Oral mucosal diseases: Mucous membrane pemphigoid

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Accepted 19 July 2007
Available online 4 September 2007

Abstract

Subepithelial vesiculobullous conditions are chronic autoimmune disorders that arise from reactions directed against components of the hemidesmosomes or basement membrane zones (BMZ) of stratified squamous epithelium to which the term immune-mediated subepithelial blistering diseases (IMSEBD) has been given. Mucous membrane pemphigoid (MMP) is the most common, but variants do exist.

Non-immune disorders that involve these epithelial components typically have a genetic basis—the main example being epidermolysis bullosa.

All subepithelial vesiculobullous disorders present as blisters and erosions, and diagnosis must be confirmed by biopsy examination with immunostaining, sometimes supplemented by other investigations.

No single treatment reliably controls all subepithelial vesiculobullous disorders; the immunological differences within IMSEBD may account for differences in responses to treatment. Currently, as well as improving oral hygiene, immunomodulatory treatment is used to control the oral lesions of MMP, but it is not known if its specific subsets reliably respond to different agents.

Keywords: Pemphigoid; Skin; Autoimmune; Corticosteroids; Immunosuppressants; Oral

Introduction

The bullous diseases to be first recognised were pemphigus and dermatitis herpetiformis; most vesiculobullous disorders were then grouped under those diagnoses. When immune deposits (mainly IgG and C3) were detected in some patients along the epithelial basement membrane zone of stratified squamous epithelium, the term pemphigoid was coined as the disease followed a less severe course than pemphigus.

However, it later became evident that pemphigoid consisted of a family of chronic immune-mediated, subepithelial, blistering diseases that included conditions such as bullous pemphigoid, pemphigoid (herpes) gestationis, cicatricial pemphigoid, dermatitis herpetiformis, and linear IgA disease. This heterogeneity led to the introduction of the term immune-mediated subepithelial blistering diseases (IMSEBD), and it was recognised that, in pemphigoid, IgG autoantibodies can be directed against various antigens of the epithelial basement membrane zone because most of the autoantibodies have immune deposits that are located on the floor of salt-split epithelial biopsy specimens.

Pemphigoid came to include cicatricial pemphigoid (now renamed mucous membrane pemphigoid (MMP)), bullous pemphigoid, pemphigoid gestationis, anti-p200, anti-p105, and anti-p450 pemphigoid, lichen planus pemphigoides, dermatitis herpetiformis, linear IgA disease, epidermolysis bullosa acquisita, bullous systemic lupus erythematosus, and paraneoplastic pemphigus. However, it is now known that MMP itself is heterogeneous.

Pemphigoid of the mucous membranes

The clinical phenotype that is acquired and consists of vesicles, bullae or erosions, or both, and that mainly affects
mucosa, often in the mouth, is called mucous membrane pemphigoid (MMP). It predominantly affects women, with an age range at onset of 51–62 years.

MMP is neither a single clinical nor immunological homogeneous entity; recent molecular biological advances have unravelled its heterogeneity. At least 10 different and distinct components of the basement membrane zone have now been identified as autoantigens in various IMSEBDs: MMP is usually associated with autoantibodies to bullous pemphigoid antigen 2 (BP230 or BP180), and less often to bullous pemphigoid antigen 1 (BP180), laminin 5 (epiligrin), type VII collagen, or to the α6β4 subunit of integrin.

These variations in antigens and antibodies might be reflected in variations in pathogenetic mechanisms, clinical presentations and response to therapy.

**Aetiology and pathogenesis**

The initiating factor for the autoimmune response in MMP is usually unknown, but is occasionally a drug such as furosemide. There may be an immunogenetic background and an association with HLA DQB1*0301, which may have a role in T-lymphocyte recognition of antigens in the basement membrane zone.

The autoantibodies involved in MMP are directed against these antigens, either in the basement membrane or hemidesmosomes. In MMP, immune deposits that reflect autoantibody reactions can be detected in the epithelial basement membrane zone, and are typically IgG (97%) with C3 (78%), but others such as IgA (27%) or IgM (12%) may be seen, which confirm the heterogeneity of antibodies and hint at the heterogeneity of the antigens.

