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. 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.

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%. 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.

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. 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.

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-
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 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 of a ring infiltrate with stromal edema, the differential diagnosis pyon, had 2+ cells, and was of normal depth. The lens was clear. The corneal epithelium was intact and the anterior chamber was clear. The lens was clear.

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 intrastral voriconazole. The subsequent randomized trial by Narayana et al. (the MALIN study) validated Sharma’s observations and also noted an unexpectedly high number of perforations in patients treated with intrastromal voriconazole. 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 unexpectedly high number of perforations in patients treated with intrastromal voriconazole. 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 unexpectedly high number of perforations in patients treated with intrastromal voriconazole.
active against Acanthamoeba strains which produce high levels of serine proteases. 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. 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 Acanthamoeba 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. 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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