Case Report

Mycobacterium-related Ocular Inflammatory Disease: Diagnosis and Management

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Abstract

   Introduction: Worldwide, there are approximately 8 million new cases and 3 million deaths from tuberculosis (TB) each year. TB affects the entire body and the eye. Although ocular TB is considered rare, its incidence has varied widely across time, patient populations, and geography. We report 2 patients with unique presentations of ocular TB and detail the treatment and outcome of the disease. **Materials and Methods**: Two cases of ocular inflammation, one with a medical history of systemic TB and the other, with that of presumed systemic TB, were examined. Choroidal granuloma developed in one, and scleritis developed in the other. The literature on ocular TB was comprehensively reviewed. **Results**: Both patients were diagnosed with ocular TB. The histology of the systemic TB lesions was also illustrated. They responded to aggressive anti-TB and anti-inflammatory therapies. **Conclusions**: The diagnosis and management of ocular TB can pose a significant challenge. Physicians and ophthalmologists must include TB among the differential diagnoses of patients with ocular inflammatory diseases and treat ocular TB with a combination of anti-TB and immunosuppressive medications as needed. Immunosuppressive medications applied in this setting must be cautioned and only prescribed by ophthalmologists who are familiar with these agents.

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Key words: Anti-TB therapy, Granuloma, Ocular infection, PPD test, Tuberculosis

"If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious disease such as bubonic plague, Asiatic cholera, must rank far behind tuberculosis."

Robert Koch, 1882

Introduction

   Tuberculosis (TB) is an ancient disease that has been detected in 3000-year-old Egyptian mummies.[1] Robert Koch's discovery of the tubercle bacillus as the aetiologic agent of this disease in 1882 led to the acceptance of "Koch's postulates," which remain the gold standard for linking a pathogen to a disease.[2] In humans, TB is caused by one of the members of the *Mycobacterium tuberculosis* complex: *M. tuberculosis, M. bovis,* and *M. africanum;* most commonly by *M. tuberculosis.*[3] TB is estimated to affect 1.7 billion individuals, with 8 million to 10 million new cases and 1.7 million deaths each year worldwide, ranking only second to the human immunodeficiency virus (HIV) as a leading cause of infection-related deaths. The

majority of TB manifestations are pulmonary, with extrapulmonary TB comprising only about 15% of reported cases.[4] After infection with the bacillus, around 85% to 90% of individuals successfully eliminate the systemic infection and never suffer from clinical illness. A significant proportion acquires latent TB, wherein the infection is controlled but not eliminated.[5]

   The methods currently available to test for latent TB are a skin tuberculin skin test [i.e., positive purified protein derivative (PPD) skin test] and commercially available gamma interferon assays to mycobacterial antigens [such as the Center for Disease Control (CDC)-approved Quantiferon assay validated in specified groups and Early Secretory Antigen Target (ESAT)-6] that measure the response of the patient's lymphocytes to exposed specific antigens and are still undergoing modifications.[3,6] These 2 new tests may improve myco-bacteria interspecies differentiation and decrease the incidence of confounding reactions against ubiquitous atypical mycobacteria.[3] The CDC-recommended flow chart is cited here (Fig. 1). One-third of the world population is estimated to have latent TB

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[World Health Organization (WHO) 2003 report]. A history of a bacillus calmette-guerin (BCG) vaccine (>15 years) in a patient with a positive PPD skin test for TB or gamma interferon assay to mycobacterial antigens does not rule out true TB infection and warrants further work-up.[7,8]

TB has a characteristic histopathologic presentation, with classical caseating granulomas.[9,10] The granuloma consists of a central caseating necrosis surrounded by macrophages or epithelioid cells, lymphocytes, and multinucleated giant cells (Langerhan's giant cells), in which the nuclei are arranged at the periphery in a horseshoe shape. Although reactive and primary TB are histologically similar, caseating granulomas tend to occur more in reactivated TB.[4] Occasionally, TB granulomas may not show central caseation, even in immunocompetent individuals. Special stains for acid-fast bacillus (AFB) demonstrating sequestered microorganisms need to be performed.

