Mycobacterium tuberculosis Infection Complicated by Eales Disease with Peripheral Neuropathy

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Eales disease, which is reported mainly in patients from the Indian subcontinent, is characterized by ophthalmic abnormalities that are sometimes followed by neurologic sequelae, and it is associated with previous Mycobacterium tuberculosis infection. We describe the first patient, to our knowledge, to receive a diagnosis of active tuberculosis and concurrent, severe neurological Eales disease, including peripheral neuropathy. The patient recovered completely after receiving steroid therapy. Eales disease is characterized by retinal periphlebitis, peripheral neovascularization, and vitreous hemorrhage [1]. It is most commonly reported in young men from the Indian subcontinent, and it frequently causes massive vitreous hemorrhage and temporary unilateral blindness. In addition, a spectrum of CNS complications associated with Eales disease has been reported, although these are very rare [2–7]. The precise etiology of Eales disease is uncertain, but it is generally considered to be an unwanted, immune-mediated hypersensitivity response to Mycobacterium tuberculosis. However, cases of active tuberculosis infection with concurrent Eales disease are unusual, and, to our knowledge, a case of neurological Eales disease that has complicated active M. tuberculosis infection has not been previously reported. We describe such a case, which includes the first report of Eales disease associated with peripheral neuropathy, and we also briefly review this M. tuberculosis–associated phenomenon.

Case report. A 24-year-old Sri Lankan man with no past medical history presented to a UK hospital that specializes in eye care with acute unilocular blindness in the right eye due to a vitreous hemorrhage. Retinal periphlebitis and neovascularization were noted, and a diagnosis of Eales disease was made. The patient underwent vitrectomy and endolaser therapy, with successful restoration of vision. No samples obtained during vitrectomy were sent to a laboratory for any mycobacterial analysis. Chest radiography performed during this hospitalization revealed right-side mediastinal and paratracheal lymphadenopathy, but the patient did not return for follow-up.

Sixteen months later, the patient presented to a second hospital with malaise, weight loss of 5 kg, a nonproductive cough, and fever. Chest radiography revealed bilateral infiltrates, with upper right zone opacification, and a thoracic CT scan confirmed that there was extensive cavitary disease. The WBC count was $5.2 \times 10^9$ cells/L, and the C-reactive protein level was elevated (125 mg/L). Acid-fast bacilli were detected on examination of a bronchoalveolar lavage specimen, and they were confirmed to be drug-sensitive M. tuberculosis on culture. The results of HIV antibody testing were negative. Antituberculous therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol plus pyridoxine was commenced, and compliance with therapy was assessed as good. There was initial symptomatic improvement and resolution of fever and nocturnal sweats. Three months after the patient began receiving treatment, his weight had increased by 5 kg, to 55 kg. However, during the next few weeks, there was a marked clinical deterioration, with recurrent weight loss and fever. The patient gradually developed increasing difficulty walking and passing urine as well as numbness below the knees. He was readmitted to his local hospital, where he continued to receive supervised antituberculous therapy. His neurological symptoms progressed, and he developed bilateral foot drop. He was transferred to our hospital for further treatment.

The patient had intermittent high fevers (temperature, >38°C) and was cachectic (weight, 51 kg) and barely able to walk. There were upper right zone crackles on auscultation of the chest. There was smooth, nontender splenomegaly (length, 20 cm). On neurological review, the patient had a spastic paraparesis with increased tone in both lower limbs, patellar clonus, and globally diminished power. Knee jerks were brisk, but ankle jerks were absent. All sensory modalities were impaired distally, which is consistent with peripheral neuropathy. Ophthalmological assessment confirmed that there had been no change in the retinal disease. The C-reactive protein level remained elevated at 48 mg/L, and the erythrocyte sedimentation rate was
74 mm/h. Sputum samples were repeatedly smear- and culture-negative for *M. tuberculosis*. MRI with gadolinium enhancement showed no spinal cord abnormalities. The findings of CSF examination were unremarkable, and CSF specimens did not yield pathogens on standard or mycobacterial culture. The findings of electromyography were consistent with distal axonal polyneuropathy. Very extensive investigations excluded other disease processes, including systemic vasculitis, syphilis, sarcoid, and amyloidosis.

