

# Treatment of recalcitrant Acanthamoeba Keratitis with Photoactivated Chromophore for Infectious Keratitis Corneal Collagen Cross-Linking (PACK-CXL)

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## ABSTRACT

**Purpose:** To describe a case of recalcitrant Acanthamoeba Keratitis (AK) complicated by medical non-compliance and medication intolerance that was successfully treated with photoactivated chromophore for infectious keratitis corneal collagen cross-linking (PACK-CXL).

**Observations:** A 31-year-old male presented with right eye pain and redness in the setting of fresh water exposure and scleral contact lens wear. He had lack of a response to treatment with antiviral therapy for 3 months by an outside provider. Cultures were found to be positive for *Acanthamoeba* and the patient was treated with an extended course of various anti-amoebic therapies with poor compliance due to pain and toxicity. He was eventually treated with intrastromal voriconazole and Miltefosine without improvement and eventually had PACK-CXL with resolution of his infection and pain.

**Conclusion:** PACK-CXL was associated with a dramatic improvement in a case of recalcitrant *Acanthamoeba* keratitis unresponsive to both traditional and novel therapies and may be a viable alternative or adjunctive therapy for *Acanthamoeba* keratitis.

## 1. Introduction

*Acanthamoeba* keratitis (AK) was first described in 1973.<sup>1</sup> *Acanthamoeba* are free living protozoans commonly found in water and soil. These single-celled organisms exist as vulnerable freely mobile trophozoites or as characteristic double walled cysts which are extremely resistant to temperature extremes, desiccation, irradiation, antimicrobial agents, and other environmental changes.<sup>1</sup> The main risk factors for AK are contact lens wear, trauma, swimming in contact lenses, and poor contact lens hygiene. Approximately 1 case of AK occurs per 1 million contact lens users per year.<sup>2</sup> In early stages of the disease, approximately 75–90% of cases can be misdiagnosed.<sup>3</sup> Common therapeutic options include diamidines, biguanides, neomycin, and voriconazole. Although therapeutic or optical penetrating keratoplasty is an option if all other measures fail, these surgeries carry a high risk of infection recurrence or graft failure. In this case report, we describe a case of AK that was recalcitrant to topical therapy and was ultimately treated with Miltefosine and photoactivated chromophore for infectious keratitis corneal collagen cross-linking (PACK-CXL).

## 2. Case report

A 31-year-old South Asian male with a history of bilateral keratoconus presented for right eye pain and redness. The patient was diagnosed with keratoconus at the age of 17 in India. In his left eye he had undergone deep anterior lamellar keratoplasty (DALK) at age 24 and photorefractive keratectomy (PRK) one year later. In his right eye he had apical corneal scarring and had worn scleral contact lenses for the past 3 years. He denied sleeping in his contact lenses. Four months prior to presentation, he developed eye irritation and photophobia in his right eye after swimming in a lake in India while wearing contact lenses in both eyes and subsequently rinsing his eyes with tap water in an airplane bathroom. He was evaluated by an outside ophthalmologist and diagnosed with an infectious corneal ulcer in the right eye. His uncorrected distance visual acuity (UDVA) was 20/400 pinhole 20/200 in the right eye. Slit lamp examination of the right eye was notable for a central circular anterior stromal opacification consistent with an apical scar, a dendritiform epithelial lesion, and no perineuritis. Bacterial, fungal, and *Acanthamoeba* cultures and confocal microscopy were negative for *Acanthamoeba*. He was treated with valacyclovir 1 g three times a day

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and ganciclovir 0.15% gel three times a day in the right eye. The patient was followed for 3 months and was switched to famciclovir and loteprednol drops with a stable clinical course. The patient presented to Wilmer Eye Institute after 3 months of treatment. Uncorrected distance visual acuity was 20/400 pinhole 20/70 with an oval ring of sub-epithelial granular opacities, overlying epithelial elevation, and negative fluorescein staining (Fig. 1). We performed corneal epithelial debridement with instillation of 5% povidone iodine drops every 2 minutes for a total of 10 minutes and treated the patient with ofloxacin drops 0.3% every hour and Neomycin/Polymyxin/Bacitracin ointment 3.5 mg/10,000 units four times a day. *Acanthamoeba* cultures consisting of non-nutrient agar with *E. coli* overlay were positive and the patient was started on chlorhexidine 0.02% every hour, topical voriconazole 1% every hour, ofloxacin 0.3% every 2 hours, and Neomycin/Polymyxin/Bacitracin ointment 3.5 mg/10,000 units at bedtime. Five days later, polyhexamethylene biguanide (PHMB) 0.02% was added every hour. At this point in his clinical course, the patient had UDVA 20/400 pinhole 20/125 in the right eye with slit lamp exam of the right eye showing 2–3+ punctate epithelial erosions and central subepithelial haze.