The presentation of ocular TB may be subtle, and a high index of suspicion is critical in a relevant setting due to the possibility of irreversible visual consequences if it is misdiagnosed. TB may manifest in the eye in disseminated primary infection,[11,12] reactivated latent infection or occasionally in the form of "immune"-mediated disease with usually no viable *M. tuberculosis* detectable by culture or biopsy.[13] TB has been reported in almost all ocular tissues,[14] manifesting as eyelid abscesses,[15] orbital cellulitis,[15] dacrocystitis,[16] lacrimal gland infiltration,[17] corneal ulcers,[18] chronic conjunctivitis,[19] phylectenules,[20] iris infiltrations,[21] optic neuritis,[22] neuroretinitis,[23] vitritis,[24] choroidal tubercles,[25] chorioretinitis,[26] and intraocular masses simulating tumours.[27] Immune-mediated manifestations include scleritis,[14,24,28] keratitis,[14] anterior uveitis, intermediate uveitis (including pars planitis),[29] posterior uveitis,[11,30] panuveitis,[31,32] and retinal vasculitis.[33] We present 2 patients with challenging immune-mediated ocular TB and detail the unique therapeutic approaches with varying outcomes.

Case Reports

Patient 1

In September 2000, a 33-year-old Filipino-American female was evaluated at the National Eye Institute (NEI) for complaints of painful red eyes accompanied by decreased vision that had waxed and waned for 3 years. In February 1997, she noticed decreased vision along with mild pain in the left eye in the Philippines while working as a veterinarian. She was diagnosed with unilateral diffuse scleritis. The differential diagnosis considered included rheumatoid arthritis, polyarteritis nodosa, and Wegener's granulomatosis. However, after clinical evaluation and laboratory testing, the aetiology was unclear. Therapy consisted of oral non-steroidal anti-inflammatory drugs (NSAIDs) and 3 serial periocular injections of triamcinolone with resulting improvement in vision OS (left eye) from 20/60 to 20/40 over a few months, coincident with relief of pain. After 3 months, she developed ocular inflammation OD (right eye) and was diagnosed with nodular scleritis. She was treated successfully using the same therapy as OS. By late 1999, the patient started noticing decrease of vision OU (both eyes). Vision was 20/40 OU, but she did not respond to the therapy. In January 2000, her vision further decreased to 20/100 OD. Choroidal masses were found in that eye. A systemic work-up was initiated, erythrocyte sedimentation rate (ESR) was 106 mm/h, and a brain MRI revealed a right subdural mass. The patient was referred to the NEI.

The patient had a history of abdominal TB (probable *M. bovis*) contracted through unpasteurised milk that was diagnosed 6 years ago by laparotomy and omental biopsy (Fig. 2). She had received anti-TB therapy with 4 drugs [isonicotinic acid hydrazide (INH), rifampin, ethambutol and pyrazinamide] for 13 months but admitted that she had not been entirely compliant with therapy. She was well until early 1997, when she developed skin lesions on her left upper arm that were biopsied and consistent with skin TB. She was again placed on the same 4-drug regimen, with improvement in the skin lesions. After discontinuing the anti-TB medications for 4 to 6 weeks, she experienced the first episode of ocular inflammation. She denied significant respiratory symptoms or weight loss. She was positive to skin PPD testing from 1998 to the year of examination.

