Mycobacterial Ocular Inflammation

Delay in Diagnosis and Other Factors Impacting Morbidity

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Importance: The reported outcomes of ocular mycobacterial infection are commonly unfavorable. This study is among the first to elucidate factors associated with poor outcomes, as well as highlight the continued controversies in therapy, particularly the role of oral corticosteroids.

Objective: To describe presentations and outcomes of mycobacterial ocular disease in the Midwestern United States.

Design: Retrospective case series.

Setting: A university-based uveitis clinic.

Participants: Twenty-six eyes of 17 patients with mycobacterial ocular inflammatory disease seen at University of Illinois at Chicago from 1995 to 2010.

Main Outcome Measures: Bivariate and regression analyses were performed to assess factors associated with delay in referral, relapse, and irreversible visual acuity loss (≤20/200).

Results: Of 17 patients, 13 had isolated ocular disease, 1 had miliary tuberculosis (TB), 2 had TB lymphadenopathy, and 1 had active pulmonary TB. Fourteen had Mycobacterium tuberculosis and 3 had nontuberculous mycobacterial infection. Chest imaging was consistent with granulomatous disease in 46.7%. Average delay from ocular disease onset to uveitis service referral was 755.3 days. Posterior uveitis and non-Hispanic white race were associated with increased delay. A relapsing course was observed in posterior uveitis (odds ratio [OR], 20.0; 95% CI, 1.39-287; P=.03) and those treated with systemic steroids for eye disease (OR, 10.1; 95% CI, 1.60-64.0; P=.01). Disease control was achieved in 81%, although 38.5% had profound visual loss, associated with age older than 50 years and delay in diagnosis. Patients diagnosed after 500 days from initial ocular symptoms were more likely to lose vision (OR, 20.0; 95% CI, 1.41-282; P=.03).

Conclusions: Ocular mycobacterial infection occurs in nonendemic areas and cannot be ruled out with negative chest imaging. Tuberculosis and atypical mycobacterial infection should be in the differential diagnosis of ocular inflammation, regardless of patient ethnicity. Significant delays exist in instituting antimicrobial treatment, associated with increased morbidity. Early referral is necessary for patients not responding appropriately to anti-inflammatory therapy.

investigations. Current recommended criteria for diagnosis of presumed ocular TB include positive tuberculin skin test, interferon gamma release assay, chest radiograph, or confirmed extracellular TB and supportive clinical ocular findings. More direct evidence, including acid-fast smear, tissue culture, and polymerase chain reaction (PCR) for bacterial DNA from ocular tissues, provides definitive support for the diagnosis. However, because of low bacterial load and natural inhibitors of Taq polymerase, the sensitivity of PCR in vitreous samples remains low, ranging from 33.3% to 46.9%. In addition, obtaining ocular fluids and tissue can be associated with ocular morbidity and might be of low yield. In fact, ocular TB was microbiologically identified in only 3.8% (6 of 157) of suspected cases in a study from Singapore.

Ocular TB can be difficult to treat and is associated with significant morbidity. Therapy has been reported to be effective in only 40% to 70% of published cases, with an enucleation rate of up to 30%. Factors influencing treatment outcomes are yet to be elucidated. Some have postulated the potential for multidrug-resistant bacteria, although extrapulmonary disease is typically negatively associated with multidrug resistance.

The aim of this study was to describe our experience with ocular mycobacterial disease (TB and non-TB mycobacterial infection) in the Midwestern United States, evaluating factors impacting delay in diagnosis and treatment outcomes.

### METHODS

We conducted a retrospective review of consecutive patients diagnosed with mycobacterial ocular inflammatory disease at the University of Illinois at Chicago Eye and Ear Infirmary uveitis clinic from 1995 through 2010. Institutional review board approval was obtained, adhering to Health Insurance Portability and Accountability Act requirements and tenets within the Declaration of Helsinki. Ocular mycobacterial disease included infection with *Mycobacterium tuberculosis* (TB) or any other *Mycobacterium* species in the eye. To be included, patients had to meet 1 of the 4 criteria listed in Table 1. In brief, patients had to have evidence of mycobacterial disease in the body and response of eye disease to anti-tuberculous therapy alone (without systemic corticosteroids or other immunosuppressive therapy) or direct biopsy or culture evidence of mycobacterium from the eye, regardless of response to therapy. Other inclusion criteria included 1 or more of the following clinical presentations: scleritis, granulomatous anterior uveitis, posterior uveitis including retinitis, vasculitis, choroiditis, serpigineous-like choroidopathy, and granulomatous panuveitis. Patients were excluded if clinical and/or laboratory investigation revealed another cause for the eye disease, including Behçet disease, syphilis, or sarcoidosis.

