Intraocular Tuberculosis

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Introduction

Tuberculosis (TB) is an endemic disease in many countries of the developing world and is associated with severe morbidity and mortality. Intraocular tuberculosis (IOTB) is a rare condition that may present with severe visual debilitating symptoms and often presents as a diagnostic challenge due to its protean manifestations (Gupta et al. 2007, 2015b). IOTB often presents as posterior uveitis (Gupta et al. 2015b). Thus, early recognition of IOTB and its prompt management with specific therapy are an important aspect of uveitis practice especially in developing countries.

IOTB can affect various ocular structures resulting in a wide spectrum of clinical manifestations. Due to its widespread involvement of the ocular tissue, there can be various reasons for visual loss and the patient may present with a wide range of ocular symptoms and signs. Involvement of the anterior chamber can result in inflammation involving the iris and ciliary body. The choroid is the most common site of IOTB due to its high vascularity. *Mycobacterium tuberculosis* may reside inside retinal pigment epithelial (RPE) cells resulting in various posterior segment manifestations. TB-related posterior uveitis can present as choroidal tubercles, choroidal granulomas/subretinal abscesses, serpiginous-like choroiditis (also known as multifocal serpiginoid choroiditis), retinal vasculitis, neuroretinitis, endophthalmitis, and panophthalmitis (Bansal et al. 2012; Gupta et al. 2003, 2015a, b; Ni et al. 1982).

The index chapter focuses on the clinical and imaging features of patients with IOTB including anterior as well as posterior segment disease. In addition, the treatment of TB and its challenges such as drug-resistant TB have been highlighted.

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Intraocular Tuberculosis

IOTB is often a bilateral disease resulting in severe visual symptoms (Bansal et al. 2012). In case the disease is unilateral, it can recur in the opposite eye if not treated with appropriate anti-tubercular therapy (ATT). Patients with IOTB are diagnosed on the basis of positive laboratory evidence of active or latent TB, in contrast to patients with autoimmune serpiginous choroiditis. In addition, there may be evidence of radiological features of past (or present) active TB in the form of lung parenchymal involvement or presence of lymphadenopathy.

Prevalence of IOTB is reported differently in worldwide literature. In developed countries, the incidence rate of IOTB is much lower than the developing countries such as India. In India, IOTB may represent one of the most common causes of posterior uveitis based on studies from North and South India. IOTB has no age or sex predilection. *Mycobacterium tuberculosis* can affect any part of the eye.

IOTB is a predominately a paucibacillary disease that is believed to represent an immune-mediated hypersensitivity reaction to the acid-fast bacilli sequestrated in the ocular tissues, notably the RPE. The exact role of various cytokines and interleukins involved in the pathogenesis of IOTB is yet to be elucidated in the literature.

Manifestations of Ocular Tuberculosis

Anterior Uveitis

IOTB presenting as anterior uveitis is classically a chronic granulomatous disease, although a non-granulomatous uveitis may also occur. Anterior uveitis is characterized by mutton-fat keratic precipitates which may be few or diffuse, broad-based posterior synechiae and iris nodules (Fig. 16.1). Uncommonly, it may be associated with granulomas in the angle of the anterior chamber. Chronic, recurrent course of inflammation in the anterior chamber

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produces posterior synechiae, which are typically broad-based and have been identified as having high specificity for TB etiology as compared to other causes of uveitis. However, IOTB may also present as non-granulomatous inflammation including hypopyon uveitis that can mimic noninfectious variety of uveitis related to spondyloarthropathies (Helm and Holland 1993; Karaconji et al. 2013; Velu et al. 2013).

Chronic recurrent anterior uveitis may be complicated with the development of posterior subcapsular cataract. In addition, the posterior synechiae may lead to pupillary block and secondary glaucoma. Band keratopathy and iris neovascularization are other associations in anterior segment disease.