The pathogenesis of MMP probably includes an autoantibody-induced complement-mediated sequestration of leucocytes (mainly neutrophils) with a resultant release of cytokines and leucocyte enzymes, and the detachment of the basal cells from the basement membrane zone, and possibly some complement-mediated lysis of cells.

**Variants of MMP with oral lesions**

At least six variants or subsets of MMP with different antigenic specificity of autoantibodies and patterns of immunopathology are now recognised, but new immune-mediated, sub-epithelial, blistering diseases with oral lesions that simulate MMP have also been described.

The main oral variants are as follows.

**Oral pemphigoid or OMMP (oral lesions only)**

The target antigen for oral pemphigoid is still not clear, though antibodies against a 168-kDa oral mucosal protein have been seen in a few patients, and a structural variant of the α6 integrin is probably involved in some forms.

Oral pemphigoid has a low incidence of findings on indirect immunofluorescence and little or no serological reactivity to bullous pemphigoid antigens or to other currently recognised antigens of MMP.

**Pemphigoid with more widespread clinical features (oral and extraoral lesions)**

In most cases this is associated with reactivity of antibodies to multiple antigens of the basement membrane zone, as well as to multiple components of bullous pemphigoid 180 antigens.

Antiepiligrin cicatricial pemphigoid is an important clinical type that is clinically indistinguishable from other forms of cicatricial pemphigoid. It usually involves the mouth, eyes, and skin, and is characterised by the binding of circulating IgG autoantibodies that target laminin 5, on the dermal side of salt-split human skin on immunofluorescence microscopy.

**Clinical features**

The clinical phenotype known as MMP is therefore not a single entity; it includes patients with oral lesions alone, those with involvement of other mucous membranes or the skin, or both; and some variant may have systemic complications.

Ocular involvement has serious consequences; when limited to the conjunctiva, the term ocular cicatricial pemphigoid is used.

**Oral lesions**

The oral mucosa is often the initial site of lesions in many variants of MMP. Patients often have pain, dysphagia, or peeling of the mucosa. Vesicles or bullae may occur anywhere on the oral mucosa (Figs. 1–3), and there can be a positive Nikolsky sign as in pemphigus. The blisters rupture and leave irregularly shaped erosions with a yellowish...
slough and surrounding inflammatory halo that are persistent and rarely scar.

Patients with MMP often have gingival lesions. MMP is one of the main causes of desquamative gingivitis, which is its main oral feature, and may be the initial sign of presentation. The desquamation can vary from mild, almost insignificant, small patches to widespread erythema with a glazed appearance, and can present with chronic soreness (particularly when eating acidic foods), and gingival erythema and loss of stippling that extends apically from the gingival margins to the alveolar mucosa. Patients also have more inflammation of the gingiva than controls, and higher indices of plaque than those in remission. When patients with MMP who were diagnosed more than 5 years ago were compared with those diagnosed less than 5 years ago, they had significantly more Class I furcation, and facial and lingual recession.

About 40% of patients with oral MMP eventually develop ocular disease with an incidence for the development of ocular disease of 0.03/person/year over 5 years. Ocular involvement usually begins as chronic conjunctivitis with symptoms of burning, irritation, photophobia, and excessive tears. The symptoms usually affect one eye initially but, if left untreated, also involve the other eye within 2 years. Scarring can lead to the fusion of the scleral and palpebral conjunctivae (symblepharon) or of the superior and inferior palpebrae (ankyoblepharon). The conjunctivae may also contract and invert the margins of the eyelid (entropion), leading to inversion of the eyelashes on to the surface of the cornea with subsequent irritation (trichiasis) that can lead to blindness.

Skin lesions

Involvement of the skin is uncommon (up to a quarter of patients) and is restricted to the face, neck, scalp, axilla, trunk, and extremities.

Association with systemic disease

MMP may occasionally be associated with other autoimmune disorders, including pemphigus, and occasionally other autoimmune conditions. Some cases of cicatricial pemphigoid have been associated with B-cell lymphoproliferative disorders. Patients with antiepiligrin cicatricial pemphigoid have a higher incidence of solid cancer than the normal population.