On examination at the NEI, the vital signs were within normal limits. There were neither palpable lymph nodes nor skin nodules. Visual acuity was 20/80 OD and 20/32 OS. There was no afferent pupillary defect. The external ocular examination was normal. There were bilaterally active superior 2 quadrant scleritis with thinning and a scleral nodule was evident in the left eye in the super-temporal quadrant. The anterior chamber revealed trace cells and 1+ flare OD, and 1+ cell and 1+ flare OS. The corneas were clear bilaterally. There were posterior synechiae bilaterally, OS >OD. The lenses demonstrated mild bilateral posterior subcapsular cataracts (PSC). The vitreous showed trace vitreous cells and haze bilaterally. A chorioretinal lesion was seen near the super-temporal arcade of the right macula that was clinically consistent with a choroidal granuloma accompanied with retinal pigment epithelial involvement (Fig. 3a). There was cystoid macular oedema. The optic nerves were unremarkable. Fluorescein angiograms (FA) demonstrated bilateral retinal vascular leakage, right more evident. The right chorioretinal lesion did not leak (Fig. 3b). There was no demonstrable choroidal thickening on B-scan bilaterally and the angles were bilaterally normal on ultrasound biomicroscopy.

Conjunctival swab and blood cultures were negative for AFB and fungi.

A diagnosis of bilateral nodular sclerouveitis was made. Central nervous system TB was considered. Wegener's granulomatosis, rheumatoid arthritis, lupus, sarcoidosis, syphilis, and herpetic diseases were the differential diagnoses. Laboratory investigations showed normal serum chemistries and blood counts; negative serology for anti-neutrophilic cytoplasmic antibody (ANCA), syphilis; and normal angiotensin converting enzyme (ACE) level. Erythrocyte sedimentation rate (ESR) was 114/h. There was lupus anticoagulant with elevated partial thrombo-plastin time (PTT) (correctable with mixing studies). Chest x-ray was normal. Magnetic resonance imaging (MRI) brain revealed meningeal enhancement with IV contrast and a right ill-defined subdural mass of uncertain size with accompanying brain oedema. Spinal fluid chemistry and microbial examination were non-conclusive. Due to the uncertain diagnosis, including the possibility of lymphoma, a brain dural biopsy was undertaken. Histopathological exam of the parietal dura revealed no caseating granulomas but heavy infiltration of plasma cells, lymphocytes, and macrophages. No malignant cells were identified. Although the pathological diagnosis was atypical TB meningitis, the culture for mycobacteria was negative. Infectious disease consultation was non-contributory.

Due to the progressive loss of vision and bilateral severe scleritis, the patient was placed on topical prednisolone, q.i.d. bilaterally. Since there was a possibility of the drug-resistant TB being rendered lethal by immunosuppressive corticosteroids, 4 anti-TB drugs were also initiated for 2 weeks and subsequently, oral prednisone was added to the anti-TB regimen at 20 mg/day, titrated to 30 mg per day (0.75 mg/kg/day) over 4 weeks. There was both subjective and objective improvement in the patient's condition in a few months. By September 2001, the patient's vision had improved to 20/50 OD and 20/20, OS. The scleritis had resolved with bilaterally thinning 120° OD and 360° OS. There were only trace cells and trace flare bilaterally. The posterior segment was free of haze and cells bilaterally. FA did not demonstrate significant vascular leakage. Brain MRI showed significant resolution of oedema. The anti-TB medications were discontinued after 12 months and oral prednisone was tapered.

In September 2001, her vision worsened to 20/125 OD and 20/80 OS. There was no evident scleritis. The anterior chamber showed only bilateral trace flare. However, the patient had developed bilateral PSC1+, 2+; OD and OS, respectively. There was significant bilateral macular oedema, which was confirmed on FA (Figs. 3c and 3d). Prednisone was re-instituted at 50 mg daily in conjunction with the previous regimen of anti-TB drugs. After 4 months

of therapy, her vision had improved to 20/80 OD and 20/32 OS. The patient was continued on the therapeutic regimen with B6 and multivitamins. Bisphosphonates *(*alendronate 70 mg) once a week and calcium supplements were also added to retard osteoporosis associated with corticosteroid use. After 12 months, the oral prednisone was tapered to 7.5 mg daily and the anti-TB medications were discontinued. The vision remained stable at 20/80 and 20/32 in the presence of significant bilateral cataracts, with no clinically evident macular oedema at the last visit in early August 2004 (Fig. 3e). On telephone follow-up, her vision was stable as of May 2005, on less than 7.5 mg of prednisone for 8 months.

