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CASE REPORT

Intrastromal injection of azithromycin and amikacin for recalcitrant non-tuberculous mycobacterial keratitis

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Antibiotics, atypical mycobacteria, infectious keratitis, intrastromal injection, non-tuberculous mycobacteria

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Abstract

This study aims to describe intrastromal injection of antibiotics in the management of non-tuberculous mycobacterial (NTM) keratitis. NTM can be a devastating infectious keratitis which does not resolve with only topical treatment. A case report of a 48-year-old male with sight-threatening, culture-positive NTM after corneal trauma who had been treated unsuccessfully with topical antibiotics. The patient underwent injections of intrastromal antibiotics. Using a 30G needle, amikacin 5% and azithromycin 1% were injected to the corneal stroma from the corneal limbus and deposited around the corneal infiltrate in the deep stroma. This procedure was repeated a month later. Progression of the infiltrate was arrested while sparing the visual axis. The patient's final corrected visual acuity was maintained at 0.7 and there was no need for therapeutic keratoplasty. Intrastromal bleeding occurred after the injections but resolved without sequelae.
Clinical Significance: Patients with confirmed NTM resistant to topical treatments can benefit from the early injection of intrastromal antibiotics. This may arrest progression and preserve vision while avoiding the need for a corneal transplantation.

Introduction

Non-tuberculous mycobacteria (NTM) keratitis though rare is increasing in incidence.[1,2] Diagnosis is often delayed because of the low level of suspicion and a long latency period before presentation. Atypical mycobacteria are ever more resistant to medical treatments and require periods of treatment. Corneal transplantation is frequently needed to control the infection and visual outcomes are poor in cases of *Mycobacterium abscessus*.[3,4] We report a case of NTM keratitis (NTMK) after corneal trauma successfully managed with intrastromal injection of antibiotics, preventing further vision loss and, possibly, keratoplasty in future.

Case Report

A 48-year-old healthy man presented to our clinic with a right eye (RE) lesion evolving for 5 months following trauma by a metallic foreign body. He was treated in another center for suspected herpetic keratitis and bilateral central serous chorioretinopathy (central serous retinopathy [CSR]), the latter considered incidental. The patient had no history of steroid use before the development of CSR and was treated with subconjunctival injections of corticosteroids in each eye. He presented with RE blurred vision, redness, mild pain and sensation of irritation. Visual acuity (VA) was 0.5 in the RE and 1.0 in the left eye (LE). The RE was injected with a homogenous corneal infiltrate in the periphery measuring 2 mm × 3 mm. Underlying stroma was hazy and thin with a solitary central keratic precipitate, limbal vascularization, and epithelial surface irregularities [Figure 1]. The rest of the examination in both eyes was unremarkable except for retinal lesions with subretinal fluid (SRF) corresponding to bilateral CSR [Figure 2].

Our patient was hospitalized, corneal scrapings for microbiology were collected and empirical treatment with fortified cefazolin 5% drops and fortified gentamycin 1.4% drops every hour was initiated. Microscopy, staining, and cultures for bacteria, *Acanthamoeba*, and fungi came back negative as well as polymerase chain reaction tests for *Acanthamoeba*, 26S-28SrDNA and ITSrDNA for fungi. After 6 days of treatment with no improvement, new corneal scrapings were sent for analysis and 4 days later, *M. abscessus* grew from the second set of corneal samples. Sensitivity tests showed sensitivity to

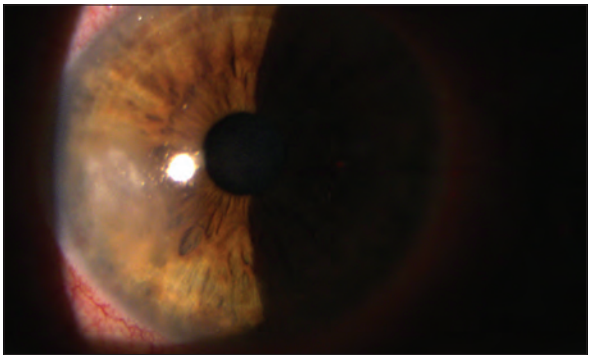

Figure 1: Corneal infiltrate

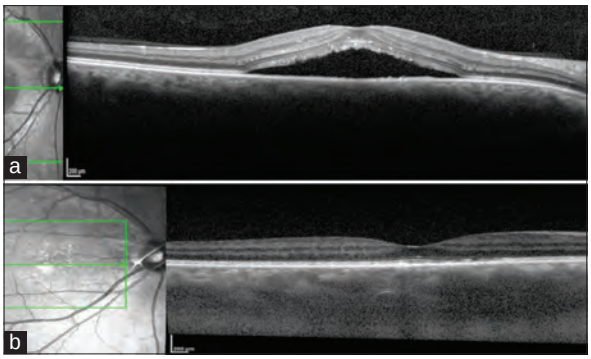

Figure 2: (a) Subretinal fluid corresponding to central serous retinopathy. (b) Complete resolution of subretinal fluid

