Ocular Tuberculosis

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Abbreviations

anti-VEGF	anti-vascular endothelial growth factor
ATT	anti-tuberculosis treatment
FAF	fundus autofluorescence
FFA	fundus fluorescein angiography
ICGA	indocyanine green angiography
IGRA	interferon-gamma release assay
IOTB	intraocular TB
OCT	optical coherence tomography
OCTA	OCT angiography
PCR	polymerase chain reaction
RPE	retinal pigment epithelium
TAU	TB-associated uveitis
TAU	tubercular anterior uveitis
TB	tuberculosis
TB SLC	tubercular serpiginous-like choroiditis
TBP	TB panuveitis
TBU	tuberculous uveitis
TIU	tubercular intermediate uveitis
TPU	tubercular posterior uveitis
TRV	TB retinal vasculitis
TST	tuberculin skin test
UWF	ultra-wide field

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Introduction

Mycobacterium tuberculosis affects a third of the world's population, with a reported 8.7 M new cases each year and approximately 1.4 M deaths annually [1, 2]. It is estimated that only 10 percent of infected people manifest with symptoms, mostly involving the lungs and the respiratory tract. In 2017, only 14% of symptomatic tuberculosis cases were reported to be extrapulmonary. The worldwide incidence of intraocular tuberculosis is variable and has shown a wide range in the literature—from 1.4% to 18% [3–7].

Tuberculosis (TB) is an airborne infection caused by *Mycobacterium tuberculosis.* It is much more common in the developing world and is associated with severe morbidity and mortality. Intraocular TB (IOTB) is a rare condition that often presents without clinical evidence of active pulmonary TB and may be the first and only manifestation of the infection [1, 8].

Posterior uveitis is the most common form of ocular TB, and early recognition with initiation of specific therapy is of paramount importance especially to prevent its visually debilitating manifestations [1, 9]. Patients with posterior uve-

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itis due to TB represent the most challenging entities to diagnose and manage due to the diagnostic conundrums and similarity with other uveitic entities. Therefore, these cases are often misdiagnosed and incorrectly treated [10, 11].

IOTB can affect various ocular structures resulting in a wide spectrum of clinical manifestations. Some of these may be due to direct mycobacterial invasion of the ocular tissue, while others may be due to delayed hypersensitivity reaction to the bacteria. The disease may manifest with a variety of clinical signs and symptoms causing visual loss due to multiple reasons. Tuberculous uveitis (TBU) may present as anterior, intermediate, posterior, or panuveitis and can mimic various other infective as well as non-infective diseases [1, 9, 11, 12].

Establishing the diagnosis of IOTB is especially a challenge due to several reasons: (1) the disease can affect all ocular structures causing protean clinical manifestations; (2) gold standard tests like smear and/or culture positivity from ocular fluids have a poor yield owing to the difficulties in obtaining ocular samples combined with paucibacillary nature of the disease; and (3) high prevalence of TB in endemic countries makes it difficult to differentiate between true TBU and uveitis associated with unrelated latent TB [8, 11]. Thus, in real-world clinical practice, the phenotype recognition is a very important component of suspecting IOTB combined with corroborative evidence to make the diagnosis and initiate anti-TB therapy [9, 10]. Also it is very important to rule out other possible infections that might be prevalent in that geographic region.

Pathogenesis

M. tuberculosis is an aerobic acid-fast bacillus that has a high amount of lipid content in its cell wall. Humans are its only host and reservoir. As *M. tuberculosis* organisms are acquired via the inhalation route, they are engulfed by alveolar macrophages and dendritic cells. The organisms are then transported to the hilar lymph nodes and potentially to other distant extrapulmonary sites. This process is followed by increased cytokine production particularly IL-12 and TNF- alpha which in turn activate the TH1 cell-dominant adaptive immune response. The CD4 TH1 cell consequently produces IFN-gamma and TNF-alpha, which are crucial in the development of the cell-mediated immune response to *M. tuberculosis* and to granuloma formation [13]. Specific antigens like the early secretory antigenic target (ESAT-6) and culture filtrate protein (CFP-10) found in patients with TB can elicit vigorous helper T-cell responses causing cell lysis and subsequent bacterial dissemination [14, 15].