Data collected included age, race, sex, birth country, bacillus Calmette-Guérin (BCG) status, TB contacts, travel history, duration of symptoms, predominant site of disease, use of immunosuppressive agents for eye disease prior to referral to our facility, and systemic immunosuppression including human immunodeficiency virus (HIV) status. Further diagnostic and outcome data collected included results of tuberculin skin and QuantiFERON-TB Gold In-Tube testing (Cellestis Inc); results of chest imaging; clinical course including time to diagnosis, control of disease, and relapse; visual acuity data; ocular surgical interventions; and results of cultures, PCR testing, and biopsies. At each visit, the specialists typically instituted standard first-line RIPE therapy (rifampin, 600 mg daily; isoniazid, 300 mg daily; pyrazinamide and ethambutol hydrochloride dosed by weight), although rifabutin and other therapies were discontinued when deemed appropriate. Control of disease was defined by Standardization of Uveitis Nomenclature Working Group criteria for anterior and intermediate uveitis. Other forms of inflammation required complete clinical resolution (Table 2).

### RESULTS

Twenty-six cases of suspected ocular mycobacterial disease were identified from a cohort of 3606 newly re-
ferred patients with uveitis evaluated between 1995 and 2010. Three cases were excluded because of inadequate follow-up. Five cases of suspected TB were excluded for negative TB screening/confirmatory examination findings or tissue diagnosis, despite good response to antimycobacterial therapy. One additional case was excluded for concomitant diagnosis of Behçet disease.

Seventeen patients with ocular mycobacterial disease were included in the analysis, of whom 14 were diagnosed with M. tuberculosis infection and 3 with nontuberculous mycobacterial infection. Average age at presentation was 47.1 years (range, 28-69 years). Eleven patients (64.7%) were female; 8 (47.1%) were born in the United States. Twelve patients (70.6%) had a history of possible TB contacts (7 were born in an endemic country, 2 had extensive travel in endemic countries, 3 had family contacts, and 3 had possible work exposure) (Table 4). Thirty percent had no identified exposure risk. All patients with known TB contacts had M. tuberculosis complex infection, whereas 2 of the 5 patients with no known TB contacts had atypical mycobacterial disease (P = .05). Nine patients (52.9%) had bilateral disease, for a total of 26 involved eyes. Of the 26 affected eyes, 4 had scleritis (15.4%), 2 had granulomatous anterior uveitis (7.7%), 11 had posterior uveitis (+2.3%), and 9 presented with panuveitis (34.6%) (Table 5). Posterior uveitis was associated with bilateral disease (P = .001), while scleritis was encountered only unilaterally (P = .02).

Four of the patients (23.5%) were systemically immunosuppressed prior to their eye disease: 2 from HIV infection and 2 from long-term immunosuppression therapy for systemic conditions (systemic lupus erythematosus and heart transplant). Atypical nontuberculous mycobacterial infection was associated with weakened systemic immune status (P = .02), because 2 of 3 affected patients were immunocompromised before disease onset, 1 from HIV and the other from a heart transplant. Seven additional patients (41.2%) were immunosuppressed for their eye disease prior to presentation to our facility: 6 with oral corticosteroids and 1 with antimetabolite immunomodulatory therapy.

Twelve of 13 patients (92.3%) with available tuberculin skin test results tested positive, while 7 of 8 (87.5%) QuantiFERON-TB Gold In-Tube test results were positive. Thirteen of 15 patients (86.7%) screened had 1 or both test results positive. The 2 patients with negative screening test results had localized nontuberculous mycobacterial infection confirmed by biopsy. Only 4 of 15 (26.7%) with available results had chest radiography findings consistent with tuberculous disease, while 5 of 9 (55.6%) had positive computed tomography chest imaging. Combined, chest imaging was consistent with current or prior granulomatous disease in only 7 of 15 patients (46.7%). Other demographics are shown in Table 4 and Table 5.

