Evaluation of Ocular Tuberculosis

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S. R. Rathinam and P. Lalitha

Introduction

Mycobacterium tuberculosis is a slow-growing acid-fast bacteria. It causes an airborne communicable disease. Inhalation of a droplet containing bacilli reaches alveoli and causes primary tuberculosis (TB) or gets cleared by the immune system. Alternatively, a patient may develop asymptomatic, latent TB. If the infection is not cleared by the immune system, the bacilli spread from regional lymph nodes to the lungs and give rise to pulmonary TB. Subsequent lymphatic and hematogenous dissemination result in extrapulmonary disease.

Ocular tuberculosis is a form of extrapulmonary disease which can affect all ocular layers. It can occur in isolation or with a pulmonary or with another extrapulmonary focus. It presents with a variety of clinical manifestations and may mimic several other uveitis. Confirming the etiology remains a challenge because of varying clinical picture and paucibacillary nature of ocular tuberculosis. Early diagnosis and an appropriate treatment are most essential for prompt regression of inflammation (Cunningham et al. 2015).

Epidemiology

Tuberculosis is the ninth leading cause of death worldwide. Poverty, human immunodeficiency virus (HIV), and drug resistance are major drivers of the global tuberculosis epidemic. The highest rates (higher than 100 per 100,000) occur in sub-Saharan Africa, India, and Southeast Asia. Intermediate rates of TB (26–100 cases per 100,000) are seen in China, Central and South America, Eastern Europe, and northern Africa. Low rates (less than 25 cases per 100,000 inhabitants) are seen in the United States, Western Europe, Canada, Japan, and Australia. In 2016, there were 600,000 new cases with resistance to rifampicin (RRTB), the first-line drug, of which 490,000 had multidrug-resistant TB (MDR-TB). Almost half (47%) of these cases were in India, China, and Russia. However, globally, the TB mortality rate is falling at about 3% per year. TB incidence is falling at about 2% per year with a declining trend in TB prevalence and mortality over the last decade (WHO 2017a, b).

Systemic Tuberculosis

Patients may present with pulmonary or extrapulmonary TB (EPTB) (Gonzalez et al. 2003) or a combination of both. Depending upon the organ involved, the patients present with specific symptoms and signs. Respiratory symptoms, fever, appetite loss, weight loss, and easy fatigability are common in pulmonary tuberculosis. Organs affected in EPTB include lymph nodes, central nervous system, eyes, musculoskeletal system, genitourinary tract, and gastrointestinal tract. Patients may have palpable lymph nodes, abdominal pain, diarrhea, monoarticular arthralgia, nerve palsies, seizures, meningism, or infertility. Extrapulmonary tuberculosis patients may have neither respiratory symptoms nor an abnormal chest X-ray. Ophthalmologists have to include appropriate questions in the history and relevant systemic examination. Based on the clinical examination, tailored laboratory workup is performed to rule out both pulmonary TB and EPTB.

Ocular Tuberculosis

Tuberculosis is one of the common causes that affect episclera, sclera, cornea, and all intraocular structures, and ocular TB is now recognized more often than before (Rathinam and Namperumalsamy 2007). Ocular TB manifests as either unilateral or asymmetrically bilateral disease. Course may be

S. R. Rathinam (✉) · P. Lalitha
Department of Ophthalmology and Uveitis Services, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Madurai, Tamilnadu, India
e-mail: rathinam@aravind.org

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recurrent, chronic, and insidious. Anatomically, it may present as anterior, intermediate, posterior, or panuveitis, more often a granulomatous than non-granulomatous uveitis (Gupta et al. 2010; Krassas et al. 2018).

Ocular TB can cause recurrent nodular episcleritis, scleritis, sclerokeratitis, and sclerokeratouveitis. When cornea is involved, the deeper layers of the cornea get inflamed with a clear superficial layer. The course is usually chronic, recurrent, and insidious. Anterior segment may show granulomatous mutton-fat keratic precipitates (Fig. 17.1), iris granulomas, Bussaca nodules, broad posterior synechiae, and complicated cataract with scanty flare and cells in the anterior chamber. Tubercular granulomas and hypopyon can be seen in tubercular inflammation. In developing countries, tubercular uveitis can cause anterior uveitis and band keratopathy in children. It is very important to differentiate it from juvenile idiopathic uveitis.

