Oral mucous membrane pemphigoid: updates in diagnosis and management

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Key points

Mucous membrane pemphigoid (MMP) is a rare, vesiculobullous disease that can manifest as ulcerations, erosions, blisters, or desquamation of tissue. Thorough clinical examination is key during appointments.

Patients with MMP may manifest with extra-oral signs, such as eye and skin involvement. A thorough review of systems in office can help differentiate MMP from other conditions.

In practice, general dentistry providers may recommend avoidance of trauma to the tissue in order to reduce the risk of ulceration or blister formation.

Abstract

Mucous membrane pemphigoid (MMP) is a rare, immune-mediated, vesiculobullous disease that predominantly affects the oral cavity and conjunctiva. In MMP, autoantibodies are directed against hemidesmosomal proteins in the basement membrane zone, most commonly BP180. Clinical signs and symptoms include gingival desquamation, erosions, and ulcerations. Differential diagnoses include other immune-mediated blistering diseases, such as bullous pemphigoid. Definitive diagnosis is reached through history taking, physical examination, tissue biopsy and/or serology testing. MMP, although not curable, is typically managed with topical or systemic corticosteroids, in addition to immunosuppressive therapies and biologic agents in recalcitrant cases. Untreated MMP can lead to life-threatening complications, such as blindness. As a condition that affects the oral cavity, it is important that dentists understand how to recognise, diagnose and manage the disease.

Introduction

Mucous membrane pemphigoid (MMP) is an immune-mediated, vesiculobullous disease, characterised by mucosal subepithelial or subepidermal blistering primarily in the oral mucosa and conjunctiva.[1,2] Anogenital tissues and upper digestive tract may also be impacted, with skin involvement occurring in about 25% of cases.[3] As one of several subepithelial blistering diseases, autoantibodies are directed against structural proteins of the hemidesmosome in the basement membrane zone.[1,2,3,4] The main target in MMP is structural protein BP180 (or type XVII collagen). Other targets may include BP230 (BPAG1), laminin 332, integrin α6/β4 subunit and type VII collagen.[4,5]

The oral cavity and conjunctivae are the most common locations of disease activity, followed by the nasopharynx, genitalia, and more rarely, the larynx, oesophagus, trachea and skin.[5,6] The exact pathogenesis of the condition is poorly understood, though several mechanisms involving target autoantigens are known. Early diagnosis via tissue analysis and/or serology testing, as well as pharmacologic management, are key to ensuring a more favourable prognosis for patients. In some cases, without treatment, life-threatening complications include airway obstruction, oesophageal strictures and conjunctival scarring, which may lead to blindness.[4,5]

Epidemiology

MMP is a rare condition with varied incidence based on geographic location. Approximately two million people per year are diagnosed with the condition in central Europe, specifically, 1.3–2 million in France and Germany.[7,8] The mean age of onset is approximately 55–65 years. Children and adolescents are rarely affected by the condition. Women are more affected than men at a ratio of nearly 2:1.[7,8] MMP is predominantly seen in white individuals.[8] HLA DQB*0301 (human leukocyte antigen) is associated with MMP and T-cell recognition of antigens in the basement membrane zone.[8]

Pathogenesis

Several mechanisms of disease activity have been proposed in the pathogenesis of MMP. The inflammatory response of the condition is believed to be a consequence of loss of tolerance to basement membrane proteins, which results in the production of plasma cells. These plasma cells produce circulating immunoglobulin G (IgG) and/or immunoglobulin A (IgA) autoantibodies. As these autoantibodies deplete the target antigens, the disease results in subepithelial separation.[3,4,9] Components of the basement membrane zone that are target antigens of MMP include BP180, laminin 332, BP230, type VII collagen and α6/β4 integrin (Fig. 1).[3,4,9]

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BP180 is a constituent of the hemidesmosome and is the target in approximately 75% of patients. It is a type II collagenous transmembrane protein with a molecular weight of 180 kD. Laminin 332 is a primary component of anchoring filaments and a ligand between transmembrane proteins.[3,9] BP230 is a member of the plakin family and a constituent of the hemidesmosomal plaque.[3,8,9]