Pathogenesis of Intraocular Tuberculosis

There are several mechanisms through which *M. tuberculosis* can infect the eye. Most commonly, it can spread via the hematogenous route—it disseminates via the bloodstream to the eye from a remote primary source of infection [7]. In this pathway, the ciliary body and the choroid are the most frequently involved structures given their high vascular content and increased regional oxygen tension [16]. The retinal pigment epithelium (RPE) cells express Toll-like receptors which may actively phagocytose *M. tuberculosis* that reaches the inner choroid via the hematogenous route [17]. Once the intracellular *M. tuberculosis* reaches a sufficient number, a cytotoxic cell-mediated response leads to destruction of the macrophages and surrounding tissue and the formation of caseation [17].

Another process of ocular infection develops through primary exogenous infection of the eye. This is when *M. tuberculosis* directly infects the eyelids and the conjunctiva. Alternatively, a secondary infection can occur via direct extension from the eye's contiguous structures. For example, orbital TB (which is a rare form of ocular TB) is believed to be spread via the paranasal sinuses, presenting as periostitis, orbital soft tissue tuberculoma, or cold abscesses [18].

Finally, tuberculosis of the eye can present as an immune-mediated or hypersensitivity reaction to circulating *M. tuberculosis* antigens. In this mechanism, there is an inflammatory response to

either an active tuberculosis infection outside the eye or to a latent infection. Phlyctenular keratoconjunctivitis, for instance, is a form of conjunctivitis derived from a delayed hypersensitivity response in the cornea or conjunctiva secondary to various pathogens such as *M. tuberculosis*, *Staphylococcus* species, and certain parasites [19, 20]. It presents as a nodule at the limbus or on the conjunctiva.

Overall, among these proposed mechanisms of disease, the precise events leading to tuberculous uveitis and intraocular tuberculosis remain unclear and continue to be controversial [21]. There is no experimental model that can explain all the clinical manifestations of TBU, and thus it is quite likely that different mechanisms may be playing role to produce different manifestations.

Clinical Features

Clinical manifestations of IOTB are variable, which pose a challenge for diagnosis. The commonest form of reported uveitis in TB is tubercular posterior uveitis (TPU) followed by tubercular panuveitis (TBP), tubercular intermediate uveitis (TIU), and tubercular anterior uveitis (TAU) [1, 8–10, 22]. Tuberculosis can potentially involve any part of the eye, and thus, there is no single pathognomonic presentation. Aside from tuberculosis, there are other etiologies for granulomatous inflammation of the eye which may present with similar ophthalmologic findings and may thus, at times, cause diagnostic uncertainty. Differential diagnoses include sarcoidosis, syphilis, sympathetic ophthalmia, uveitis associated with multiple sclerosis, lens-induced uveitis intraocular foreign body, Vogt-Koyanagi-Harada syndrome, and other infectious etiologies [23].

The incidence of ocular involvement in patients with pulmonary TB is variable ranging from 1.4% to, more recently, 6.8%, in a later study [4, 24, 25]. Its incidence rate may vary with location. It has been reported to be 0.3% in South India [26], while it is 11.7% in North India [27].

Among HIV-positive patients, choroidal granuloma has been the most common presentation described in studies [28]. In a retrospective case series of patients coinfected with HIV and tuberculosis in South India, 15 out of 766 patients were diagnosed to have ocular TB. These patients presented with choroidal granuloma (52%), subretinal abscess (37%) some of which worsened to panophthalmitis, and lastly a case each of conjunctival tuberculosis (5.2%) and panophthalmitis (5.2%). All these patients had concomitant pulmonary tuberculosis, and CD4 counts ranged from 14 to 560 cells/μL (mean 160). Severity and incidence of ocular manifestations were not found to correlate with CD4 counts. The relatively higher number of panophthalmitis cases were attributed to presence of impaired cell-mediated immunity in this population of patients. One case of panophthalmitis had happened after a robust rise in CD4 cell counts following antiretroviral treatment and was felt to be from paradoxical worsening or immune reconstitution inflammatory syndrome (IRIS) [28].

