Chapter 16.

Ocular and Oral Mucous Membrane Pemphigoid (Cicatricial Pemphigoid)

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Conflict of Interest: None.

Abstract (100 words)

Mucous membrane pemphigoid, a heterogeneous group of autoimmune blistering diseases, affect primarily the mucous membranes. While both oral and ocular mucosae can be affected in a given patient, patients have involvement restricted to oral mucosae tend to have a benign outcome, whereas those with ocular disease commonly face treatment resistance and result in scarring and blindness. Diagnosis requires a direct immunofluorescence microscopy demonstrating a linear deposition of IgG, IgA, or C3 at the epithelial basement membrane. While the target antigens vary, subsets of patients affected exclusively by oral and ocular mucosal diseases have autoantibodies targeting alpha-6 and beta-4 integrins, respectively.

Definition and Etiology

Mucous membrane pemphigoid (MMP, also known as cicatricial pemphigoid) is defined as a heterogeneous group of putative autoimmune sub-epithelial blistering diseases primarily affecting any mucous membranes, such as oral cavity, ocular mucosae, or mucous membranes of nose, larynx, esophagus, rectum, penis, and vagina [1]. Autoantibodies binding to the epithelial basement membrane zone have been clearly demonstrated in these patients and some of these autoantibodies can induce subepidermal separation in skin organ culture [1-5]. Furthermore, Fab fragments antibodies against laminin-5 are able to induce subepithelial blisters of mucous membranes and skin in neonatal mice, lending more support for MMP being an autoimmune disease [6]. Many clinical papers also pointed to a possible involvement of a mechanism of "epitope spreading", where a prior inflammatory event might expose the previously "hidden" epithelial basement membrane components to autoreactive T cells, leading to a secondary autoimmune phenomenon and the eventual development of MMP [7]. In fact, several patients who had suffered an episode of Stevens-Johnson syndrome affecting the ocular mucosae subsequently developed ocular MMP [8]. In addition, cases of patients developed ocular MMP in the context of ocular Sjogren's syndrome have been reported [9]. Many epithelial basement membrane components have been identified as potential targets of MMP, these include bullous pemphigoid antigen 2 (type XVII collagen) [1], type VII collagen [1], laminin 332 (laminin-5) [3], laminin-6 [10], alpha-6 and beta-4 integrin subunits [4], and a 120-kD undefined epithelial antigen [8]. Currently, there is no definite evidence pointing to the mechanism that links the binding of autoantibodies to epithelial basement membrane and the subsequent scarring process, which actually post the single most difficult challenge to the physicians who care for this group of patients. Over the years, investigators have attempted to subdivide this heterogeneous group of diseases into more unique subsets [2, 4, 11]. For example, patients with exclusive involvement of ocular mucosae possess autoantibodies to an epithelial basement membrane antigen, beta-4 integrin subunit, different from those who have other mucosal and skin diseases [2, 4]. Other investigators also proposed that patients with exclusive oral mucosae involvement should be categorized to another distinct subset of disease (oral pemphigoid), with autoantibodies targeting the alph-6 subunit of integrin [11]. It has been well documented that this group of "oral pemphigoid" patients tend to encounter a relative benign course compared to those with skin and other mucosal diseases [11]. Several papers have documented the association of MMP with MHC class II HLA-DQB1*0301 [12-14].

Clinical Manifestations

While skin and multiple mucous membranes can be affected in a given patients [1], there are apparently distinct subsets of patients where the affected sites are restricted to ocular or oral mucosae [2, 4, 11]. In patients who have restricted oral mucosal lesions, the prognosis is excellent and this group of patients tends to have a mild to moderate disease process [1, 11]. Scarring is usually absent from this group of patients who have only oral lesions [1]. The individual lesions can be erythematous patches, blisters, erosions, or pseudomembrane-covered erosions [15]. Any oral cavity locations, including attached gingivae, buccal mucosae, palate, pharynx, labia, and tongue, can be involved. Fig. 1 illustrates a patient with oral mucosal involvement.

