Ocular Manifestations of Whipple Disease

An Atypical Presentation

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A 62-year-old man developed bilateral granulomatous iridocyclitis after uncomplicated cataract surgery. On ophthalmic examination, we found moderate inflammation in the anterior chamber and vitreous, with granular crystalline deposits on the iris, intraocular lens, and capsular bag. Biopsy of the lens capsule and vitreous revealed periodic acid–Schiff–positive, diastase-resistant bacilli consistent with *Tropheryma whippelii*. Electron microscopy and polymerase chain reaction confirmed the diagnosis of Whipple disease. A jejunal biopsy specimen also revealed *T whippelii*. Treatment with trimethoprim-sulfamethoxazole, cefixime, rifampin, and doxycycline resulted in improvement of systemic symptoms, but intraocular inflammation persisted. Intraocular inflammation was eventually reduced with the intravenous administration of ceftriaxone sodium.

Whipple disease usually affects the gastrointestinal system, but can also affect the neurologic, hemopoietic, rheumatologic, cardiac, pulmonary, and ocular systems. Ocular involvement may result in inflammation, vitreous hemorrhage, or optic disc edema. Whipple disease predominantly affects white, middle-aged men and is attributed to an as-yet uncultured, periodic acid–Schiff–positive, diastase-resistant bacillus, *Tropheryma whippelii*. We report a case in which biopsy of the vitreous established the diagnosis.

REPORT OF A CASE

A 62-year-old white man was referred to us with a 5-month history of bilateral uveitis that was resistant to topical, oral, and subtenon's corticosteroids. Seven months previously, he had undergone uncomplicated bilateral cataract extractions with implantation of posterior chamber intraocular lenses at a 13-day interval. His medical history included arthritis, which required oral corticosteroids, and fever of unknown origin, which lasted for several months.

Visual acuity was 20/20 OU. Grayish white granular aggregates adhered to the iris margin in the left eye (Figure 1). The patient had aqueous cell and flare (1+) and vitreous cell and haze (2+) in both eyes. Intraocular pressures were 23 mm Hg OD and 17 mm Hg OS. Fundus examination revealed optic disc drusen and posterior vitreous detachments in both eyes. A chest radiograph showed no abnormalities; test findings for rapid plasma reagin, fluorescent treponemal antibody absorption, and angiotensin-converting enzyme and serum lysozyme levels were also normal.

A diagnosis of phacoanaphylactic uveitis was made. During the next 6 weeks, despite treatment with corticosteroids, the patient’s visual acuity decreased to 20/40 OD and 20/25 OS, and he had aqueous cell and flare (2+) and vitreous cell and haze (3+) in both eyes. Prominent granular crystalline clumps were present on the intraocular lenses, lens capsule, and iris in both eyes (Figure 2).

The patient underwent posterior chamber intraocular lens removal, capsulotomy using α-chymotrypsin, anterior vitrectomy, and anterior chamber intraocular lens implantation in the right eye. Examination of the specimen revealed only bladder cells; no organisms or inflammatory cells were identified. As the scarcity of cells was attributed to α-chymotrypsin, the procedure was repeated in the left eye.
eye without enzyme. Periodic acid–Schiff–positive, diastase-resistant material was seen in macrophages that adhered to the vitreal surface of the lens capsule and in the vitrectomy specimen (Figure 3). Electron microscopy showed degenerating epithelial cells containing intracytoplasmic bacilli (Figure 4, left) with a thick laminated capsule and vacuolated cytoplasm, consistent with *T whippelii* (Figure 4, right). The polymerase chain reaction of the lens capsule, performed using techniques described by Ramzan et al, was diagnostic of Whipple disease (Figure 5).

The patient then reported a recent episode of diarrhea. A jejunal biopsy specimen revealed bacilli in macrophages in the lamina propria and epithelium, consistent with *T whippelii*. Intravenous trimethoprim-sulfamethoxazole produced intolerable side effects. Treatment with oral cefixime, 400 mg/d, did not improve systemic symptoms, and intraocular inflammation worsened with recrudescence of granular deposits on the iris margins and posterior lens surfaces. Polymerase chain reaction of the blood was still positive. Treatment was changed to oral rifampin, 600 mg/d, and oral doxycycline, 100 mg twice daily, which resulted in improvement of arthritis and diarrhea, although intraocular inflammation worsened.
The patient developed bilateral hypopyons (Figure 6), elevated intraocular pressure in both eyes, and macular edema in the right eye. Two grams per day of intravenous ceftriaxone sodium was also administered, resulting in a decrease in inflammation within 2 weeks, and involution of the iris and lenticular deposits within 1 month. At the last ophthalmic examination, visual acuity was 20/25 OD and 20/30 OS, with minimal ocular inflammation. The patient continues to receive oral rifampin and doxycycline, intravenous ceftriaxone, oral and topical corticosteroids, and antiglaucoma medications.

The ocular history and lack of systemic symptoms in this patient initially suggested phacoanaphylaxis or latent endophthalmitis. Absence of organisms in the biopsy specimen and the bilateral nature of the disease made endophthalmitis unlikely. The diagnosis of Whipple disease rather than phacoanaphylaxis was made histopathologically.

The bacilli-laden macrophages on the iris margin and lens capsule had a granular crystalline quality, perhaps owing to the high polysaccharide and peptidoglycan content of the Whipple bacillus. Similar crystalline deposits have been described on the corneal endothelium in a patient with Whipple disease. We propose that the distinct crystalline granular appearance may be a useful clinical sign. To our knowledge, direct involvement of lens epithelium by the Whipple bacillus has not been reported previously. The bacilli most likely entered the vitreous and the lens epithelium through the retina, as previously described in detailed histopathologic studies.

Since Whipple disease is a chronic disease, recrudescence of inflammation is not unusual; the cause of systemic improvement with persistent ocular inflammation as seen in our patient is unknown. Antibiotics used in previous cases of Whipple disease with ocular involvement have included trimethoprim-sulfamethoxazole, tetracycline, erythromycin, penicillin, streptomycin, and chloramphenicol. Our patient was intolerant of the drug of choice, trimethoprim-sulfamethoxazole. Doxycycline and rifampin have good intraocular penetration, thus the initial persistence of ocular inflammation despite systemic improvement is difficult to explain. It is possible that our patient did not achieve therapeutic levels of doxycycline and rifampin in the eye or that the persistent inflammation was a response to dead bacilli.

Intravenous ceftriaxone has been shown to achieve aqueous levels in the minimum inhibitory concentration range for many gram-positive and gram-negative bacteria. The reduction of intraocular inflammation with the addition of ceftriaxone may be due to high organism susceptibility to this drug, or to improved intraocular penetration because of progressive breakdown of the blood-ocular barrier. It is also possible that the improvement resulted from a synergistic effect of ceftriaxone, doxycycline, and rifampin.

Polymerase chain reaction analysis in this case played a confirmatory role. It was not needed in making the diagnosis because of the existence of overwhelming histopathologic evidence. However, its role may be essential in cases where the diagnosis is less clear. It may also be helpful in cases of recrudescence, as histologic findings in these cases are often negative or equivocal, while polymerase chain reaction remains positive.

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