# Ocular Cicatricial Pemphigoid, Keratomycosis, and Intravenous Immunoglobulin Therapy

*Barbara Iaccheri, MD,* Manolette Roque, MD,* Tito Fiore, MD,* Thekla Papadaki, MD,* Benjamin Mathew, MD,† Stefanos Baltatzis, MD,* Barry Emara, MD,‡ A. C. Tokarewicz, MD,‡ and C. Stephen Foster, MD**

**Purpose:** To report the case of a patient developing fungal keratitis in the context of uncontrolled ocular cicatricial pemphigoid (OCP), which, despite intravenous immunoglobulin (IVIg) and other immunomodulatory therapy, progressed to end-stage pemphigoid, with corneal opacification, ankyloblepharon, and xerosis. Keratoprosthesis (KPro) restored functional vision for the patient.

**Methods:** A 39-year-old man presented with uncontrolled CP and corneal ulcer in the left eye. Conjunctival biopsy diagnosed OCP; corneal scraping and biopsy diagnosed the cause of the corneal ulcer. OCP was treated with systemic steroids, immunosuppressive drugs, and IVIg. Visual rehabilitation was accomplished with Ahmed valve and a type II Dohlman KPro.

**Results:** Immunohistology of the biopsied conjunctiva showed IgG at the epithelial basement membrane zone, confirming the clinical diagnosis of OCP. Microbiologic studies of the corneal biopsy specimen were negative for *Acanthamoeba* and herpes but positive for *Aspergillus niger*. The patient's keratomycosis resolved with topical antifungal therapy. Treatment with Dapsone, intravenous-pulse steroid, oral cyclophosphamide, and intravenous immunoglobulin (IVIg) failed to control the OCP, with resultant complete conjunctivization of the cornea. Keratoprosthesis improved the patient's visual acuity from hand movements to 20/20.

**Conclusions:** Patients with uncontrolled OCP are at increased risk of corneal infection. The difficulty in diagnosing keratomycosis and the relatively rare occurrence of OCP explain the uniqueness of our reported case. OCP may progress to "end-stage" disease despite therapy. Keratoprosthesis can restore vision in selected otherwise seemingly hopeless cases.

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From the *Ocular Immunology and Uveitis Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA; †University of Ottawa Eye Institute, Ottawa, Ontario, Canada; and ‡Ivey Institute of Ophthalmology, University of Western Ontario, London, Ontario, Canada.

Reprints: C. Stephen Foster, MD, Ocular Immunology and Uveitis Service, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114 (e-mail: fosters@uveitis.org).



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Cicatricial pemphigoid (CP) is a systemic autoimmune disease. It is characterized by involvement of skin and mucous membranes. The effects of CP on the eye are chronic cicatrizing conjunctivitis, progressive conjunctival subepithelial fibrosis, with resultant fornix foreshortening, symblepharon formation, trichiasis, meibomian duct obstruction, and eventual lacrimal duct compromise with reduced tear supply to the ocular surface.[1] Secondary microbial keratitis is common, but fungal keratitis has never before been described. Topical therapy is not effective for this systemic disorder; systemic treatment is necessary. High doses of systemic steroids are effective, but the risks of long-term corticosteroid treatment are well established.[2] Studies have shown that immunosuppressive chemotherapy is effective in controlling the progression of this disease.[1,3,4] Recently IVIg therapy was proposed for patients with OCP who did not respond to conventional immunomodulatory regimens.[5]

We describe a patient who developed a corneal ulcer with subsequent *Aspergillus niger* infection that was successfully treated, but the OCP progressed to "end-stage" disease with bilateral hand movements vision. Keratoprosthesis was the only potentially viable option for vision rehabilitation because all cornea experts agree that no keratoplasty ever survives in the bone-dry keratinized environment of stage IV (end-stage) pemphigoid.

## CASE REPORT

A poorly compliant 39-year-old man with cicatricial pemphigoid (CP) affecting both eyes and oral mucosa presented in October 1999 to the University of Ottawa Eye Institute with a 3-day history of photophobia and severe pain in his left eye. The CP was previously diagnosed by conjunctival biopsy in 1997. The patient's visual acuity was 20/50 in both eyes. Slit-lamp examination disclosed thickened up-

per eyelids, severe conjunctival injection, foreshortening of superior and inferior fornices, and symblephara in both eyes. A 1.3 mm × 2.5 mm peripheral corneal ulcer with 75% stromal loss was present in the left eye (Fig. 1).