A long delay until institution of antimycobacterial therapy was observed. Average delay from the onset of

Table 3. Case Descriptions and Antimicrobial Therapy Administered

<table>
<thead>
<tr>
<th>Case</th>
<th>Presenting Examination Findings</th>
<th>Therapy</th>
<th>Additional Systemic Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nodular scleritis, iritis with anterior chamber cell, and greasy keratic precipitates</td>
<td>RIPb</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Panuveitis: AC cell with fibrin, KP, posterior synechiae, vitreous cell haze, multiple white retinal/choroidal lesions</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Active multifocal choroiditis with mild vitritis</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Active serpiginous-like choroiditis</td>
<td>RIPEc</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Active multifocal choroiditis</td>
<td>RIPEc</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Necrotizing nodular scleritis, panuveitis (granulomatous anterior uveitis, vitritis, multifocal choroiditis, disc edema with an optic nerve head granuloma, exudative retinal detachment)</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Panuveitis, including active macular choroidal lesion with large submacular neovascular membrane</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Serpiginous-like choroiditis, interstitial keratitis</td>
<td>RIPEc; then rifabutin, isoniazid, and oral moxifloxacin</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Panuveitis</td>
<td>RIPEc</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Panuveitis with single 20-disc diameter choroidal tuberculum and multifocal choroiditis</td>
<td>RIPEc</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Panuveitis with large iris granuloma, interstitial keratitis</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Necrotizing nodular scleritis, interstitial keratitis, anterior uveitis</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Panuveitis with granulomatous anterior and intermediate uveitis with a choroidal lesion</td>
<td>RIPEc</td>
<td>clarithromycin and oral gatifloxacin</td>
</tr>
<tr>
<td>14</td>
<td>Necrotizing nodular scleritis</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>Multifocal indolent necrotizing scleritis, nonnodular with thinned moth-eaten appearance, peripheral marginal keratitis</td>
<td>RIPEc</td>
<td>Clarithromycin and discontinuation of immunosuppression therapy</td>
</tr>
<tr>
<td>16</td>
<td>Chronic granulomatous iridocyclitis with iris nodules</td>
<td>RIPEc</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Active choroidal granuloma with disc edema</td>
<td>RIPEc</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: AC, anterior chamber; KP, keratic precipitates; RIP, rifampin, isoniazid, and pyrazinamide therapy; RIPE, rifampin, isoniazid, pyrazinamide, and ethambutol therapy.

a Addition of corticosteroids occurred after the initial response to antimicrobial therapy only.
b Rifampin, 600 mg daily; isoniazid 300 mg daily; and pyrazinamide.
c Rifampin, 600 mg daily; isoniazid 300 mg daily; pyrazinamide, and ethambutol dosed by weight.
symptoms to initiation of antimycobacterial therapy was 802.3 days (range, 29-3073 days). The average delay in referral to the uveitis service by the treating ophthalmologist was 755.3 days (range, 7-3017 days). Race was associated with delay in referral to a uveitis specialist on bivariate analysis. All non-Hispanic white patients were referred to the uveitis service after 3 years of symptoms, while Asian patients from endemic countries were sent within 6 months of onset of ocular symptoms (P = .045). Posterior uveitis was also associated with longer delays in referral: 1587 days vs 478 days for other manifestations of disease (P = .03; r² = 0.30). Delay in diagnosis was associated with negative computed tomography chest imaging. The 5 patients with positive computed tomography chest examination findings were diagnosed with TB on average 241 days from symptom onset compared with 989 days for the 4 patients with negative imaging (P = .03; r² = 0.61).

Ten eyes (38.5%) of 8 individuals (47.1%) had profound loss of vision, defined as irreversible vision loss secondary to TB with best-corrected visual acuity of 20/200 or less in the affected eye: 3 eyes from multifocal choroiditis involving the macula, 2 from multifocal choroiditis with optic nerve involvement, 2 from scleritis recalcitrant to therapy, 1 from endophthalmitis, 1 from multifocal serpiginidoid chorioidopathy, and 1 from a subretinal neovascular membrane associated with a choroidal tuberculum. Four of the 13 patients (30.8%) with disease controlled with antimycobacterial therapy had irreversible profound vision loss, whereas all 4 patients with uncontrolled disease had vision loss (P = .03). Profound loss of vision secondary to mycobacterial infection was associated with delay in diagnosis (Table 6). Patients diagnosed and treated after 500 days from initial symptoms were more likely to have vision loss than those diagnosed earlier (OR, 20.0; 95% CI, 1.41-282; P = .03). Those who had profound irreversible vision loss were diagnosed in 1260 days on average, compared with 475 days for those without irreversible visual loss. This association was further upheld on linear regression, as delay from time of initial symptoms to initiation of antimycobacterial therapy was significantly associated with profound loss of vision (P = .03; r = 0.62).