Patient 2

A 77-year-old diabetic African-American female was referred for bilateral painful necrotising scleritis, which first developed 3 months prior. Her medical history included a longstanding seizure disorder partially controlled on phenytoin, borderline hypertension, and non-deforming arthritis for 20 years. Her diabetes was controlled on metformin 500 mg twice daily. She had developed skin lesions that were diagnosed by biopsy to be pyoderma gangrenosum (Figs. 4a and 4b). Immunosuppressive therapy for her skin disease included prednisone 30 mg daily, and oral methotrexate initiated at 5 mg weekly and titrated upwards to 20 mg weekly. After 2 months on the immunosuppressive, the patient complained of ocular pain and was diagnosed with bilateral necrotising scleritis. Investigations revealed a positive rheumatoid factor, negative serologies for ANCA (p and c) and syphilis. The ESR was 106 mm/h. PPD skin testing was positive with a measurement of 30 mm while on immunosuppressant therapy. The patient was referred to the NEI.

On examination, the vital signs were normal. The vision was 20/40 OD and 20/80 OS. The adenexae were within normal limits. The sclerae were markedly injected in all 4 quadrants with the multiple necrotic foci evident superiorly OD, and multiple areas of thinning bilaterally (Figs. 5a and 5b). The corneas were clear bilaterally. The anterior chambers were deep and quiet bilaterally. The irides were normal and the lenses had 2+ nuclear sclerotic changes bilaterally. The anterior vitreous was free of cells and haze bilaterally. There was mild hypertensive retinopathy. The optic nerve heads were unremarkable other than mildly increased cupping bilaterally.

Laboratory investigations revealed normal serum chemistries and blood counts. The ESR was 84 mm/h. Chest X-ray demonstrated chronic calcified nodular opacities. High-resolution computed tomographic (CT) scans of the chest revealed multiple nodular lesions in the lung parenchyma consistent with granulomatous lung
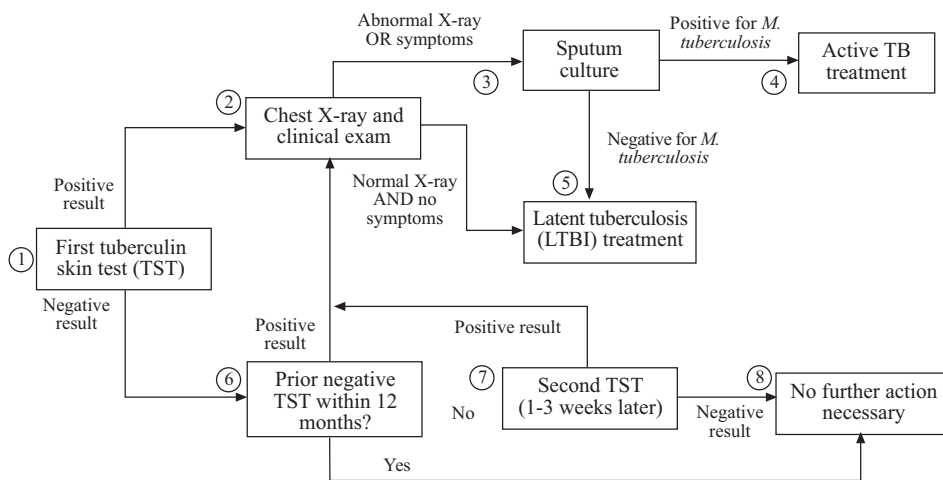
Fig. 1. Two-step tuberculin skin testing (TST) flow chart from CDC, USA.