Despite admission to the hospital and treatment with fortified topical antibiotics and cycloplegia, the ulcer progressed, and the patient's visual acuity decreased to 20/200, left eye. The corneal scraping grew α-hemolytic *Streptococcus* sp. and *Staphylococcus aureus* sensitive to aminoglycosides and to cefazolin. The patient was transferred to Boston in November 1999 and was hospitalized urgently for his nonhealing and progressive corneal ulcer (left eye). A partial-thickness corneal biopsy was performed because of the suspicion of *Acanthamoeba,* herpes, or fungal keratitis superimposed on the original α-hemolytic *Streptococcus*. The specimen was processed for special stains (Gram, PAS, Giemsa, methenamine silver, calcofluor white), immunoprobing studies (fungi, *Acanthamoeba,* herpes), and cultures. A conjunctival biopsy was also performed to confirm the previous diagnosis of CP. The topical antibiotic regimen continued while awaiting the results of the laboratory studies. Immunohistology of the biopsied conjunctiva showed IgG at the epithelial basement membrane zone. Preliminary microbiologic studies were negative for herpes, *Acanthamoeba,* and fungus. But on the eighth day after corneal biopsy, *Aspergillus niger* was isolated. The patient was then treated with topical antifungal therapy (0.15% amphotericin B drops every hour) in Ottawa. The patient's keratomycosis resolved, with resultant visual acuity of 20/60 in the left eye (Fig. 2). The patient's previous treatment with Dapsone, intravenous pulse steroid, and oral cyclophosphamide had failed to control his bilateral cicatrizing conjunctivitis secondary to CP. Therefore, we suggested high-dose intravenous pulse cyclophosphamide, subcutaneous cytosine arabinoside, or IVIg therapy.

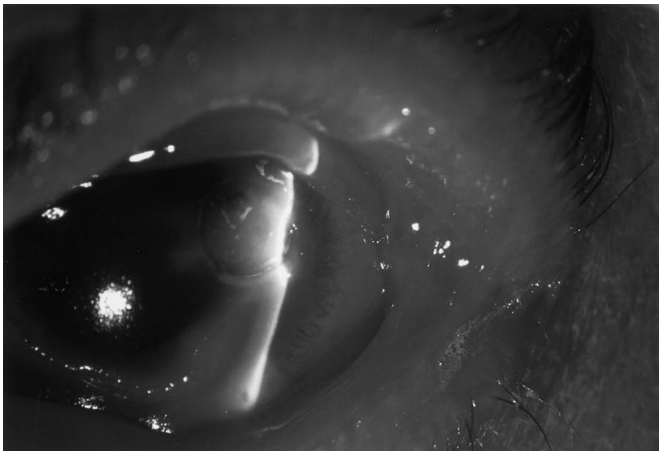

**FIGURE 1.** Slit-lamp examination of the right eye at presentation to the Massachusetts Eye and Ear Infirmary. Note the severe thickening of the eyelids, conjunctival injection, and the peripheral corneal ulcer with associated stromal loss.

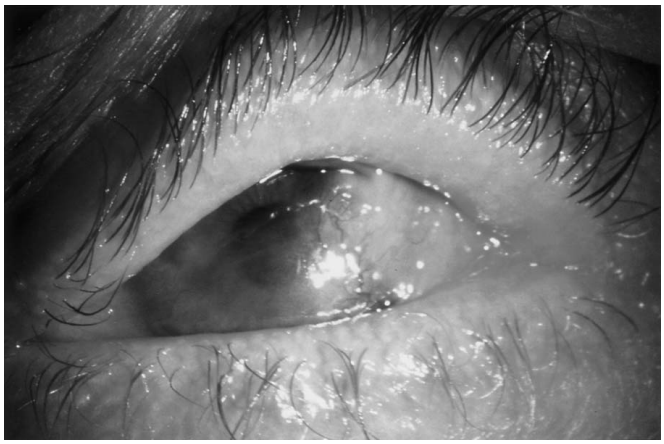

**FIGURE 2.** Slit-lamp examination of the right eye on completion of topical antifungal therapy. Scarring and neovascularization cover the area of the healed ulcer.

