ELSEVIER
SAUNDERS

Dent Clin N Am 49 (2005) 91–106

THE DENTAL
CLINICS
OF NORTH AMERICA

Mucous membrane pemphigoid

Thomas P. Sollecito, DMD[a,*], Ernesta Parisi, DMD[b]

[a]*Department of Oral Medicine, University of Pennsylvania School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104, USA*
[b]*Department of Diagnostic Sciences, University of Medicine and Dentistry of New Jersey–New Jersey Dental School, 110 Bergen Street, D-860 Newark, NJ 07103, USA*

Mucous membrane pemphigoid (MMP) is a chronic, subepithelial autoimmune disease, which predominantly involves mucosal surfaces and results in mucosal blistering, ulceration, and subsequent scarring. The condition belongs to a group of mucocutaneous autoimmune blistering disorders often collectively referred to as subepithelial bullous dermatoses (SEBDs). These disorders result in blistering of the skin or oral mucosa and include bullous pemphigoid (BP), MMP, linear IgA disease (LAD), chronic bullous dermatosis of childhood (CBDC), and epidermolysis bullosa acquisita (EBA).

On a molecular level, each of these specific diseases is based on various and distinct antigens to which the patient reacts. The clinical signs and symptoms of these disorders are usually the same, but there are some notable exceptions that, when combined with histopathology and immunohistochemical techniques, can help a clinician differentiate one disorder from the other. A final diagnosis may be reached by combining the clinical signs of the patient with the immunohistopathologic findings. For example, BP usually affects the patient's skin, and oral involvement is also common. Overall, it is the most common of the SEBDs. Oral lesions also are frequently seen in LAD, CBDC, and EBA. Because MMP almost always involves the oral cavity, the focus of this article is on MMP.

On a clinical level, MMP involvement may include the eyes, oral cavity, and pharyngeal mucosa of patients usually over the age of 50 years. Although MMP is a blistering disease predominantly involving the mucosal surfaces, up to 30% of patients may also have skin involvement [1]. On an immunohistopathologic level, autoantibodies produced by MMP patients target one of

* Corresponding author.
E-mail address: tps@pobox.upenn.edu (T.P. Sollecito).

doi:10.1016/j.cden.2004.07.004 dental.theclinics.com

several different autoantigens in the mucosal or epithelial basement membrane zone (BMZ). This antibody and antigen interaction causes the cleaving of fibrils in the basement membrane, as well as the activation of complement with the recruitment of neutrophils, which eventually results in subepithelial blistering [2].

Over the past 20 years, several different epithelial basement membrane components have been identified as antigens possibly involved in a broad clinical diagnosis of pemphigoid. Distinct subgroups of MMP, based on these antigens, have been identified using advanced immunopathologic and immunochemical techniques (Table 1). MMP described in the literature is generally based on both clinical features and antigenic specificities [3].

Epidemiology

The true incidence of MMP is unclear [4]. Data in the dermatology literature suggests that MMP is approximately seven times less common than BP [5]. Ocular pemphigoid may occur in 1 of every 15,000 to 40,000 individuals seen by an ophthalmologist [6]. Retrospective immunofluorescent studies in oral mucosal diseases suggest that MMP occurs up to three times more frequently than pemphigus [7].

MMP is an autoimmune condition, predominately affecting women, with a mean age at onset over the age of 50 years [8]. Children are rarely affected. There is no known racial or geographic predilection. The cause is usually unknown, but there are a few reports of MMP triggered by medications [9,10]. A possible immunogenetic link that is especially notable in pemphigoid affecting the eyes is HLA DQB1*0301 [11,12].

Table 1
Autoantigens involved in pemphigoid

Subepithelial bullous dermatoses-clinical classification	Autoantigens
Mucous membrane pemphigoid (MMP)	BPAG2 (180 kDa) BPAG1 (230 kDa) Laminin-5 (epiligrin) α6 β4 integrin
Bullous pemphigoid (BP)	BPAG1 (230 kDa) BPAG2 (180 kDa) 105-kDa antigen
Linear IgA disease (LAD)	BPAG1 (230 kDa) BPAG2 (180 kDa) 45 kDa 97 kDa
Bullous pemphigoid of childhood	45 kDa 97 kDa
Epidermolysis bullosa aquisita (EBA)	Type VII collagen

Clinical presentation

Oral lesions occur in more than 90% of individuals with MMP [1], whereas oral involvement may be present in up to 50% of those with BP [13]. Oral manifestations of MMP are variable and often include desquamative gingivitis associated with severe gingival erythema and frank ulceration. Ulceration or atrophy of the buccal and labial mucosa, palate, and tongue are also frequently observed (Fig. 1). An intraoral ulcer may present with a pseudomembrane consisting of a necrotic eschar covering. Intact vesicles (filled with clear fluid or blood) are rare in the oral cavity but may be observed (Fig. 2).

Most patients are symptomatic, often complaining of oral pain caused by mucosal ulceration and desquamation. Patients with gingival involvement frequently have poor oral hygiene because of the inability to clean the dentition effectively secondary to mucosal pain. Thus patients may often present with bleeding gums. Patients typically describe the inability to eat certain types of foods for fear of exacerbating the symptoms. Occasionally patients may complain of halitosis, from lack of maintaining good oral hygiene. Other common clinical observations include delayed or incomplete healing following scaling and root planing or peeling of the gingival tissue with simple prophylaxis. Soft tissue management during dental restoration may also be compromised and associated with extensive bleeding. Consequently, impression taking and retraction cord placement can be difficult in patients with MMP.

