Chapter 14
Ocular Tuberculosis

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Tuberculosis is an airborne communicable disease caused by the acid-fast bacillus (AFB) *Mycobacterium tuberculosis* and most commonly involves the lungs. It can also affect any other part of the body and remains the most common single cause of morbidity and mortality worldwide [1].

Periocular or intraocular infection mainly by *Mycobacterium tuberculosis* or by *Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti* is defined as "ocular tuberculosis" (ocular TB) [2].

Primary ocular tuberculosis is the ocular disease without systemic involvement or in which the eye is the entry of the mycobacterium into the body, and secondary ocular TB is ocular involvement as a result of hematogenous spread from a distant organ or direct invasion from adjacent tissues, like the sinus or cranial cavity.

Although it is estimated that 1.4% of patients with pulmonary TB will eventually develop ocular disease, ocular TB may not be associated with clinical evidence of pulmonary TB [3]. Also, nearly 60% of patients with evidence of extrapulmonary TB may not have evidence of pulmonary TB [1].

The most common clinical presentation of ocular tuberculosis is uveitis while posterior uveitis being the most common followed by anterior uveitis, panuveitis, and intermediate uveitis [4].

In the nineteenth century, TB was considered as the common cause of uveitis. In the 1940s, Guyton and Woods placed TB as the cause of 80% of all granulomatous uveitis [5]. However, with new diagnostic tests, diagnostic criteria for ocular tuberculosis have become more strict, and previously undefined causes like sarcoid, toxoplasmosis, and histoplasmosis were defined; the number of uveitis cases attributed to *M. tuberculosis* declined [5]. Since the 1980s, reports in the literature cite tuberculosis (TB) as an etiology of uveitis from 0 to 4% [5–9]. The region-specific

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prevalence for presumed ocular tuberculosis is reported as 0.4–9.8% for India, 4% for China, and 7% for Japan [10–13].

TB is reported as a prominent cause for chronic iridocyclitis, disseminated choroiditis, and periphlebitis in Denmark and for posterior uveitis in Russia [14, 15].

Singh et al., in their study with PCR, defined intraocular fluid and reported that 30% of the patients with uveitis had infectious origin, the two thirds being intraocular TB [12].

TB is defined as etiological factor in 0.3% of the uveitis patients in the tertiary centers in Turkey [16].

14.1 Signs and Symptoms

Blurred vision, photophobia, and redness of the eye are the most common symptoms. However patients may also be asymptomatic or have complaints like headache, flashes, and floaters.

14.2 Clinical Manifestations of Ocular TB

Ocular TB is a hematogenous dissemination of the pulmonary and extrapulmonary TB, and primary ocular infection through conjunctiva may rarely be seen in children. Symptomatic disease is usually due to reactivation of silent lesions in the ocular tissues rather than primary infection.

The presence of eye lesions due to *M. tuberculosis* antigen hypersensitivity from a distant focus like the lungs, without the presence of bacillus in the eye, is another form of ocular TB [1].

Ocular TB is usually unilateral and asymmetric. It may affect ocular surface, eyelid, conjunctiva, cornea, sclera, uvea, choroid, retina, orbital, lacrimal gland, and optic nerve extending to the central nerve system [5, 17].

14.3 Major Clinical Manifestations

1. *Uveitis* is the most prominent clinical manifestation of the ocular TB predominantly posterior uveitis, followed by anterior uveitis, panuveitis, and intermediate uveitis. It has a variety of uveitis presentations making the TB an important masquerading, in uveitis patients.

   Posterior uveitis with disseminated choroiditis is the most common manifestation of tuberculous uveitis and is often bilateral [18]. Multiple, discrete, yellow lesions uni- or bilaterally may be seen in the posterior pole in wide range of diameters in size (choroidal tuberculoma). As lesions progress, their borders

may become more distinct, and the center becomes paler leading to an atrophic scar. Subretinal neovascularization, subretinal abscess, and choroiditis may later develop.