Diagnosis of MMP

Blisters that rupture leaving irregularly shaped erosions, and a positive Nikolsky sign are not specific to pemphigoid or any other IMSEBD. The main differential diagnoses of MMP may also include lichen planus, pemphigus, erythema multiforme and systemic lupus erythematosus, as well as subtypes of pemphigoid.

Diagnosis must be confirmed by examination of biopsy specimens with histological and direct immunofluorescent techniques. It is necessary to biopsy a vesicle or perilesional tissue, not an erosion, as this will show the loss of the epithelium that one wishes to study. Some authors have even suggested that a vesicle should be induced by rubbing the mucosa before taking the biopsy specimen. If possible, it is better to avoid taking biopsy specimens of gingival lesions, as it may cause a periodontal defect, and the chronic inflammation of gingivitis may confuse the histological picture.

The following recommendations in the Consensus Statement may improve the accuracy of biopsy results: in patients with involvement of a single mucosal site, a biopsy specimen should be taken from tissue next to the areas of inflammation; when patients present with involvement of
multiple sites, the biopsy specimen should be taken from tissue adjacent to an inflamed non-ocular site; patients who present with involvement of both skin and mucosa should have a biopsy specimen taken from an inflamed lesion on the skin; biopsy specimens must be taken carefully from patients with ocular involvement to minimise injury and avoid additional scarring.

Specimens should be transferred in a specific transport medium (Michele’s solution) or snap-frozen in liquid nitrogen, and must be processed without delay.

Histologically MMP is characterised by junctional separation at the level of the basement membrane, that gives rise to a sub-basilar split with a chronic inflammatory infiltrate in the lamina propria that contains eosinophils, lymphocytes, and neutrophils (Figs. 4 and 5). Direct immunofluorescence shows deposits, usually of IgG and C3, in a homogeneous linear manner in the basement membrane zone along the epitheliomesenchymal junction. A positive result confirms the diagnosis of IMSEBD and can also differentiate the IgG-mediated diseases (bullous pemphigoid, MMP, pemphigoid gestationis, and acquired epidermolysis bullosa) from the IgA-mediated diseases (dermatitis herpetiformis and linear IgA disease).94

Indirect immunofluorescence and immunoblot assays can be used to detect circulating antibodies. Indirect immunofluorescence using salt-split mucosa provides a more sensitive assay,95 can show antibasement membrane zone antibodies,96 and distinguishes between antigens on the epithelial side of the split (β4 integrin and BPAG2) and those on the lamina propria side (laminin 5).96–98 Immunoblot assays are more specific than indirect immunofluorescence.10,11

Management of MMP

Patients should try to avoid hard foods,9–12 and should improve oral hygiene.

There have been few clinical trials of treatments for MMP; most include patients with heterogeneous entities,17 and few include more than a limited number of patients, so reliable data from randomised controlled trials are unavailable.99

The main treatments available, shown in Fig. 6, are anti-inflammatory, or immunosuppressive, or both.

Patients with oral lesions alone

Patients with MMP who have oral lesions alone have a relatively benign course compared with those with other variants of pemphigoid involving the oral cavity,17 and are best treated with topical drugs.

Topical drugs

Corticosteroids. Topical corticosteroids and intralesional steroid injections9–12 are the main treatments,8,100–105 though some advocate systemic dapsone.

The more potent fluorinated steroids such as fluocinonide 0.05% or clobetasol propionate 0.05% (2–3 applications daily for 9–24 weeks) in an adhesive medium,1,100,101,103,104 or used in a vacuum-formed customised tray or veneer for gingival lesions,79,100,106–109 are usually required. Triamcinolone acetonide 0.1–0.5% as an aqueous rinse or ointment is rarely adequate to control MMP,105 but intraesionally (in a dilution of 5.0–10 mg/ml)9 can be useful to treat isolated erosions.110

Candidosis may complicate treatment with steroids, but can be prevented by adding antimycotics such as miconazole gel or chlorhexidine mouthwashes, or both.100

Calcineurin antagonists. Topical ciclosporin may be effective in the treatment of oral lesions,111,112 but it is expensive. Topical tacrolimus has been used,113–117 but the Food and Drug Administration (USA) has discouraged its use in view of potential carcinogenicity.