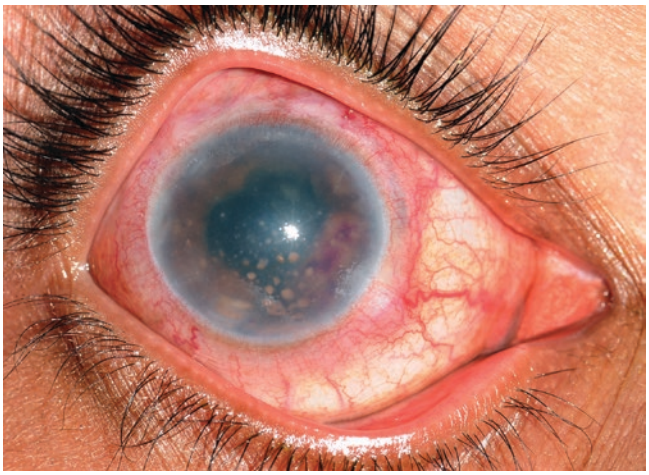

Fig. 17.1 Anterior chamber color photograph showing circumcorneal congestion with chronic pigmented granulomatous keratic precipitates and iris granuloma

Intermediate uveitis of TB and sarcoidosis mimic each other as both are granulomatous and recurrent. Ciliary body tuberculoma can be demonstrated with ultrasonic biomicroscopy. Other findings include vitritis, pars plana snowballs, snow banking, peripheral granulomas, pigmented pars plana scars, and cystoid macular edema.

Posterior segment findings include focal or multifocal yellow choroidal granulomas (Fig. 17.2) or multifocal chorioretinal pigmented scars specifically along retinal vessels (Fig. 17.3) (Gupta et al. 2010). The retinitis may be seen with an associated choroiditis, although a direct retinal involvement is rare. Other signs include subretinal granuloma or abscesses, retinal vasculitis, optic neuritis, retrobulbar neuritis, neuroretinitis, optic disc granuloma, and disc edema. TB can cause serpiginous-like choroiditis (SLC) which sometimes mimic a classic serpiginous choroidopathy (SC). Tubercular SLC show multifocal, scattered, highly pigmented lesions with significant vitreous cells. Unlike classic SC, SLC do not respond to corticosteroid therapy, and inflammatory control is achieved only after anti-TB treatment (Vasconcelos-Santos et al. 2010).

Rarely, an acute and robust inflammatory response may result in hypopyon in tubercular panuveitis. Yellowish subretinal abscess can rupture into the vitreous and result in endophthalmitis or panophthalmitis.