Occasionally the signs and symptoms of MMP may be subtle. Anecdotally, some patients may notice a superficial sloughing of the oral mucosa. Other patients may describe a transient fluid-filled blister that ulcerates and quickly heals. On the other hand, long-standing lesions related to MMP may be secondarily infected, sore, and slow to heal.

Extraoral manifestations of MMP can involve the conjunctiva, genitalia, esophagus, trachea, and larynx [14]. Involvement of the esophagus may

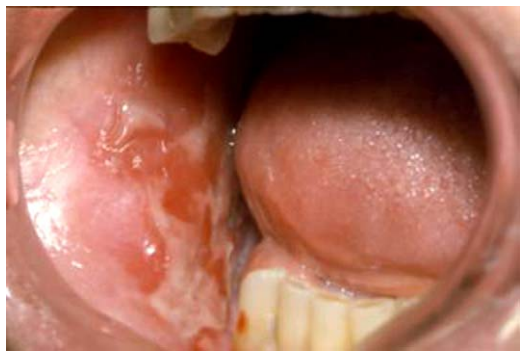

Fig. 1. Buccal mucosa of a patient with MMP. Notice the ulceration and the scarring.

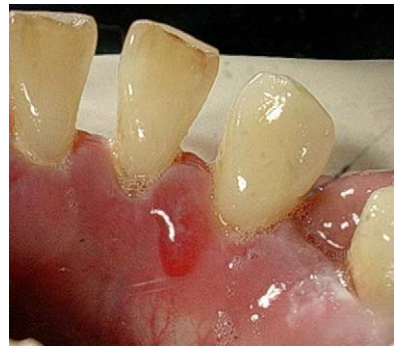

Fig. 2. Intact blood-filled vesicle.

result in dysphagia and odynophagia, whereas tracheal involvement may lead to hoarseness. Eye involvement may initially be characterized by conjunctival injection. Later, symblepharon formation may occur. Symblepharon formation results from the scarring and adhesion of the bulbar to the palpebral conjunctiva (Fig. 3). As a result, corneal damage is common, and progressive scarring can lead to blindness. Genital involvement results in mucosal ulceration and may lead to sexual dysfunction resulting from pain. Although MMP is considered a subepithelial blistering mucosal disorder, MMP involves the skin in up to 30% of patients [1]. Most of the other subepithelial blistering disorders are much more likely than MMP to involve the skin and should be considered in a well-developed differential diagnosis if both the oral mucosa and skin are involved.

Pathophysiology

The pathophysiologic mechanism of MMP is complex and is not yet completely understood. There is clearly a defect in the immune regulation involving the formation of autoantibodies, usually of the IgG class, directed against normal components (antigens) of the BMZ. This interaction triggers

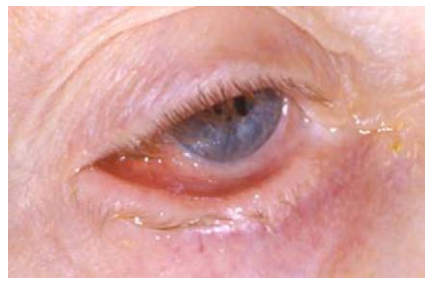

Fig. 3. Symblepharon formation resulting from the scarring of the bulbar and palpebral conjunctiva.

a complicated web of immunologic events resulting in the expression of inflammatory mediators that induce migration of lymphocytes, eosinophils, neutrophils, and mast cells to the BMZ. The separation of epithelium from the underlying tissue within the BMZ may be the result of direct cytotoxic action or the effect of lysosomal proteolytic enzymes [15,16]. Fibroblasts also are activated secondary to the production of inflammatory cytokines. The collagen produced may lead to cicatrization of the eye or mucous membranes. This process is of particular importance in MMP affecting the eyes, where fibrosis or subsequent cicatrization can cause profound tear insufficiency, symblepharon formation, trichiasis, keratinization of the cornea, and several other defects.

To understand this process better, a basic knowledge of the components in the BMZ is necessary. There are several components to the BMZ that can be schematically divided into keratinocytes, lamina lucida, lamina densa, and sublamina densa [17]. Within this zone, hemidesmosomes anchor keratinocytes to the basement membrane. Components of the hemidesmosome are proteins, which include the bullous pemphigoid antigen 1 (BPAG1) {a 230-kDa protein}, the bullous pemphigoid antigen 2 (BPAG2) {a 180-kDa protein}, BP230, the α6 β4 integrin, plectin, and laminin-5, also called epiligrin (Fig. 4).

BPAG1 is an intracellular protein, whereas BPAG2 and α6 β4 integrins are transmembrane proteins. The major ligand between the transmembrane proteins and the anchoring filaments is thought to be laminin-5 [18,19,20]. Therefore laminin-5 serves as a critical molecule in this adhesive structure [18]. Anchoring fibrils, composed of type VII collagen, are located deeper in the lamina densa. Although the relationship is complex, a general understanding of the cellular relationship of these proteins will provide insight to the pathophysiologic mechanism that occurs in the various subtypes of SEBD, and specifically MMP.