Source: Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Morb Mortal Wkly Rep 2000;49(RR-6):1-51.
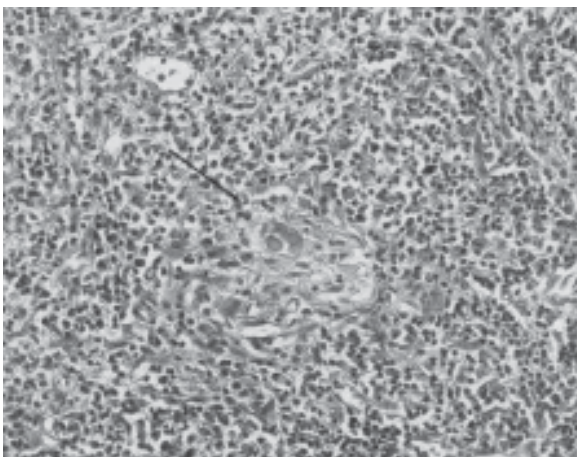

Fig. 2. Case 1. Microphotograph showing a granuloma (arrow) surrounded by numerous lymphocytes in the omental biopsy (haematoxylin & eosin, x100).
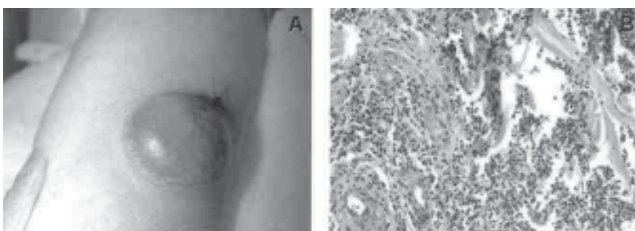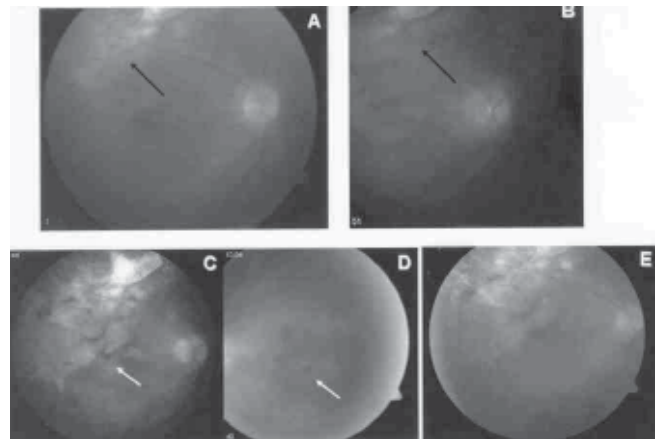

Fig. 3. Case 1. Fundoscopic photographs showing (A) a large elevated choroidal granuloma (arrow) in the superior temporal region and hazy vitreous of the right eye; (B) no leakage of the granuloma (arrow) by FA; (C) intraretinal accumulation of fluorescein in the macula (arrow) and choroidal lesion of the right eye; (D) a petaloid pattern (arrow) indicating macular oedema of the left eye; (E) a resolving choroidal granuloma with pigmentation and clear vitreous of the right eye.

Fig. 4. Case 2. Photographs showing (A) a large skin lesion with a violaceous border and a surrounding halo of erythma; (B) pathology of the skin lesion with a heavy infiltration of lymphocytes and neutrophils (haematoxylin & eosin, x100).
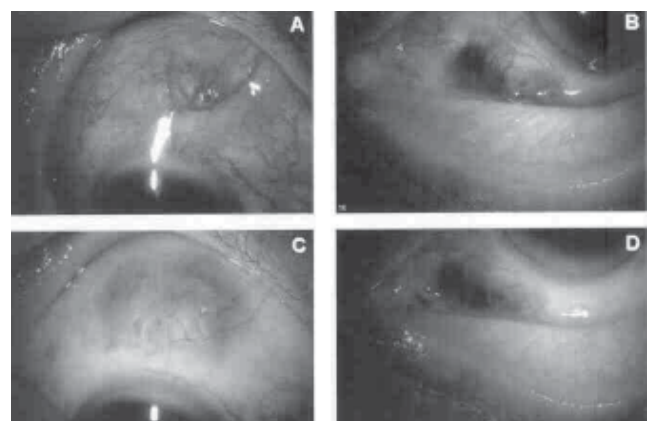

Fig. 5. Case 2. Slit lamp photographs showing (A) a blue-greyish linear lesion (due to thinning, which allows the underlying choroids to show) and engorged deep episcleral blood vessels in the thinning, oedematous sclera of the right eye; (B) a large blue-grey, brownish appearance covered by a thin inflamed sclera of the left eye; (C) after anti-TB and anti-inflammatory treatment healed scleritis of the right eye; (D) resolving scleritis of the left eye.

disease. The patient underwent a bronchoalveolar lavage (BAL) that was non-diagnostic.

