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Voriconazole in the successful management of a case of Acanthamoeba-Cladosporium keratitis

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ABSTRACT

Purpose: Acanthamoeba and fungal infections can be recalcitrant to therapy - more so when the deeper layers of the corneas are involved. We describe the diagnosis and successful management strategies employed in a case of deep keratitis due to co-infection with Acanthamoeba and Cladosporium sp.

Observations: Once the diagnosis of co-infection with both Acanthamoeba and Cladosporium was made, treatment was initiated with a combination of PHMB, chlorhexidine, natamycin, and voriconazole; to which the response was favorable. Signs of relapse with spread of the infection to the deeper plane and the presence of endothelial exudates were noted at 5 weeks. This was attributed to poor compliance. Though the response to re-initiation of therapy under direct supervision was once again favorable; it was only after the introduction of intrastromal voriconazole repeated at timely intervals that rapid and complete resolution was obtained.

Conclusions: Severe keratitis due to fungi or Acanthamoeba very often requires surgical intervention. Complete resolution with medical therapy was obtained only after the introduction of intrastromal voriconazole; thereby avoiding a therapeutic keratoplasty. The addition of voriconzole both topically and particularly intrastromally facilitated faster resolution as well as restricted the duration of therapy with more toxic drugs such as phmb and chlorhexidine.

1. Introduction

The management of fungal keratitis can be challenging, with size and depth of the lesion being important predictors of successful medical management. Superficial keratomycosis responds fairly well (albeit with some exceptions) to topical antifungal therapy; natamycin 5% suspension being the drug of choice for most filamentous fungal keratitis. This approach works in most circumstances considering that Fusarium species is the most commonly identified fungus in South India.[1] Treatment of deep fungal keratitis however remains challenging, irrespective of the causative organism. The uses of broad spectrum antifungal agents such as voriconazole, as well as alternate routes of administration such as intracorneal injections, have been used to treat deep or resistant fungal keratitis.[2,3,4]

Cladosporium spp are rare causes of fungal keratitis. They are Ascomycota fungi that are commonly found on plants. Indoors, they can be found on moist surfaces. Cladosporium is a fairly uncommon cause of keratitis with the incidence being variably reported from 1.3% to 3%.[5,6] Guidelines for the management of Cladosporium keratitis are scarce. Although this fungus is known to be refractory to topical natamycin and systemic antifungals, it has been reported that voriconazole could be effective in the treatment of Cladosporium keratitis.[7]

Acanthamoeba keratitis is also a difficult to treat infection, especially when the deeper layers of the cornea are involved. Although Acanthamoeba and fungi share similar environments, and are widely distributed in nature, coexistent Acanthamoeba and fungal infections in non-contact lens users are considered scarce, with documentation of a case each by Gupta and Lin, respectively.[8,9] However, it is increasingly evident that co-infections with Acanthamoeba and fungi can occur, and more importantly, can also present with features traditionally considered exclusive to bacterial, fungal, or Acanthamoeba keratitis.[10]

This case report discusses the successful management of an advanced case of combined Cladosporium and Acanthamoeba keratitis. To the best of our knowledge, only 2 cases of successful medical therapy of co-

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infection involving Acanthamoeba and fungi in non-contact lens users have been described.[8,9]

1.1. Case report

A 36-year old male in apparently good health was seen 3 weeks after exposure to cement particles in the right eye. He reported vigorous washing of the eye with tap water and subsequent consultation with an ophthalmologist who treated him for suspected viral keratitis with a combination of topical ganciclovir eye ointment and topical steroids. Since there was no symptomatic relief over a period of 8 days, the patient discontinued his medications; he then presented to us 2 weeks later with complaints of increasing redness, pain and defective vision in his right eye.