Signs and symptoms

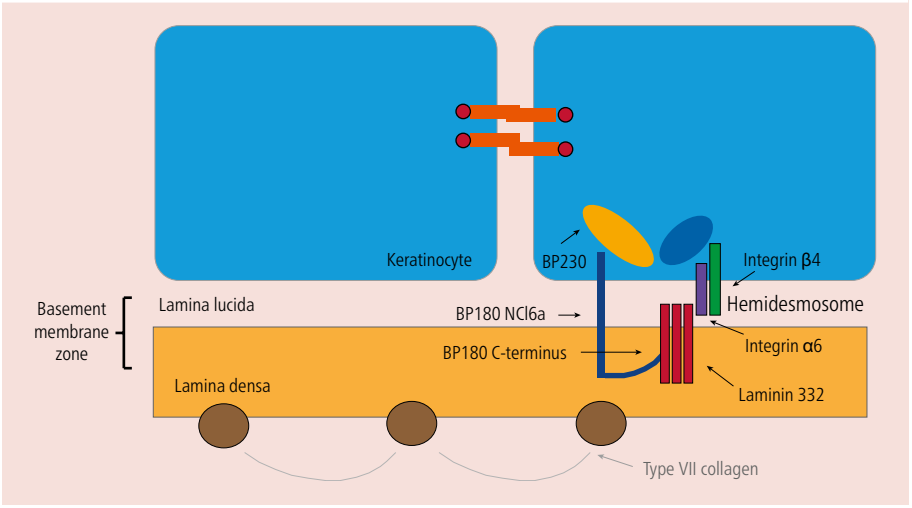
MMP can present clinically in several ways and with variance in disease severity. The oral mucosa is the most commonly affected site.[1,2,3,4] Other sites involved include conjunctivae, nasal mucosae, skin, anogenital area, pharynx, larynx and oesophagus, in descending order of occurrence.[3,4,8] Mild cases may appear as erythema or range from erosions to extensive ulcerations. Desquamation of gingival and palatal tissues are common oral manifestations of MMP, with lesions observed less commonly on the buccal mucosa and tongue (Fig. 2).[10] Other signs may include vesicles or bullae.[1,2,3,8] Blisters may easily rupture, which turn into erosions. However, intact blisters are more commonly seen in MMP as compared to other blistering diseases. Patient symptoms may include soreness, pain (particularly with food intake), bleeding (especially while brushing) and a peeling sensation.[1,2,3,8]

Given the chronic nature of the condition, patients may experience periods of disease exacerbation and remission. Chronic lesions intra-orally can affect a patient's ability to maintain proper oral hygiene, attain adequate nutrition and overall, decrease quality of life.[3,8]

Differential diagnosis

The differential diagnosis of MMP includes other autoimmune disorders, such as bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa and linear IgA disease (Table 1).[11] Subepithelial blistering conditions can be differentiated through site of clinical involvement and histopathologic analysis. Clinically, MMP predominantly involves mucosal surfaces. MMP can be differentiated from pemphigus through direct immunofluorescence (DIF) microscopy.[3,8,11] In oral MMP, differential diagnoses may also include oral lichen planus, pemphigus vulgaris, or lupus erythematosus.[3,8,11] Accurate history taking and thorough physical examination are essential for diagnosing.

Fig. 1 Diagram of cellular components in MMP



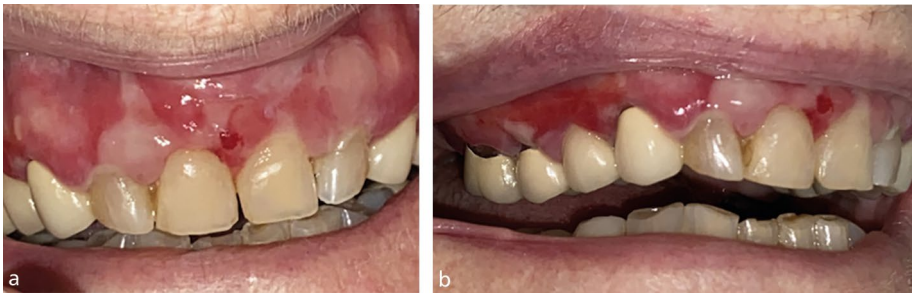


Fig. 2 a, b) Clinical photos depicting desquamation and ulceration of the gingival tissues as seen in MMP. Image courtesy of Dr Eric Stoopler, University of Pennsylvania

Table 1 Differential diagnosis table

Condition	Target autoantigens	Direct immunofluorescence findings	Indirect Immunofluorescence findings
Bullous pemphigoid	BP180, BP230	Linear IgG and C3 at the basement membrane	Subepithelial IgG
Pemphigus vulgaris	Desmoglein 1, desmoglein 3	Intercellular IgG and C3	Intercellular IgG
Epidermolysis bullosa acquisita	Type VII collagen	Linear IgG, IgA and C3 at the basement membrane junction	Subepithelial IgG
Linear IgA disease	LAD-1, type VII collagen	Linear IgA and C3 at the basement membrane junction	Epithelial and subepithelial IgA

