Mucous Membrane Pemphigoid

Hong-Hui Xu, MD, PhD[a,b], Victoria P. Werth, MD[b,c,*], Ernesta Parisi, DMD[d,e], Thomas P. Sollecito, DMD, FDS RCSEd[f]

KEYWORDS

• Cicatricial pemphigoid • Mucous membrane • Subepithelial autoimmune disease • Oral • Ocular

KEY POINTS

- Mucous membrane pemphigoid is a heterogeneous subepithelial blistering disease predominantly affecting oral, ocular mucous membrane and occasionally the skin.
- Like other forms of pemphigoid, the disorder is characterized by the formation of autoantibodies against structural proteins of the dermal-epidermal junction.
- Early diagnosis is critical and immunosuppressive treatment may prevent scarring.

INTRODUCTION

Mucous membrane pemphigoid (MMP) is a heterogeneous group of chronic, autoimmune subepithelial blistering diseases that predominantly involves the mucous membranes and occasionally the skin. In vivo, it is characterized by linear deposition of immunoglobulin (Ig)G, IgA, or C3 along the epithelial basement membrane zone.[1,2]

Conflict of Interest: The authors have nothing to disclose.
This material is supported by the National Institutes of Health, including NIH K24-AR 18 02207 (Werth), by the Department of Veterans Affairs, Veteran Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development and by Innovative Research Teams in Universities, Liaoning Bureau of Education (LT2012012).
A version of this article appeared as Sollecito TP, Parisi E. Mucous membrane pemphigoid. Dent Clin N Am 2005;49:91–106.
[a] Department of Dermatology, No.1 Hospital of China Medical University, 155 North Nanjing Street, Shenyang 110001, China; [b] Department of Dermatology, Philadelphia VA Medical Center, 3900 Woodland Avenue, Philadelphia, PA 19104, USA; [c] Department of Dermatology, Perelman Center for Advanced Medicine, University of Pennsylvania, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104, USA; [d] Private Practice, 224 Union Boulevard, Totowa, NJ 07512, USA; [e] Department of Diagnostic Sciences, NJ Dental School, UMDNJ, 110 Bergen Street, Newark, NJ 07103, USA; [f] Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, 240 South 40th Street, Philadelphia, PA 19104, USA
* Corresponding author. Perelman Center for Advanced Medicine, University of Pennsylvania, Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104.
E-mail address: werth@mail.med.upenn.edu

Dent Clin N Am 57 (2013) 611–630
http://dx.doi.org/10.1016/j.cden.2013.07.003 **dental.theclinics.com**
0011-8532/13/$ – see front matter Published by Elsevier Inc.

Although the oral and ocular mucosae are the most common sites affected, the nasopharynx, esophagus, larynx, and anogenital region also may be involved. This disorder results in mucosal and/or skin blistering, ulceration, and subsequent scarring. The disease severity and distribution are highly variable, from mild cases involving only the oral mucosa, to severe cases involving the ocular, genital, and esophageal mucosa. Involvement of the larynx or esophagus can give rise to strictures, which may be life-threatening. Because the consequences of this disease can be severe and limited therapeutic options are available once scarring develops, early diagnosis is critical.[3] However, as the disease is rare and the early presenting symptoms are nonspecific, MMP is often unrecognized in the early inflammatory stage.

Other nomenclatures for MMP include cicatricial pemphigoid, oral pemphigoid, ocular cicatricial pemphigoid (OCP), ocular pemphigoid, and benign mucous membrane pemphigoid.

Autoantibodies to one or several autoantigens in the mucosal or epithelial basement membrane zone (BMZ) have been identified in patients with MMP.[4–10] The association of MMP with human leukocyte antigen (HLA) major histocompatibility class II HLA-DQB1*0301 has been demonstrated.[11–13] The cause is usually unknown, but there are a few reports of MMP triggered by medications, such as methyldopa, clonidine, and D-penicillamine.[14,15]

EPIDEMIOLOGY

The true incidence of MMP is unclear. A recent study from the United Kingdom demonstrated that ocular MMP accounted for 61% of the cases of newly diagnosed cicatricial conjunctivitis and the incidence was calculated as 0.8 per million population.[16] The incidence of MMP was estimated to be 1.3 to 2.0 per million per year in France and Germany.[17,18] MMP predominantly affects women more often than men with a female-to-male ratio of nearly 2:1.[19] MMP mainly occurs in the elderly population, commonly observed between 60 and 80 years of age.[20] Albeit rare, children may also be affected. Approximately 20 cases of childhood-onset MMP have been reported, among whom the youngest one was 10 months old.[21–23] There is no known racial or geographic predilection.

PATHOGENESIS

The pathogenesis of MMP is complex. MMP has been found to be heterogeneous with several different antigens implicated. The pathogenic relevance of autoantibodies in MMP has been demonstrated in vivo and in vitro.

Circulating IgG and/or IgA autoantibodies against components of the BMZ found in the serum of patients with MMP indicate that MMP is mediated by a humoral immune response.[24,25] Loss of immunologic tolerance to structural proteins in the BMZ results in development of autoantibodies. By use of immunoblotting and immunoprecipitation techniques, a variety of autoantigens, including the bullous pemphigoid antigen 1 (BPAg1) (a 230-kDa protein, BP230), the bullous pemphigoid antigen 2 (BPAg2) (a 180-kDa protein, BP180),[24,25] integrin subunits $\alpha 6/\beta 4$, laminin-332 (also called epiligrin and laminin-5), laminin-6, and collagen type I have been identified (**Table 1**). BPAg1 is an intracellular protein, whereas BPAg2 and $\alpha 6/\beta 4$ integrins are transmembrane proteins. The most frequently targeted autoantigen in MMP is BPAg2. Laminin-5 is thought to be the major ligand between the transmembrane proteins and the anchoring filaments.[26] Anchoring fibrils, composed of type VII collagen, are located deeper in the lamina densa (**Fig. 1**). These autoantigens are not exclusive to MMP. Autoantibodies to both BPAg1