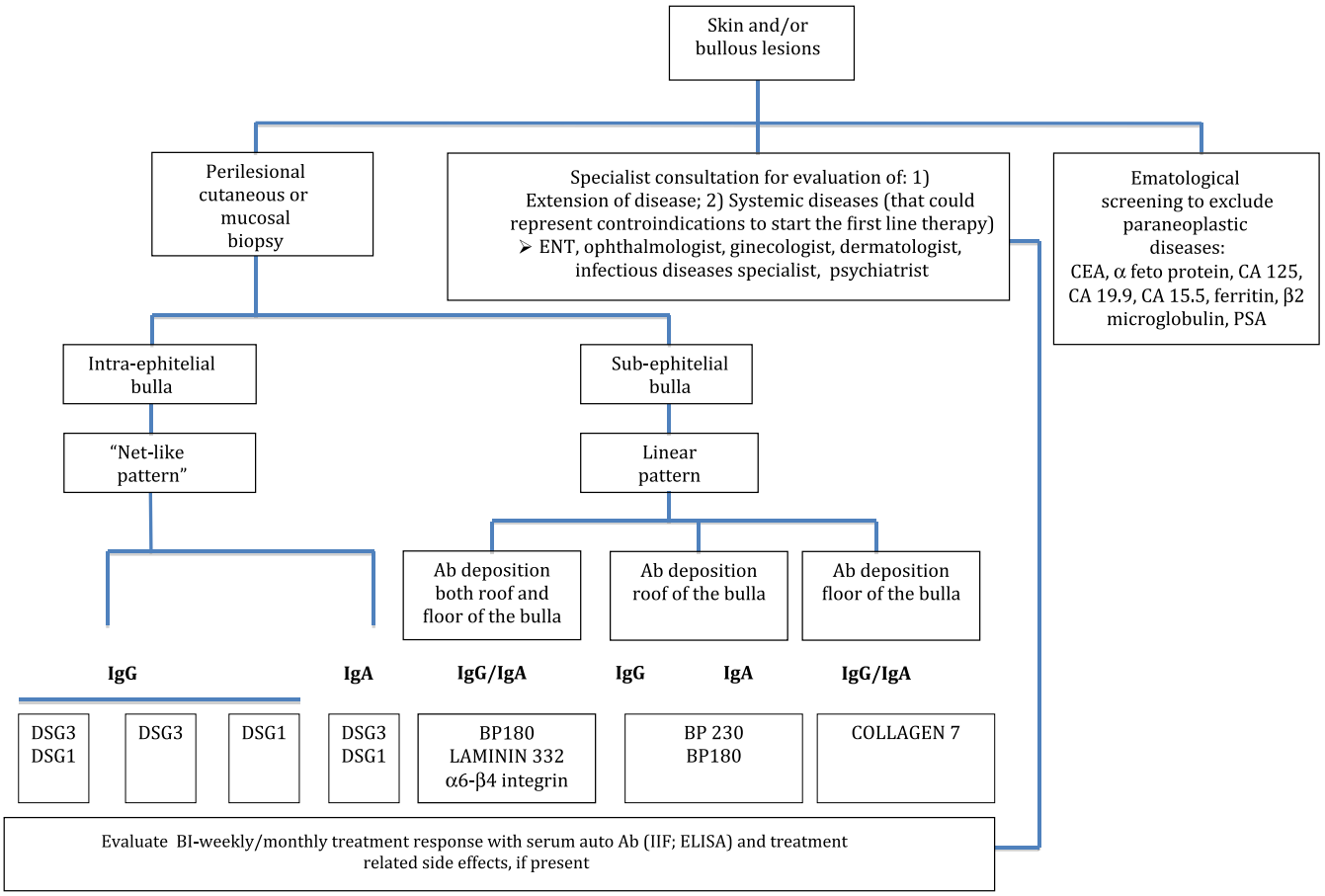

FIGURE 18 Algorithm of clinical management of patients affected by autoimmune blistering disorders. BP180, collagen alpha-1(XVII) chain; BP230, dystonin; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; DSG, desmoglein; ENT, ear, nose, and throat; PSA, prostate-specific antigen

phase). Other reportedly useful medications include prednisone, sulfamethoxypyridazine, colchicine, dicloxacillin, mycophenolate mofetil, and intravenous immunoglobulin.[40,84,85] As second-line therapies, in patients unresponsive or partially responsive to dapsone/sulfapyridine, the addition of a medium dose of steroid (prednisone, 0.5 mg/kg) may be effective. In very severe cases refractory to steroids, a high dosage of intravenous immunoglobulins (2 g/kg/cycle) could be indicated.

7 | CONCLUSIONS

The health of the epithelium depends essentially on the integrity of cadherin-type adhesion molecules inside and outside desmosomal structures that mediate cell-cell adhesion.[1] Autoimmune blistering disorders compromise the epithelial/basal membrane zone architectural arrangement through humoral immunogic processes against a large group of antigens and the result is the onset of mucocutaneous vesiculobullous lesions, erosions, or ulcerations that characterize many disorders with different prognoses. Clinical management of patients affected by autoimmune blistering disorders is summarized in Figure 18.

The prevalence of oral involvement in autoimmune blistering disorders is well known and varies enormously in frequency among the diseases and seriousness of involvement among patients. Early manifestations are common in adults and typically have a chronic course.[16] Intact oral bullous lesions are rare during oral examination because they readily rupture, forming erosions or ulcerations depending on the type of intra- or subepithelial bulla. Gingival lesions, often referred to as "desquamative genigivitis", may frequently appear; if this is the sole manifestation, then recognition of bullous lesions is difficult. Gingival lesions are very resistant to treatment. They heal much more slowly than cutaneous lesions because of the peculiar micro-environment represented by teeth and the periodontal complex, and the specific and polymorphic bacterial biofilm that exacerbates and prolongs the local inflammation. As a consequence, complete clinical remission is usually delayed. Oral lesions cause pain, discomfort, burning sensations, and swelling and contribute to significant morbidity affecting quality of life and psychological well-being. It is to be hoped that all clinicians (dermatologists, ear, nose, and throat specialists, general practitioners, dentists, and oral medicine specialists) are familiar with the clinical presentations and diagnostic procedures of oral bullous lesions in autoimmune blistering disorders in order to define an early diagnosis, which is crucial for the patient's health. Dentists play a key role in this sense and should have a high level of awareness, making an early diagnosis or asking for a specialized consultation.

New horizons in the understanding of autoimmune blistering disorders will lead to new molecular and immunologic mechanisms in the pathogenesis and consequently improved therapeutic strategies for management of patients.

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