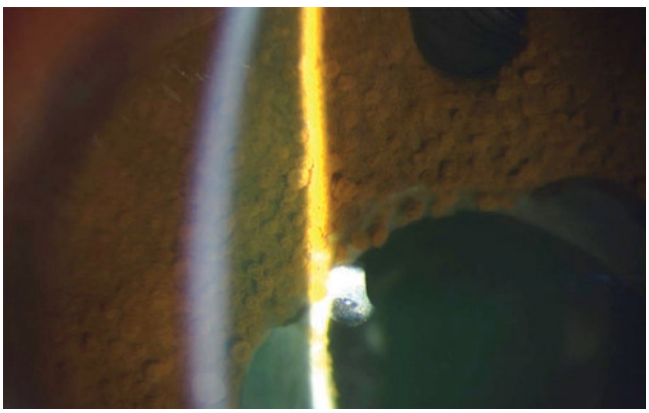

Fig. 16.1 A 4-year-old female presented with vision decrease for the past 6 months. Examination of the anterior segment revealed cells 1+ and flare 2+. The iris was studded with diffuse nodules suggestive of granulomatous inflammation. Her tests for tuberculosis were positive. She was initiated on oral steroids and anti-tubercular therapy

Intermediate Uveitis

IOTB may also present as intermediate uveitis that has nonspecific presentation, but vitritis with snowballs and peripheral retinal phlebitis is common (Parchand et al. 2011). This phenotype is most commonly likely to be mistaken for pars planitis, a disease that has typical phenotype but is believed to be idiopathic.

Intermediate uveitis typically presents with a wax-and-wane course. There may be pars plana exudates, snow balls, and moderate-to-severe vitritis. Usually, there is a presence of cystoid macular edema and peripheral vascular sheathing (Fig. 16.2). Ciliary body tuberculomas may be detected on ultrasound biomicroscopy.

Posterior and Panuveitis

Posterior uveitis is the most common form of uveitis in TB (Gupta and Gupta 2005). Posterior segment manifestations of ocular TB include *serpiginous-like choroiditis* (or *multifocal serpiginoid choroiditis)*, tubercular granulomas or tubercles, subretinal abscesses, neuroretinitis, retinal vasculitis, and rarely endophthalmitis or panophthalmitis (Gupta et al. 2007, 2010; Gupta and Gupta 2005). The following sections describe clinical and imaging characteristics of tubercular lesions that primarily involve retina or choroid.

1. *Choroidal Tubercles/Tuberculoma:*
   Choroidal tubercles were the earliest sign described in IOTB, mostly in association with disseminated TB. They appear as round, small, multiple, well-defined lesions. Choroidal granulomas or tuberculomas or subretinal granulomas are larger in size, solitary, unilateral, and usually in the posterior pole with surrounding exudative retinal detachment (Gupta et al. 2015b; Singh et al. 2012).

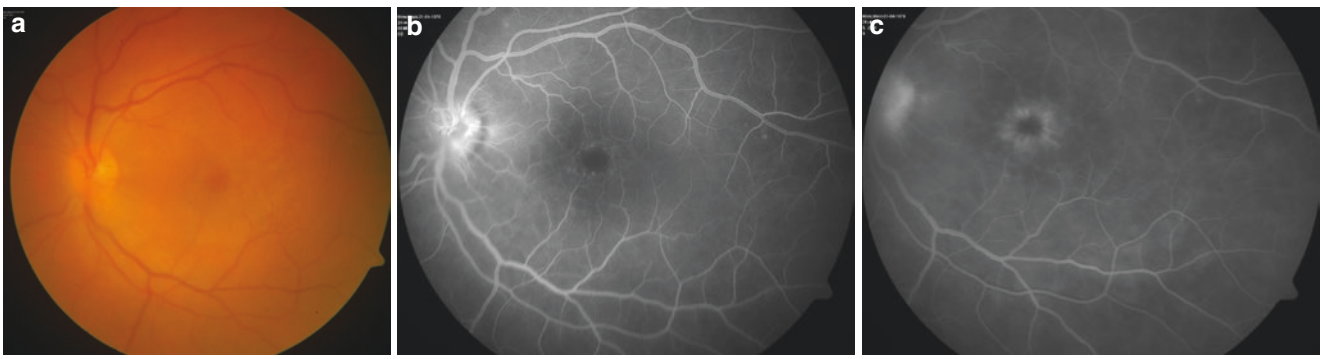

Fig. 16.2 A 30-year-old female presented with decreased vision in both eyes for the past 1 month (only left eye shown). Ocular examination revealed 1+ cellular reaction in the anterior chamber. (**a**) There was significant vitritis in both eyes. (**b**, **c**) Fluorescein angiography revealed early disc hyperfluorescence with late leakage and petalloid pattern of dye accumulation in the macula suggestive of cystoid macular edema. She was diagnosed as probable tubercular intermediate uveitis since her immunological and radiological investigations were positive. She received intravitreal dexamethasone depot injection in both eyes and anti-tubercular therapy