Acute or chronic granulomatous anterior uveitis may be seen with mutton-fat keratic precipitates, iris or angle granulomas, posterior synechiae, hypopyon, secondary cataract, vitritis, and secondary glaucoma [19]. Intermediate uveitis is seen with pars planitis like signs as snow banking, low-grade chronic vitritis, peripheral vascular sheathing, and peripheral retinochoroidal granulomas [19].

Disc edema, periphlebitis, vasculitis, and vitritis may be present.

2. *Retinitis and Retinal Vasculitis*

   Retinal manifestation is usually due to choroidal manifestation. Retinal vasculitis mostly is in the retinal veins with perivascular cuffing; arteries may rarely be associated.

3. *Optic Neuropathy and Neuroretinitis*

   Optic neuropathy may be the result of the direct invasion of the microorganism or hypersensitivity to the microorganism. Optic neuritis, papillitis, papilledema, retrobulbar neuritis, and neuroretinitis may be other manifestations [19–22].

4. *Endophthalmitis and Panophthalmitis*

   This form is acute and progressive, leading the hypopyon fill the anterior chamber and vitreous cavity. Subretinal abscess may occur, and liquefaction necrosis may result in perforation of the globe [19].

5. *Choroidal Tubercles*

   These lesions are the most recognized lesions in intraocular TB and are an indicator of hematogenous spread of the mycobacteria.

   Choroidal tubercles are unilateral, yellowish lesions with poorly defined borders and typically elevated centrally, ranging from 1–4 to several optic disc sizes in diameter, usually less than five in number and may become more pigmented as time passes. Tubercles near or at macula present with diminished visual acuity otherwise may be asymptomatic.

   In an autopsy series, choroidal tubercles are found in nearly 50% of the cases [23].

6. *Orbital involvement* occurs most commonly in children, although rare cases have been reported in adults. Findings may include a draining sinus tract with/or radiographic evidence of bony destruction.

7. *Tuberculous conjunctivitis* has been reported in the literature: usually unilateral, chronic conjunctivitis, occasionally associated with an ulcer, subconjunctival nodule, pedunculated polyp, or conjunctival mass or ulceration. Most do not have systemic manifestations of TB and may represent primary ocular tuberculosis.

8. *Eyelid involvement:* Tuberculosis can also present as an eyelid abscess or chalazion-like mass. Spontaneous drainage of abscess can form draining sinus tract.

9. *Lacrimal gland involvement* (dacryoadenitis) may be indistinguishable clinically from bacterial infection.
10. *Scleritis:* Scleral involvement, although rare, may also apply. There are biopsy-proven cases of TB scleritis.
11. *Phlyctenulosis* is a type IV hypersensitivity reaction that presents as an inflammatory mass on the cornea and can be associated with *Staphylococcus aureus* as well as tuberculosis.
12. *Eales' disease.* This is a rare disorder that is not associated with *M. tuberculosis* specifically but with a positive tuberculin skin test. It is characterized by recurrent vitreous hemorrhages in young men.

14.4 Diagnosis

The diagnosis of ocular TB is often problematic due to the masquerading nature of the disease and it is impractical to obtain biopsy for culture and direct visualization of the microorganism to provide definitive proof of ocular TB [24]. Definitive diagnosis may be achieved by examination of smears and staining for acid-fast organisms, cultures of intraocular tissue/fluid for *Mycobacterium tuberculosis.* Historically, the only way to prove the ocular TB was enucleating the eye for histopathological evaluation. Recently obtaining intraocular specimens via pars plana vitrectomy or chorioretinal biopsy makes it possible to obtain a histopathological diagnosis while keeping the eye intact. However, usually the bacillus obtained from the intraocular fluids is low in number making it difficult to diagnose the microorganism by direct microscopy and culture test. However smears from lesions with caseification necrosis or endophthalmitis may show acid-resistant dye positivity for the bacillus [19]. Due to amount limitations of the intraocular fluid, PCR became an important diagnostic tool by requiring small amounts of specimen. Anterior chamber fluid; vitreous, subretinal fluid; and rarely chorioretinal biopsy specimens or epiretinal membrane obtained by vitrectomy may be analyzed by PCR [19].