A higher incidence of ocular involvement (18%) was noted among 100 patients with tuberculosis admitted to a general hospital in a prospective study of microbiologically confirmed tuberculosis cases done in the AIDS era [5]. The study group included both HIV-positive and HIV-negative patients. Like the prior study, the authors similarly did not detect a significant difference in CD4 counts among HIV-infected patients who had ocular tuberculosis versus those who did not. All 18 patients with ocular tuberculosis had concomitant systemic tuberculosis, with 11 not reporting any ocular symptoms. Multivariable analysis showed that miliary disease (odds ratio 43.92, $p = 0.002$), ocular symptoms (odds ratio 6.35 and $p = 0.0143$), and decreased visual acuity (odds ratio (0.04, $p = 0.012$) were the independent risk factors that predicted for ocular involvement. Miliary disease was the most significant risk factor in both HIV-infected and HIV-negative groups. The presence of HIV infection by itself was not found to be statistically associated with ocular tuberculosis.

In TB-endemic areas, broad-based posterior synechiae, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis have been found to be highly specific for tubercular uveitis with a specificity, likelihood ratio, and

posttest probability of 79%, 93%, and 90%, respectively [29]. Gupta et al., in their retrospective comparative case study, proposed that a patient with these clinical features should further undergo testing for active or latent tuberculosis by proceeding with tuberculin skin test, QuantiFERON-TB Gold test, or chest imaging in the form of chest x-ray or CT chest [30].

In non-endemic areas, however, the diagnosis of ocular tuberculosis may be more challenging and is typically made presumptively. There are no uveitis features that are pathognomonic, and various ocular features may range from nongranulomatous anterior uveitis to occlusive retinal vasculitis [31]. Radiographic studies do not typically show abnormalities or signs of pulmonary involvement. The main exam finding is a chronic resistant granulomatous uveitis [32]. Many times, the diagnosis is based presumptively on a positive QuantiFERON-TB Gold test and/or a tuberculin skin test, further confirmed retrospectively if resolution of the inflammation occurs with antituberculosis treatment.

Tubercular Anterior Uveitis (TAU)

TB anterior uveitis often presents as chronic granulomatous disease which may be unilateral or bilateral. It is characterized by large, mutton fat keratic precipitates, iris nodules which may be present near the pupillary border (Koeppe) or on the iris surface (Busacca), and broad-based posterior synechiae [8, 33]. The disease can be complicated by the development of cataract with or without accompanying vitritis. Broad-based posterior synechiae have been described as a hallmark sign of TAU, a sign that is predictive of possible tubercular etiology. Rarely, TB can also present as non-granulomatous uveitis including hypopyon [1, 8, 30, 33].

Tubercular Intermediate Uveitis (TIU)

The presentation of TIU is non-specific with a waxing and waning course. Patients generally present with smoldering, chronic uveitis characterized by the presence of vitritis, snowball opacities, and peripheral vascular sheathing and may in addition have retinochoroidal granulomas [10, 34–36]. The disease may be complicated by cystoid macular edema or cataract and less commonly by glaucoma/ocular hypertension, epiretinal membrane (ERM) formation, retinal detachment, peripheral neovascularization, or vitreous hemorrhage [1, 8].

Tubercular Posterior Uveitis (TPU) and TB Panuveitis (TBP)

Posterior uveitis is the most common ocular manifestation of IOTB and may be unilateral or bilateral. Choroid is the primary site of involvement with lesions varying from choroidal tubercles and choroidal granulomas to serpiginous-like choroiditis [8]. Retinitis as sole manifestation of TB is rare, and usually there is associated choroiditis. However, TB may present as retinal vasculitis that tends to be occlusive in nature [37, 38].