2. *Serpiginous-like choroiditis (multifocal serpiginoid choroiditis):*
   Serpiginous-like choroiditis (SLC) typically affects young to middle-aged adults from TB-endemic areas such as India and immigrants in other countries such as UK (Bansal et al. 2012; Gupta et al. 2003). Unlike autoimmune serpiginous choroiditis, tubercular serpiginous-like choroiditis occurs at a younger age, associated with mild vitritis and is bilateral in majority of the cases (Nazari Khanamiri and Rao 2013). This entity may have different morphological patterns (Fig. 16.3) (Bansal et al. 2012).
   (a) **Placoid chorioretinitis**: In this phenotype of IOTB, a diffuse plaque-like lesion is observed, which has a characteristic amoeboid pattern and active edge. The borders of the lesions are yellowish-white and elevated, whereas the center of the lesion is less elevated with pigmentary changes suggestive of a healing process in the center of the lesion.
   (b) **Multifocal choroiditis**: This phenotype of IOTB presents with discrete lesions, yellowish-white in color with well-defined margins and slightly raised edges. The edges of these lesions are non-contiguous initially and show a wave-like progression over a period of 1–4 weeks and gradually become confluent.

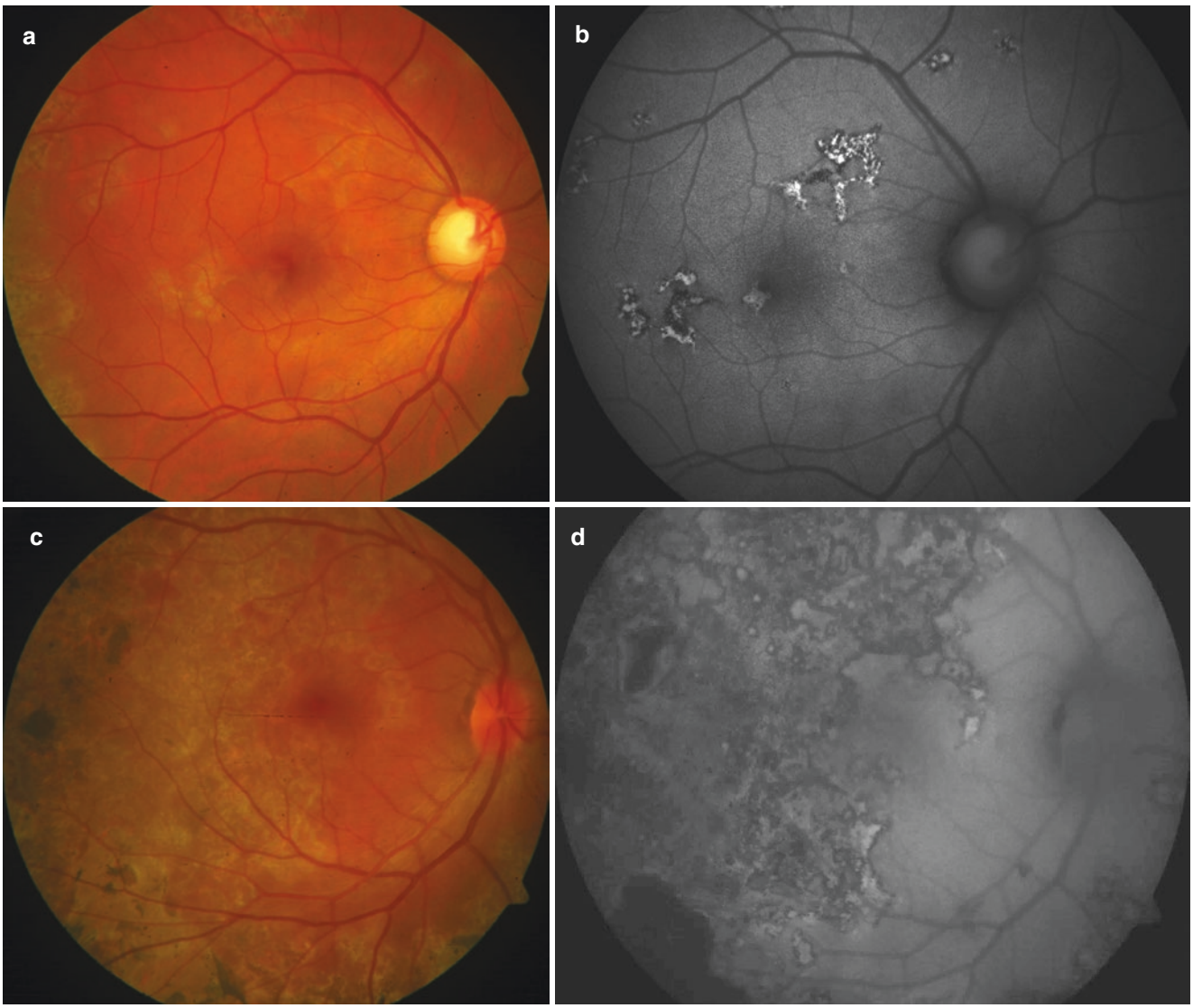

Fig. 16.3 Fundus photography and autofluorescence (FAF) imaging of two patients with tubercular serpiginous-like choroiditis. Patient #1 (**a**, **b**) shows presence of yellowish-white choroiditis lesions in the posterior pole that appear hyper-autofluorescent with hypo-autofluorescent halos on FAF imaging. Similarly, patient #2 (**c**, **d**) shows diffuse involvement of the posterior pole and mid-periphery by choroiditis lesions that appear active on FAF. The lesions show predominant hyper-autofluorescence suggestive of the need for continued anti-tubercular therapy and systemic immunosuppression

(c) **Mixed/Undetermined pattern**: These lesions of IOTB present with overlapping features of both multifocal and placoid chorioretinitis. There have been descriptions of TB choroiditis lesions that may appear as other white dot syndromes such as ampiginous choroiditis.

3. *Tubercular Subretinal Abscesses:*
TB-related subretinal abscess appears distinct and more yellowish in color compared to a small choroidal granuloma. They usually have overlying retinal hemorrhages, and have a tendency to develop retinal angiomatous proliferation over a period of time.

Imaging Features of Posterior/Panuveitis

1. *Color Photography and Ultra-wide Field Imaging*
In order to accurately study the morphology of the IOTB lesions, it is important to obtain color fundus photography at regular intervals. This greatly aids in the analysis of the fundus lesions and provides an objective assessment of change in the lesions over an extended period. Serial fundus photography (from acute stage to the stage of healing) is very useful in assessment of morphological evolution of the lesions (Bansal et al. 2012). Ultra-wide field (UWF) fundus imaging is a recent addition in the imaging modalities used for the assessment of various chorioretinal pathologies. Compared to conventional imaging (fundus photography and fluorescein angiography), UWF imaging systems aid in detection of additional features such as perivascular choroiditis, retinal vasculitis, and retinal neovascularization (Aggarwal et al. 2016). In addition, UWF imaging may be superior to conventional imaging in identifying *peripheral paradoxical worsening*, which may be otherwise missed on conventional imaging (Aggarwal et al. 2016).