As previously mentioned, autoantibodies produced in MMP target one of the several different components of the BMZ, causing immunologic events that lead to epithelial separation from the connective tissue at the BMZ level. Several distinct basement membrane components have been identified as autoantigens in various subepithelial blistering disorders, and others are likely to be elucidated in the near future [21,22]. The most frequently targeted autoantigen in MMP is BPAG2; however antibodies to BPAG1, laminin-5, and α6 β4 integrin have also been identified [14,38]. Involvement of these autoantigens is not, however, exclusive to MMP, because antibodies to both BPAG1 and BPAG2 also are present in BP and pemphigoid gestationis [23].

Diagnosis

In the past, diagnosis of MMP was based on clinical presentation and occasionally on the presence of certain immunopathologic features. The first international consensus statement on MMP has recently recommended

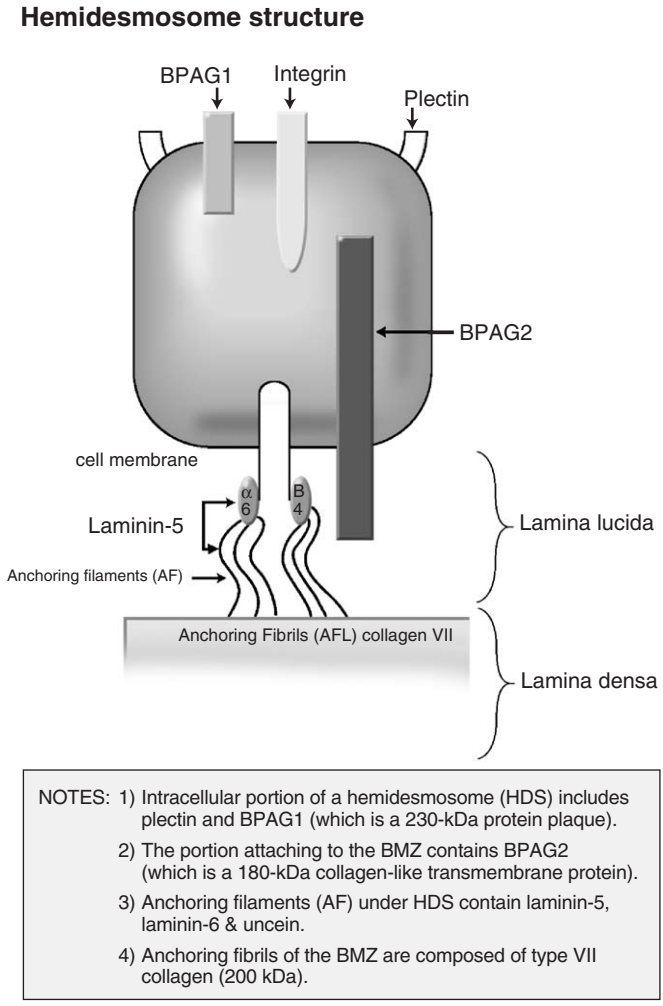

Fig. 4. Components of the basement membrane zone.

uniform nomenclature since the lack of clear diagnostic criteria in the past has led to a nonconcurrence among clinicians [24]. To better characterize MMP, the consensus discouraged the use of site-specific terms in the diagnosis of MMP (ie, ocular pemphigoid or oral pemphigoid). This recommendation is understandable, because site-specific diagnosis often does not acknowledge that many patients have multiple sites of involvement.

As discussed in the section on pathophysiology, attempts have been made to define and diagnose MMP solely on the basis of the autoantibody produced or the autoantigen (target) involved. The theory would follow that even if the clinical features were the same in several patients, the sera obtained from different patients may target different autoantigens. To date,

however, there is no firm correlation between clinical presentation and targeted autoantibodies [24]. MMP patients who present with only ocular involvement rarely exhibit circulating IgG antibodies, but patient selection and laboratory methods used can influence the sensitivity of indirect immunofluorescence (IIF) [14]. Also, patients with MMP confined the oral cavity often do not have circulating IgG autoantibodies but do have linear deposits of complement and immunoglobulin, particularly IgG, along the BMZ on direct immunofluorescent (DIF) studies [14]. Another subgroup of MMP includes patients who exhibit both mucosal disease and skin lesions. In this subset of MMP patients, circulating IgG autoantibodies to BPAG2 can usually be detected. There is also is a heterogeneous subgroup of MMP that involves multiple mucosal surfaces (ie, eye, mouth, and genital mucosal involvement) without significant skin disease and in which the expression of circulating IgG autoantibodies is also quite variable.

Mindful of this information, the consensus concluded that any diagnostic classification of pemphigoid, including subgroups of MMP, must be based on clinical presentation as well as on the presence of certain immunopathologic features. To this end, the consensus panel proposed clear clinical criteria defining MMP and distinguishing MMP from other oral conditions, and these clinical criteria must be interpreted with proper histopathologic and immunopathologic analysis [24].

Based on the consensus statement, when a patient is suspected of having a subepithelial blistering disease, tissue samples must be obtained. Therefore, any patient suspected of having MMP must have two biopsy specimens taken for pathologic evaluation. One specimen should be submitted for routine histopathologic analysis with hematoxylin and eosin staining. A second specimen should be obtained from perilesional tissue for immunologic testing including DIF analysis. As discussed later, the DIF analysis aids in antibody identification.