On examination, his best corrected visual acuity in the right eye was 6/60 and 6/6 in the left eye. Slit-lamp examination of the right eye was significant for circumcorneal congestion, and the presence of a central corneal ring infiltrate 5mm × 7.6mm in diameter with an overlying epithelial defect 8.3mm × 8mm in size. The infiltrate extended up to the mid-stroma and was associated with deep stromal edema and Descemet's membrane folds. The anterior chamber was devoid of any hypopyon, had 2+ cells, and was of normal depth. The lens was clear. Digitally, the intra-ocular pressure was normal in the right eye. Slit-lamp evaluation of the left eye was within normal limits. Given the combination of a ring infiltrate with stromal edema, the differential diagnosis included Acanthamoeba keratitis, viral keratitis, and co-infection with Acanthamoeba and fungus.[10]

Confocal microscopy using Heidelberg Retinal Tomograph 3 (with Rostock Cornea Module) was carried out - which showed multiple cysts. The corneal infiltrate was then scraped and inoculated onto blood agar, non-nutrient agar, and potato dextrose agar. Additional scrapings were taken for smears for direct microscopy. The Gram stain as well as the potassium hydroxide mount were positive for hyphae. Accordingly, therapy was initiated with polyhexamethylene biguanide (PHMB) 0.04%, chlorhexidine 0.04%, and natamycin 5% eye drops on an hourly basis, along with homatropine hydrobromide eye drops twice daily. Given the presence of two organisms as well as the prior history of treatment with steroids, he was advised to undergo treatment as an in-patient. Four days later, Acanthamoeba trophozoites were identified on the non-nutrient agar. A day later fungal colonies were detected on the agar plates; subsequently identified as Cladosporium species. Topical voriconazole drops (Vozole 1%, Aurolab, Madurai, India) was added to the treatment regimen once cultures were positive for fungi. The initial response to the therapy was good with peripheral scarring and resolution of the epithelial defect. The patient was discharged with recommendations to continue the same medications, i.e. hourly PHMB, chlorhexidine, natamycin, and voriconazole. When seen on follow-up over the next few weeks the infiltrate continued to reduce in size. However, when reviewed 5 weeks from the onset of treatment, and due to poor compliance (the patient had discontinued his hourly drops since he claimed to have felt much better), his vision had deteriorated to hand movements and his condition had worsened with involvement of the deep stroma and recurrence of the epithelial defect. The peripheral region remained scarred, and pigmented keratic precipitates were noted on the back of cornea. Endothelial exudates were also noted. The patient was re-admitted and therapy continued with hourly PHMB (0.04%), natamycin 5%, and voriconazole 1% eye drops. Chlorhexidine was withheld due to concerns regarding toxicity. Oral ketoconazole 200mg twice-a-day was added.

Approximately 10 days after re-admission, there was an anterior-to-deep stromal infiltrate measuring 4.4mm × 3.9mm with an overlying epithelial defect; peripheral scarring was also noted. Given the recalcitrance of the central lesion to therapy, intrastromal voriconazole 50 μg/0.1ml. (Vozole PF, Aurolab, Madurai, India) was administered under topical anesthesia. There was significant improvement in a week's time with the infiltrate reducing to 2.8mm X X 3.3mm. An increase in intraocular pressure necessitated the addition of topical anti-glaucoma medication. He was once again discharged. The second intrastromal injection was repeated 10 days later with subsequent injections spaced approximately a week apart. Approximately 50 days after presentation, medications were tapered to 8 times a day. When the 5th injection was administered, the surface had healed with a small residual infiltrate in the anterior stroma. All-in-all he received 6 injections of intrastromal voriconazole. Rapid taper of topical medications was instituted after the last dose of intrastromal voriconazole (13weeks after starting therapy). Natamycin was stopped a month later, followed by PHMB 2 months later. Topical voriconazole eye drops was discontinued after another month. Uncorrected visual acuity had improved to 6/36 (Fig. 1a, b, 1c).

2. Discussion

Ring infiltrates and deep stromal infiltration with endothelial exudates usually indicate advanced disease, with most cases requiring keratoplasty. Except for the 3-week delay in diagnosis prior to his presentation, the patient was treated with a combination of PHMB, chlorhexidine, and natamycin, with the subsequent addition of voriconazole early in the course of the disease. Two potentially toxic anti-amoebic drugs were administered concurrently because of the reported combined greater efficacy in eradicating cysts[11] and also because of the presence of a ring infiltrate which indicates advanced disease. The 2 antifungals natamycin and voriconazole were administered concurrently because of the paucity of literature on the management of Cladosporium keratitis, and the initial favorable response to treatment.

