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Case report

Corneal cross-linking for *Acanthamoeba* keratitis in an orthokeratology patient after swimming in contaminated water☆

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ABSTRACT

Purpose: To report a case of *Acanthamoeba* keratitis diagnosed using confocal microscopy in a patient corrected by orthokeratology and treated with corneal crosslinking (CXL) after failure to respond to medical treatment.
Methods: After diagnosis, the patient was treated with several medications until CXL was applied during one 30-min session using ultraviolet A radiation and application of riboflavin. The clinical signs of the disease observed using slit-lamp biomicroscopy and confocal microscopy were evaluated and the visual acuity was measured during the course of the infection and treatment over a period of 30 months including 12 months of medical treatment, 9 months after cross-linking and amniotic membrane transplant and 9 months after penetrating keratoplasty and cataract extraction.
Results: In this case, confocal microscopy facilitated early diagnosis of an *Acanthamoeba* infection even if other signs and symptoms might be confounding. CXL was more effective than aggressive medication against the microorganism. After CXL, the symptoms and the corneal appearance improved significantly but the ulcer did not heal completely. After amniotic membrane transplantation, the patient underwent penetrating keratoplasty (PK) with no rejection, and the visual function substantially improved over 9 months of follow-up.
Conclusions: Swimming in contaminated water might represent a risk for orthokeratology patients. CXL was effective for treating *Acanthamoeba* keratitis in an orthokeratology patient to eliminate active and cystic forms of the microorganism. Confocal microscopy was useful to confirm the diagnosis in the presence of confounding clinical signs observed during a conventional slit-lamp examination. Both CXL and confocal microscopy are essential to the outcome of PK.

1. Introduction

Acanthamoeba species (spp.), is a unicellular protozoa capable of forming amoeba cysts, are present in air, soil, and fresh water (baths, swimming pools, and stagnant water). In humans they are among the normal oral flora. They are resistant to many disinfecting agents, changes in temperature, and dry environments. The first case of an *Acanthamoeba* ocular infection was reported in 1974 [1]. Since then many cases have been reported, most of which were unilateral. Binocular cases also have been described. In non-contact lens wearers, infection traditionally has been associated with previous trauma and subsequent exposure to contaminated water or soil [2]. This infection is also commonly associated with contact lens wear, particularly disposable soft contact lenses [3,4]. *Acanthamoeba* has demonstrated to adhere to rigid, rigid gas permeable and soft contact lenses and it has been hypothesized as a potential risk for infection [5,6]. In the literature we can find *Acanthamoeba* infection associated also to rigid gas permeable lenses for orthokeratology [7] and also to hybrid lenses [8]. *Acanthamoeba* infection related with contact lens wear use to be associated with poor compliance or contact with contaminated water sources [9,10]. *Acanthamoeba* has been associated to one of the more recent contact lens related infections outbreaks in the USA [11], and continuous efforts are being done by care solutions manufacturers to increase the efficacy against this resistant microorganism [12–14].

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The pathophysiology of *Acanthamoeba* infection includes severe corneal necrosis; establishing the diagnosis is usually difficult and results in delayed administration of appropriate treatment. The outcomes can range from partial loss of corneal transparency to corneal transplant or even enucleation. The differential diagnosis includes herpes simplex, fungal keratitis, or torpid evolution keratitis [15]. Early treatment is essential for appropriate management, and confocal microscopy is a powerful tool in this regard [15].

In 2003, Wollensak et al. [16] introduced corneal cross-linking (CXL), which consists of application of ultraviolet-A (UVA) radiation onto the cornea after epithelial debridement and irrigation with isomolar riboflavin solution at 0.1% at regular intervals to cross-link the corneal stroma and strengthen the corneal tissue. CXL is effective for stabilizing keratoconus and post-refractive surgery ecstatia [17]. In vitro studies also have shown the bactericidal effect of UV radiation, which seems to be enhanced with riboflavin. The treatment is effective against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, multiresistant *P. aeruginosa*, and drug-resistant *Streptococcus pneumonia* [18]. More recently, the combined application of amphotericin B and riboflavin with UV radiation was effective against *Candida albicans*, *Fusarium* spp., and *Aspergillus fumigatus* [19].

2. Case report

A 34-year-old woman, who had been wearing corneal refractive therapy lenses for myopia correction for 3 years, presented with the complaints of tearing, burning, photophobia, and moderate pain of 4 days duration after having bathed in a swimming pool that was poorly maintained. The patient worn the current lenses for 9 months at the time of the event and was compliant with the care regime consisting of a multipurpose care solution for gas permeable lenses (Boston Simplus, Bausch & Lomb), a monthly protein removal (Progent, Menicon) and preservative free artificial tears to apply with lens insertion and immediately after waking every morning (Aquify, Ciba Vision). When she was informed that she might have an ocular infection, the patient spontaneously reported that other users of the swimming pool she used to attend had recently developed ocular infections and other adverse events potentially related to the quality of the pool water.