In view of his history of distinctive retinal disease, we suspected that this patient had an unusual neurological manifestation of Eales disease associated with tuberculosis. Prednisolone therapy (20 mg) was commenced, and there was a dramatic clinical improvement within 72 h. The fever abated, and the C-reactive protein level decreased to 16 mg/L within a few days and eventually normalized. The patient’s weight had increased to 64.5 kg at 6 months. Neurological signs resolved such that the patient was walking normally 3 months after commencing treatment, but prednisolone therapy (5 mg) was continued for 6 months, because neurological improvement continued for this period.

**Discussion.** This case was a rare complication of a common infectious disease. Eales disease is a well-defined clinical entity, although its pathogenesis is poorly understood. Recent data from the Indian subcontinent, where the incidence of Eales disease is high, have demonstrated the presence of a novel 88-kDa protein in the vitreous humor and serum of patients with Eales disease but not in unaffected control subjects or patients with proliferative diabetic retinopathy [8]. A causal link between *M. tuberculosis* and Eales disease remains unproven, but the most widely held view is that Eales disease is an immunemediated hypersensitivity process resulting from prior exposure to *M. tuberculosis*, although the evidence for this is poor [9]. Consistent with this view is the observation by a research group in Madras, India, that 11 of 23 patients with Eales disease tested positive for the *M. tuberculosis* genome on nested PCR analysis of the epiretinal membrane, compared with 3 of 27 subjects in a control group [10]. Three of the patients in that series for whom nested PCR was negative for *M. tuberculosis* previously had had documented pulmonary tuberculosis. The authors postulated that sequestrated mycobacteria in the eyes may be a trigger for Eales disease. However, PCR for detection of *M. tuberculosis* remains an investigational tool, and the significance of such data remains limited.

In the case we report, the patient had lymphadenopathy and probable tuberculosis at the time of his first presentation with vitreous hemorrhage, which directly links active infection with Eales disease. Because he did not receive treatment for *M. tuberculosis* infection at the time, it is possible to temporally link the neurological sequelae of Eales disease with ongoing tuberculous infection. To our knowledge, this has not been reported elsewhere. The most common neurological complications of Eales disease are myelopathy [6, 9] and stroke [2, 7]. In the only available series to have described postmortem findings, which comprised 9 such patients, the histopathological findings were inflammatory venopathy with perivenular demyelination [11]. None of these patients had clinically active tuberculosis at the time of presentation. The CNS vasculopathy was similar to the retinal periphlebitis described in Eales disease. Other CNS complications of Eales disease that have been reported include encephalopathy, internuclear ophthalmoplegia, and psychiatric conditions [3–5]. To our knowledge, peripheral neuropathy, which occurred in our patient, has never been reported. It is extremely unlikely that this condition was secondary to isoniazid toxicity, because isoniazid therapy was continued throughout the period of improvement, and the patient had received prophylactic pyridoxine since the start of antituberculous treatment. It is theoretically possible that the drug-induced killing of *M. tuberculosis* organisms released additional antigens that increased the severity of the clinical deterioration in our patient.

The standard therapeutic approach for patients with Eales disease is based on symptoms. Treatment includes administration of systemic corticosteroids (usually tapering doses of oral prednisolone) and ophthalmological intervention with photoocoagulation therapy, cryotherapy, or vitrectomy, as appropriate. In one review, empiric addition of antituberculous therapy was advocated for severe cases, although it was acknowledged that there is a lack of evidence for this recommendation [1]. Almost all patients with neurological complications have undergone a therapeutic trial of steroids with varying degrees of success. In our patient, there was a dramatic response that was consistent with suppression of an acute inflammatory process. Similar success has been reported by others [12]. However, in one series, the response was mixed, although the patients in that study varied widely with regard to the time between the onset of symptoms and the institution of corticosteroid therapy [11]. We suggest that an early therapeutic trial of steroids in patients with neurological Eales disease may be appropriate, as long as active tuberculosis has been excluded or treated. It is important for the treated patients’ compliance with therapy to be closely monitored.

In summary, we report a case of active tuberculosis complicated by both ocular Eales disease and neurological sequelae, including the previously unreported finding of peripheral neuropathy. Complete resolution of the neurological features of the disease occurred after the patient received treatment with oral corticosteroids. As international travel and migration increases, it is important that all infectious diseases physicians be aware of this complication of tuberculosis as well as the therapeutic options.
References