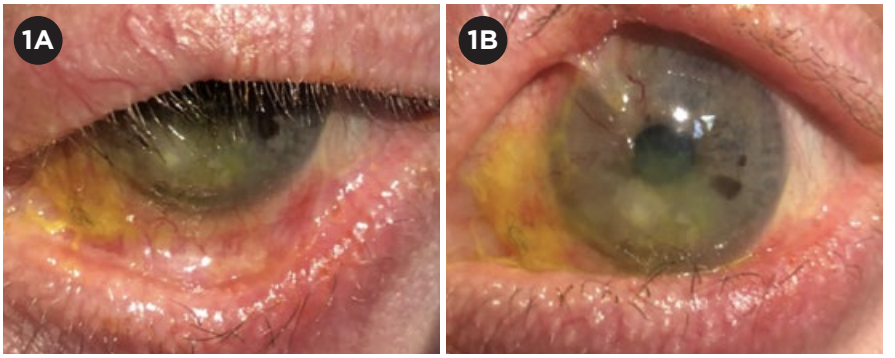
# Mucous Membrane Pemphigoid With Ocular Involvement: A Primer

Mucous membrane pemphigoid (MMP) with ocular involvement, also known as ocular cicatricial pemphigoid, is a chronic autoimmune cicatrizing conjunctivitis. MMP can have serious, vision-threatening complications as well as systemic manifestations in the mouth, oropharynx, esophagus, skin, and genitoperineal region. Thus, it is important to diagnose MMP early in its clinical course, to treat it in a timely manner, and to prevent its adverse sequelae.




***PATIENT WITH MMP.*** *Photos of patient's left eye highlight (1A) inferior fornix shortening and (1B) superior eyelid symblepharon. Other notable features are erythematous and edematous eyelids, entropion, conjunctivitis, superior forniceal shortening, symblephara, corneal opacities, and corneal vascularization.*

## Prevalence and Epidemiology

MMP with ocular involvement is a rare disease, with one study in the United Kingdom reporting an incidence of 0.8 per 1 million.[1] Patients are typically over 60 years old at the time of diagnosis. Women are more commonly affected than men, at an estimated ratio of 2:1. There is no known racial or geographic predilection. MMP is associated with other autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, and HLA-B27 spondyloarthropathies.

## Pathophysiology

Although the pathophysiology of MMP with ocular involvement is not fully known, its pathogenesis can generally be broken down into three phases. In the injury phase, circulating autoantibodies to antigens in conjunctival basement membrane (e.g., beta-4-subunit of alpha-6 beta-4 integrin of hemidesmosomes in lamina lucida) in susceptible individuals activate a complement cascade. This leads to the acute inflammation and proliferation phase, which involves proinflammatory cytokine release and immune cell recruitment and activation. Finally, in the fibrosis phase, there is fibroblast activation, remodeling of the extracellular matrix, and, ultimately, fibrosis.[2]

## Clinical Features

While oral involvement is the most common manifestation of MMP, ocular involvement is also frequent and portends a poorer prognosis.[3] Ocular involvement tends to be bilateral, asymmetric, and chronically progressive.

Early signs and symptoms of MMP with ocular involvement are nonspecific, which often delays diagnosis (Table 1). In the intermediate stages of MMP with ocular involvement, there is evidence of subconjunctival fibrosis and shortening of the inferior fornix (Fig. 1A); the latter is characteristic of cicatrizing conjunctival diseases. The pathognomonic signs of MMP with ocular involvement present later in the course of disease. The most pertinent of these is symblepharon, an adhesion between the palpebral and bulbar conjunctiva (Fig. 1B). Other late signs include flattening of the plica and keratinization of the caruncle. Corneal opacification and fusion of the upper and lower eyelids, known as ankyloblepharon, are signs of further progression.

Recurrent cycles of inflammation and fibrosis can lead to destruction of goblet cells and lacrimal gland obstruction, ultimately causing ocular surface disease, including fibrosis and tear film deficiency. Serious sight-threatening

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complications may ensue, including epithelial breakdown, corneal ulceration, microbial keratitis, corneal melt, and perforation. Other complications include trichiasis, entropion, lagophthalmos, and glaucoma.

