Microsporidial Stromal Keratitis

Microsporidia are spore-forming, obligate eukaryotic protozoan parasites that belong to the phylum Microspora. The ophthalmic manifestations of ocular microsporidiosis exhibit characteristic clinical features depending on the genus involved. With the genus Encephalitozoon, infection is limited to the epithelial cells of the cornea and conjunctiva, producing a diffuse punctate epithelial keratoconjunctivitis. With the genera Nosema and Microsporidium, the infection typically involves the corneal stroma, including the kerocytes.1

To date, only 5 case reports of microsporidial stromal keratitis have been published.2-6 We report an additional case caused by Vittaforma corneae (formerly known as Nosema corneum), which was confirmed by histological analysis and electron microscopy.

Report of a Case. A 65-year-old white man was referred with a 4-month history of progressive redness, pain, and decreased vision in the right eye. The patient denied any history of herpes zoster, vesicular eruptions, trauma, and contact lens wear. Ophthalmic examination revealed a best-corrected visual acuity of 20/40 OD and 20/20 OS. Findings from an examination of the left eye were normal. The right eye showed moderate diffuse conjunctival hyperemia with a central area of stromal infiltration and edema without suppuration (Figure 1). The anterior chamber had 1+ cells and flare with a 3% hypopyon inferiorly. Findings from the remainder of the ocular examination were unremarkable. The patient was treated with 1% prednisolone acetate and 1% trifluridine, both 6 times a day in the right eye for presumed herpes simplex stromal keratitis. Conjunctival and corneal swabs and scrapings collected for bacterial, chlamydial, fungal, and herpes-virus cultures were all negative for microorganisms.

Over the next 2 months, the visual acuity improved to 20/25 OD, with gradual resolution of the stromal edema. Four weeks later, while the patient was taking a tapering regimen of prednisolone acetate and trifluridine, stromal keratitis recurred with a disciform appearance associated with central epithelial defect as well as superficial corneal vascularization superiorly (Figure 2). Visual acuity was 20/200 OD. Repeated cultures revealed only a few colonies of Staphylococcus epidermidis. Despite appropriate antimicrobial treatment, a persistent epithelial defect ensued with progressive stromal thinning centrally. Ten months after onset of symptoms, the right cornea perforated. The patient underwent a penetrating keratoplasty, the visual acuity improved to 20/25 OD. A blood sample tested with an enzyme-linked immunosorbent assay was negative for antibodies to human immunodeficiency virus. The subsequent postoperative course was complicated by severe microbial keratitis secondary to Pseudomonas aeruginosa infection, leading to perforation. A second penetrating keratoplasty was performed in the right eye.

Transmission electron microscopy 1-µm sections revealed scattered sporoblasts, displaying a distinct cell wall with dikaryotic arrangement of the nuclei, which is characteristic of Vittaforma corneae (Figure 3). A diagnosis of microsporidial stromal keratitis caused by Vittaforma corneae was made.

Six months after the penetrating keratoplasty, the visual acuity improved to 20/25 OD. A blood sample tested with an enzyme-linked immunosorbent assay was negative for antibodies to human immunodeficiency virus. The subsequent postoperative course was complicated by severe microbial keratitis secondary to Pseudomonas aeruginosa infection, leading to perforation. A second penetrating keratoplasty was performed in the right eye.
approximately 1 year after the first grafting. Histopathological examination of the keratectomy specimen showed acute necrotizing and suppurative keratitis with stromal thinning. No evidence of microsporidial organisms was present.

At the last follow-up examination, approximately 15 months after the second penetrating keratoplasty, the graft remained clear, and visual acuity was 20/40 OD.

Comment. Well-documented cases of microsporidiosis involving the corneal stroma are rare. Only 2 genera, *Nosema* and *Encephalitozoon*, are known to cause ocular infections.6

Deep stromal infections of the cornea have been described in association with trauma leading to stromal scarring and vascularization,2 with atraumatic perforated corneal ulcer manifesting with keratouveitis and hyphema,3 and with foreign body and persistent corneal ulcer.4 In addition, spontaneous stromal keratitis mimicking herpes simplex virus infection has also been described.3 Lastly, stromal microsporidiosis has also been reported in a patient with persistent stromal keratitis, which was initially managed as a case of herpes simplex stromal keratitis.6 Likewise, our patient was first seen with stromal keratitis resembling herpes simplex virus infection, which ultimately progressed to corneal thinning and perforation, leading to a penetrating graft. Thus, microsporidial ocular infections should be considered in the differential diagnosis of culture-negative stromal keratitis refractory to conventional medical treatment.