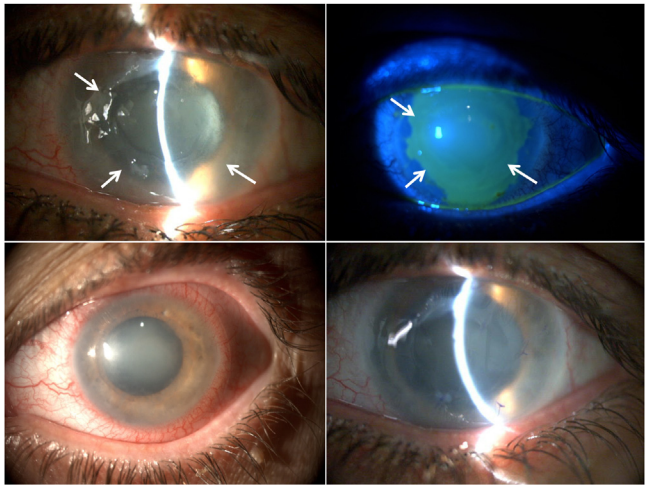

Fig. 1. Ulcer formation and follow-up after CXL treatment. Top left, the ulcer after CXL treatment; top right, the ulcer after CXL stained with sodium fluorescein; bottom left, progression of the ulcer after CXL covered with a therapeutic contact lens; bottom right, after an amniotic transplantation procedure. Images obtained at 10× (top right) and 12× magnification.

Slit-lamp examination confirmed a mild inferior superficial keratitis. Considering the suspicion of an inflammatory adverse event, a topical antibiotic (Tobrex, Tobramycin, Alcon, Spain) (1 drop, 4 times/day) was prescribed, and cessation of contact lens wear was recommended until resolution of the infection. After 5 days of treatment, the pain and photophobia increased, and an examination revealed infiltration with a dendritic fluorescein pattern compatible with a herpetic infection. Acyclovir ointment (GlaxoSmithKline, Spain) five times daily was prescribed. The lack of improvement within the next 72 h and increasing pain led us to consider the possibility of *Acanthamoeba* keratitis. Suspect of polymicrobial infection was considered and epithelial specimens were collected for culture assays of bacteria, fungi, and *Acanthamoeba*. The solution in the contact lens case also was analyzed. The diagnosis of *Acanthamoeba* was confirmed by confocal microscopy (Fig. 1) based on the presence of subepithelial cysts [20,21]. All other laboratory cultures were negative.

Treatment consisting of topical chlorhexidine (0.02%), polymyxin, neomycin, gramicidin (Ophthalmowell, Farmasierra Manufacturing SL, Madrid, Spain), and propamidine isethionate 0.1% (Brolene, Sanofi Aventis, Surrey, UK); the medications were instilled hourly during the day and every 4 h at night. Cyclopentolate 0.1% (Colircusi Ciclopleji co, Alcon, Barcelona, Spain) was prescribed every 8 h and systemic ketoconazole (Panfungol, Laboratorios Dr. Esteve SA, Barcelona) 100 mg every 12 h.

After a few weeks of treatment, perineuritis was present, and the typical ring-shaped infiltrate characteristic of *Acanthamoeba* keratitis was observed at a later stage.

After 4 months of intensive treatment with no substantial improvement, propamidine isethionate 0.1% was replaced with hexamidine 0.1% (Desomedine, Pharma Intenracional, Spain), and chlorhexidine 0.02% was replaced with polyhexamethylene biguanide (PHMB) from Moorfields Eye Hospital, London, UK.

After 1 year, the corneal conditions worsened with ulceration and recurrent uveitis, and CXL was performed. Topical anesthesia of the cornea was obtained using oxybuprocaine and tetracaine drops, alternating every 3 min for 9 min. During this time period, pilocarpine 2% eye drops were also instilled twice. After a lid speculum was inserted, a 9.0-mm diameter corneal abrasion was created. Ribofl avin 0.1% drops were instilled every 3 min for 30 min. The ribofl avin drops were prepared immediately before treatment by mixing aqueous ribofl avin 0.5% solution with dextran T-500 20% solution. UVA radiation was applied at a rate of 3 mW/cm^2 with a CMB XLINKER (Ophthaltec, Barcelona, Spain), and riboflavin solution was applied every 5 min for 30 min. During irradiation, the cornea was moistened every 5 min with ribofl avin 0.1% drops and oxybuprocaine drops every 10 min.

After CXL, the corneal appearance improved significantly and the symptoms resolved. The signs of inflammation also resolved almost immediately, although *Acanthamoeba* treatment was interrupted only 3 months later. Confocal microscopy at this stage showed no cysts in the area of analysis.

Six months after CXL, amniotic membrane implantation was performed to resolve the deficient corneal re-epithelization. Fig. 2 shows the ocular condition at different time points after CXL.

After this stage, corneal melting developed about 8 months after CXL and 20 months after first onset of the infection with resultant glaucoma and a triple procedure that included glaucoma and cataract surgeries and penetrating keratoplasty (PK) was scheduled. The surgeries were performed when no *Acanthamoeba* cysts were seen on confocal microscopy. The triple procedure was uneventful and the patient has had no signs of rejection of the implant or other complications. Fig. 3 shows the current appearance of the eye with recovery of the best-corrected visual acuity to 20/60.