The patient returned to his home state and was then lost to follow up for 2 months due to the COVID-19 pandemic. He had been instructed to follow up with a local ophthalmologist and according to records, developed perineuritis after self-discontinuing voriconazole. The patient was given Neomycin/Polymyxin B/Dexamethasone 3.5 mg/10,000 units/0.1% ophthalmic ointment and continued on PHMB 0.04%, Propamide (Brolene) 0.1%, and oral voriconazole 400 mg daily with concern for medication non-adherence. He also developed severe eye pain that did not improve with topical lubrication or oral acetaminophen and had been prescribed narcotics for this. Two months later he returned to our clinic and was found to have hand motion visual acuity in the right eye with slit lamp exam of the right cornea notable for disciform endotheliitis, keratic precipitates, and perineuritis (Fig. 2). The patient was continued on topical voriconazole 1%, PHMB 0.04%, chlorhexidine 0.02% every 2 hours and all other therapies were stopped. Two intrastromal injections of voriconazole (50 µg/0.1 mL) were administered one week apart with mild reduction in the infiltrate density, but the patient refused additional intrastromal injections due to eye pain. The patient developed a consolidating ring infiltrate and was started on oral miltefosine 50 mg three times a day. The patient reported difficulty tolerating oral voriconazole and miltefosine due to gastrointestinal upset. One month after starting miltefosine and despite topical therapy and two intrastromal injections of voriconazole, the infiltrate continued to worsen (Fig. 3). Given his worsening clinical status and intolerance to medications, PACK-CXL was performed using the Dresden protocol.<sup>4</sup> The corneal epithelium was loosened with ethanol and debrided, riboflavin 5'-phosphate in 20% dextran ophthalmic solution 0.146% (Photrex® Viscous) was instilled onto the cornea every 2 minutes for 30 minutes, and the presence of anterior chamber flare was verified via slit lamp examination. Because the corneal thickness was less than 400 µm, hypotonic Photrex® (riboflavin 5'-phosphate ophthalmic solution) 0.146% was instilled every 5 minutes until a



Fig. 1. Slit lamp photo showing sub-epithelial granular opacities and epithelial elevation.

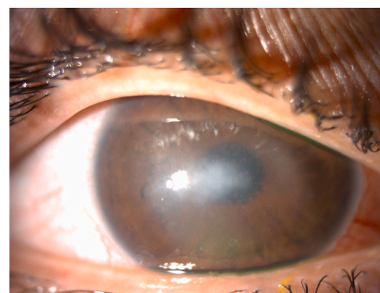


Fig. 2. Slit lamp photo showing disciform endotheliitis, keratic precipitates and perineuritis.

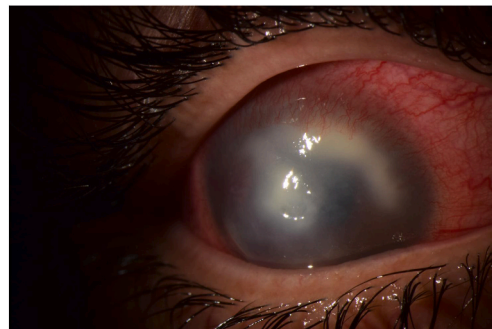


Fig. 3. Slit lamp photo showing worsening infiltrate size and density.

thickness of 400 µm was reached, and the eye was irradiated for 30 minutes at 3 mW/cm<sup>2</sup> with continuation of Photrex® Viscous every 2 minutes for 30 minutes. Afterward the patient was continued on chlorhexidine and PHMB. The patient's pain completely resolved four weeks after PACK-CXL and the infiltrate decreased in both size and density over the next ten weeks (Fig. 4). At last follow-up three months after PACK-CXL, the patient continued to be pain-free and his vision was count fingers at 2 feet, with central corneal scarring and neovascularization without signs of active infection.