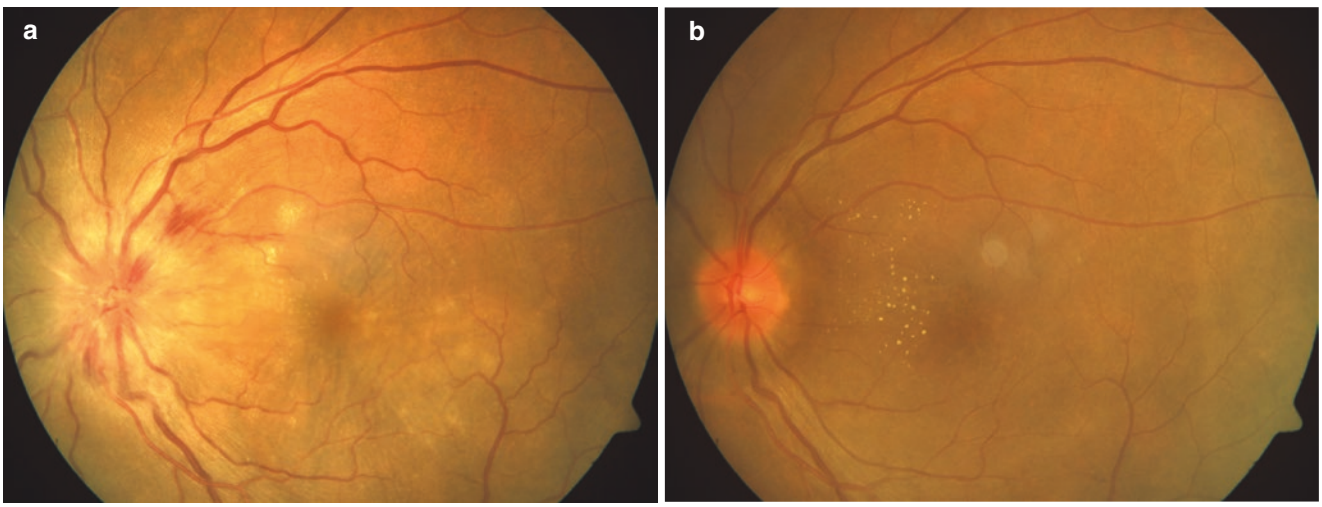

Fig. 17.2 (**a**) A 45-year-old woman presented with optic nerve granuloma, superficial hemorrhage, and multifocal choroidal granulomas. Her Mantoux test was necrotic positive. (**b**) Resolution of fundus findings and choroidal granulomas were observed after 3 months of antituberculous treatment. Edema is resolved leaving white proteinaceous material

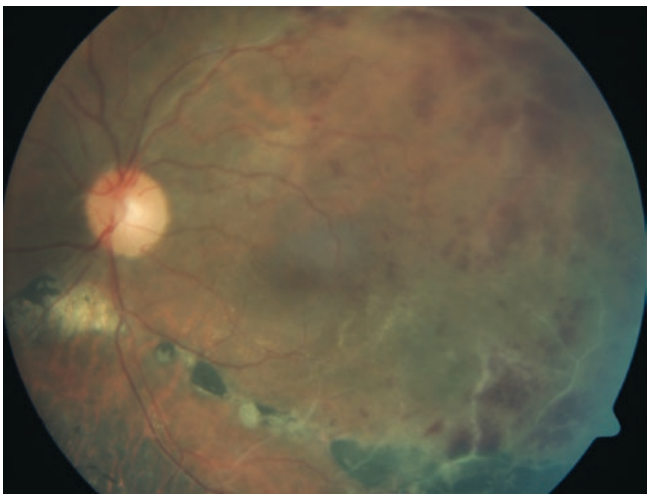

Fig. 17.3 Fundus photography of left eye showing healed multifocal choroiditis with highly pigmented scars along the blood vessels. Superior quadrant shows multiple hemorrhagic spots because of branch retinal vein occlusion

Latent TB

The term latent TB infection (LTBI) is used when an asymptomatic person presents with a positive tuberculin skin test (TST) with no clinical or radiographic signs of active TB. Usual interpretation is that they are infected but not diseased. Among these, 5–15% may progress to active disease in future when the environmental conditions are favorable. However, they cannot spread the disease to other people. Decision for prophylactic treatment for this population varies among countries.

Differential Diagnosis

Differential diagnosis includes other granulomatous uveitis such as sarcoidosis, Vogt–Koyanagi–Harada disease, sympathetic ophthalmia, herpetic infection, phaco-antigenic uveitis, syphilis, and leprosy. Other causes of choroidal granulomas include sarcoidosis, syphilis, and fungal lesions (Babu 2013; Vasconcelos-Santos et al. 2010).

Diagnostic Criteria and Laboratory Tests

Definitive diagnosis of ocular TB is possible only when the bacilli are isolated from the ocular tissues. As definitive evidence of *Mycobacterium tuberculosis* is rarely found in intraocular specimens, its diagnosis is usually clinical, supported by laboratory tests and favorable response to antitubercular therapy. The diagnosis is considered presumed ocular TB when the clinical picture is consistent with known clinical signs (broad-based posterior synechiae, retinal vasculitis with choroiditis, choroidal granuloma, or pigmented SLC) and supported by a positive tuberculin skin test or QuantiFERON TB Gold test or any other relevant anxillary tests, such as chest radiography and computed tomography. Inflammatory control after anti-tubercular treatment and absence of recurrence further supports the diagnosis of presumed ocular TB (Gupta et al. 2010).

The confirmation of etiological diagnosis of ocular tuberculosis remains a clinical challenge because of difficulty in getting a specimen from inflamed eye and paucibacillary tuberculosis. Ocular TB is diagnosed on the basis of a combination of clinical signs such as chronic granulomatous uveitis, choroidal granulomas, and multifocal pigmented chorioretinitis. Microbiological, histopathologic, or molecular evidences assist the confirmation of the diagnosis. Sometimes supportive evidences such as radiographic features (infiltrates, fibrosis, and cavitation in chest x-ray/computerized tomography (CT) chest) aid the diagnosis (Fig. 17.4).