Age greater than 50 years was also correlated with worse outcomes. Sex and year of diagnosis were not associated with any outcome variables. Older patients were more likely to have uncontrollable disease (P = .03) and were 10 times more likely to have irreversible vision loss (OR, 10.5; 95% CI, 1.1-98.9; P = .04). Loss of the eye was also directly correlated with advanced age on linear regression (P = .05; r = 0.14). In contrast, disease was controllable in all 9 patients younger than 50 years.

Average time to control of disease (in those patients for whom disease could be controlled) was 137.8 days (range, 42-252 days) after initiation of antimycobacterial therapy. Five cases took more than 200 days to achieve control. Supplemental use of steroids to control inflammation after initiation of antimycobacterial therapy was not associated with shorter periods until control of disease but was associated with increased relapse rate (P = .01).

Ten eyes (38.5%) of 6 patients (35.3%) had a relapsing course of disease. Relapse in disease was defined as a 2-step increase in inflammation as defined by Standardization of Uveitis Nomenclature criteria or new or reactivated retinitis, choroiditis, or scleritis. Only 2 patients relapsed after a complete course of therapy as directed by the infectious disease specialist, both of whom had multifocal serpiginidoid-like chorioidopathy. One patient had been treated with 8 months of isoniazid and rifabutin, while the other had received 9 months of RIFE...
therapy. Both of these patients responded to reinstatement of antitubercular therapy without additional corticosteroids or immunosuppressive therapy. Three patients with multifocal choroiditis (2 panuveitis and 1 posterior uveitis) relapsed with a decrease in antitubercular coverage between 1 and 4 months but responded when multidrug therapy was reinstituted. One patient with posterior uveitis secondary to a non-tuberculous mycobacterium also relapsed with a decrease in antitubercular coverage after 3 months but responded to reinstatement of multidrug therapy. Disease control, as defined in the Methods section, was eventually achieved in 21 eyes (80.8%) of 13 patients (76.5%). Three required enucleation of the involved eye because of uncontrolled infection/inflammation despite multidrug antitubercular and anti-inflammatory therapy, 2 after spontaneous perforation from uncontrolled necrotizing nodular scleritis.

A relapsing course of disease was observed in 80% of patients with posterior uveitis, compared with 17% of patients with other manifestations of infection, including panuveitis (P = .03). Relapse was also associated with supplemental steroid use in the treatment of disease-related inflammation. Those treated with supplemental oral corticosteroids after instituting antimicrobial therapy were 10 times more likely to relapse compared with those not treated with steroids on univariate analysis (OR, 10.1; 95% CI, 1.60-64.0; P = .03). No correlation between relapse rate and cumulative dose or duration of steroid treatment (data not shown). Both posterior uveitis and supplemental steroid use remained independently associated with relapse on multivariate regression analysis. In the multivariate model, those with posterior uveitis had a 13 times higher chance of relapse (OR, 13.1; 95% CI, 1.16-148; P = .04), while those treated with systemic steroids were 15 times more likely to respond to reinstitution of multidrug therapy. Disease control, as defined in the Methods section, was eventually achieved in 21 eyes (80.8%) of 13 patients (76.5%).

Table 6. Outcome Measures and Their Risk Factors

<table>
<thead>
<tr>
<th>Eyes, No. (%)</th>
<th>Risk Factors</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent loss of visual acuity (&lt;20/200)</td>
<td>Age &gt;50 y</td>
<td>10.5 (1.1-98.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Relapsing disease</td>
<td>Delay in diagnosis (&gt;500 d)</td>
<td>20.0 (1.41-282)</td>
<td>.03</td>
</tr>
<tr>
<td>Uncontrolled disease</td>
<td>Posterior uveitis</td>
<td>13.1 (1.16-148)</td>
<td>.04</td>
</tr>
<tr>
<td>Loss of eye</td>
<td>Supplemental systemic steroids</td>
<td>14.9 (1.40-160)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Ocular mycobacterial infection is uncommon. In this series, 0.7% of 3606 new patients with uveitis seen at a US tertiary referral uveitis service over a 15-year period were suspected of having ocular mycobacterial disease, and only 0.5% met study inclusion criteria. This is in accordance with rates reported in the United States and other developed countries. Even in endemic countries, TB uveitis is not very common, with 1 tertiary center in southern India reporting a prevalence of 0.39% among patients with uveitis. Other endemic regions report higher rates of 6% to 10%, although case inclusion criteria vary significantly between series.