During the calendar year 2000 the patient was seen in multiple locations, with poor compliance for medications and follow-up visits. In January 2001, his treatment consisted of systemic prednisone (50 mg daily) and IVIg (every two weeks). This therapy continued throughout 2001, with suboptimal control of the OCP, development of keratopathy, right eye, and diminished visual acuity (20/100). The prednisone was gradually tapered and stopped by April 2001. By December 2001 the patient's keratopathy had progressed to complete keratinization and corneal neovascularization. The patient returned to Boston in May 2002 with visual acuity of hand movements in both eyes. Slit-lamp examination disclosed trichiasis, symblepharon with complete obliteration of superior and inferior fornices, and complete conjunctivization of the cornea in both eyes (Fig. 3). The anterior chamber and the fundus could

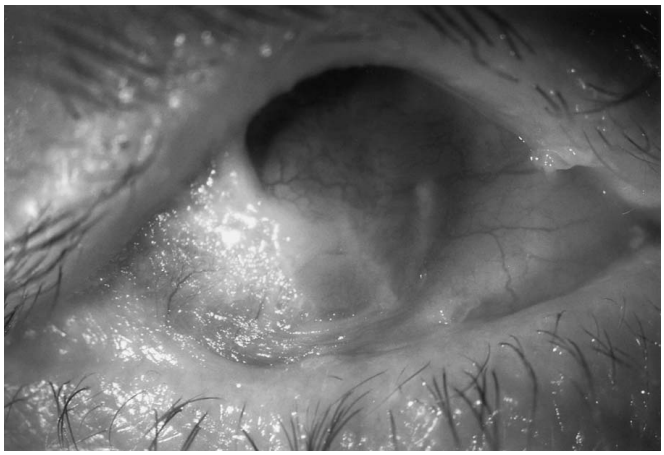

**FIGURE 3.** Despite treatment OCP has progressed from stage III to stage IV. Note the complete obliteration of the fornices and the conjunctivalization of the cornea.

not be evaluated because of the ocular surface. In an attempt at visual rehabilitation via keratoprosthesis (KPro), an Ahmed glaucoma valve shunt with an extension to the maxillary sinus was implanted in June 2002 in the right eye. IVIg twice a month was continued. A type II Dohlman KPro (through the upper eyelid) was implanted in the right eye 3 weeks later (Fig. 4). Two days later, the visual acuity was 20/20, right eye, with a correction of + 5.50 spherical lens; the tactile pressure was 5–10 mm Hg. The patient's visual acuity as of December 2003 was 20/25 (uncorrected), and the keratoprosthesis remains in situ.

## DISCUSSION

Mucous membrane pemphigoid with ocular involvement is a rare chronic autoimmune disorder that may lead to blindness. Profound keratopathy can develop secondary to trichiasis, entropion, meibomanitis, tear insufficiency, and corneal exposure. Corneal epitheliopathy, persistent epithelial defects, corneal stromal ulceration, and neovascularization may develop slowly or rapidly. Secondary microbial keratitis is common on the debilitated cornea, and eventually the cornea is completely scarred, vascularized, and keratinized.[1] We have described here a patient with uncontrolled OCP developing fungal keratitis.

Fungi do not invade the cornea easily. The pathogenesis of mycotic keratitis appears to involve agent factors, such as invasiveness and toxigenicity, and host factors, such as trauma and intrinsic defects in resistance.[6] Ocular surface defects of patients with uncontrolled OCP provide an excellent opportunity for microbial keratitis. But to the best of our knowledge, based on a computerized search of the world's medical literature (Medline), fungal keratitis in patients with OCP has never been described. This can reflect in part the difficulty in diagnosis of keratomycosis.