Detection of acid-fast bacilli (AFB) from anterior chamber granuloma or from vitreous is possible with Ziehl–Neelsen staining. Alternatively, histopathological examination can demonstrate caseous necrosis and Langerhans giant cells. The conventional diagnostic method like isolation of the pathogen may not be possible in all patients, as ocular TB is paucibacillary (Vasconcelos-Santos et al. 2009).

In patients with co-existence of pulmonary or extrapulmonary TB, detection of acid-fast bacilli (AFB) in the sputum samples or in the lymph nodes is performed with Ziehl–Neelsen and auramine–rhodamine fluorescent dye. Culturing

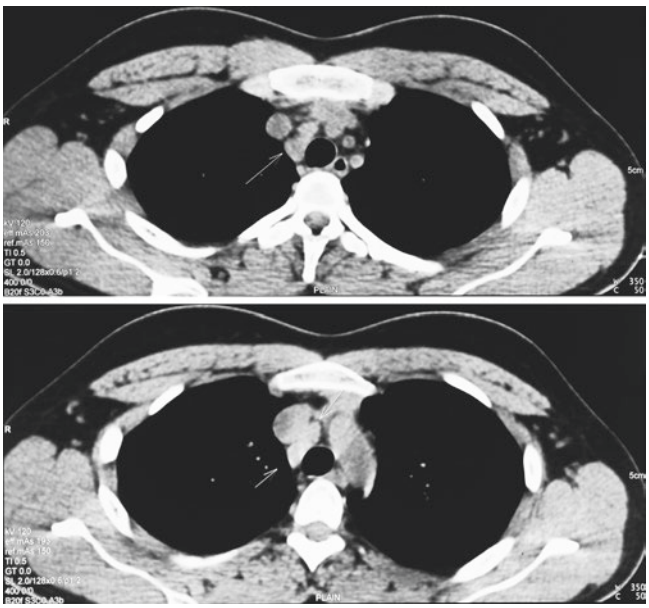

Fig. 17.4 Chest computed tomography revealed enlarged mediastinal lymph nodes (arrow) with necrosis with the largest lymph node measuring 1.89 × 1.35 cm

in liquid media using semi-automated and automated systems are popular for quicker process of less than 2 weeks. Isolation of the organism allows testing for antibiotic resistance as well.

Positive Mantoux or TST (tuberculin skin test) following intradermal injection of tuberculin purified protein derivative (PPD) indicates a successful cellular immune response after exposure to TB bacilli. However, it has limited specificity as the antigen can cross-react with other species of Mycobacterium. The American Thoracic Society and Center for Disease Control (CDC) considers reactions of 5 mm or more to be positive in very high-risk patients (e.g., chest x-ray sign and HIV patients), 10 mm or more in high-risk patients (e.g., patients from endemic areas), and 15 mm or more in patients with no identified risk factors. However, negative test does not rule out TB. In a study on patients with histopathologically proven ocular tuberculosis, 40% had negative TST results.

Molecular studies and sequencing of the *M. tuberculosis* genome have identified specific and highly immunogenic antigens, ESAT-6 and CFP-10 proteins. Using these antigens, novel in vitro tests have been developed, namely QuantiFERON (QFT) and TSPOT.TB. They are named as Interferon Gamma Release Assays (IGRA). They can be used to study the immune response of the patients. QuantiFERON (QFT) and TSPOT.TB are now commercially available. The CDC guidelines state that IGRAs can replace the TST. Canada and the United Kingdom national guidelines suggest using IGRAs only to confirm a positive TST (Schluger and Burzynski 2010). These tests were initially designed to screen latent tuberculosis; however, they were found to be useful in both active systemic and ocular tuberculosis cohorts.

A positive skin test or an IGRA indicates exposure to TB, but it does not necessarily indicate active infection. The lack of a gold standard for the diagnosis of TB infection challenges interpretable comparison of the IGRAs and the TST in ocular tuberculosis. In addition, predictive values of IGRA depend on prevalence of TB in the study population. In low endemic countries, the results of IGRA have to be interpreted with caution as false-positive tests may be seen in patients with sarcoidosis (Albini et al. 2008).