Ocular TB typically occurs without clinically apparent systemic disease. This has been observed since the time of Verhoeff, who stated that clinical evidence of TB elsewhere in the body is “slight or entirely lacking” in patients with tuberculous chorioretinitis. Furthermore, pulmonary TB is rarely associated with ocular TB, though other systemic manifestations are more closely correlated. A study in India demonstrated concomitant ocular disease in only 1.2% of those with pulmonary TB, as compared with 16.2% and 23.2% in those with TB meningitis and TB lymphadenopathy, respectively. Of the 17 patients with ocular mycobacterial disease in this study, 13 had active disease limited to the eyes, 2 had systemic lymphadenopathy, 1 had miliary TB, and only 1 had active pulmonary TB. This rate is similar to those reported in other studies but deserves reemphasis because many clinicians are unwilling to diagnose TB in the absence of pulmonary disease.

Given the lack of association between ocular and pulmonary TB, it is not surprising that chest imaging was not able to adequately identify cases of TB in this series. Chest imaging was consistent with current or prior granulomatous disease in only 46.7% of patients with ocular mycobacterial disease in this series, 43% in the Armed Forces Institute of Pathology study, and 28% in a UK series. Furthermore, patients with negative chest computed tomography scans in this series had a 2- to 3-fold longer delay in diagnosis, perhaps suggesting an overreliance on imaging.

Two cases of necrotizing nodular scleritis in this series resulted in perforation and enucleation, despite systemic anti-TB therapy and later addition of immunosuppressive therapy. Corneoscleral perforation is not uncommon in TB uveitis, with 1 study reporting a 12% enucleation rate secondary to perforation. There is debate as to whether TB scleral nodules represent an exaggerated response of that seen in phlyctenulosis, ie, a hypersensitivity reaction to tuberculin proteins, or whether it represents direct infection. Cases with evidence of direct infection have been reported, with a pathology study suggesting that perforation occurs as a result of long-standing infection. Evidence from our series further supports the latter hypothesis, as 3 scleritis cases had...
direct evidence of infection: 1 culture-positive case, 1 PCR-positive lesion, and 1 PCR-positive biopsy specimen of a conjunctival granuloma in a patient with necrotizing scleritis, with caseating necrosis seen on pathologic examination of the sclera at the time of enucleation.

The etiology of TB-related posterior uveitis has also been debated. Verhoeff identified TB as an etiology of choroidal granulomatous disease based on characteristic histologic findings. Over time, however, the hypersensitivity hypothesis gained momentum, secondary to the lack of ability to directly identify the bacillus in ocular specimens. More recently, however, Rao et al were able to demonstrate acid-fast bacilli in necrotic retinal pigment epithelial cells in an enucleated eye of a patient with panuveitis treated only with steroids, with the diagnosis confirmed by PCR for M tuberculosis. Because the process of granuloma formation sequesters and encapsulates bacteria but does not necessarily destroy them, mycobacteria may inhibit binding of phagosomes and avoid microbicidal activity, remaining protected from the immune system within the cell. The disease may then be reactivated in times of relative immunosuppression, such as with systemic disease or immunosuppressive therapy. As retinal pigment epithelial cells share phagocytosis-like activity with macrophages, TB may be able to evade the phagosome activity of these cells, which may be an explanation for the relapsing nature of posterior disease observed in this series. The independent effect of steroids on relapsing disease also suggests an inability of host immunity to effectively clear mycobacteria. It is possible that posterior segment relapse represents reactive inflammation, active infection, or a combination of the two. However, given that those patients who received a full course of antimycobacterial therapy tended not to relapse, and those who relapsed responded to an expanded course of therapy, we suggest that recurrence represents reactivation of sequestered organisms in retinal pigment epithelial cells and that relapse necessitates retreatment with antimycobacterial therapy.