Bilateral necrotising scleritis was diagnosed and the differential diagnosis included TB, Wegener's granulomatosis and polyarteritis nodosa. Pulmonary consult also suggested phenytoin-induced pulmonary granulomatous disease. Reactivated TB was considered most likely due to the florid PPD reaction even under significant

immunosuppression and due to persistent scleritis in spite of the institution of methotrexate. She did not qualify for rheumatoid arthritis by the American College of Rheumatology (ACR) criteria. ANCA was negative (p and c). There was no clinical evidence of granulomatous airway disease or renal symptoms such as haematuria. Due to the bilateral vision-threatening scleritis, the patient was admitted as an inpatient and anti-TB medications were instituted. Infectious disease consultation suggested a shorter 9-month course of anti-TB therapy for the patient in view of her age and morbid conditions. INH 300 mg, rifampin 600 mg, ethambutol 800 mg, and pyrazinamide 1000 mg once daily was the starting regimen and oral prednisone 20 mg was added after a week. The necrotising scleritis improved in 1 week. The patient was discharged home. The necrotic foci of her skin were completely epithelialised in 4 weeks. The patient was instructed to continue the 4 anti-TB medications for 2 months. The original plan was to continue INH and rifampin in conjunction with oral prednisone, all at the same dose except for prednisone, which would be slowly tapered. However, the patient developed hyperuricaemia, and pyrazinamide was stopped and the uric acid levels reverted to baseline while she was in the hospital. Phenytoin was replaced by carbamazepine, as recommended by a pulmonary specialist. The patient was followed in the outpatient clinic and the corticosteroids were tapered over 3 months to 12.5 mg daily. Oral calcium supplements and alendronate were added to her regimen. On follow-up with her internist, she discontinued the anti-TB medications but remained on prednisone. Six weeks later, she presented with bilateral scleritis and unchanged vision. Four anti-TB medications in conjunction with 40 mg of oral prednisone were again prescribed and the patient responded favourably. Currently, the patient is on only 2 drugs for TB (INH and rifampin) and 20 mg of prednisone with normal liver function tests. The bilateral scleritis was completely resolved with thinning (Figs. 5c and 5d) and her vision was 20/80 OD, 20/60 OS, in the presence of significantly worsened cataracts.

Discussion

Two patients presented with ocular inflammatory disease and past medical histories of systemic TB and presumed systemic TB. Partially treated ocular TB was diagnosed in one and TB-associated scleritis was diagnosed in the other.

In the first patient, the social history of immigration, occupational hazards and medical history of treated systemic TB with manifestation of granulomatous panuveitis led to the clinical diagnosis. Although drug-resistant TB was suspected initially, the history of self-interruptions in therapy suggested that a full course of anti-TB therapy would be beneficial. After the completion of the full course of therapy, her macular oedema was managed as a non-infectious autoimmune complication. The reasoning for this approach was that the chorioretinal lesions were resolving and no new lesions were evident bilaterally.

In the second patient, the frankly positive PPD while on significant immunosuppression made TB the most likely diagnosis, although infective isolated scleritis is an unusual manifestation of ocular TB. Interestingly, there are reports that have associated pyoderma gangrenosum with systemic TB.[34] The patient later confirmed that a close relative was infected with TB, lending more support to the diagnosis. Phenytoin hypersensitivity was not considered,[35] because the ocular inflammation recurred on carbamazepine (tegretol).[35] Furthermore, there was a rapid clinical response to the anti-TB medications in combination with low-dose steroids. With discontinuation of anti-TB therapy, the scleritis promptly recurred, supporting the diagnosis of presumed ocular TB.