**Staging.** The clinical progression of MMP with ocular involvement is typically characterized through two staging systems: the Foster system, which is based on increasing severity of clinical signs; and the Mondino and Brown system, based on loss of inferior fornix depth (Table 2). However, neither system has been proven to correlate with disease progression or to predict the need for immunosuppression.[4]

## Diagnosis

The differential diagnosis for cicatrizing conjunctivitis includes the following conditions:

- infections (e.g., adenovirus, *Chlamydia trachomatis, Corynebacterium diphtheriae*)
- allergic eye disease (e.g., atopic keratoconjunctivitis)
- drug-induced disorders (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
- autoimmune disorders (e.g., lichen planus, systemic lupus erythematosus, sarcoidosis scleroderma, linear IgA dermatosis, MMP with ocular involvement)
- chemical, thermal, or radiation injury
- medicamentosa
- pseudopemphigoid
- neoplasia
- ocular rosacea
- trauma

It is particularly difficult to distinguish pseudopemphigoid from the ocular manifestations of MMP, as their presentations are identical. Pseudopemphigoid is caused by long-term use of topical ophthalmic medications such as pilocarpine, timolol, and epinephrine, and it resolves with cessation of the agent.[5] Clinical information on laterality, skin and mucous membrane involvement, associated systemic diseases, medication use, and the presence of specific clinical signs can aid in distinguishing the etiology of cicatrizing conjunctivitis.

**Table 1: Signs and Symptoms of MMP With Ocular Involvement**

| Category | Nonspecific Signs/Symptoms |
|---|---|
| General | Tearing, burning, light sensitivity, foreign body sensation |
| Conjunctival | Diffuse hyperemia, papillary reaction, keratoconjunctivitis sicca |
| Corneal | Punctate epithelial erosions, exposure keratitis, epithelial defects, peripheral infiltrates, ulcers, vascularization |
| Palpebral | Blepharitis, trichiasis, entropion, lagophthalmos |

**Testing.** In addition to clinical signs, a conjunctival biopsy sent to a pathology lab capable of performing direct immunofluorescence testing is used for definitive diagnosis. Conjunctival biopsy of an involved area, typically the inferior conjunctival fornix, is recommended, but biopsies of active oral lesions may also be taken. Linear staining of the epithelial basement membrane zone is consistent with diagnosis of MMP. A biopsy yielding negative immunohistochemical results has been reported in up to 60% of cases that were clinically consistent with the disease and its evolution. Negative biopsy results can be attributed to inflammatory destruction of the subepithelial membrane or therapies used prior to biopsy.[6]

## Management

A multidisciplinary team that includes specialists in other medical fields such as rheumatology, hematology/oncology, and dermatology can be useful in managing MMP with ocular involvement, particularly its concurrent systemic symptoms. Such specialists can also contribute expertise in the use of systemic immunomodulatory agents, which are typically required to control MMP.

**Topical therapy.** Topical treatments such as artificial tears, punctal occlusion, steroids, tacrolimus, and cyclosporine A are useful adjuncts for relief of ocular surface disease symptoms. However, they have little effect in halting disease progression.

**Systemic medications.** Systemic anti-inflammatory and immunomodulatory medications are the mainstay of treatment for MMP with ocular involvement. A stepwise approach to systemic agents is taken depending on the severity of disease, presence of sight-threatening complications, and adverse effects of medications. The main categories of systemic agents are alkylating agents, antimetabolites, biologic immune modulators, interleukins, and T-cell inhibitors.

**In mild ocular disease,** dapsone is a common first-line anti-inflammatory and immunomodulatory agent. Its adverse effects, which include gastrointestinal distress, anemia, hepatotoxicity, and leukopenia, can decrease adherence to treatment. Sulfapyridine and sulfasalazine are alternate first-line agents that have a lower adverse effects profile.