### 3. Discussion

Management of *Acanthamoeba* keratitis can be difficult for a number of reasons. Because the condition can be very painful due to perineuritis, scleritis and topical medication toxicity, patients may struggle with medication adherence. The treatment course is often prolonged and can be marked by relapses.

Miltefosine is an alkylphosphocholine effective against protozoal infections such as visceral leishmaniasis, *trypanosoma cruzi*, and *Entamoeba histolytica*.<sup>5</sup> In vitro and in vivo studies have demonstrated the amoebicidal activity of Miltefosine without a negative effect on cell viability.<sup>6,7,8</sup> In 2016, oral miltefosine received orphan drug designation from the United States (U.S.) Food and Drug Administration for

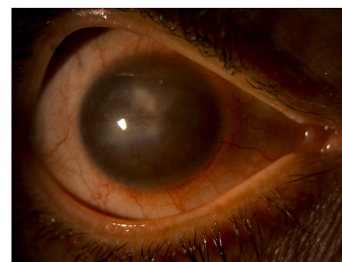


Fig. 4. Slit lamp photo showing decreased infiltrate with residual stromal scarring.

treatment of *Acanthamoeba* keratitis. Use of miltefosine is typically reserved for recalcitrant cases of AK in which patients have failed to improve after 4–6 weeks of treatment with other anti-amoebic therapies including oral voriconazole.<sup>5</sup> The recommended dosage is 50 mg bid for 30–44 kg body weight and 50 mg TID for  $\geq 45$  kg body weight, and serial liver function testing should be performed to monitor for hepatotoxicity.<sup>5</sup> Case series have shown miltefosine may be a viable adjunctive therapy for recalcitrant AK but its use may be associated with a severe inflammatory reaction in the cornea that is typically seen after 2 weeks of treatment.<sup>9</sup>

PACK-CXL is another potential treatment for recalcitrant AK, particularly in light of antimicrobial resistance, topical medication toxicity, and high risk of infection recurrence with therapeutic keratoplasty.<sup>10</sup> In vivo and in vitro experimental studies have failed to show amoebicidal or cysticidal effects of riboflavin-UVA crosslinking.<sup>11,12,13</sup> In vitro studies have also shown that riboflavin/ultraviolet (UV)-A in doses up to 10 times higher than recommended for corneal crosslinking does not enhance the cysticidal effect of either PHMB or chlorhexidine.<sup>14</sup> However, there are multiple case reports describing successful treatment of AK with PACK-CXL with improvement seen in cases where PACK-CXL was used as an adjunctive treatment or as monotherapy.<sup>12,13,15,16</sup> Beyond potential amoebicidal activity due to release of free radical molecules, it is possible that the collagen stabilizing effect of cross-linking prevents further tissue damage, makes the cornea more resistant to enzymatic digestion by collagenases, and prevents amoeba reproduction. It is possible that the epithelial debridement performed prior to cross-linking may decrease amoebic load within the corneal epithelium. In severe cases of *Acanthamoeba* keratitis with deeper stromal invasion, creation of an epithelial defect may also facilitate penetration of anti-amoebic medication into the deeper stroma where microbes reside. However, when our patient initially presented to us, a complete epithelial debridement was performed in clinic with the instillation of 5% povidone iodine drops every 2 minutes for a total of 10 minutes and anti-amoebic therapy was resumed without any improvement. As has been reported with cross-linking for keratectasia, riboflavin/UV-A may reduce corneal nerve density in the sub-basal plexus which could explain the dramatic reduction of pain in this patient.<sup>17</sup> However, the true anti-*Acanthamoeba* efficacy of riboflavin/UV-A is still debatable.

#### 4. Conclusion

This is a case of recalcitrant *Acanthamoeba* keratitis unresponsive to maximal medical therapy and complicated by loss to follow up during the COVID-19 pandemic, poor medication adherence, and intolerance of oral and topical medications due to side effects. Oral miltefosine did not appear to offer additional benefit. PACK-CXL was associated with a dramatic improvement in the infiltrate size and density as well as resolution of severe eye pain.

#### Patient consent

The patient consented to publication of the case in writing and orally.

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#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

#### Declaration of competing interest

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