Full-thickness corneal transplantation appears to be the only procedure that has proven to be successful for the treatment of deep stromal microsporidiosis. In one of the reported cases, a deep lamellar keratoplasty was unable to prevent the recurrence of the disease. Furthermore, the use of both topical fumagillin and oral albendazole failed to control the infection, even after lamellar keratoplasty. Of the 4 case reports of corneal microsporidiosis4-6 including our own, no recurrences of microsporidial infection occurred at the last follow-up examination following a full-thickness penetrating corneal graft. Therefore, one should consider performing a full-thickness penetrating graft rather than a lamellar graft to avoid the possibility of recurrences in the graft.

Identification of microsporidial ocular infections require cytologic and histopathological examination of corneal or conjunctival biopsy specimens combined with transmission electron microscopy, which is essential for accurate species characterization. Distinguishing features, including the clinical findings and ultrastructural features of *Encephalitozoon hellem* and *Vittaforma corneae*, are depicted in the Table. In our patient, dikaryotic arrangement of the nuclei was

<table>
<thead>
<tr>
<th>Feature</th>
<th><em>Encephalitozoon hellem</em></th>
<th><em>Vittaforma corneae</em></th>
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</thead>
<tbody>
<tr>
<td>Host status</td>
<td>Immunocompromised</td>
<td>Immunocompetent</td>
</tr>
<tr>
<td>Tissue</td>
<td>Confined to corneal and conjunctival epithelium</td>
<td>Corneal stroma</td>
</tr>
<tr>
<td>No. of nuclei</td>
<td>Monokaryotic</td>
<td>Two abutted nuclei</td>
</tr>
<tr>
<td>Autophagic vacuole</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

*Vittaforma corneae was previously known as *Nosema corneum*. 

Figure 3. Thick sections (1 µm) depict swollen stromal keratocytes containing numerous intracellular round to oval organisms measuring 2.5 to 4.0 µm in maximal diameters (toluidine blue stain, original magnification ×252).

Figure 4. An electron micrograph depicts a sporoblast with 2 abutted nuclei (N), which is highly characteristic of *Vittaforma corneae*. 

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Epstein-Barr Virus–Related Bilateral Acute Retinal Necrosis in a Patient With X-linked Lymphoproliferative Disorder

X-linked lymphoproliferative disorder (XLPD) is a hereditary disease that stems from a deletion Xq 23-25 that negates the functions of an immune response to the Epstein-Barr virus (EBV). Males who inherit the mutation develop a spectrum of conditions that include fatal infectious mononucleosis, hypogammaglobulinemia, B-cell lymphomas in extranodal sites, and aplastic anemia after EBV infection.1 Although the virus has previously been implicated in chorioretinitis and retinal vasculitis in patients with infectious mononucleosis,2 to our knowledge there is only 1 report in the literature of retinal necrosis associated with XLPD.3 Herein we present the case of a 10-month-old boy with XLPD and pathologically confirmed retinal necrosis.

Report of a Case. A 10-month-old boy was referred for a dilated fundus examination prior to bone marrow transplantation for aplastic anemia secondary to XLPD. The patient’s serologic test results were positive for EBV, cytomegalovirus (CMV), and herpes simplex virus (HSV). He was able to fix and follow with the left eye, but the right eye did not appear to see. Examination of the anterior segment in the right eye revealed an afferent pupillary defect, posterior synechiae, and rubecosis. The vitreous in the right eye was hazy owing to cellular infiltration. Funduscopy revealed widespread yellow-white retinal opacification and multiple retinal hemorrhages. A retinal detachment was present in the superior nasal quadrant. Left eye examination revealed 3 small vitreous fluff balls, pronounced white swelling and hemorrhaging of the optic nerve head, whitish infiltration of the retina (Figure 1) with retinal hemorrhages, and inflammatory sheathing of some retinal blood vessels. Numerous round and oval-shaped atrophic-appearing retinal pigment epithelial lesions measuring approximately 300 μm in diameter were scattered throughout the entire peripheral fundus (Figure 2). Some of these lesions coalesced into large geographic areas of atrophy.

The patient underwent a diagnostic 3-port pars plana vitrectomy and retinal biopsy in the blind right eye. Two 1 × 1-mm sections of retina with active-appearing infiltrates were excised from the nasal and superior quadrants. Vitreous samples were submitted for cultures, and the retinal specimens were submitted for cytology and in situ hybridization for CMV, EBV, HSV, and herpes zoster virus (HZV).

The retinal biopsy specimen showed linear sections of hemorrhagic and necrotic retinal tissue (Figure 3), with diffuse replacement of the photoreceptor layer by irregular layers of large multinucleated cells with enlarged nuclei. These hyperchromatic nuclei exhibited vesicular chromatin with prominent chromocenters, shallow indentations, and focal lobulation. The surrounding cytoplasm was sparse and syncytial. A mixed population of T cells and B cells was demonstrated by immunohistochemical staining.

Figure 1. Fundus photograph of the left eye demonstrating whitish infiltration of the retina with retinal hemorrhages, and inflammatory sheathing of some retinal blood vessels in a patient with Epstein-Barr virus–related acute retinal necrosis.