Blistering Mucocutaneous Diseases of the Oral Mucosa — A Review: Part 1. Mucous Membrane Pemphigoid

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ABSTRACT

Oral mucous membranes may be affected by a variety of blistering mucocutaneous diseases. In this paper, we review the clinical manifestations, typical microscopic and immunofluorescence features, pathogenesis, biological behaviour and treatment of mucous membrane pemphigoid (MMP). As MMP is a relatively common condition, the general dentist must be able to diagnose, treat and monitor the progress of their affected patients or refer when appropriate.

MeSH Key Words: mouth mucosa; pemphigoid, benign mucous membrane/diagnosis; pemphigoid, benign mucous membrane/therapy

The most common blistering conditions of the oral and perioral soft tissues are viral infections, especially *Herpes simplex*, but also *Varicella zoster* (chicken pox or shingles) and various forms of Coxsackie virus infections.[1] In normal immunocompetent patients, these self-limiting conditions resolve spontaneously, usually within days.

Oral erythema multiforme is a mucocutaneous blistering disease that usually heals spontaneously within 2 to 3 weeks. Several clinical forms occur, including major and minor types. The minor forms involve the skin, with characteristic "target" or "bull's eye" lesions, and the oral mucous membrane. The major types include Stevens-Johnson syndrome, an acute form occurring in young patients, and toxic epidermal necrolysis — both of which are characterized by large blister formation.[1]

Other blistering mucocutaneous diseases are associated with persistent suffering for months and years. Oral lesions are frequently the first manifestation of these and may be the only lesions suffered by some patients. Some rare hereditary forms of blistering diseases, such as epidermolysis bullosa, usually have onset in infancy.[1] Bullous lichen planus is a rare blistering variant of lichen planus, a common disease that has been reviewed by Edwards and others.[2] Other blistering conditions, such as contact or systemic allergic reactions, bullous pemphigoid and linear IgA disease,[3] more commonly affect the skin.

Mucous membrane pemphigoid (MMP) is 1 of the 2 most common chronic immunopathogenic diseases to cause chronic oral blistering. (In part 2 of this 2-part article, we discuss the other: pemphigus vulgaris.)

Normal Epithelial–Connective Tissue Interface

Oral mucous membranes consist of an epithelial covering of underlying connective tissues (**Fig. 1a**). The adhesion of the epithelium to the connective tissue is complex, involving a number of proteins that link intermediate filaments inside basal keratinocytes through hemidesmosomes and the basement membrane zone (BMZ) to anchoring type VII collagen in the underlying connective tissue. Intermediate keratin filaments are bound to

hemidesmosome plaque proteins, such as bullous pemphigoid antigen 1 (BP230), which are in turn connected to transmembrane proteins such as bullous pemphigoid antigen 2 (BP180) and α6β4 integrin. In the lamina lucida — a thin electron-lucent zone below the basal keratinocyte plasma membrane — these transmembranous proteins are linked to laminins, which in turn are linked to underlying lamina densa proteins such as type IV collagen or fibronectin. Finally, these proteins are linked to type VII collagen (**Fig. 1b**).

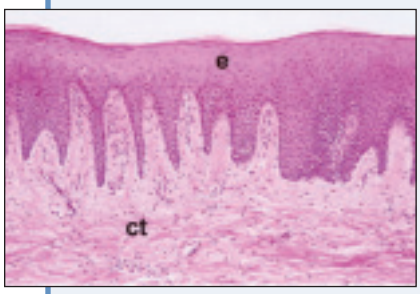

Figure 1a: Most oral mucosa is surfaced by stratified squamous epithelium (e), which is firmly anchored to the underlying connective tissue (ct) as seen in this microscopic section of normal gingiva. (Hematoxylin and eosin staining, magnification ×200)

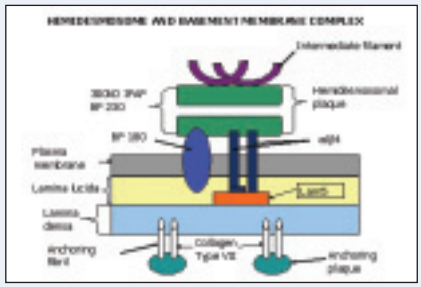

Figure 1b: Schematic of details of the protein linkages in the epithelium–connective tissue interface.

Mucous Membrane Pemphigoid

Mucocutaneous diseases, which are characterized by separation of epithelium from connective tissue, involve alterations in one or more of the linked anchoring proteins caused by either genetic abnormalities (e.g., hereditary epidermolysis bullosa) or autoantibodies. MMP is the most common group of autoimmune mucocutaneous diseases to affect the oral cavity.