clarithromycin (minimal inhibition concentration [MIC] 2 mg/L), amikacin (MIC 128 mg/L), ciprofloxacin (MIC >32 mg/L), and doxycycline (>256 mg/L). Clarithromycin was the drug of choice,[3] but unavailable in our setting. We changed the treatment to oral doxycycline 100 mg daily combined to amikacin 5% and ciprofloxacin 0.3% drops every hour. These were gradually tapered down. The patient also received spironolactone 50 mg daily for 6 weeks for CSR.

The follow-up period was marked by progression of corneal vascularization toward the corneal center and satellite corneal infiltration. All corneal samples from corneal debridement done to reduce the infectious load came back positive for *M. abscessus*. On sensitivity tests, clarithromycin stayed the drug of choice with MIC of 2 mg/L and 4 mg/L at initial cultures and 3 months later, respectively. Amikacin had an MIC of 128 mg/L initially and 4 mg/L on sensitivity tests at 3 months. Doxycycline had an MIC at >256 mg/L for all the duration of its use [Table 1]. After 10 weeks of treatment with ciprofloxacin 0.3% and amikacin 5% drops, progression of the infection led us to change to topical moxifloxacin 0.5%, amikacin 5%, and azithromycin 1% 8 times daily. Occurrence of lid edema and toxic epitheliopathy after prolonged treatment with this regimen guided maintenance dosages at 8 times daily, not hourly.

The lesion progressed despite intensive combination therapy, so we opted for intrastromal injection of antibiotics. In a sterile setting using a 30-gauge needle, 0.1 ml of amikacin 5% and 0.1 ml of azithromycin 1% were injected around the corneal lesions at about two-thirds stromal depth. A limbal approach was used with the needle guided bevel up toward the corneal center and antibiotics were delivered with gentle pushes on the syringe plunger creating corneal edema that extended into the lesions [Figure 3]. This procedure was repeated twice, 1 month apart. Both sessions were followed by incidents of intrastromal bleeding that gradually cleared. The infiltrate slowly resolved and an arrest in progression of corneal vascularization was noticed after 7 months of follow-up [Figure 4]. All topical antibiotics were tapered down and discontinued. At last follow-up 7 months after, the patient had a VA of 0.7, a mild corneal opacity that looked scarred, with regressed vascularization in the temporal cornea, all sparing the visual axis. There was also complete resolution of the CSR [Figure 2b].

Discussion

NTM also known as atypical mycobacteria are increasingly causing infectious keratitis. According to the Runyon classification, Group IV mycobacteria also known as the "rapid growers" are the most common cause of ocular infections, with *Mycobacterium fortuitum* group and *Mycobacterium chelonae-abscessus* group responsible for up to 83.5% of keratitis cases caused by NTM.[1] Risk factors include ocular trauma, refractive surgery, and systemic or local immunosuppression with corticosteroids. An important risk factor for the development of NTMK is corneal trauma which breaches the intact corneal epithelium resulting in a dysfunctional innate immune system.[3] We think predisposing factors for our patient included trauma and local immunosuppression from the subconjunctival corticosteroids he had received as treatment for CSR.

The onset of NTMK is characterized by a long period of latency of up to 10 weeks. Symptoms include variable degrees of ocular pain, decreased vision, and photophobia. A dense solitary or multiple corneal stromal infiltrates can be found. Satellite spread is a hallmark of progression and present with infiltrates that can result in the characteristic "cracked windshield" appearance of a crystalline keratopathy.[1,2] Our patient had a solitary infiltrate progressing toward the visual axis with satellite infiltrates, vascularization, and edema. NTMK mimic several other forms of infectious keratitis including herpetic, fungal, and *Acanthamoeba* keratitis and a definitive diagnosis through laboratory confirmation is often needed to initiate treatment. This was the case of our patient who had been previously treated as a case of herpetic keratitis. Laboratory diagnosis of NTM is challenging, often delaying diagnosis. NTM are Gram variable but stain better with acid fast stains like Ziehl–Neelsen. Lowenstein-Jensen media and MacConkey agar are recommended culture media. Microscopy is of, however, low yield (22–78% sensitivity) when compared to cultures.[2,5]

M. abscessus is a subgroup of *M. chelonae/abscessus* group and is the most virulent, rapid growing, and antibiotic resistant