2. *Fundus Autofluorescence*
Studies have shown that fundus autofluorescence (FAF) is a very useful noninvasive imaging modality in the management of IOTB, specifically TB serpiginous-like choroiditis. Staged of lesions using FAF (Gupta et al. 2012) is as follows: active lesions demonstrate ill-defined hyper-autofluorescence throughout the lesions. Thus, the lesions have a diffuse, amorphous appearance (Stage 1). In the stage of early healing (Stage 2), a thin rim of hypo-autofluorescence is seen surrounding the lesion, which remains predominantly hyper-autofluorescent with a stippled pattern. With further healing, the lesion becomes predominantly hypo-autofluorescent (Stage 3) on FAF imaging. On complete healing, the lesions become uniformly hypo-autofluorescent without hyper-autofluorescent areas (Stage 4) (Gupta et al. 2012).
3. *Fluorescein Angiography*
Fluorescein angiography (FA) is a very useful modality in the diagnosis and follow-up of patients with IOTB. TB choroiditis lesions appear hypofluorescent in the early phase and show hyperfluorescence in the late phase. Due to RPE damage and choriocapillaris atrophy, the areas of healing may demonstrate window defects (Bansal et al. 2012). Thus, FA is very helpful in demonstrating the activity of the lesions. In addition, complications of the disease such as inflammatory choroidal neovascularization may be detected using FA, though it may be very challenging in the absence of high index of suspicion (Bansal et al. 2016).
4. *Indocyanine Green Angiography*
On Indocyanine green angiography (ICGA), active lesions of TB SLC remain hypofluorescence from early to late phase on ICGA. ICGA is very useful in detecting choriocapillaritis and presence of choriocapillaris hypoperfusion among patients with IOTB. Other changes of tubercular uveitis include presence of numerous hyperfluorescent spots, fuzzy appearance of choroidal vessels in the intermediate phase, and late choroidal hyperfluorescence due to dye leakage, which tends to regress after the completion of treatment with ATT and corticosteroids.
5. *Optical Coherence Tomography*
Spectral-domain OCT, especially enhanced-depth imaging (EDI) OCT, has provided numerous insights into the pathogenesis of IOTB. OCT permits identification of peripapillary retinal atrophy, disruption of the photoreceptor and other outer retinal layers, thinning of the RPE, mild cystic changes as well as subretinal fibrosis in area of old choroidal neovascularization and marked attenuation of the interdigitation zone in the outer retina (Punjabi et al. 2008; Rifkin et al. 2015). TB choroiditis may also result in alteration of the ellipsoid and the myoid zones in the outer retina along with choriocapillaris thinning. Active edges of the lesions show localized, fuzzy area of hyper-reflectivity in the outer retinal layers involving the RPE, photoreceptor outer segment tips, external limiting membrane, and the outer nuclear layer without increased backscattering from the inner choroid. As the lesions begin to heal from the center, the hyper-reflective fuzzy areas begin to disappear and are replaced by irregular, hyper-reflective knobbly elevations of the outer retinal layers. Eventually, there is loss of RPE and outer retinal layers, and persistent increased reflectance from the choroid on OCT (Bansal et al. 2011).