The diagnostic tissue biopsy technique is important. The biopsy may be difficult to obtain because of the tendency of the epithelium to dislodge from the underlying connective tissue while being manipulated. Because hemidesmosomes are affected in this disease, the epithelium easily detaches from the underlying connective tissue, rendering an improperly taken biopsy specimen nondiagnostic. The routine histopathology of a properly obtained specimen demonstrates the sub-basilar cleavage. Routine biopsy, however, may not be sufficient to differentiate the disease from other mucocutaneous disorders such as lichen planus or erythema multiforme. It is therefore important to use immunopathologic methods in making the diagnosis.

Generally, two types of immunologic studies are readily available and are often used to help diagnose a patient with suspected pemphigoid, DIF and IIF. DIF demonstrates autoantibodies already attached to the patient's tissue, whereas IIF demonstrates autoantibodies in the patient's serum.

DIF often is helpful in making a broad diagnosis of pemphigoid. In DIF a tissue sample is obtained from a site adjacent to a new vesicle or bulla. The

tissue sample should not be ulcerated but should include intact perilesional tissue. The specimen should be immediately placed in and transported in a specific buffered hypertonic saline solution, Michele's solution. The specimen must be processed in a timely manner to ensure minimal immune degradation. In the laboratory, the tissue sample is incubated with fluorescein-coupled antibodies against specific immunoglobulins (autoantibodies), complement, and fibrinogen, and then is examined using a fluorescent microscope. In pemphigoid, the DIF study shows a uniform, apple-green, linear deposition of IgG and complement along the BMZ of perilesional tissue.

The biopsy specimen should not be obtained from lesional tissue because a false-negative interpretation may be given; that is, there is no significant linear staining of IgG at the membrane zone because of the loss of immunoreactants in longstanding lesions. In some cases, additional biopsies may be necessary to demonstrate the presence of immune deposits in the BMZ. To ensure consistency, the consensus statement recommends the following to enhance positive biopsy results [24]:

- In patients with single mucosal site involvement, whether it involves the eye, genital, or oral mucosal, the biopsy specimen should be obtained from tissue next to the areas of inflammation.
- When patients present with multiple-site involvement, the biopsy should be taken from tissue adjacent to an inflamed non-ocular site.
- Patients who present with both skin and other mucosal involvement should have a skin biopsy taken from an inflamed lesion.
- For patients with ocular involvement requiring a biopsy, the procedure should be performed cautiously to minimize injury and additional scarring.

The second immunodiagnostic technique often used is IIF. This technique can be used to detect autoantibodies circulating in a patient's serum. IIF is performed by incubating patient serum with an epithelial substrate, such as monkey esophagus or rat bladder, and marking the specific antigens with fluorescein-labeled anti-human IgG. Using this method, serial logarithmic dilutions are made so that circulating antibody titers to autoantigens within the BMZ can be determined. Using immune reactivity testing with conventional skin substrates, early studies of MMP failed to show the association between antibody titer and disease activity [25]; however, Setterfield et al [26] demonstrated that both the presence and titers of circulating IgG and IgA autoantibodies to BMZ antigens using mucosal substrates may be predictors of disease severity and may correlate to disease activity. Circulating antibodies are more commonly seen in BP patients and are less predictably seen in MMP.

Often when a patient presents with oral lesions, it is difficult to identify the specific SEBD based solely on clinical evaluation. Therefore the clinician should be mindful of using these immunodiagnostic tools.

As noted, DIF helps in making a broad diagnosis of pemphigoid but does not distinguish MMP from anti-epiligrin pemphigoid, BP, epidermolysis bullosa, or skin-dominated LAG IgA. IIF also rarely helps with making a diagnosis of MMP. Distinction between the SEBDs may be clarified by combining the clinical findings with other sophisticated immunopathologic tests, which are routinely not requested. For instance, IIF can be used to detect circulating antibodies in a patient's serum. An enhanced method of performing this type of test is incubating patient serum with a human tissue substrate and marking the specific antigens with fluorescein-labeled anti-human IgG. To determine further which components of the BMZ are targeted by autoantibodies, a salt-split skin procedure may be performed on the human tissue substrate used [27].

In the salt-split skin technique, normal human skin substrate is incubated with 1 mol/L of sodium chloride solution. This incubation results in a separation of the two layers of the skin (ie, the epidermis from connective tissue) at the site of the lamina lucida portion of the BMZ. Antigens of the BMZ are exposed, improving the sensitivity for detection of binding serum antibodies directed against the substrate [28]. Antigens on both the epidermal side of the split (upper lamina lucida) and the dermal side of the split (lower lamina lucida) can be identified. Most patients with MMP and BP have autoantibodies against antigens in the epidermal side of the salt-split skin, where BPAG2 antigens are found, whereas those with autoantibodies to antigens on the dermal side of the split are targeted toward epiligrin.

Anti-epiligrin–directed pemphigoid may have significant implications [29]. There have been multiple reports in the literature associating anti-epiligrin MMP with malignancies. Before the development of advanced immunohistologic techniques, a distinction between autoantigenic subgroups of MMP did not exist. There was, however, some association of clinically diagnosed MMP, in general, with cancer. In one case report, a squamous cell carcinoma of the conjunctiva was detected within 2 months of the diagnosis ocular pemphigoid [30]. Other case reports of anti-epiligrin MMP associated with various malignancies can also be found in the literature [31–35]. Some include lung adenocarcinoma in an HIV-infected patient [36].