Table 1: Treatment timeline and minimal inhibitory concentrations of drugs used

Drug / Months	1	2	3	4	5	6	7	8	9
Amikacin	MIC 128 mg/L				MIC 4 mg/L				
Azithromycin									
Ciprofloxacin	MIC >32 mg/L								
Doxycycline	MIC >256 mg/L								
Moxifloxacin									

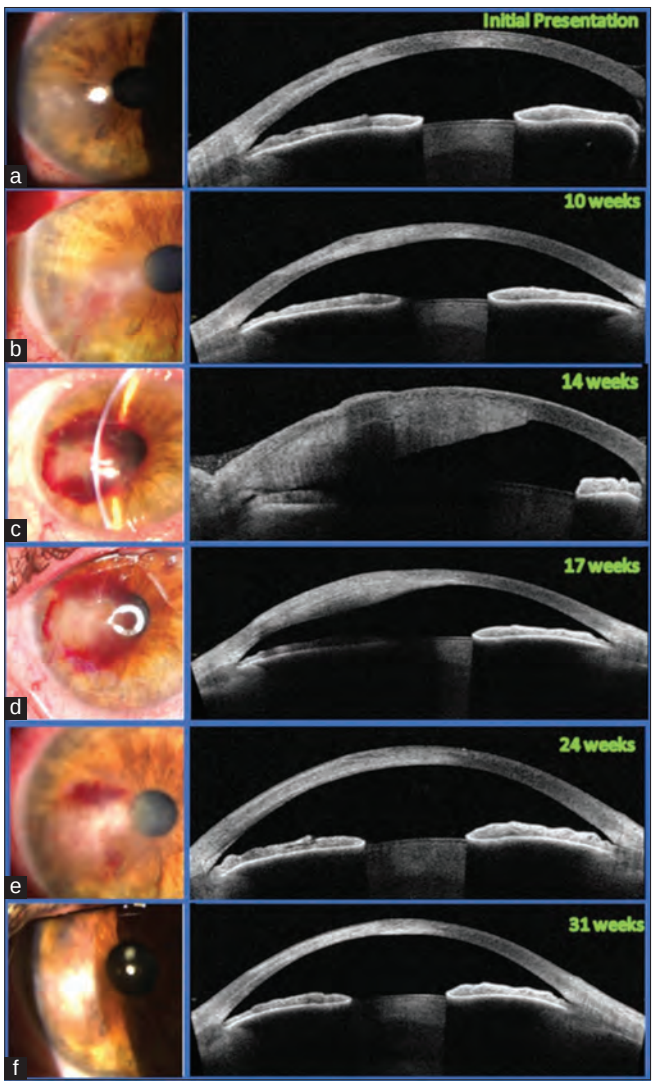

Figure 3: Intrastromal injection. (a) Limbal approach with a 30G needle. (b) Bevel up, delivery of intrastromal antibiotics around infiltrate. (c) Stromal edema created at end of procedure

of all the NTM. Several studies show that aminoglycosides, macrolides, and fluoroquinolones are active against NTM *in vitro*. While *in vitro* activity does not always reflect *in vivo* efficacy, MIC levels are used to guide therapeutic decisions.[2,3,6] Combination therapy is often used to overcome the problem of resistance linked to monotherapy in these patients that need

