Microsporidial Keratoconjunctivitis in Healthy Individuals

A Case Series

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Purpose: To present a series of 6 cases of microsporidial keratoconjunctivitis in healthy, nonimmunocompromised individuals.

Design: Retrospective, noncomparative case series.

Participants: Six individuals with unilateral keratoconjunctivitis.

Methods: Cornea epithelial scrapings were taken and evaluated by modified trichome staining. Blood was taken for human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay in all cases and for CD4 and CD8 T-lymphocyte counts in 5 cases.

Main Outcome Measures: The individuals were evaluated based on symptoms, visual acuity, slit-lamp biomicroscopy, and pathologic examination of the corneal scrapings.

Results: All cases occurred in men whose ages ranged from 16 to 37 years. Initial symptoms included unilateral pain and redness. All experienced subsequent worsening of symptoms and blurring of vision after using topical steroids prescribed by general practitioners. Slit-lamp biomicroscopy revealed coarse, multifocal, punctate epithelial keratitis in all 6 cases, anterior stromal infiltrates in 2 cases, with accompanying conjunctivitis in all cases. Modified trichrome staining of corneal epithelial scrapes revealed pinkish to red spores characteristic of microsporidia in all cases. Results of an HIV enzyme-linked immunosorbent assay were negative in all cases, and CD4 and CD8 T-lymphocyte counts and ratios were normal in all 5 tested cases. On diagnosis, topical steroid therapy was stopped in all cases. Treatment with topical Fumidil B (bicyclohexylammonium fumagillin; Leiter’s Park Ave Pharmacy, San Jose, CA) together with oral albendazole was given in 3 cases, oral albendazole alone in a single case, and broad-spectrum antibiotic treatment with topical norfloxacin or chloramphenicol in two cases. Two cases had keratic precipitates with mild cellular activity in the anterior chamber and one such case was restarted subsequently on topical steroids. All six cases showed resolution of epithelial keratitis but with residual visually inconsequential subepithelial scars by the end of 1 month of treatment.

Conclusions: Microsporidial keratoconjunctivitis can occur more commonly than expected in healthy, nonimmunocompromised individuals. Topical steroids seem to contribute to the persistence of this infection and may be a predisposing factor in these cases by creating a localized immunocompromised state. The clinical course is variable and may be self-limiting with cessation of topical steroid use. Ophthalmology 2003;110:1420–1425 © 2003 by the American Academy of Ophthalmology.

Microsporidia are obligate, intracellular, spore-forming protozoan parasites that belong to the phylum Microspora. Microsporidiosis, the disease caused by these organisms, has been recognized in both vertebrates and invertebrates. The first case of microsporidial keratitis in humans was reported by Ashton and Wirasinha in 1973. Two distinct clinical entities have been described since: deep corneal stromal infection occurring in immunocompetent patients and bilateral diffuse punctate epithelial keratopathy in immunocompromised patients with AIDS.

In 2001, we reported an unusual case of microsporidial epithelial keratitis in a healthy, nonimmunocompromised contact lens wearer occurring after topical steroid use. The keratitis that was described in this case was a superficial, multifocal, coarse, punctate epithelial keratitis, the morphologic features of which were more in keeping with the keratitis that is said to occur in immunocompromised individuals. We since have found 5 other cases of similarly healthy individuals with this unique unilateral epithelial keratitis. We now describe this series of 6 cases.
Materials and Methods

Six patients with unilateral keratoconjunctivitis initially treated by general practitioners were referred to the Singapore National Eye Center from the period February 1999 through September 2001. The patients were examined initially by comprehensive ophthalmologists in the Center and referred subsequently to the Cornea Service, where the patients were seen by the 4 authors. They were evaluated based on symptoms, visual acuity, and slit-lamp biomicroscopy results. Corneal epithelial scrapings were taken and sent for modified trichrome staining by a microbiologist. Blood was taken for human immunodeficiency virus enzyme-linked immunosorbent assay in all cases and for CD4 and CD8 T-lymphocyte counts in 5 cases. The cases were analyzed retrospectively based on entries in the case records. The follow-up period ranged between 2 months to 15 months (mean period, 8 months). Because this was a retrospective analysis, there was no standardized follow-up schedule.