With the introduction of advanced technologies such as EDI and swept-source (SS)-OCT, there has been tremendous advancement in the diagnostic capabilities in the field of IOTB. Recent introduction of OCT angiography, a dye-less noninvasive technique to obtain photographs of retinochoroidal endoluminal networks, has furthered our capabilities to understand the pathological involvement in IOTB.

Tubercular Endophthalmitis

IOTB may rarely present as severe vitritis with hypopyon and no view of the retina, with echoes in the vitreous cavity on ocular ultrasonography mimicking infectious endophthalmitis. In such cases, the diagnosis may be established by a high index of suspicion and evaluation of ocular fluids for mycobacteria. Therapeutic response to ATT and corticosteroids is observed in these patients.

Other Manifestations

Mycobacteria may rarely affect the scleral tissue leading to either diffuse or nodular tubercular scleritis (Fig. 16.4). There are few case reports where authors have demonstrated acid fast bacilli (AFB) either by microscopy or by culture from enucleated eyes and scleral biopsy. In a series of 42 enucleated eyes, 1–2 bacilli were found close to areas of necrosis (Wroblewski et al. 2011). These cases may be challenging to diagnose and differentiate from autoimmune scleritis.

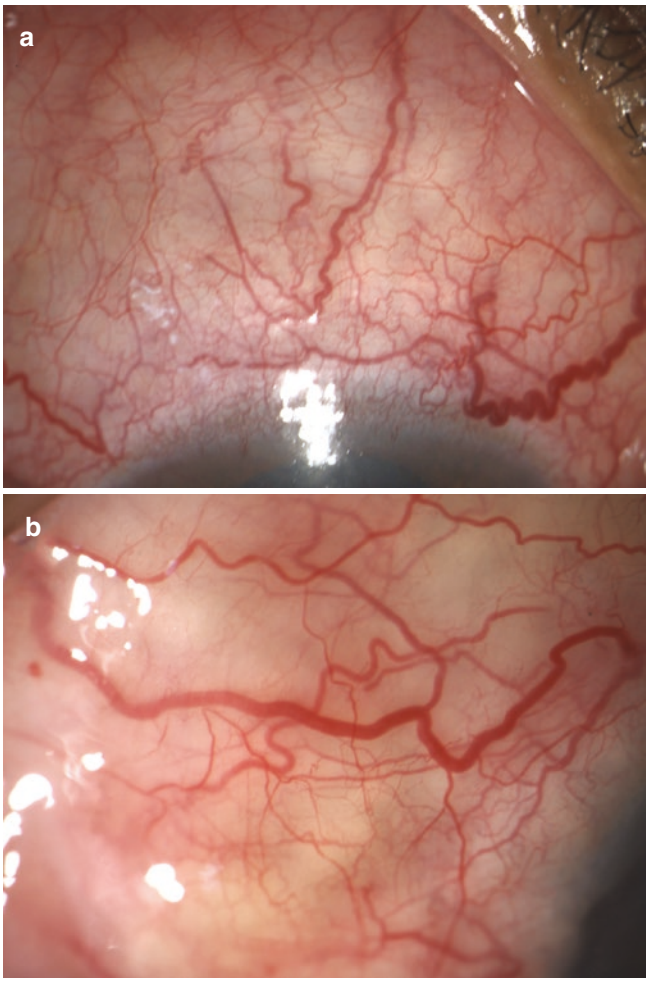

Fig. 16.4 A 35-year-old female presented with bilateral diffuse scleritis and panuveitis with a history of decreased vision and pain for the past 4 weeks in both eyes (**a**, **b**). Her Mantoux text was highly positive and QuantiFERON TB Gold® was positive. Chest computerized tomography (contrast-enhanced) revealed mediastinal lymphadenopathy. She was diagnosed with probable tubercular scleritis and started on oral corticosteroids and anti-tubercular therapy

Retinal vasculitis has long been recognized feature of IOTB in young healthy males, previously known as Eales disease (Gupta and Gupta 2005). However, recent studies have indicated that so-called Eales disease indeed is a phenotype of tubercular uveitis. Typically, the veins are more commonly affected than arteries and is accompanied by vitritis, perivascular cuffing by the exudates, choroiditis lesions (active or healed), cystoid macular edema, occlusive features in the form of capillary non-perfusion, vitreous hemorrhage, or neovascularization of the optic disc/retina. Though the presence of occlusive vasculitis with/without perivascular choroiditis scars is likely to be tubercular in origin, many other diseases such as sarcoidosis and collagen vascular diseases can have similar phenotype (Singh et al. 2012).

