CASE REPORT

Importance of clinical signs leading to the diagnosis in a case of microbiological smear negative ocular microsporidiosis

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SUMMARY

A 28-year-old patient presented to us with multifocal coarse raised epithelial lesions in the left eye associated with pain watering redness and blurred vision with a visual acuity of 20/40 in the left eye. The patient had been managed elsewhere with a course of topical moxifloxacin eye-drops four times a day and topical steroids (prednisolone acetate) 1% three times a day for 2 weeks without any resolution, which was stopped 2 days ago prior to presentation at our centre. Gram stain was negative for bacteria as well as microsporidial spores. 10% KOH was negative for fungal hyphae. Based on strong clinical signs of corneal microsporidiosis, in spite of the negative microbiology smear, the patient was started on voriconazole eye-drops five times a day. The lesions started resolving in 5 days and completely healed after 17 days of therapy. No relevant history pertaining to exposure of contaminated water, swimming or history of trauma could be elicited.

was treated elsewhere prior to presentation with topical moxifloxacin eye-drops four times a day and topical steroids for 2 weeks without any resolution. She discontinued all the treatment 2 days prior to presentation. Examination revealed multifocal coarse raised epithelial lesions with epithelial defect in the left cornea (figure 1).

INVESTIGATIONS

Under topical anaesthesia with 0.4% oxybuprocaine hydrochloride eye-drops, diagnostic corneal epithelial sampling was performed and two glass slides were prepared. One smear was stained with Gram's stain for microsporidial spores and the other with 10% KOH for fungal hyphae. HIV testing was also performed with ELISA.

DIFFERENTIAL DIAGNOSIS

Adenoviral keratitis, fungal keratitis, herpetic keratitis, recurrent epithelial erosion syndrome, basement membrane dystrophy.

TREATMENT

Based on strong clinical evidence of corneal microsporidiosis, the patient was started on voriconazole eye-drops five times a day for 10 days. The drops were reduced to two times a day on day 11 for another 1 week. The total duration of treatment was 17 days.

OUTCOME AND FOLLOW-UP

The epithelial defect healed and the lesions started fading with mild subepithelial haze (figure 2)

BACKGROUND

Microsporidia are obligate intracellular eukaryotes that are spore forming and are closely related to fungi and primarily cause keratoconjunctivitis and stromal keratitis.¹⁻³ Microsporidial keratoconjunctivitis, although more prevalent, is often misdiagnosed as adenoviral keratoconjunctivitis and is under-reported due to the lack of literature.^{4,5}

Microsporidial spores can be seen on Gram stain, 1% acid-fast stain and on 10% potassium hydroxide (KOH) with calcofluor white stain under fluorescent microscopy.⁴ Das *et al*⁴ reported a sensitivity of 90% for Gram stain in detecting microsporidial spores.

This case highlights the importance of clinical signs in determining the diagnosis, when laboratory investigations and microbiological smears are negative. The clinical signs are of paramount importance in the absence of a definitive microbiological diagnosis which dictates the initial treatment, thereby preventing morbidity and subsequent visual loss because of delayed treatment.

CASE PRESENTATION

A 28-year-old patient presented to us with pain watering redness and blurred vision in the left eye, with a best-corrected visual acuity of 20/40. There was no relevant history of contact with contaminated water or contact lens usage. The patient

Figure 1 Multifocal coarse raised epithelial lesions with epithelial defect in the left cornea.

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Figure 2 Fading lesions with mild subepithelial haze.

and completely healed with a resolution of subepithelial haze (figure 3) after 17 days of therapy.

There were no recurrences on subsequent follow-up of 2 months. The corneal epithelium and stroma remained clear on follow-up of 2 months with an uncorrected visual acuity of 20/20.

DISCUSSION

Microsporidia are obligate intracellular eukaryotes that are spore forming and are closely related to fungi.^{1 3} Corneal microsporidiosis is an underdiagnosed entity, often being misdiagnosed as viral keratoconjunctivitis and treated with antibiotics and steroids or antiviral medications.² These patients present as simple viral keratoconjunctivitis and are treated with antibiotics and steroids.⁵

Theng *et al*,⁶ Chan *et al*⁷ and Kwok *et al*⁸ have identified contact lens use, exposure to foreign body and soil as risk factors for microsporidial keratoconjunctivitis.

Immunocompromised states like HIV are a known risk factor.⁹ Long-standing keratoconjunctivitis refractory to antibiotics with classic raised white epithelial lesions having stuck on appearance leaving small depressions or micropits after swabbing is a classic clinical presentation for epithelial microsporidiosis.

The various stains used for microbiological diagnosis are 10% KOH with calcofluor white, Gram's stain, Giemsa stain and modified Ziehl-Neelsen (1% sulphuric acid H₂SO₄)

Figure 3 Completely healed with resolution of subepithelial haze.

stain.⁴ Literature search reports a sensitivity of 90% on Gram staining,⁴ but sometimes the specimen is inadequate and the stain is negative for microsporidial spores.

Differentiating features from adenoviral punctate keratitis is that the microsporidial keratitis is more coarse and raised above the surface, with a stuck on appearance as compared with small infiltrates of adenoviral keratitis which are flat and after scraping microsporidial lesions leave small depressions/micropits on the cornea, unlike adenoviral keratitis.

We took this finding as an important clinical clue to start empirical treatment in the absence of definitive microbiological diagnosis because of negative smears.

0.3% fluconazole eye-drops have been used by Agashe *et al*,² in their case series of established smear-positive corneal microsporidiosis. We have used 1% voriconazole eye-drops because of the non-availability of fluconazole eye-drops with similar efficacy. The prognosis is fairly good if the treatment is started well in time before the subepithelial scarring sets in.² Various drugs have been reported to be useful in the treatment of microsporidial keratitis namely polyhexamethylene biguanide (PHMB), fumagillin, itraconazole, voriconazole, fluoroquinolones and albendazole.⁹⁻¹³ Das *et al*¹³ compared the time to heal and time to cure between PHMB and placebo in a randomised controlled trial and concluded that PHMB did not offer any advantage over placebo. The treatment is continued till complete resolution of lesions.² Khandelwal *et al*¹⁴ have used topical azole for 4 weeks in tapering doses. Delayed treatments with ongoing inflammation cause epithelial and subepithelial scarring, subsequent visual loss and the need for cornea transplant surgeries.¹⁵

In cases where voriconazole fails, other alternate therapies namely fumagillin, itraconazole, voriconazole, fluoroquinolones and albendazole can be tried.²

Patient's perspective

I'm very happy after the treatment as I was being treated elsewhere since 2 weeks without any improvement.

Learning points

- ▶ This is an unusual case with smear-negative report which highlights the importance of clinical signs in clinching the diagnosis, when laboratory investigations and microbiological smears are negative.
- ▶ The clinical diagnosis is of paramount importance in the absence of a definitive microbiological diagnosis. The clinical signs help in formulating the initial treatment, thereby preventing morbidity. Delayed treatments with ongoing inflammation cause epithelial and subepithelial scarring and subsequent visual loss and the need for cornea transplant surgeries.
- ▶ Microsporidiosis can be easily confused with adenoviral keratitis and the treatment approach to each disease is different. Adenoviral keratitis is treated with topical steroids whereas antifungals are used for treating ocular microsporidiosis because of an organism closely related to fungi. Voriconazole binds and inhibits ergosterol synthesis by inhibiting cytochrome P450-dependent 14-alpha sterol demethylase. The inhibition of 14-alpha sterol demethylase results in depletion of ergosterol in fungal cell membrane thereby acting as fungicidal.

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