Cheng et al. and Marcomini et al. have discussed the favorable impact of topical and oral voriconazole in Cladosporium keratitis.[7,12] We did not administer systemic voriconazole but after significant resolution of the infiltrate in the periphery (at 6 weeks) the central almost-full-thickness infiltrate persisted. Several studies had shown successful resolution via the use of voriconazole as an adjunct (topically or intrastromally) or as a stand-alone intrastromal.[3,4,14–18] We decided to attempt the same, and the infiltrate responded swiftly to the administration of intrastromal voriconazole. The rapid response facilitated the taper and subsequent withdrawal of PHMB with only voriconazole being continued as maintenance therapy.

Natamycin has poor penetration and its bioavailablity is only about 2% after topical administration.[13] The formation of a biofilm is considered to be the cause of resistance to natamycin. Voriconazole having broad spectrum activity and a higher intraocular penetration is a good choice for refractory fungal keratitis.[12,13] Intracorneal injection of the antifungal agent provides high concentration of the drug at the target site and affords adequate fungicidal effect in deep mycosis.[2] A comparative study done between intrastromal and topical voriconazole by Solaiman et al. has shown intrastromal injections to be more effective than topical in resistant fungal keratitis, and more so in deep infiltrations.[3] Voriconazole has a dose-dependent action. It is fungistatic at low concentration and fungicidal at higher concentrations.[13] Kalaiselvi and coworkers, in a case series of 25 patients with mycotic keratitis resistant to topical antifungals (natamycin and voriconazole), reported a healing rate of 72% with intrastromal voriconazole.[14]

The evidence for or against the efficacy of voriconazole is conflicting, with the initial study by Sharma et al. finding no incremental benefit in treating patients with intrastromal voriconazole. The subsequent randomized trial by Narayana et al. (the MALIN study) validated Sharma's observations and also noted an unacceptably high number of perforations in patients treated with intrastromal voriconazole.[19,20] This was, however, not our experience, and our patient received 6 injections in total.

Chlorhexidine and PHMB are usually administered in combination with the diamidines in the treatment of Acanthamoeba keratitis; one recent review suggests that PHMB as monotherapy is perhaps the best approach to the treatment of Acanthamoeba keratitis.[21] Cabello-Vílchez et al. in their study showed that voriconazole and chlorhexidine are