Diagnosis

The diagnosis of MMP is based on history, clinical examination, histopathologic analysis and serology. MMP often goes undiagnosed as early manifestations may not be obvious or may appear similar to other conditions, causing a diagnostic delay of approximately 12 months.[3,8,11]

Gold standard for diagnosis is incisional biopsy, either through a scalpel or punch (3–4 mm). Two specimens are typically obtained: one for haematoxylin-eosin staining and one for DIF microscopy. Epithelium is needed for histopathologic diagnosis; therefore, a biopsy should be performed by an experienced provider given the fragile nature of this tissue. The specimen for routine histology is typically obtained from affected tissue. Specimens should not be obtained from ulcerated tissue as they lack epithelium needed for histopathologic analysis. The specimen for DIF is typically obtained from perilesional tissue (within 1 cm) or from

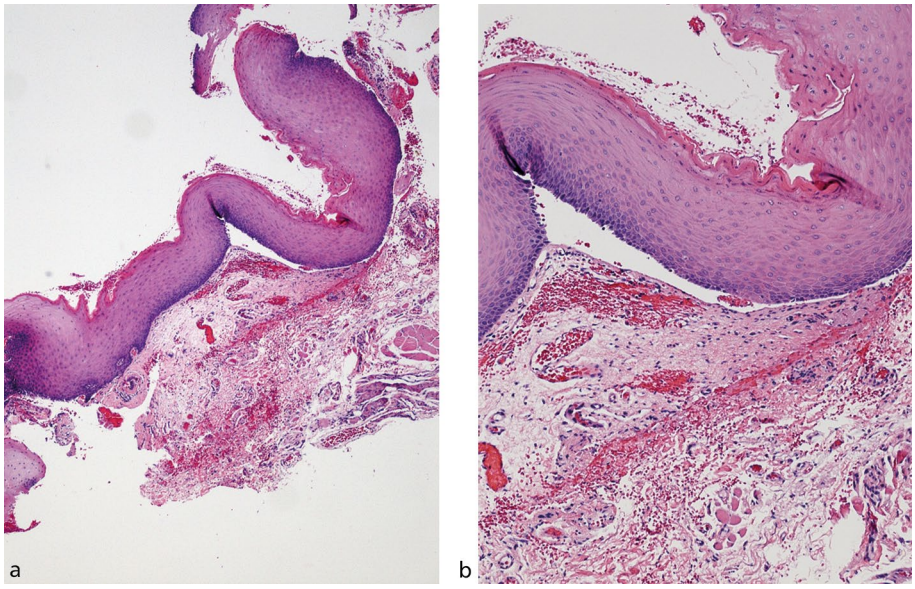


Fig. 3 Haematoxylin-eosin slide revealing surface epithelium detached from the underling connective tissue at the point of the basement membrane zone, as seen in MMP. a) Magnification x40. b) Magnification x100. Images courtesy of Dr Faizan Alawi, University of Pennsylvania

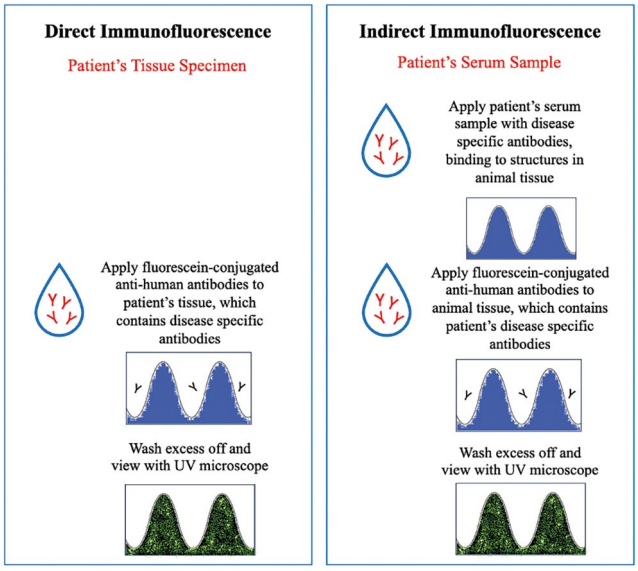


Fig. 4 Diagram of direct and indirect immunofluorescence. Reprinted and adapted from *Dental Clinics of North America*, Vol 57, F. Santoro *et al.*, 'Pemphigus', pp 597–610, Copyright 2013, with permission from Elsevier

normal appearing tissue.[3,8] The specimen for haematoxylin-eosin analysis is placed in formalin solution while the specimen for DIF is placed in Michel's solution, a simple salt solution that is used to preserve and transport the specimen.