Unlike pulmonary TB, where cultured sputum or biopsy is feasible, intraocular TB is less likely to be diagnosed via microbiological or histological evaluation. To illustrate this point, the incidence of intraocular TB in surveys of patients with intraocular inflammatory disease is around 0% to 0.16% and that in patients with systemic TB is 0.27% to 1.4%. Thus microbiologically or histologically proven cases of intraocular TB are relatively rare. Although molecular analysis (polymerase chain reaction) has assisted the detection of TB and is rapidly becoming a method of choice for the detection of TB DNA,[14] this technique does not make it any easier to obtain an intraocular specimen in an inflamed eye.[36] These patients represent typical scenarios in the ocular immunology clinic where evaluation of granulomatous uveitis mandates ruling out TB. Often, sampling non-ocular tissues where relevant may help in this endeavour.

The management of immune-mediated ocular disease associated with TB poses a challenge, as a judicious mix of antimicrobial and immunosuppressive regimens in varying combination often has to be titrated to clinical effect.[37] Intraocular TB should be managed as central nervous system (CNS) TB.[11] Due to the blood-brain barrier, blood levels of anti-TB drugs may not reflect their levels in the CNS.[38] Both patients responded to the combination of anti-TB therapy in conjunction with carefully monitored immunosuppressive therapy.[37] This approach addressed both the infectious and inflammatory components, although the margin between the infection and autoimmunity may be constantly changing.[39,40] The clinical decision to institute immunosuppressive therapy for scleritis in the face of potentially active TB is a complicated and challenging issue. The safest approach would be to institute anti-TB therapy; if the response is inadequate, a titrated trial of

Table 1. Summary of Relevant Anti-TB Medications

Anti-TB drugs	Action	Adverse effects
Isoniazid (INH)	Bactericidal intracellular and extracellular	Hepatic enzyme elevation, peripheral neuropathy, hepatitis, hypersensitivity
Rifampin	Bactericidal against both intracellular and extracellular organisms, maintains activity against very slowly metabolising bacilli	Orange discolouration of secretions (contact lens discolouration) and urine: nausea, vomiting, hepatitis, febrile reaction, purpura
Pyrazinamide	Bactericidal only at acidic pH such as within cells, greatest activity in first few months of therapy	Hepatotoxicity, hyperuriacaemia, arthralgias, skin rash, gastrointestinal upset
Ethambutol	Bacteriostatic against both intracellular and extracellular organisms	Optic neuritis (decreased red-green colour discrimination, decreased visual acuity), skin rash

immunosuppression combined with anti-TB therapy is recommended.

TB has a propensity to reactivate in conditions of relative immunosuppression.[4] This explains the higher incidence in extremes of age[41] and is further evident in patients who receive anti-tumour necrosis factor therapy for inflammatory diseases, including uveitis, and develop TB.[42] The adverse effects related to anti-TB medications are not trivial, and prior to therapy careful consideration must be given to the risks versus benefits of therapy.[43] Infectious disease consultation is necessary in every case of suspected TB not only for therapeutic advice but also epidemiologic considerations. There should be a solid primary care infrastructure to provide follow-up care and avoid complications (Table 1) related to the medications. In suspected *M. bovis* infection, directly observed therapy may be a safer approach as this microorganism is notorious for inherent drug resistance and interrupted therapy may aggravate this problem.[44,45] This described scenario may not be entirely applicable to areas where TB is highly endemic.

TB bacillus is well known to be highly immunogenic.[7,46] The vaccines that are currently undergoing clinical trials under the auspices of the National Institutes of Health[47] may prove to be effective in battling this pandemic; however, it remains to be seen whether the immunogenicity of the bacillus itself would induce autoimmune disease.[46] Drug-resistant HIV in AIDS patients could conceivably contribute to TB epidemics, even in developed countries.[48] TB remains a huge problem worldwide, and ophthalmologists must be aware of the severe consequences of failing to include TB among the differential diagnosis of patients with ocular inflammatory diseases.

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