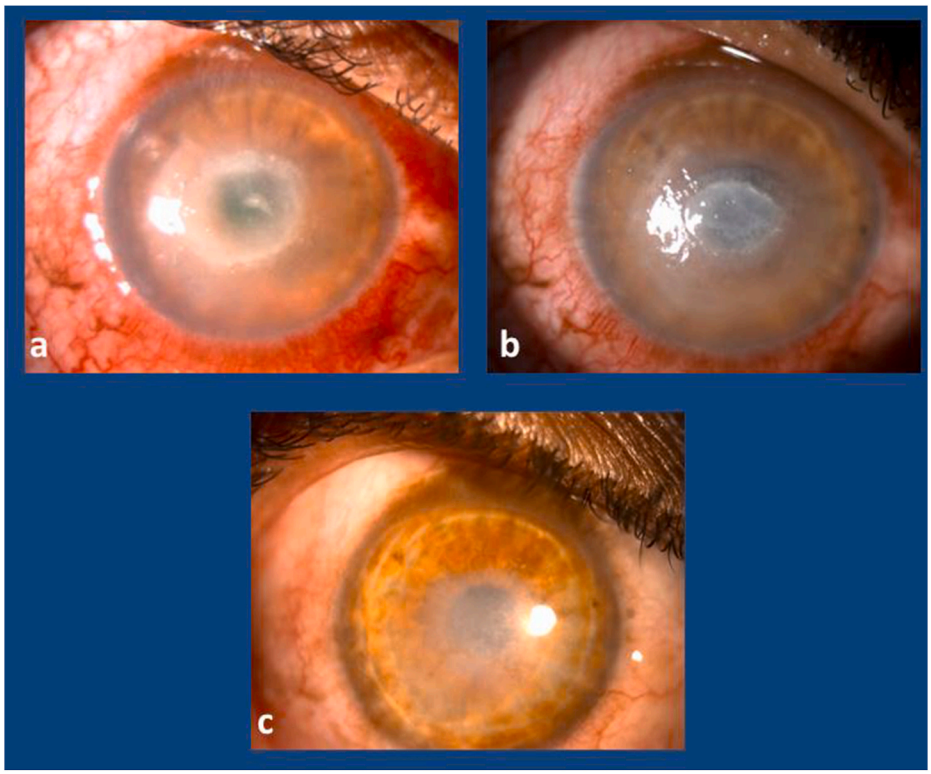

Fig. 1. a. Prior to initiation of i/s voriconazole (@ 3 weeks after presentation). b. 3 weeks after initiation of i/s voriconazole. c. Complete resolution (@ 5 months after presentation). Note: i/s = intrastromal.

active against Acanthamoeba strains which produce high levels of serine proteases.[22] However, we had discontinued chlorhexidine approximately 6 weeks after initiating therapy. Though the initial response had been satisfactory at the time of discontinuing the chlorhexidine, the infiltrate had worsened. In their case report Tu et al. has suggested that while a small proportion of chronic acanthamoebal stromal keratitis may be immune rather than infectious, the resolution of inflammation in their patients with oral voriconazole treatment strongly suggests continued infection.[23] Our patient too exhibited a persistent deep stromal infiltrate, though the initial resolution was achieved in the superficial and peripheral regions. Once voriconazole was introduced to the deeper plane and possibly at higher concentration by means of intrastromal injection, complete resolution was achieved. The resolution achieved was further maintained and consolidated by continuation of topical voriconazole even after discontinuation of topical anti-acanthamoebal therapy. Intrastromal voriconazole used judiciously probably acted as a double edged sword in resolving both the fungal and the Acanthmoeba components of this infection.

A recent synergy study by Talbott et al. on the combined MICs of various antiamoebic agents, showed that voriconazole when administered simultaneously with chlorhexidine renders the latter ineffective in treating Acanthamoeba infections.[24] It is however possible that like in the case of the antifungals, the in vitro efficacy of chlorhexidine may be at variance with the in vivo effect. This needs to be explored further. However, for our patient, since chlorhexidine was discontinued early in the course of treatment, it may have facilitated the action of voriconazole on both the organisms.

3. Conclusion

Since co-infections with Acanthamoeba and fungal species are more common than previously realized, a high element of suspicion should be maintained in evaluation of keratitis with ring infiltrates and those with yellow feathery edges. Considering that both organisms can have multiple strains as well as species involved, an initial rapid resolution to curtail the spread should be attempted with combined medication both broad spectrum anti-fungal and amoebicidal medications. Co-infections being more likely to be recalcitrant, a tailor-made approach of medication is required after initial resolution to balance possible drug toxicity and resistance to treatment. Oral as well as intracorneal injections provide a more direct approach to deeper tissues and help to reduce the usage of topical medications which are toxic to the ocular surface. An integrated and responsive algorithmic approach can sustain and achieve resolution in these cases.

We believe that the administration of voriconazole probably hastened the resolution of both the Acanthamoeba as well as the fungal keratitis. It also allowed a very rapid taper of PHMB - and maintenance therapy was by voriconazole only - thereby avoiding potential toxicity from the PHMB. It is also possible that the withdrawal of chlorhexidine did not have a deleterious effect on the Acanthamoeba component because of the simultaneous administration of voriconazole. As more such cases are diagnosed and treated, a clearer picture would emerge on appropriate therapeutic approaches to such co-infections.

Importance

1. Coinfection of Acanthamoeba with a rare fungus such as Cladosporium for which treatment guidelines are not yet established.
2. Successful resolution in a ring infiltrate due to a coinfection; ring infiltrates being indicative of advanced Acanthamoeba keratitis.
3. The potential of voriconazole for treating both Acanthamoeba and fungal keratitis.

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Authorship

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Declaration of competing interest

The Authors declare that they have No Conflict of Interest, or Financial Stake in this Study.

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