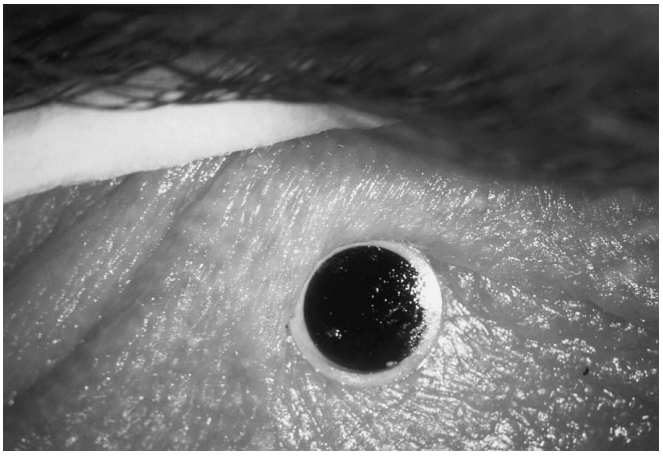

**FIGURE 4.** Left eye 2 days after implantation of a type II Dohlman keratoprosthesis.

It is impossible to diagnose keratomycosis only on the basis of the clinical features, although these have been well described.[7,8] The definitive diagnosis of keratomycosis requires confirmation of the existence of fungal elements in the corneal lesions. Various stains, immunoprobing studies, and cultures are valuable for diagnosing keratomycosis by corneal scraping. However, corneal scraping is not always diagnostic because fungus can spread deep into the corneal stroma, where the organisms are inaccessible to scrapings.

Therefore, as noted in other reports, vigorous scraping should be performed, and the diagnostic efforts not abandoned if initial scraping and cultures are negative in the presence of high clinical suspicion.[9–11] If keratomycosis is the primary clinical suspicion, but the smear and the cultures are negative after 48 to 72 hours, and the patient is not improving on the initial broad-spectrum antibacterial therapy chosen, corneal biopsy is recommended.[12] This was diagnostic in our case. The delay of the diagnosis even after corneal biopsy may itself be a negative prognostic factor in the treatment of keratomycosis. As reported in our case, 8 days was required to isolate the fungus from the biopsied corneal tissue.

Medical therapy for OCP has evolved during the past 30 years. In 1970, systemic prednisone was used to treat this systemic disease, but the doses of corticosteroid required to control OCP were unacceptable because of the side effects. Since 1974 different types of immunosuppressive drugs were introduced. Dave and Vicers[13] successfully used azathioprine for treatment of OCP in 1974. Brody and Pirozzi[3] treated a patient with cyclophosphamide in 1977. Further, randomized, masked clinical studies were also performed to test the safety and effectiveness of systemic immunomodulatory therapy.[1,2,4] These studies showed that 10% of patients with OCP progressed despite therapy.[14] A recent preliminary study showed that IVIg is an alternative therapeutic approach for OCP otherwise resistant to treatment, although the necessity of additional studies with follow-up longer than 1 year was suggested to evaluate long-term remission in patients refractory to the standard therapy.[5] We suggested treating our patient with IVIg because systemic antiinflammatory and immunosuppressive agents had been ineffective. But IVIg therapy also failed to control the disease progression. The imperfect response to IVIg treatment may have been related to the poor compliance of the patient for medications and follow-up visits.

The lack of control of inflammation in our patient led to complete conjunctivization and xerosis of the cornea. Keratoprosthesis was then employed in an attempt at visual rehabilitation of one eye. KPro is indicated in cases of corneal blindness for which conventional treatment with penetrating keratoplasty is highly unlikely to succeed. Such cases include end-stage OCP. The prognosis of KPro depends on the preoperative diagnosis. Different prognostic categories have

recently been described,[15] and OCP occupies a middle ground in terms of probable outcome. Yaghouty et al showed the outcome of patients with OCP following KPro surgery. Seventy-two percent of patients had a visual acuity of 20/200 to 20/20 after 2 years of follow-up, although the percentage decreased to 43% after 5 years from surgery.[15]

Recent advances in the surgical techniques and modifications of postoperative care have improved the prognosis after KPro surgery. But the use of KPro continues to be associated with a significant rate of both early and late complications.[16] Glaucoma is of particular concern in patients with OCP who require KPro surgery. Netland and al[17] reported that the elevation of intraocular pressure (IOP) is common in patients with KPro, and glaucoma drainage implants are effective in preventing this. Dohlman routinely implants a glaucoma valve shunt, as was done by him in this case, 3 weeks before the KPro surgery.

This report highlights the susceptibility of the distressed ocular surface affected by OCP to corneal infection, including fungal keratitis, the continuing challenge posed to the ophthalmologist by treatment-resistant OCP, and the hope provided by the current generation of the Dohlman keratoprosthesis for restoration of vision in those patients who have been blinded by this disease.

## ACKNOWLEDGMENT

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