When it is impossible to get a specimen by surgery, it is important to evaluate the chest X-ray for infiltration, cavitation, or pleural effusion. Acid-fast stains and cultures can be performed from urine, spinal fluid, or sputum.

14.5 Diagnostic Criteria for Ocular TB

Although there are not well-defined criteria for ocular TB, the guidelines for ocular tuberculosis reported in several studies in the literature were presence of any suggestive ocular findings like uveitis (anterior, intermediate, posterior, or panuveitis), retinitis, retinal vasculitis, neuroretinitis, optic neuropathy, endophthalmitis, or panophthalmitis, living in areas of endemic TB, contact history with patients with TB diagnosis, exclusion of any other causes of uveitis, positive tuberculin skin test

(TST), evidence of healed or active lesion on chest radiography, demonstration of acid-fast bacillus (AFB) or culture of *Mycobacterium tuberculosis* from the ocular fluids, positive PCR from ocular fluids for IS 6110 or other conserved sequences of *Mycobacterium tuberculosis* genomes, positive interferon-gamma release assays (IGRAs), and a positive response to conventional antituberculous therapy (ATT) over a period of 4–6 weeks without recurrence [1, 25–28].

These guidelines categorized the ocular tuberculosis into two categories as confirmed or presumed [27–30].

In 2015, Gupta et al. proposed new guidelines which provide three categories as confirmed, probable, and possible intraocular tuberculosis [28]. This new proposed classification of intraocular tuberculosis provides more certain diagnosis with more case definition criteria [28].

Positive response to four-drug antituberculous therapy (isoniazid, rifampicin, ethambutol, pyrazinamide) in 4–6 weeks duration is defined as therapeutic test. This therapy should be started by a TB specialist and the ocular response to this therapy should be evaluated by an ophthalmologist [19, 27–30].

14.6 Ocular Imaging Techniques for Intraocular TB

Fundus fluorescein angiography is the most common imaging modality, as well as indocyanine green angiography, optical coherence tomography (OCT), orbital ultrasound, and ultrasound biomicroscopy [19, 28–29].

14.7 Medical Therapy

The current treatment of intraocular TB consists of use of four drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) taken for a long period of time (total 9–15 months) [29, 30].

Combination therapies should be preferred in order to prevent resistance. Centers for disease control (CDC) suggest four-drug therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) for 2 months, followed by two-drug therapy (isoniazid, rifampicin) for 4 months. In immunosuppressed patients two-drug therapy may be extended to 7 months [19, 31, 32].

Although ideal treatment duration is unknown, extended therapy is suggested [19, 32].

Corticosteroids may be added to four-drug ATT for 4–6 weeks to reduce the ocular damage from type IV hypersensitivity. Corticosteroids should never be used alone in order to prevent reactivation of a latent infection or flare up of the systemic infection [30].

14.8 Ocular Side Effects of Antituberculosis Drugs

Ethambutol may lead to dose-related toxicity. All patients should be evaluated for visual acuity, visual field testing, and color vision test before ethambutol therapy. Doses below 15 mg/day rarely result in ocular side effects. Most common signs for toxicity are optic neuropathy, acquired red-green dischromatopsy, central scotoma, disc edema, disc hyperemia, peripapillary splinter hemorrhages, optic atrophy, retinal edema, and pigmentary changes of the macula. Patients under ethambutol therapy should be followed up by an ophthalmologist once in every 2–4 weeks for doses over 15 mg/day and once in every 3–6 months for lower doses [19, 33].

Optic neuritis and optic atrophy are rarely reported for isoniazid [19].

Ocular TB is a masquerading disease with different clinical manifestations, with no gold standard test for a certain diagnosis. An empirical clinical approach, including evaluation of clinical symptoms, ocular and systemic examination findings, and positive laboratory results with detection of the bacillus in the intraocular fluids and tissues by direct microscopy, culture, or PCR, makes a definitive diagnosis permitting antituberculous treatment with a four-drug combination therapy in an extended duration.

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