Imaging studies include both ocular imaging and systemic imaging. Computed tomography (CT) is the method of choice in detecting early bronchogenic spread, hilar and abdominal lymphadenopathy, and also in characterization of the infection as active or not (Fig. 17.4) (Bansal et al. 2018). Chest CT is more sensitive than plain chest radiographs. Magnetic resonance imaging (MRI) is considered superior to CT for the detection of tuberculosis of bone and joints and central nervous system TB.

Intraocular TB can involve various tissues in the eye and can be demonstrated by several ocular imaging techniques such as fluorescein angiography, ultrasonography (Fig. 17.5), and optical coherence tomography (Fig. 17.6). These imaging tests are used individually or in combination with follow-up response to treatment and find out any sequelae of intraocular TB.

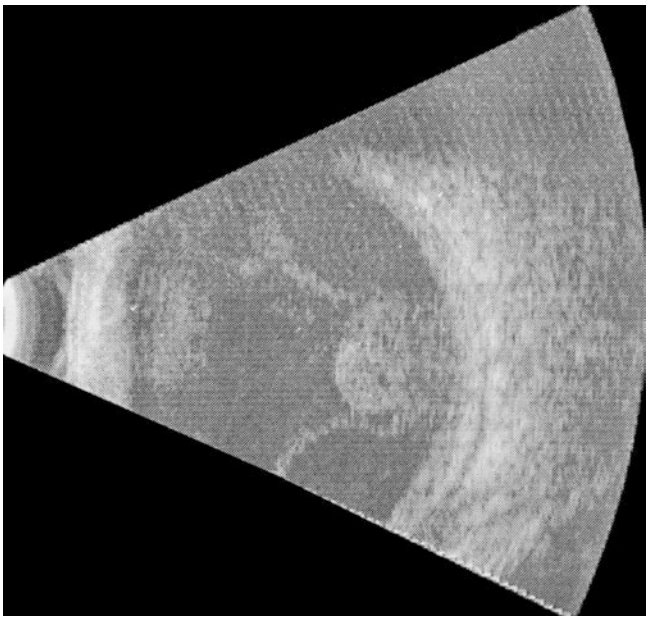

Fig. 17.5 Ocular ultrasonography of a patient with a massive choroidal tubercular granuloma with choroidal detachment

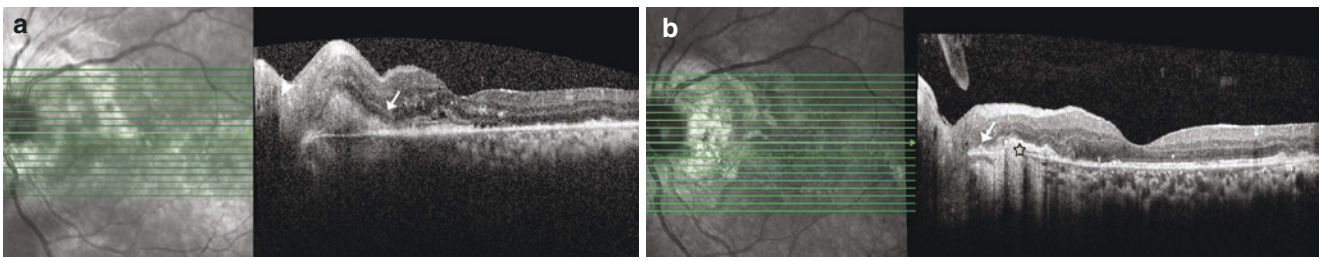

Fig. 17.6 A 23-year-old female with decreased vision in her left eye. (**a**) Spectral-domain optical coherence tomography showed subretinal hyperreflective choroidal tubercular granuloma (arrowhead) temporal to the disc with minimal subretinal fluid and exudates at macula (arrow). (**b**) After intravitreal bevacizumab injection, the hyperreflective lesion regressed (arrow) with resolution of subretinal fluid and disruption of IS-OS junction (asterisk)

Molecular diagnostic tests such as PCR (or RT-PCR) are rapid tests, and detection of rifampicin and isoniazid resistance can also be achieved. Several new primers have been published (Kharel Sitaula et al. 2018).

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