Routine histology reveals subepithelial split with mixed inflammatory infiltration of eosinophils and neutrophils (Fig. 3).[8,9] DIF reveals linear IgA, IgG, or C3 along the basement membrane zone.[8,9] DIF serves as the most accurate diagnostic test for MMP, with a sensitivity between 60% and 90%.[12,13] If there is a concern for a false negative DIF and high clinical suspicion of MMP, repeat biopsies may be warranted. Based on current diagnostic guidelines, repeat biopsies for DIF increase sensitivity from 70% to 95%.[12,13] Indirect immunofluorescence microscopy may also be used for diagnosis (Fig. 4). Human skin, mucosa, or monkey oesophagus may be used as a media to test for serum autoantibodies in pemphigoid conditions.[3,14] Autoantibodies against BP180 and BP230 may be detected via ELISA (enzyme-linked immunosorbent assay) testing. MMP may contain low titres (eg 1:10–1:40) and in a lower percentage as compared to bullous pemphigoid.[3,14]

Management

Typical treatment of MMP involves corticosteroids in conjunction with immunosuppressants. Non-steroid immunomodulatory agents include methotrexate, dapsone, azathioprine, tetracycline, or nicotinamide. Recalcitrant lesions may be treated with intravenous immunoglobulin (IVIg) or rituximab.[3,8]

In mild cases of MMP, high or ultra-high potency topical corticosteroids may be used at the local site(s). Topical corticosteroids are effective in the management of oral MMP.[15,16,17] They can vary in potency, vehicle of action and method of application. Corticosteroid gels are typically used intra-orally as they adhere better to the affected mucosal tissues over other formulations of topical corticosteroids.[18] Gels may be used, whether applied by finger, gauze, or occlusive tray, as a method of treatment when gingival lesions predominate. Antifungal prophylaxis may be indicated when prescribing high or ultra-high potency corticosteroids, as the anti-inflammatory properties of the medication create susceptibility to the development of fungal infections, especially in those who are at higher risk (for example, patients with dry mouth or immunosuppressed). Other treatments may include intralesional steroid injection (for example, triamcinolone 40 mg/mL) to focally affected areas.[8,17,19] In oral MMP, emphasis on oral hygiene is key in reducing gingival inflammation and bleeding.[8]

Systemic treatment modalities for moderate or severe cases include corticosteroids, steroid-sparing immunosuppressive agents and biologic therapies.[3,8,17,19] First-line agents may include dapsone, methotrexate, or doxycycline in addition to topical or systemic steroids. Second-line agents may include the above, mycophenolate mofetil, or azathioprine.[3,8,17,19] Off-label use of rituximab, a CD20 target monoclonal antibody, has been used to treat severe cases with some benefit, though further investigation is needed.[17] Third-line agents for severe or recalcitrant cases may include IVIg or a tumour necrosis factor α inhibitor.[3,8,17,19]

Prognosis

MMP is not a curable disease but rather one that can be managed. Given the chronicity of the condition, patients may experience times of high activity or states of remission. Patients with oral involvement only or oral and skin involvement have a better prognosis than patients with ocular or anogenital tract lesions.[3,4,8] Active MMP requires continuous surveillance and treatment to reduce risk of life-threatening complications. These may include oesophageal strictures, airway obstruction and conjunctival scarring which may progress to blindness.[3,4,8] Cases of MMP associated with laminin-332 have been associated with higher risk of developing malignancy, though conclusive evidence is still being established. The most common type documented are adenocarcinomas, with haematological malignancies rarely being reported.[8]

Conclusion

Given the oral cavity is the most common site involved in MMP, it is important for dentists to clinically recognise the condition, understand when and how to refer their patients for diagnosis and management, and work on an interdisciplinary team to improve overall outcomes for their patients.

Ethics declaration

The authors declare no conflicts of interest.

Author contributions

Roopali Kulkarni: writing and editing. Eric T. Stoopler: editing. Thomas P. Sollecito: editing and supervision.

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