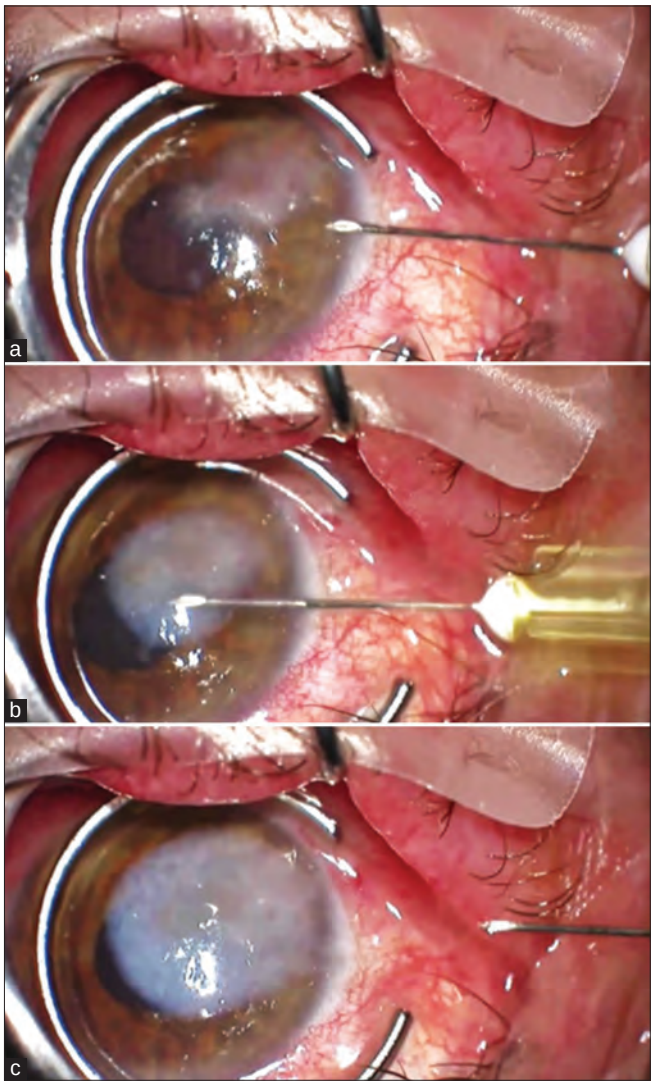

Figure 4: Progression and resolution of corneal infiltrate after intrastromal injections. (a) Slit-lamp and anterior segment -optical coherence tomography images of peripheral corneal infiltrate on initial presentation. (b) Progression of corneal infiltrate and vascularization. (c) Intrastromal bleeding after intrastromal injection of antibiotics. (d) Complete resolution of bleeding, clear visual axis, mild scarring, and resolved infiltration

long-term antibiotherapy. John *et al*. reported that 50% and 21% of patients with NTM infectious keratitis after LASIK need treatment with a combination of three and four antibiotic medications, respectively.[3] The initial treatment regimen of our patient with topical amikacin and ciprofloxacin combined to oral doxycycline was guided by sensitivity tests and MIC levels. Clarithromycin had the lowest MIC at 2 mg/L and would have been the drug of choice but is commercially unavailable in our setting. The lack of improvement after 10 weeks of treatment prompted us to reevaluate our initial treatment regimen. Azithromycin has been used in combination therapy to treat keratitis caused by rapidly growing NTM with good clinical outcomes.[7] It has comparable activity to clarithromycin *in vitro* with a similar resistance profile.[8] In a study on New Zealand, white rabbits inoculated with NTM, Yao *et al*.[9] showed that azithromycin was effective in arresting the disease, while another study by Reddy *et al*.[10] showed that *in vitro*, clarithromycin, and azithromycin had similar activity against NTM with MIC levels lower than that of amikacin. Azithromycin became our obvious macrolide of choice since its topical form could be compounded by our hospital pharmacy. We decided to change the topical fluoroquinolone to moxifloxacin even without sensitivity tests because it is reported to have a superior effect *in vivo* against *M. abscessus* compared to ciprofloxacin.[11]

Combination therapy though effective, often results in topical toxicity and ocular surface irritation. These together with prolonged treatments decrease patient compliance. Medical treatments are often inadequate and the majority of patients

will need a surgical procedure (68–85%) at some point in the course of the infection.[1,12] Our patient had an intact epithelium at presentation probably preventing sufficient antibiotic concentrations from reaching the deep-seated infected area [Figure 4]. The deep and peripheral location of infection in our case would have made infection site amputation or emergency penetrating keratoplasty unsuccessful in eradicating the infection, without causing severe ocular damage. We considered intrastromal injections a less invasive treatment, and a safe mode of antibiotics delivery to the deep-seated lesions, avoiding the deleterious effects of a hot keratoplasty in a peripheral location. There are only two of such reports on intrastromal injection of antibacterial agents in humans. Khan *et al.*[12] used intrastromal cefuroxime for the treatment of an infectious crystalline keratopathy caused by coinfection with *Streptococcus mitis* and *Streptococcus parasanguis*, and Liang and Lee[13] reported on the use of intrastromal tobramycin in the management of a recalcitrant keratitis caused by a coagulase-negative staphylococcus.

Our patient had a unique presentation of *M. abscessus* keratitis associated with CSR which we think was incidental and unrelated to the keratitis. Our patient has a type-A personality and was very anxious over the thought of losing vision in an eye throughout the treatment period. On last follow-up, there was a complete resolution of the SRF in both eyes. We think that the CSR resolved spontaneously and was not linked to any of the treatments (subconjunctival corticosteroids and spironolactone) received by the patient given the time elapse between the treatments and SRF resolution; 11 months for subconjunctival corticosteroid injections and 5.5 months for spironolactone. In literature, we did not find any reports on CSR occurring alongside microbial keratitis.

Conclusion and Clinical Significance

To the best of our knowledge, this is the first description of intrastromal antibiotics for the treatment of NTMK. We hypothesize that enhanced drug delivery through intrastromal injections arrested the infection and preserved the patient's vision. Although few studies are available on the pharmacokinetics and pharmacodynamics of intrastromal delivered antibiotics, we propose intrastromal injections of antibiotics as an adjuvant treatment in deep-seated infections like those often seen in NTMK.

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