Leverkus et al [37] documented further evidence of a possible relationship between malignancy and anti-epiligrin MMP in an investigation of the frequency of anti-epiligrin MMP in patients with the clinical phenotypic MMP. Leverkus found that 5 of 16 patients with clinical MMP produced anti-epiligrin autoantibodies. Of these five, two patients had associated malignancies.

It is still difficult, based solely on DIF and IIF, to distinguish BP from MMP, because they both often react to BPAG2. Other, more specific immunochemical procedures have demonstrated that autoantibodies are directed against a specific domain of the BPAG2 autoantigen. Antibodies produced by MMP patients bind at the C-terminal portion of the BPAG2 antigen, whereas antibodies produced by patients with BP bind to the NC16A

domain of the same autoantigen [38]. This finding suggests that the autoantibody response may be more epitope specific than antigen specific. Despite the identification of selective epitopes and the advances in identification of the antigens involved, the diagnosis of MMP cannot be defined by a specific target antigen, because multiple antigens have been identified by the autoantibodies produced in various clinical presentations of MMP.

To date, the distinction between the various forms of pemphigoid has led to a further understanding of the pathophysiology of this disease. In the future the combination of clinical information with histologic and immunopathologic findings may allow clinicians to define the prognosis of patients with various presentations of MMP [38].

Although distinct subgroups of MMP have been identified by the use of advanced immunopathologic and immunochemical techniques to identify reactants and are described in the literature [3,14], diagnosis should still be made on the basis of clinical presentation combined with immunohistologic analysis.

Perhaps as molecular techniques become used more frequently and careful clinical criteria and standard reporting are initiated, various subgroups of pemphigoid based on the molecular findings will be better defined clinically.

Management

Management of MMP is similar to other chronic disorders: it depends on the severity of the disease and the patient's response to a particular therapy. Treatment should be individualized for each patient depending on the severity of disease, age, general health, medical history, and any contraindications to the use of systemic medications. Clearly, disease involving the eye, throat, or skin requires the evaluation and treatment of that patient by the respective medical specialist. Combining the expertise of various medical specialists will improve overall patient outcome.

Often, MMP involves only the mouth, and the severity of the oral lesions dictates the treatment. Patients with mild oral disease, characterized by erythema and erosions involving a minimal portion of the oral mucosa, may be managed with topical high-potency or ultra–high-potency corticosteroids, such as fluocinonide 0.05% or clobetasol propionate 0.05% and betamethasone dipropionate 0.05%, respectively. Most topical steroid formulations include either a cream, ointment, or gel base. Adherence and local penetrance seem to be better with the gel-based formulation than with the ointment or the cream preparations, which are better used for skin lesions.

A common complaint from patients with MMP is desquamative gingivitis. Desquamative gingival lesions from MMP may be managed effectively with the application of topical corticosteroids to the tissue and then placement of a resilient vacuum-formed occlusive splint that covers the involved gingiva (Fig. 5). The topical corticosteroids remain without being

washed away by normally occurring salivary flow. While using an occlusive tray with the immunosuppressive steroid, a patient is more susceptible to secondary opportunistic infections such as candidiasis. As discussed in the article on oral fungal infections in this issue, concomitant treatment with an antifungal agent is usually in necessary. Additionally, systemic absorption of the steroid is enhanced if an occlusive tray is used or if large areas of desquamated mucosal tissue are covered.

Although often overlooked, meticulous oral hygiene is extremely important to decrease the plaque-induced gingival inflammation in patients with gingival lesions. Patients must be closely monitored; frequent dosing over an extended period of time should be avoided.

In addition to topical steroid preparations, a corticosteroid suspension may also be injected directly into the lesions. Intralesional corticosteroids are useful for treating recalcitrant lesions or as an adjunct to topical steroid delivery. Intralesional injections of a steroid suspension usually result in prompt healing (Fig. 6). One must consider the concentration of the steroid and inject the proper amount, because excessive steroid injections may result in tissue necrosis.

When topical or intralesional therapies prove ineffective, or if there is involvement of the patient's eyes, throat, or skin, systemic medications should be used for treatment. Various systemic medications have been proposed as effective treatment for MMP. All systemic medications recommended for the treatment of MMP have an anti-inflammatory component. Systemic glucocorticosteroids and antimetabolites such as azathioprine or mycophenolate mofetil may be used for the treatment of MMP. Their use should be considered in relation to the patient's disease activity because these medications, when used chronically, have significant side effects. Certainly patients with extraoral involvement (ie, eye, esophageal, or severe skin involvement) may require these medications.

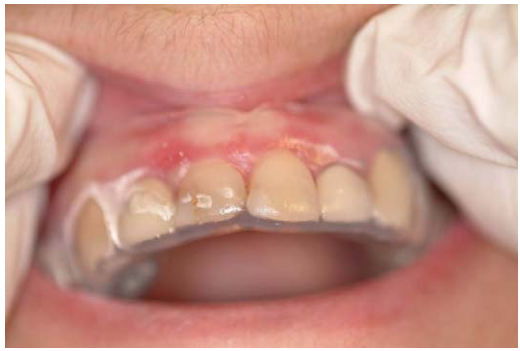

Fig. 5. A resilient splint serving as an occlusive dressing over the attached gingiva.