Results

The results are summarized in Table 1. The 6 individuals were male, with ages ranging from 16 to 37 years (mean age, 29.5 years). All had prior consultation with general practitioners and were being treated with topical steroids for a “red eye” that was presumed to be viral conjunctivitis. Initial symptoms included unilateral pain and redness after the use of topical steroids, all described definite worsening of symptoms with blurring of vision. One patient (patient 1) gave a history of contact lens wear and another patient (patient 4), had a history at presentation of dust particles entering the affected eye. There was no history of trauma or exposure to other environmental agents in the other 4 patients. Snellen visual acuity varied between 20/25 and 20/100. Slit-lamp biomicroscopy revealed unilateral diffuse, multifocal, coarse, punctate epithelial lesions in all the patients (Figs 1 and 2). The lesions stained with fluorescein (Fig 3). In 2 patients, the lesions appeared to be at a deeper subepithelial and anterior stromal level but with a similar morphologic appearance. A mild, nonpurulent conjunctivitis was associated in all cases, with papillary reaction noted in the upper and lower tarsal conjunctivae in two cases. Keratic precipitates with 1+ cellular activity in the anterior chamber also were noted in an eye (patient 1). Another patient (patient 4) also experienced similar anterior chamber activity, but this occurred 2 days after starting Albendazole.

Modified trichrome staining of the corneal epithelial scrapes revealed the typical intracellular pinkish to red spherical bodies characteristic of microsporidia spores in all cases (Fig 4). All patients were healthy individuals who, apart from their ocular symptoms, were otherwise systemically well and symptom free. Results of a human immunodeficiency virus enzyme-linked

Table 1. Clinical Course of Six Patients with Unilateral Keratoconjunctivitis in Healthy Individuals

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/ Gender</th>
<th>Race</th>
<th>Symptoms</th>
<th>Trauma/Contact Lens</th>
<th>Topical Steroids</th>
<th>Best-corrected Visual Acuity</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37/M</td>
<td>White</td>
<td>Pain and redness (3 days)</td>
<td>Contact lens</td>
<td>Dexamethasone 0.1%</td>
<td>20/25</td>
<td>Multifocal coarse punctate epithelial keratitis, anterior stromal infiltrates, papillary conjunctivitis, 1+ cellular activity in the anterior chamber, pigmented keratic precipitates</td>
</tr>
<tr>
<td>2</td>
<td>37/M</td>
<td>Chinese</td>
<td>Pain and redness (3 wks)</td>
<td>Nil</td>
<td>Dexamethasone 0.1%</td>
<td>20/40</td>
<td>Multifocal coarse punctate epithelial keratitis; diffuse conjunctivitis</td>
</tr>
<tr>
<td>3</td>
<td>36/M</td>
<td>Chinese</td>
<td>Pain and redness (4 days)</td>
<td>Nil</td>
<td>Dexamethasone 0.1%</td>
<td>20/25</td>
<td>Multifocal coarse punctate epithelial keratitis; diffuse conjunctivitis</td>
</tr>
<tr>
<td>4</td>
<td>28/M</td>
<td>Indian</td>
<td>Pain, redness, and visual blurring (1 wk)</td>
<td>Dust particles entering eye</td>
<td>Betametasone 0.1%</td>
<td>20/30</td>
<td>Multifocal coarse punctate epithelial keratitis, anterior stromal infiltrates, diffuse conjunctivitis, 1+ cellular activity in the anterior chamber, and keratic precipitates developing 2 days after starting Albendazole</td>
</tr>
<tr>
<td>5</td>
<td>23/M</td>
<td>Chinese</td>
<td>Pain, redness, and visual blurring (9 days)</td>
<td>Nil</td>
<td>Dexamethasone 0.1%</td>
<td>20/40</td>
<td>Multifocal coarse punctate epithelial keratitis, papillary conjunctivitis</td>
</tr>
<tr>
<td>6</td>
<td>16/M</td>
<td>Chinese</td>
<td>Redness and visual blurring (1 wk)</td>
<td>Nil</td>
<td>Dexamethasone 0.1%</td>
<td>20/100</td>
<td>Multifocal coarse punctate epithelial keratitis, diffuse conjunctivitis</td>
</tr>
</tbody>
</table>

AC = anterior chamber; b.d. = twice daily; om = one in morning; on = once at night; qds = 4 times a day.
immunosorbert assay were negative in all cases and CD4 and CD8 T-lymphocyte counts and ratios were normal in all 5 tested cases.