In general, MMP patients with ocular disease tend to follow a progressive disease process [1, 16]. Recurrent conjunctiva inflammatory process usually results in subepithelial fibrosis, leading to fornix shortening, symblepharon and ankyloblepharon formation, and then subsequently trichiasis and entropion. Blisters are rarely observed. Fig. 2 illustrates a patient with ocular involvement. Later in the disease stage, limbal stem cell deficiency, tear deficiency, and lid malposition can occur, ending in total keratinization of the entire ocular surface [1, 16].

The epidemiological data for MMP is not very well established. In a survey of a large series of 28 MMP patients, it was found that 64% of them had ocular disease, with mean age of 73 years old and 61% being female [17]. In this survey, the complications of ocular diseases are many, including entropion, recurrent epithelial erosions, corneal ulcers, keratitis, and corneal perforation [17]. Despite the control of inflammation, visual loss occurred in 53% of eyes and reading visual acuity was maintained in only 35% of eyes [17].

Diagnostic Work Ups

Differential diagnoses of MMP include pemphigus vulgaris, paraneoplasic pemphigus, and Stevens-Johnson syndrome. It is essential that a direct immunofluorescence microscopy is performed to document the disease before we commit the patients to long-term immunosuppressive treatments. An international consensus meeting recommends that a mucosal biopsy should be performed in oral mucosa for the test [1]. This consensus also recommends against biopsy the ocular mucosa tissue, since it may aggravate the existing inflammation. The finding of linearly deposited IgG, IgA, or C3 (Fig. 3) at the epithelial basement membrane is considered to be sufficient for the diagnosis in the context of consistent clinical findings, and a lesional histopathology is recommended only if a biopsy can be performed in non-ocular mucosae such as oral mucosae or skin. Some physicians may also perform an indirect immunofluorescence microscopy (IIF) in order to identify the presence and characteristic of autoantibodies using the patients' sera on a normal human skin substrate split by 1.0 molar NaCl or 20 m molar of Na EDTA. Although the sensitivity is low in IIF, a positive finding of autoantibodies binding to the roof or the floor of the split will allow physicians to subdivide groups of patients with autoantibodies targeting upper lamina lucida antigens (bullous pemphigoid antigen 2, alpha 6 beta 4 integrins) or lower lamina lucida/sub-lamina densa antigens (laminin-5, laminin-6, type VII collagen), respectively. ELISA test for target antigen is a more sensitive test, but its availability is currently limited to a few academic centers. Since a subset of patients, who developed MMP and possessed anti-laminin-5 autoantibodies, were found to have internal malignancies developed around the time of MMP onset [18], it is essentially that an age-appropriate cancer screening to be performed in this sub-group of patients.

Therapeutic Strategies

An international consensus meeting recommends that patients should be subdivided into two clinical categories: 1). patients with mucosal lesions restricted to oral mucosae and 2). patients with ocular, laryngeal, esophageal, or genital lesions, for the purpose of strategic therapy [1, 15]. For the first group of patients with milder disease, an initial treatment of topical corticosteroid should be tried [1, 11, 15]. In patients with moderate to severe of oral mucosal disease, dapsone (50-200 mg/day) and low dose of prednisone (0.5 mg/kg/day) should be initiated [1, 11, 15]. If satisfactory response is not obtained by dapsone and prednisone, then an immunosuppressive (azathioprine 100-150 mg/day or mycophenolate mofetil 1 g/day) could be added to the regimens.

For the second group of patients, a more aggressive starting treatment plan is recommended [1, 15]. The available medications for the later group of patients include dapsone, systemic corticosteroids, azathioprine, mycophenolate mofetil, and cyclophosphamide. For patients with slow to moderate progression of disease, dapsone (50-200 mg/day), plus systemic corticosteroids (1 mg/kg/day) and an immunosuppressive (either azathioprine 100-150 mg/day or mycophenolate mofetil 1-1.5 g/day) should be initiated. For patients with rapid progression of disease, cyclophosphamide (1-2 mg/kg/day) plus systemic corticosteroids (1-1.5 mg/kg/day) is preferred since cyclophosphamide has a faster onset of action [1, 15]. When treating patients with immunosuppressive, careful monitoring of the medication side effects is an essential part of the management. Azathioprine and mycophenolate mofetil could cause severe liver toxicity; cyclophosphamide could cause hemorrhagic cystitis, whereas all of these immunosuppressive could induce severe bone marrow suppression.