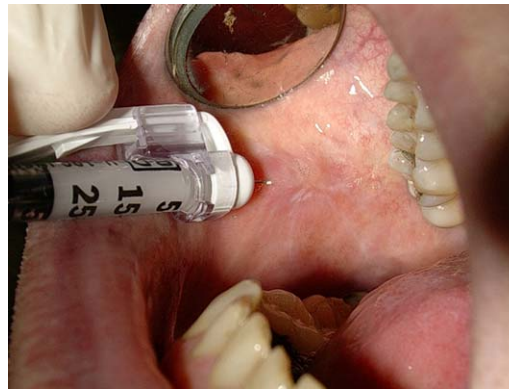

Fig. 6. Intralesional injection of steroid preparation.

Another medication widely reported in the literature for the treatment of MMP is dapsone, a synthetic sulfone with significant anti-inflammatory properties. There is evidence that dapsone suppresses neutrophil function and inhibits the synthesis of prostaglandin (E_2) by neutrophils [39,40]. Dapsone also inhibits neutrophil activity by suppressing neutrophil adherence to the endothelium, and it seems to interfere with the chemotaxis [41,42]. It has been used to treat a variety of disorders. For example, dapsone has been clinically used for many years to treat leprosy and malaria. It also has proved useful as an anti-inflammatory medication, as evidenced by its use in treating dermatitis herpetiformis [43]. Dapsone has been reported to treat idiopathic thrombocytopenia purpura effectively [44], and to manage cutaneous leukocytotoxic vasculitis and immune complex diseases [45].

Various studies have reported the effectiveness of dapsone in treating MMP. A study originating from the Mayo clinic describes the successful management of 77 patients with pemphigoid using dapsone [46]. A protocol for using dapsone to treat MMP has been published by the same author. Ciarrocca and Greenberg [2] reported on the management of 11 patients with MMP who were treated with topical steroids and with dapsone. In this report, 7 patients showed complete resolution, and 4 patients showed significant improvement with the dapsone therapy.

Dapsone does have significant side effects, all of which must be monitored while using this medication. The major side effect is hemolysis and may result in a severe hemolytic anemia. The development of significant methemoglobinemia is also a significant side effect. Before therapy is initiated, patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency. Individuals who are G6PD deficient may develop extensive hemolysis [47]. The enzyme G6PD prevents oxidation of hemoglobin to methemoglobin. Individuals who are G6PD-deficient will develop severe hemolysis resulting in hemolytic anemia or formation of significant

methemoglobinemia. These adverse side effects may be reduced by the use of cimetidine, 400 mg/day, and vitamin E, 800 units/day [48,49]. Dapsone hypersensitivity syndrome is another potential complication of dapsone use. It is characterized by fever, lymphadenopathy, hepatic damage, and generalized erythematous pustules. This syndrome, if it does occur, usually presents during the first 4 to 5 weeks of dapsone therapy [50].

The protocol for using dapsone includes closely monitoring for side effects. Monitoring of the patient's hemoglobin as well as liver function is essential while using dapsone to manage MMP. The protocol recommends a starting dose of 25 mg. The patient's hemoglobin should be checked during the first week of therapy. If there is no significant development of anemia, dapsone should be increased slowly by 25 mg every 3 days pending acceptable results of hemoglobin evaluations and a negative review of systems for questions pertaining to symptoms of anemia. A patient may need to stay at a certain dosage of dapsone for weeks before increasing to allow stabilization of the patient's hemoglobin. The usual effective dose is between 100 mg and 200 mg/day.

Minocycline, a tetracycline-type antibiotic, has also been reportedly effective in treating MMP [51]. Minocycline has been used as an effective anti-inflammatory medication and, in low doses, is used to treat periodontal disease. The benefit in the treatment of MMP may be related to the anticollagenase activity, suppression of leukocyte chemotaxis, and other anti-inflammatory and immunosuppressive actions. The dosage of minocycline is between 50 to 100 mg/day. Minocycline also has unwanted side effects including nausea, vomiting, dizziness, photosensitivity, and hyperpigmentation [52]. Other rare but serious side effects reported during minocycline use include drug-induced lupus, serum sickness–like reaction, and hypersensitivity syndrome reaction [53].

Other combination therapies using multiple medications can also be used to treat MMP. One such combination consists of tetracycline use with nicotinamide [54]. Nicotinamide is a vitamin B_3 or niacin derivative, usually used at 2 to 3 g/day. Higher doses of nicotinamide as monotherapy have been associated with hepatotoxicity, pruritus, and flushing. These side effects have been reported only in patients taking much higher doses than those used in combination therapy [55].

Summary

A broader knowledge of the causes of chronic oral ulceration associated with vesiculobullous eruptions allows the clinician to broaden the differential diagnosis. Understanding the underlying cause of the chronic ulceration leads to a clearer diagnosis and therefore allows more effective treatment. In patients with biopsy-proven oral MMP, questions regarding extraoral involvement are necessary. If a patient has symptoms suggestive of

extraoral MMP, it is imperative that the patient be referred to the appropriate specialist for further evaluation.

Patients with oral MMP can be a challenge to treat, especially because the condition is chronic and is associated with frequent exacerbations and remissions in clinical signs and symptoms. In addition, with the advent of new diagnostic studies, clinicians should consider using the pathologic techniques described in this article to characterize more accurately patients diagnosed with MMP. Ultimately, uniformity in reporting the clinical, histopathologic, and immunopathologic findings associated with all SEBDs in general will allow a better clinical definition of various subgroups of pemphigoid based on the molecular findings.