On diagnosis of microsporidial keratoconjunctivitis, topical steroid therapy was stopped in all cases. Our first patient (patient 1) initially received treatment with oral albendazole and topical propamidine isethionate. There was initial improvement but a worsening of signs and symptoms after 1 month of treatment. The topical propamidine isethionate was stopped and replaced subsequently with topical Fumidil B (bicyclohexylammonium fumagillin; Leiter’s Park Ave Pharmacy, San Jose, CA) 0.113 mg/ml. The keratitis resolved 1 month after topical Fumidil B was started.

Two patients (patients 2 and 3) were prescribed topical Fumidil B combined with oral albendazole. Oral albendazole alone was given in one patient (patient 4).

Two patients (patients 5 and 6) received nonspecific broad-spectrum antibiotic treatment with topical norfloxacin and chloramphenicol. The decision was made not to start any specific antimicrosporidial treatment in these 2 cases, because while awaiting the microscopy results of the corneal epithelial scrapes, the patients showed spontaneous improvement in symptoms and signs after withdrawal of the topical steroids.

Patient 5 is one such case illustrating resolution of microsporidial keratoconjunctivitis after treatment with nonspecific broad-spectrum antibiotics. He was a 23-year-old university student who sought treatment at the Singapore National Eye Center with a 1-week history of right eye redness and blurring of vision. He previously saw a general practitioner, who prescribed topical dexamethasone 0.1%. At presentation, his visual acuity was 6/12 correctable to 6/6 with pinhole in the right eye and 6/6 in the left with spectacle correction. He had diffuse multifocal coarse punctate epithelial keratitis (Fig 5) in the right eye, whereas the left eye was completely normal. A clinical diagnosis of microsporidial keratoconjunctivitis was made, with a possible differential diagnosis of a viral keratoconjunctivitis. Corneal epithelial scrapes for modified trichome stain were performed and the patient was treated with topical chloramphenicol eyedrops 4 times daily with artificial tear eye-drop supplements, and instructed to stop the steroid eye-drops. After the diagnostic cornea epithelial biopsy, which removed most of the epithelial lesions, the condition improved on topical chloramphenicol treatment alone, and subsequent weekly reviews showed gradual resolution of his corneal lesions. His visual acuity returned to 6/6 with his spectacles and the cornea lesions had completely resolved with minimal subepithelial scarring by 2 months (Fig 6). Patient 4 experienced keratic precipitates with mild cellular activity in the anterior chamber during the course of treatment, and, subsequently, was restarted on low-dose topical steroids after resolution of the corneal lesions.

All 6 patients showed resolution of epithelial keratitis within 2 weeks to 2 months of starting treatment. However, all retained residual subepithelial cornea scars for a varying period of time (Fig 6). These scars, however, were visually inconsequential, with Snellen acuity at 20/20 in all cases. They were still present between 2 to 4 months later in 3 patients (patients 1, 5, and 6) and in patient 4, the scars were still visible after 13 months of the initial infection. In two patients (patients 2 and 3), the scars resolved and their corneas were clear at 15 months and 11 months, respectively.
Figure 1. Slit-lamp photograph of patient 6 showing multifocal, coarse, punctate epithelial keratitis (original magnification, ×40).

Figure 2. Slit-lamp photograph of patient 5 showing similar multifocal, coarse, punctate epithelial lesions (original magnification, ×25).

Figure 3. Slit-lamp photograph showing diffuse punctate fluorescein staining lesions in patient 1 (original magnification, ×40).

Figure 4A. Modified trichrome staining showing intracellular pinkish to red spherical bodies characteristic of microporidial spores in patient 2 (original magnification, ×100).

Figure 4B. Modified trichrome staining showing intracellular pinkish to red spherical bodies characteristic of microporidial spores in patient 2—alternative view (original magnification, ×100).

Figure 5. Slit-lamp photograph of patient 5 showing multifocal, coarse punctate epithelial keratitis at presentation (original magnification, ×40).
Two patients (patients 5 and 6) defaulted follow-up after 2 to 2.5 months of treatment. However, when contacted over the phone 6 months after the initial infection, they reported being well and symptom free.