While diagnosis and treatment can be a challenge, other factors impacting morbidity may be more easily addressed, such as the extremely long delays in referral to uveitis specialists reported herein, as well as in a series from Manchester, England. In this study, those with delays in diagnosis longer than 500 days were 20 times more likely to have irreversible vision loss and loss of the involved eye. Analysis of delay highlights potential bias in referring practices, as well as overreliance on ancillary testing. Our data demonstrate that all Asian patients born in TB endemic countries were referred within 6 months, while non-Hispanic white patients born in the United States were all referred after more than 3 years of symptoms. Nearly one-half of the patients in this study were not born in an endemic country and nearly one-third had never spent time in an endemic area. Our data, therefore, serve to highlight the need to consider the diagnosis of mycobacterial infection, even in patients who are not from or have not been to endemic countries, regardless of race. Delay was also significantly higher in patients with posterior uveitis. This difference is difficult to explain but may be due, in part, to the greater degree of comfort of referring ophthalmologists in managing posterior uveitis as compared with panuveitis or necrotizing scleritis. In those patients not adequately responding to anti-inflammatory therapy, mycobacterial infection should be entertained and consideration be given to referral to a uveitis specialist, even in the setting of normal ancillary testing.

The decision regarding whom to treat is difficult. Proposed treatment algorithms, while needed, may underestimate the complexity of disease, leading to both undertreatment and overtreatment. Gineys et al proposed treatment guidelines based on the quantitative value of interferon gamma release assay testing and tuberculin skin tests. However, use of these tests alone will result in overdiagnosis of ocular mycobacterial disease, because the majority of patients with uveitis and positive purified protein derivative or interferon gamma release assay results will not have TB uveitis and will not benefit from expensive and potentially toxic TB therapy. Sanghvi et al suggested that when definitive testing is unavailable, the use of supportive circumstantial evidence together with absence of evidence for other disease warrants 6 months of therapy. Vasconcelos-Santos et al proposed a different algorithm, using clinical history of TB exposure in the decision-making tree. Our series does not have sufficient data to support any particular algorithm but suggests the need to consider age as a modifying factor, because worse outcomes were encountered in patients older than 50 years. Given these complexities, we believe that a simple algorithm is not yet possible and suggest only that mycobacterial infection be considered in the differential diagnosis of uveal inflammation, regardless of patient ethnicity, country of origin, and chest imaging findings, particularly when disease is not responding to anti-inflammatory therapy as expected.

The optimal treatment and duration of antimycobacterial therapy are unknown. Studies have shown therapy to be effective in only 40% to 70% of cases of mycobacterial ocular infection. 80.8% of diseased eyes were able to be controlled in this study, although more than one-third of eyes had irreversible visual loss. Observations of worsening disease when therapy was tapered in this study, with response to reinstitution of multidrug therapy, suggest that longer treatment periods may be required for ocular disease than systemic disease, especially for those with posterior and panuveitis with multifocal choroiditis. The sizeable effect of systemic corticosteroids on relapse in this study is concerning. Previous clinical studies have postulated an association between systemic steroids and relapse risk, and an experimental animal model has demonstrated a prolonged course of ocular TB and higher rates of recurrence in the setting of corticosteroid therapy. Given the significantly higher risk of relapse of patients in this series treated with systemic corticosteroids, as well as lack of benefit in terms of time to control of disease and visual outcomes, steroids may have a limited role in treatment. While further elucidation is required, we think that steroids should be used judiciously to control destructive inflammatory sequelae and that some form of anti-TB therapy should be instituted for all relapsing disease.

This study is limited by its sample size, which serves to increase type I error and lead to false conclusions. It
may also have somewhat limited generalizability because it was conducted at a tertiary care facility in the Midwestern United States. It is, however, among the largest modern series from the United States, with prevalence rates similar to studies from nonendemic countries,11,12 such that there may not be an overwhelming recruitment bias. While the study conclusions must be interpreted with due caution, it is reassuring that the clinical findings and outcomes are similar to those reported in other studies. Further, this study provides statistical evidence with large strengths of association for topics long observed, debated, and in need of further elucidation, such as the effect of systemic steroids and the nature of relapsing disease. Regardless of its limitations, this study does suggest that TB must be considered in the differential diagnosis of ocular inflammation, irrespective of patient ethnicity, country of origin, or results of chest imaging; that longer periods of multidrug therapy may be required to control ocular mycobacterial infection; that systemic corticosteroids be used judiciously; and that a reduction in the delay in diagnosis could improve clinical outcomes.

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REFERENCES