Tuberculous optic neuropathy is also uncommon, and may manifest as papillitis, neuroretinitis, and optic nerve tubercle (Gupta et al. 2007). These cases may be challenging to diagnose and treat, and high index of suspicion must be maintained.

Treatment of Intraocular Tuberculosis

Systemic tuberculosis treatment consists of multidrug regimen including first-line agents such as isoniazid, rifampin, ethambutol, and pyrazinamide, and second-line agents such as levofloxacin, streptomycin, amikacin/kanamycin. Second-line agents are used in the presence of mycobacterial resistance. The duration and dosing regimen depend on the organ system involved, severity of disease, and the history of prior anti-TB therapy.

IOTB treatment comprises of four-drug regimen of isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), ethambutol (15 mg/kg/day), and pyrazinamide (20–25 mg/kg/day) along with pyridoxine divided into 2-month induction course of isoniazid, rifampicin, and pyrazinamide administered daily, followed by a continuation phase of 4–7 months of isoniazid and rifampicin. ATT is given in combination with systemic steroids (oral prednisolone 1 mg/kg/day), which is tapered off over the next 6–12 weeks depending upon the level of inflammation seen. Topical steroids may be employed in cases with anterior segment inflammation. Addition of systemic immunosuppressive agents such as azathioprine, cyclosporine, or mycophenolate mofetil may be considered when needed (Gupta et al. 2007).

Paradoxical Worsening of IOTB

A subset of patients treated with ATT may develop paradoxical worsening of ocular disease (Gupta et al. 2011). Paradoxical worsening of the disease is also known as ocular Jarisch-Herxheimer reaction that occurs due to release of tubercular antigens from the dying bacilli. These patients require increase in systemic steroids/immunosuppressive therapy to prevent damage to ocular tissues due to excessive release of inflammatory mediators. Paradoxical worsening of the disease must be differentiated from worsening of primary disease.

MDR IOTB

Recently, rifampin resistance has been demonstrated in ocular TB (Sharma et al. 2014). Drug-resistant tuberculosis with increasing cases of multidrug-resistant TB (MDR TB) as well as extensively drug-resistant TB (XDR TB) is a major challenge. Thus, it is important to obtain the sensitivity profile of the mycobacteria since resistance of this organism is increasing. Failure of response to therapy due to resistance may result in diagnostic and therapeutic challenges.

Complications of IOTB such as inflammatory choroidal neovascularization or macular edema may be treated with the use of intravitreal anti-vascular endothelial growth factor injections.

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