Discussion

There has been a growing awareness of microsporidial keratoconjunctivitis in recent years largely because of the increasing number of patients with AIDS and their susceptibility to infection by this opportunistic pathogen. In the AIDS or immunocompromised patient, a bilateral punctate epithelial keratopathy and conjunctivitis has been described. Though uncommon, there have been reported cases of microsporidial corneal infections occurring in immunocompetent patients as well. A similar form of superficial keratitis, presenting with intraepithelial and superficial stromal opacities, was described in a patient without AIDS who was immunosuppressed with oral prednisolone for severe asthma. In the case described by Davis et al, a deep, intrastromal keratitis was seen, and this has been described to occur typically in the immunocompetent individual. Our series of 6 patients has shown that the bilateral punctate epithelial involvement of the cornea that is typically described in immunocompromised individuals can also occur unilaterally in healthy, immunocompetent individuals. All 6 patients initially were prescribed topical steroids by general practitioners, who presumed the infection to be a viral conjunctivitis. It is possible that microsporidial keratoconjunctivitis was the initial cause of the red eye, with steroid therapy contributing to the persistence of the infection and worsening of symptoms. Alternatively, these patients also could have had a viral conjunctivitis in the first place, with steroid therapy creating a localized immunosuppressed state, resulting in superinfection by microsporidia. Other risk factors in these cases include a prior history of contact lens wear in one patient, and a history of possible foreign body entry into the eye in another.

Anecdotal reports of specific drug treatment for microsporidiosis include itraconazole, albendazole, propamidine isethionate, benzimidazoles, and fumagillin, but their effectiveness remains controversial. Surgical treatment has been described, and this includes diagnostic and therapeutic epithelial debridement, which therapeutically ‘de-bulks’ the load of organisms from the cornea epithelium. This, however, may increase the risk of penetration of the organism into the deep stromal layers, or increase the risk of secondary infection. The severity of this condition is emphasized by the fact that penetrating keratoplasty has been performed in cases of corneal stromal disease occurring after failed medical therapy.

Fumagillin is a naturally secreted antibiotic of Aspergillus. Fumidil B is the water-soluble form of fumagillin, commonly used to control microsporidial disease in honey bees. The mechanism of action of fumagillin is not clearly understood, although studies suggest that the drug may alter DNA content or inhibit RNA synthesis in the organism. Recurrence of symptoms and signs on transient discontinuation of the drug has been described, which implies an inhibitory rather than a parasiticidal action on the sporoblasts. Albendazole is a broad-spectrum antihelminthic that has been shown to be effective in the treatment of microsporidiosis. Three of our patients were given albendazole together with topical Fumidil B, whereas one was given albendazole alone. All 4 of these patients responded well to the treatment prescribed, with resolution of the keratitis within 1 month.

Interestingly, the last 2 patients in our series did not receive any specific microsporidial therapy, but had a spontaneous resolution of the keratitis within 2 weeks of discontinuation of the topical steroids. This reinforces our belief that topical steroids contributes to the persistence of microsporidial infection, or could be the initial predisposing factor in these patients. Discontinuation of the topical steroids removes the localized immunosuppression, and the otherwise healthy host is then able to counter the infection spontaneously, with resolution of the keratitis.

A common feature in all 6 patients was the subepithelial scars on resolution of the epithelial keratitis. These are very similar (although not identical) to the “nummular keratitis” typically seen after an episode of adenoviral keratoconjunctivitis. In fact, especially in settings where topical steroids are prescribed freely to treat the “sore eye,” we believe that microsporidial keratoconjunctivitis may in fact occur more commonly than expected. The disease is probably underdiagnosed, and to an untrained eye, the punctate epithelial lesions and subsequent subepithelial scars can be easily mistaken for an “atypical” or “unusual” adenoviral keratoconjunctivitis. A high index of suspicion is therefore required to prevent underdiagnosis of this disease.

Conclusions

Microsporidial keratoconjunctivitis can occur more commonly than expected in healthy, nonimmunocompromised individuals, especially when topical steroids have been prescribed. A multifocal, coarse, punctate unilateral keratitis associated with mild conjunctivitis appears to be the char-
acteristic manifestation of this disease. Subepithelial lesions and a mild anterior uveitis may also be present. The clinical course is variable, but may be self-limiting in certain cases with cessation of topical steroid use. A high index of suspicion is required for microsporidial keratoconjunctivitis in cases of unusual unilateral keratitis, especially if topical steroids have been prescribed.

References