In the past, MMP was known by several terms, including "benign mucous membrane pemphigoid," "cicatricial pemphigoid" and "ocular or oral–gingival pemphigoid." However, in reporting the results of the First International Consensus on Mucous Membrane Pemphigoid, Chan and others[4] recommended the term "mucous membrane pemphigoid" because the disease may not be benign when it causes blindness from ocular involvement (**Fig. 2a**) or death from laryngeal scarring[5]; it may not be scarring, as in gingival involvement; and it may affect a number of mucous membranes such as the oral and nasal mucosa, pharynx, anus, genital mucosa, esophagus and trachea. The skin may be affected, but is always a minor component.

MMP is a group of uncommon chronic blistering diseases found in 2–5 people per 100,000 population a year.[6] Orally, it primarily affects the gingiva (**Fig. 2b**) but may involve any area.[7] The disease is seen twice as often in women, primarily those middle aged and older.[8] Lesions are typically painful at first and persistent. Fluid-filled blisters develop (**Fig. 2c**) or sometimes blood-filled blisters following mild to moderate trauma. The clinician may be able to induce a blister or epithelial sloughing by applying tangential pressure to reddened areas or to apparently unaffected mucosa adjacent to lesions (a positive Nikolsky test)[1] (**Fig. 2d**). The blisters break leaving raw, painful ulcers that heal slowly over several days to weeks. Patients may complain of difficulty brushing their teeth or of sloughing bits of tissue. The severity of the disease is extremely variable, ranging from occasional blisters to continuous severe blistering and ulceration. Scarring from gingival lesions is not seen, but may occur in other oral areas, with associated reduced function.[8]

Microscopic Appearance

The intact epithelium detaches cleanly from the underlying connective tissue. There is often chronic inflammation in the connective tissue (**Fig. 2e**), but this is sometimes subtle or absent.[1,7,9]

Immunofluorescence Pattern

Direct immunofluorescence shows a linear deposit of IgG, IgA, C3 or a combination of these in the BMZ. Circulating autoantibodies are usually low in concentration although often sufficient to show linear BMZ staining by indirect immunofluorescence on either the epithelial or connective tissue surface.[4,8,9]

Pathogenesis

The pathogenesis of MMP can best be understood by considering the normal epithelial–connective tissue interface (**Fig. 2b**). Autoantibodies (IgG or IgA or both) attack 1 or more antigen sites in the molecules connecting the epithelium to the connective tissue and prevent the linkage of molecules in the hemidesmosomes and BMZ. The major antigens involved in oral MMP are believed to be BP180[10,11] and laminin 5[12,13] (**Fig. 2f**). Consequently, the epithelium is poorly anchored to the connective tissue and separates, allowing a subepithelial blister to form.

There is evidence to show that the severity of the disease is proportional to the concentration of autoantibodies and the number of classes of antibodies involved (i.e., both IgG and IgA).[4,6]

Clinical Course

Oral MMP usually appears suddenly, is painful, waxes and wanes in severity and lasts for years or may be active throughout the remainder of the patient's life. Oral

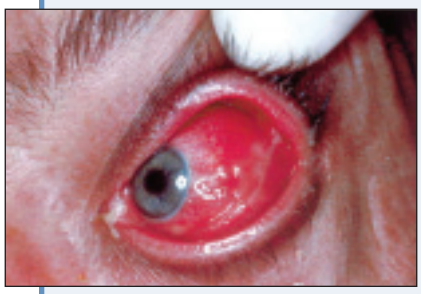

Figure 2a: Clinical appearance of severe ocular lesions in a male patient with mucous membrane pemphigoid (MMP).

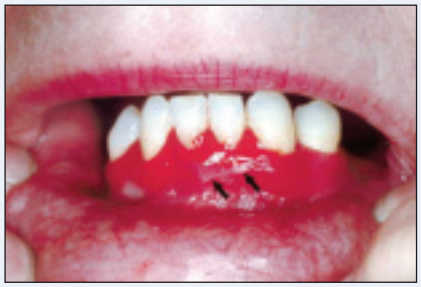

Figure 2b: Generalized erythematous, painful gingival lesions in a female patient with MMP. Sloughing of the epithelium is seen (arrows).

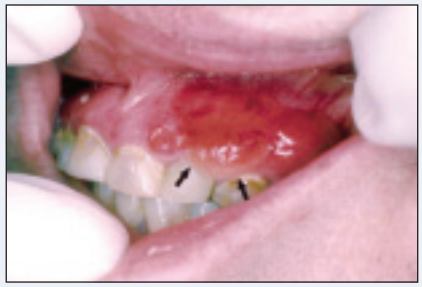

Figure 2c: An intact blister (arrows) in another female patient with MMP.

