Mucous membrane pemphigoid (MMP) is the terminology used to describe a group of chronic subepithelial inflammatory disorders that cause both inflammation and progressive cicatrisation of mucosal membranes and skin. Of greatest interest to the ophthalmologist, MMP may affect the ocular mucosa, which if left untreated is often sight threatening. However, MMP also affects the oral, anal, genital, nasopharyngeal, esophageal, and laryngeal mucosa, as well as skin, resulting in multisystem disease including life-threatening airway obstruction. Caring for patients with ocular MMP can be a frustrating experience, and not simply because this disease can be hard to manage. Delays in diagnosis are common; accurately documenting progression can be difficult; delineating active MMP from secondary ocular inflammation due to dryness, keratinization, trichiasis, and bacterial colonization is a challenge; and obtaining authorization for treatment medications, especially when there is only ocular involvement, is an ongoing battle.

Over the years, I have come up with ways to circumvent and overcome some of the difficulties in managing patients with ocular MMP on the basis of both experience and consideration of disease pathogenesis. In addition, for the past 15 years I have pretty much stopped getting biopsies of the ocular mucosa for direct immunofluorescence (DIF) to make a diagnosis of MMP. The one exception has been if the patient demands a biopsy. My rationale is straightforward. Once I rule out my relatively short list of other causes of conjunctival cicatrisation, such as trauma/chemical burns, Stevens–Johnson syndrome/toxic epidermal necrosis, atopy, hypertropic conjunctivitis, graft-versus-host disease, and medication toxicity, I need to treat chronic progressive cicatrisating conjunctivitis aggressively with systemic immunomodulatory drugs to prevent vision loss. If a conjunctival biopsy with DIF is positive, it confirms my suspicions, but if it is negative, I am going to treat anyway and refer the patient to other specialists to rule out MMP affecting nonocular regions of the body. If the patient does not have MMP elsewhere, I am still going to aggressively treat the vision-threatening chronic progression cicatrisating conjunctivitis with systemic immunosuppression. My rationale for this is 2-fold. First, if the patient has chronic progressive cicatrisizing conjunctivitis, I will need to treat him to prevent vision loss whether the diagnosis is MMP or not. Second, the sensitivity of a conjunctival biopsy with DIF for making a diagnosis of MMP in a patient with only ocular disease is unknown, although typically described as having a sensitivity ranging from 50% to 80%. As elegantly stated by Ong et al1 in the current issue (see http://www.aaojournal.org/article/S0161-6420(17)32595-2/fulltext) “…it is recognized that in ocular-only MMP, half of the patients with conjunctival disease typical of MMP have had intermittent or repeatedly negative DIF.”

A singular problem with making the diagnosis of ocular MMP without a biopsy is that it flies in the face of evidence-based medicine. In 2002, a group of well-meaning, self-appointed experts published “The First International Consensus on Mucous Membrane Pemphigoid,” in which they established diagnostic criteria for MMP.2 These criteria included the statement that “…direct immunopathology criteria are essential and must be demonstrated before a diagnosis of MMP is assigned.” I have obviously ignored this recommendation for the past 15 years. It is also clear that Ong et al1 were bothered by this recommendation, stating that “misdiagnosis, or delayed diagnosis of MMP…results in irreversible deterioration in MMP patients.” Therefore, they set out to study whether patients who met the clinical criteria for ocular MMP, but had a negative conjunctival biopsy for MMP by DIF, represented patients with a different disease from those patients who were DIF positive.

The resultant study was an investigational tour de force.1 The investigators recruited 73 patients with ocular MMP (20 of whom had no nonocular MMP), in whom the diagnosis was made on ocular findings regardless of the DIF result. Slightly more than half of the study patients (58.9%) were DIF positive, with the positive biopsy not necessarily coming from the eye. Thorough histories were obtained, and patients were examined. Examinations focused not only on the eyes but also on all anatomic sites that can be affected by MMP. The authors found no significant demographic or clinical difference between study patients with positive and negative DIF results. Furthermore, in supplemental retrospective data, they demonstrated no difference in the treatment outcome of patients who were DIF positive and DIF negative.

Another important and novel finding of this study1 was that in the 73 study patients, asymptomatic MMP disease at extraocular sites was common. More than 40% of patients with ocular and oral disease had asymptomatic disease at other sites, and more than 60% of patients with mucosal involvement of the nasopharynx were asymptomatic. For me, the implications of this are profound and will change the
way that I practice medicine. I frequently find myself as the coordinating physician for my patients with MMP. In the past, I would perform a careful review of systems and then send my patients with MMP for evaluation of symptomatic body sites to the appropriate specialist (e.g., otolaryngology and dermatology). Now, I will need to ensure that my patients are thoroughly evaluated by other subspecialists who can evaluate all possibly affected sites whether the patients are symptomatic or not.

It is interesting to note that as I was writing this editorial, Labowsky et al. published a study in the American Journal of Ophthalmology very similar to that of Ong et al., with similar conclusions. In a nutshell, Labowsky et al. found little difference in presentation, outcome, or response to therapy among patients with presumed ocular MMP who were DIF positive or DIF negative. When it rains, it pours.

I conclude with this final thought. Eminence-based consensus guidelines can be useful and potentially keep us out of legal trouble, but there is nothing like an evidence-based approach to disease management. The studies by Ong et al. and Labowsky et al. help us understand that we should not delay in using systemic immunomodulatory therapy in patients with suspected MMP simply because we have not performed a conjunctival biopsy with DIF or have obtained a DIF negative result. These studies also teach us that patients with suspected ocular MMP need to have not only a thorough review of systems but also a thorough screening of all potential sites of MMP involvement so that asymptomatic sites can be identified and followed for response to therapy. Clearly, the only way that we will continue to make clinical advances in ophthalmology is by evidence-based, rather than eminence-based, approaches to disease management, as difficult as carrying out well-designed clinical studies sometimes seems.

References


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