References

[1] Greenberg MS. Ulcerative, vesicular, and bullous lesions. In: Greenberg MS, Glick M, editors. Burket's oral medicine: diagnosis and treatment. 10th edition. Philadelphia: B.C. Decker; 2003. p. 73.
[2] Ciarrocca KN, Greenberg MS. A retrospective study of the management of oral mucous membrane pemphigoid with dapsone. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:159–63.
[3] Chan LS, Yancey KB, Hammerberg C, Soong HK, Regezi JA, Johnson K, et al. Immune-mediated subepithelial blistering diseases of mucous membranes: pure ocular cicatricial pemphigoid is a unique clinical and immunopathological entity distinct from bullous pemphigoid and other subsets identified by antigenic specificities of autoantibodies. Arch Dermatol 1993;129:448–55.
[4] Scully C, Carozzo M, Gandolfo S, Puiatti P, Monteil R. Update on mucous membrane pemphigoid: a heterogeneous immune-mediated subepithelial blistering entity. Oral Surg Oral Med Oral Pathol Endod 1999;88:56–68.
[5] Bernard P, Vaillant L, Laibelle B, et al. Incidence and distribution of sub-epidermal autoimmune bullous skin diseases in 3 French regions. Arch Dermatol 1995;131:48–52.
[6] Mondino BJ, Stuart IB. Ocular cicatricial pemphigoid. Opthalmology 1981;88:95–100.
[7] Daniels TE, Quadra-White C. Direct immunofluorescence in oral mucosal disease: a diagnostic analysis of 130 cases. Oral Surg Oral Med Oral Pathol 1981;51:38–54.
[8] Ahmed AR, Kurgis BS, Rogers RS. Cicatricial pemphigoid. J Am Acad Dermatol 1991;24: 987–1001.
[9] Van Joost T, Van't Veen AJ. Drug-induced cicatricial pemphigoid and acquired epidermolysis bullosa. Clin Dermatol 1993;11:521–7.
[10] Laskaris G, Satriano RA. Drug-induced blistering oral lesions. Clin Dermatol 1993;11: 545–50.
[11] Nayar M, Wojnarowska F, Venning V, Taylor CJ. Association of autoimmunity and cicatricial pemphigoid: is there an immunogenetic basis? J Am Acad Dermatol 1991;25: 1011–5.
[12] Delgado JC, Turbay D, Yunis EJ, et al. A common major histocompatibility complex class II allel HLA-DQB1*0301 is present in clinical variant of pemphigoid. Proc Natl Acad Sci U S A 1996;93:8569–71.
[13] Venning VA, Frith PA, Bron AJ, et al. Mucosal involvement in bullous and cicatricial pemphigoid. A clinical and immunopathological study. Br J Dermaol 1988;118:7.
[14] Fleming TE, Korman NJ. Cicatricial pemphigoid. J Am Acad Dermatol 2000;43:571–91.
[15] Eversole LR. Immunopathology of oral mucosal ulcerative, desquamative and bullous diseases. Oral Surg Oral Med Oral Pathol 1994;77:555–71.
[16] Eversole LR. Adhesion molecules and oral mucosal diseases. Oral Dis 1996;2:185–7.

[17] Dayan S, Simmons RK, Ahmed AR. Contemporary issues in the diagnosis of oral pemphigoid: a selective review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:424–30.
[18] Yancey KB. Adhesion molecules, II: interactions of keratinocytes with epidermal basement membrane. J Invest Dermatol 1995;104:1008–14.
[19] Symington BE, Takada Y, Carter WG. Interaction of integrins alpha 3 beta 1 and alpha 2 beta 1: potential role in keratinocyte intercellular adhesion. J Cell Biol 1993;120: 523–35.
[20] Burgeson RE, Chiquet M, Deutzmann R, Ekblom P, Engel J, Kleinman H, et al. A new nomenclature for the laminins. Matrix Biol 1994;14:209–11.
[21] Lin MS, Mascaro JM, Liu Z, Espana A, Diaz LA. The desmosome and hemidesmosome in cutaneous autoimmunity. Clin Exp Immunol 1997;107(Suppl 1):9–15.
[22] Dabelsteen E. Molecular biological aspects of acquired bullous diseases. Crit Rev Oral Biol Med 1998;9:162–78.
[23] Bedane C, McMillan JR, Balding SD, Bernard P, Prost C, Bonnetblanc JM, et al. Bullous pemphigoid and cicatricial pemphigoid autoantibodies react with ultrastructurally separable epitopes on the BP 180 ectodomainin: evidence that BP180 spans the lamina lucida. J Inves Dermatol 1997;108:901–7.
[24] Chan LS, Ahmed AR, Anhalt GJ, Bernauer W, Cooper KD, Elder MJ, et al. The First International Consensus on Mucous Membrane Pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol 2002;138: 370–9.
[25] Allen J, Venning VA, Nayar M, et al. Immunofluorescence studies in cicatricial pemphigoid. Br J Dermatol 1991;125:495 [Abstr.].
[26] Setterfield J, Shirlaw PF, Bhogal BS, Tilling K, Challacombe SJ, Black MM. Cicatricial pemphigoid: serial titres of circulating IgG and IgA antibasement membrane antibodies correlate with disease activity. Br J Dermatol 1999;140:645–50.
[27] Gately LE, Nesbitt LT. Update on immunofluorescent testing in bullous diseases and lupus erythematosus. Dermatol Clin 1994;12:133–42.
[28] Lazarova Z, Yancey KB. Reactivity of autoantibodies from patients with defined subepidermal bullous diseases against 1 mol/L salt-split skin: specificity, sensitivity, and practical considerations. J Am Acad Dermatol 1996;35:389–403.
[29] Egan CO, Lazarova Z, Darling TN, Yee C, Yancey KB. Anti-epiligrin cicatricial pemphigoid: clinical findings, immunopathogenesis, and significant associations. Medicine 2003;82:177–86.
[30] Sivalingam V, Shields CL, Shields JA, Pearah JD. Squamous cell carcinoma of the conjunctiva associated with benign mucous membrane pemphigoid. Ann Ophthalmol 1990; 22:106–9.
[31] Gibson GE, Daoud MS, Pittelkow MR. Anti-epiligrin (laminin-5) cicatricial pemphigoid and lung carcinoma: coincidence or association? Br J Dermatol 1997;137:780–2.
[32] Setterfield J, Shirlaw PJ, Lazarova Z, Bryant BM, Bhogal BS, Harman K, et al. Paraneoplastic cicatricial pemphigoid. Br J Dermatol 1999;141:127–31.
[33] Lenz P, Hsu R, Yee C, Yancey KB, Volc-Platzer B, Stingl G, et al. Cicatricial pemphigoid with autoantibodies to laminin-5 (epiligrin) in a patient with metastatic endometrial carcinoma. Huatarzt 1998;49:31–5.
[34] Taniuchi K, Takata M, Matsui C, Fushida Y, Uchiyama K, Mori T, et al. Antiepiligrin (laminin-5) cicatricial pemphigoid associated with an underlying gastric carcinoma producing laminin-5. Br J Dermatol 1999;140:696–700.
[35] Fujimoto W, Ishida-Yamaoto A, Hsu R, Nagao Y, Iizuka H, Yancey KB, et al. Anti-epiligrin cicatricial pemphigoid: a case associated with gastric carcinoma and features resembling epidermolysis bullosa acquisita. Br J Dermatol 1998;139:682–7.
[36] Lish KM, Washenik K, Yancey KB, Yee C, Rico MJ. Anti-epiligrin cicatricial pemphigoid in a patient with HIV. J Am Acad Dermatol 1997;36(3 Pt 1):486–8.