**In mild to moderate ocular disease,** mycophenolate mofetil is an effective and well-tolerated first-line antimetabolite agent for patients without sight-threatening complications. Methotrexate is another antimetabolite that has been recommended as a first-line agent because of its efficacy; however, it has more significant side effects, the most serious of which include hepatic and pulmonary fibrosis.

**In moderate to severe ocular disease,** or in patients whose disease is refractory to an adequate trial of first-line agents, systemic corticosteroids with concurrent immunosuppressives are commonly used. Cyclophosphamide, an alkylating agent, typically in combination with corticosteroids, is a mainstay for patients who have severe disease with sight-threatening complications. However, it should be used judiciously because of its serious adverse effects, including pancytopenia and hepatotoxicity.

**In severe refractory ocular disease,** or in those with serious adverse reactions to prior levels of treatment, biologics

## Table 2: Two Different Staging Systems for MMP With Ocular Involvement

| Stage | Foster System: Clinical Signs | Mondino and Brown System: Forniceal Depth Loss |
|---|---|---|
| 1 | Subconjunctival scarring and fibrosis | <25% |
| 2 | Forniceal shortening | 25%-50% |
| 3 | Symblepharon formation | 50%-75% |
| 4 | Ankyloblepharon formation; corneal opacification | >75% |

such as etanercept, rituximab, and intravenous immunoglobulin are used.[6] Finally, a recent study found repository corticotropin to be a well-tolerated alternate or adjunctive treatment in severe refractory MMP with ocular involvement.[7]

**Surgical management.** It is important to note that surgery can be an inciting factor for further cycles of inflammation and cicatrization. Therefore, it is important to adequately control active inflammation with medical therapy before proceeding with surgery.

Adjunctive surgical treatments for the sequelae of MMP with ocular involvement include eyelash epilation, entropion repair, tarsorrhaphy, and amniotic membrane graft. Procedures for more severe disease include limbal stem cell transplantation, mucous membrane autografts, and cultivated oral mucosal epithelial transplantation. The latter has been shown to be effective in treatment of ocular surface disease secondary to limbal stem cell deficiency.[8]

In end-stage ocular disease, corneal transplants tend to fail due to graft vascularization. However, some evidence supports the utility of keratoprostheses, particularly the Boston keratoprosthesis type II, in select patients.[9]

## Prognosis

Progression of ocular disease has been reported in 20% to 30% of patients undergoing systemic therapy.[10] It is important to monitor progression with close interdisciplinary follow-up employing serial photos and detailed clinical documentation. Of note, a significant percentage of patients with MMP with ocular involvement demonstrate a clear and quiet conjunctiva despite clinical and histologic evidence of fibrotic progression. This makes management difficult, as injection cannot be used as a sign of disease activity.[1] It has been proposed that monitoring inflammatory markers such as myeloperoxidase could be a quantitative way to track disease activity.[11]

## Conclusion

When untreated, MMP with ocular involvement can progress to blindness. Upon diagnosis, a lifelong multidisciplinary, stepwise management plan with frequent periodic monitoring should be undertaken for symptom relief, suppression of progression, and treatment of sequelae.


1 Radford CF et al. *Eye* (Lond). 2012;26(9):1199-1208.
2 Georgoudis P et al. *Ophthalmol Ther.* 2019;8(1):5-17.
3 Foster CS. *Trans Am Ophthalmol Soc.* 1986;84:527-663.
4 Elder MJ et al. *Br J Ophthalmol.* 1996;80(4):292-296.
5 Thorne JE et al. *Ophthalmology.* 2004;111(1):45-52.
6 Fremont F et al. *Cornea.* 2019;38(11):1406-1411.
7 Sharon Y et al. *Cornea.* 2022;41(1):45-51.
8 Cabral JV et al. *Stem Cell Res Ther.* 2020;11(1):301.
9 Pujari S et al. *Cornea.* 2011;30(12):1298-1303.
10 Labowsky MT et al. *Am J Ophthalmol.* 2017;183:48-55.
11 Arafat SN et al. *Ophthalmology.* 2014;121(1):79-87.



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