More recently, few cases of MMP which were treated successfully utilizing a new biologic rituximab with or without combination of IVIG have been reported in the literature [19-21]. In one recent report, combined treatment of rituximab and IVIG arrested disease progression and prevented total blindness in patients with recalcitrant disease, whereas those treated aggressively with other immunosuppressive regimens became totally blind [19].

From time to time, surgical interventions are utilized for MMP patients with ocular diseases. These procedures include entropion surgery (eye lash ablation), tarsorrhaphy, mucous membrane grafting, amniotic membrane transplantation, tectonic keratoplasty, and keratoprothesis [17]. These surgical procedures aim to achieve temporary symptom relieve, and are not curative. After receiving a procedure called “Boston keratoprothesis, patients with end-stage ocular disease secondary to MMP suffered numerous corneal melt-downs and required multiple repeat implantations [22]. Since tear deficiency is a major cause of symptom in this group of MMP patients with ocular disease, besides systemic treatment to control inflammation, lubricant without preservative is needed to improve dry eye and the accompanying blapharitis should be treated with tetracycline and lid hygiene [23].

Besides medical and surgical treatments, physicians who care for this group of patients need to pay attention to a potential association of MMP to internal malignancies. A survey of a group of 35 patients who developed MMP with autoantibodies to laminin 332 showed a relative cancer risk of 6.8, which appears to be increased [18]. However, other surveys on MMP patients who have exclusively oral mucosal disease (with autoantibodies to alpha -6 integrin) and who have exclusive ocular mucosal disease (with autoantibodies to beta-4 integrin) showed a lower than expected relative cancer risk of 0.34 and 0.29, respectively [24-25].

Research Gap, Practice Gap, and Emerging Therapeutic Options

One of the major practice gaps regarding the therapeutic option is that there is currently no medication or procedure that can be used to reverse the scarring/fibrotic process once it is established. This is particularly detrimental to those with ocular lesions. Therefore, for the future therapeutic intervention, study should be geared toward learning how we could reverse the scarring/fibrotic process.

Another area of research interest would be the link between anti-laminin 332 autoantibodies and the increased cancer development [18]. Is laminin 332 important in preventing the development of certain cancers?

There are some encouraging research data, however. One recent publication reported an increased conjunctiva expression of TNF-alpha in ocular MMP and suggests that systemic TNF-alpha antagonist could be effective in controlling severe MMP cases unresponsive to conventional immunosuppressant [26]. Interestingly, TNF-alpha stimulates conjunctiva fibroblast MMP-9 production and up-regulated CD40 and ICAM expressions, without significant effect on fibroblast proliferation or collagen lattice contraction [26]. In fact, several cases of MMP, some of them affecting ocular mucosae, have been successfully controlled by anti-TNF-alpha medication after failing the conventional treatment of immunosuppressive [27-29]. Obviously, a controlled trial in the future is needed to establish the true effectiveness of this regimen.

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Figure Legends

Fig. 1. A patient with oral mucous membrane pemphigoid develops erosion and pseudomembranous erosion.

Fig. 2. A patient with ocular mucous membrane pemphigoid develops lower conjunctiva symblepharon.

Fig. 3. Direct immunofluorescence microscopy performed in a biopsy obtained from an oral mucosa illustrates the linear deposit of C3 along the epithelial basement membrane (Original magnification 40X).

Drug Names

azathioprine: Imuran
mycophenolate mofetil: Cellcept
cyclophosphamide: Cytoxan
rituximab: Rituxan
intravenous immunoglobulin (IVIG)
dapsone
prednisone