[37] Leverkus M, Schmidt E, Lazarova Z, Brocker EB, Yancey KB, Zillikens D. Antiepiligrin cicatricial pemphigoid: an underdiagnosed entity within the spectrum of scarring autoimmune subepidermal bullous diseases? Arch Dermatol 1999;135:1091–8.
[38] Yancey KB, Egan CA. Pemphigoid: clinical, histologic, immunopathologic, and therapeutic considerations. JAMA 2000;284:350–6.
[39] Kettle AJ, Winterbourne CC. Superoxide is an antagonist of anti-inflammatory drugs that inhibit hypochlorous acid production by myeloperoxidase. Biochem Pharmacol 1993;45: 2003–10.
[40] Van Zyl JM, Basson K, Kriegler A, van der Walt BJ. Mechanisms by which clofazimine and dapsone inhibit the myeloperoxidase system. A possible correlation with their anti-inflammatory properties. Biochem Pharmacol 1991;42:599–608.
[41] Coleman MD. Dapsone: modes of action, toxicity and possible strategies for increasing patient tolerance. Br J Dermatol 1993;129:507–13.
[42] Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. J Leukoc Biol 1997;62:827–36.
[43] Hall RP. Dermatitis herpetiformis. J Invest Dermatol 1992;99:873–81.
[44] Hernandez F, Linares M, Colomina P, Pastor E, Cervero A, Perez A, et al. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol 1995;90:473–5.
[45] Nurnberg W, Grabbe J, Czarnetzki BM. Urticarial vasculitis syndrome effectively treated with dapsone and pentoxifylline. Acta Derm Venereol 1995;75:54–6.
[46] Rogers RS III, Mehregan DA. Dapsone therapy of cicatricial pemphigoid. Semin Dermatol 1988;7:201–5.
[47] Todd P, Samaratunga IR, Pembroke A. Screening for glucose-6-phosphate dehydrogenase deficiency prior to dapsone therapy. Clin Exp Dermaol 1994;19:217–8.
[48] Rhodes LE, Tingle MD, Park BK, Chu P, Verbov JL, Friedmann PS. Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. Br J Dermatol 1995;132:257–62.
[49] Kelly JW, Scott J, Sandland M, Van der Weyeden MB, Marks R. Vitamin E and dapsone-induced hemolysis. Arch Dermatol 1984;120:1582–4.
[50] Prussick R, Shear NH. Dapsone hypersensitivity syndrome. J Am Acad Dermatol 1996; 35(2 Pt 2):346–9.
[51] Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. Br J Dermaol 1995;132:784–9.
[52] Kim Y, Greenberg MS. Management of patients with severe oral mucosal disease. Alpha Omegan 2001;94:18–23.
[53] Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. Report of 13 patients and review of the literature. Arch Dermatol 1996;132:934–9.
[54] Reiche L, Wojnarowska F, Mallon E. Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. Clin Exp Dermatol 1998;23: 254–7.
[55] Fivenson DP, Breneman DL, Rosen GB, Hersh CS, Cardone S, Mutasim D. Nicotinamide and tetracycline therapy of bullous pemphigoid. Arch Dermatol 1994;130:753–8.