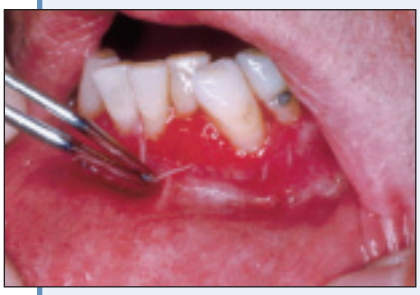

Figure 2d: This patient's clinician was able to lift and peel epithelium from the connective tissue using tissue forceps indicating a positive Nikolsky test.

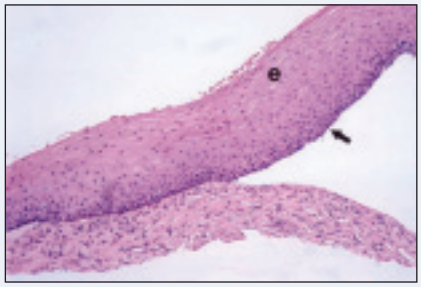

Figure 2e: Microscopically, the intact epithelium (e) has separated from the connective tissue below the basal cell layer (arrow). (Hematoxylin and eosin staining, magnification ×200)

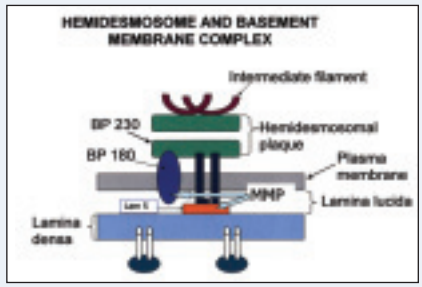

Figure 2f: Schematic diagram of MMP showing both bullous pemphigoid antigen 2 (BP180) and laminin 5 as the major antigenic sites for autoantibody attack.

lesions are not life threatening, but may be associated with considerable morbidity in severely affected patients who do not respond to medication. The attending dentist must always rule out ocular and respiratory tract lesions. Patients who respond to treatment usually require constant or at least intermittent therapy for years.

Treatment

Patients with involvement of the conjunctiva and pharyngeal, laryngeal and genital mucosa should be referred to appropriate medical personnel for therapy, which is usually more aggressive than that for patients with oral lesions only.

Patients who exhibit only mild oral lesions may require no treatment, as the risk of therapeutic side effects outweighs the benefit of the treatment. Many patients develop a tolerance to the oral lesions and cease complaining about oral discomfort despite the persistence of mild disease.

Because the disease is considered autoimmune, the first line of treatment for those with only oral lesions is the use of topical corticosteroids, such as fluocinonide.[7,14] However, this treatment often fails. Periodic bursts of systemic corticosteroids, such as prednisone, may achieve success in some patients, whereas others notice no improvement.[14] Patients resistant to corticosteroid therapy may benefit from dapsone (avlosulfone) therapy[7,14,15] or combined tetracycline and nicotinamide therapy.[12] Recently, topical tacrolimus has been used experimentally with some success on a patient with genital lesions.[16] Cyclophosphamide, azathioprine and methotrexate[14,15] are used in combination with systemic corticosteroids in severe cases. Intravenous immunoglobulin (IVIG) has been tried with some success.[14] In some patients, any combination of treatments is unsuccessful, and these patients may continue to suffer unabated for decades.

In all cases involving the gingiva, excellent oral hygiene to reduce bacterial plaque is recommended, despite the pain and potential blistering associated with brushing.

Relation to Other Types of Subepithelial Blistering Diseases

Bullous pemphigoid is generally a condition characterized by large blisters that occur on the skin in areas of friction such as the axillae and groin. The antigens are BP230 and sometimes BP180, and circulating autoantibodies are usually easily detected. Bullous pemphigoid affects may include mucosal lesions. Bullous pemphigoid and MMP cannot be distinguished by histologic or immunofluorescence features, but are separated by clinical presentation.[4]

Linear IgA disease is a blistering disease of skin characterized by a linear deposit of IgA at the BMZ by direct immunofluorescence of skin lesions. MMP lesions may also show IgA immunofluorescence but are distinguished from linear IgA disease by clinical presentation.[4]

Epidermolysis bullosa acquisita (EBA) results from autoantibody disruption of type VII collagen in the skin, causing skin blistering. MMP involving type VII autoantibodies is distinguished from EBA by clinical presentation.[4]

Conclusion

Because MMP is a relatively common condition, dental practitioners should be able to recognize and manage it, or refer their patients when appropriate. Further elaboration with regard to management and referral is provided at the end of part 2 of this paper.[17]

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