Recalcitrant pemphigoid or pemphigoid not limited to the oral cavity

Patients with large oral, or multiple oral lesions, or both, extensive involvement of the mucous membrane (particu-
larly of the eye), or recalcitrant disease, may need aggressive systemic treatment.9–12,118–120

Dapsone has often been used initially,9,121 but if patients fail to respond, systemic corticosteroids, or alternative immunosuppressants, or a combination of high-dose intravenous corticosteroids and drugs such as cyclophosphamide12 are then used.

Systemic drugs
Dapsone. Dapsone, a synthetic sulfone with anti-inflammatory properties, seems to suppress adherence of neutrophils, and inhibits synthesis of prostaglandin E2.122,123 Several authors have used it to treat patients with MMP,17,124–126 with or without topical corticosteroids,123 but others have reported disappointing results.121,127 Dapsone has often had to be discontinued because of adverse effects including headaches, haemolytic anaemia, methaemoglobinemia, suppression of bone marrow, and hepatotoxicity,121,125,127 particularly in Asian, Negro, or Mediterranean patients121 in whom glucose-6-phosphate dehydrogenase deficiency must always also be excluded.

To minimise side-effects the regimen recommended is: dapsone 25 mg daily for 3 days, then 50 mg daily for 3 days, then 75 mg daily for 3 days, then 100 mg daily for another 3 days, then rising to 150 mg daily on the seventeenth day.126 However, even with this regimen, intolerance is common.121 Dapsone plus cimetidine (Fig. 6) may reduce adverse effects.

Corticosteroids. Treatment with a systemic corticosteroid with a short plasma half-life such as prednisone128 may be effective.9,123,129,130 Short courses of high dose steroids are advocated.8 An alternative approach is to use a lower dose of systemic prednisolone or prednisone (40 mg daily for 5 days) followed by 10–20 mg daily for 2 weeks.105 Systemic steroids may be combined with high-potency topical steroids such as clobetasol to control oral lesions,100,105 or used with other immunosuppressants, or with dapsone.131,80 Immunosuppressants may take up to 6 weeks to work.121

Azathioprine or cyclophosphamide. Azathioprine (1–2 mg/kg daily) or cyclophosphamide (0.5–2 mg/kg daily) can be used9,121,131–134 but usually neither is sufficient alone,124 and both can have several adverse effects such as suppression of bone marrow. Azathioprine may induce cholestasis, whereas cyclophosphamide can induce alopecia and haemorrhagic cystitis, and is potentially teratogenic and carcinogenic.135,136
Other systemic agents. Other systemic agents proposed for the treatment of MMP include: methotrexate, thalidomide, mycophenolate mofetil, leflunomide, sulphasalazine, sulphydryl pyridine (alone, or in combination with dapsone), sulphamethoxypyridazine, and tetracyclines.

A preliminary report described a beneficial response of desquamative gingivitis to doxycycline 100 mg daily for 8 weeks. Minocycline (50–100 mg daily for 3–39 months) was successful in four patients with gingival lesions. The combined use of tetracycline and nicotinamide (500 mg to 2.5 g daily) seemed to produce a better response in isolated cases, though there is a need for controlled trials.

In patients who did not respond to conventional treatment such as high-dose systemic corticosteroids, or immunosuppressants, or both, an alternative treatment can be to use intravenous immunoglobulin. Plasmapheresis has also been effective in some patients.

Surgery. Oral hygiene and the use of local corticosteroids, followed by scaling and root planing are recommended for the treatment and maintenance of periodontal health in patients with MMP. Some may need operations to repair scars, or to prevent severe complications such as blindness, stenosis of the upper airway, or stricture of the oesophagus. Ocular lesions may be corrected with oral mucosal grafts, or by transplantation of cultured oral epithelial cells.

However, operations may aggravate the disease, so it is essential that good control is achieved before it is contemplated. This may also apply to oral procedures.

References