Choroidal Tubercles/Tuberculoma

Choroidal tubercles are one of the most characteristic intraocular manifestations of TB usually seen in disseminated disease. These tubercles have been defined as "single/multiple, small ($\leq$ 0.5 disc diameter), discreet greyish-white lesions with a central core and surrounding rim of inflammation typically in a patient with miliary disease" [39]. They are small yellowish, discrete lesions generally smaller than a quarter disc diameter with ill-defined borders, located deep in the choroid (Fig. 1.1). Associated anterior segment or vitreous inflammation is usually not seen. When healed, these tubercles appear better circumscribed with surrounding pigment and may develop into a scar [8, 39–43].

Solitary Choroidal Tuberculoma/ Subretinal Abscess

Untreated choroidal tubercles may grow in size up to 14 mm or more, to present as solitary elevated mass-like lesion known as choroidal tuberculoma. Choroidal tuberculomas have been defined as single/multiple yellowish subretinal

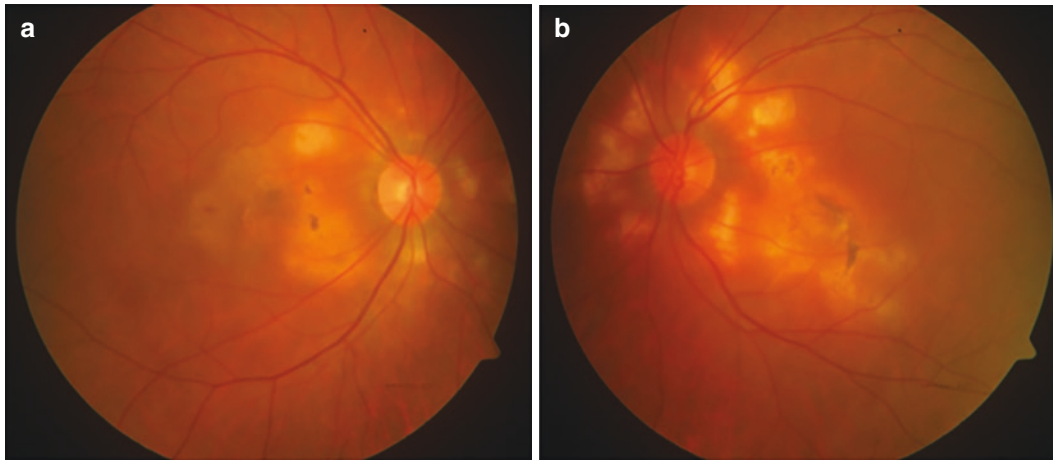

Fig. 1.1 Figure shows two patients with tubercular choroidal granulomas (tuberculomas). In patient 1 (**a**), the tuberculomas are multiple and present in the peripapillary region as yellow, raised, voluminous lesions with surrounding fluid and exudation. Similar lesions are observed in patient 2 (**b**), along with central scarring and pigmentation

lesion with indistinct borders and surrounding exudative fluid, along with oval/round lesion in the choroidal stroma. This would include tubercular subretinal abscess (severe form with exudation, rapid necrosis and tissue destruction, and overlying retinal hemorrhages) [22]. These tuberculomas may be mistaken for tumors, and eyes may be enucleated for mistaken diagnosis. There is underlying tissue destruction resulting from progressive, liquefied caseation necrosis with rapid multiplication of tubercular bacilli. They may even break into vitreous cavity and mimic subretinal abscess causing widespread intraocular inflammation [8, 44, 45].

Tubercular Serpiginous-Like Choroiditis (TB SLC)

TB SLC represents an immune-mediated hypersensitivity reaction to the acid-fast bacilli (*Mycobacterium tuberculosis*) sequestrated in the RPE. It is different from the classic autoimmune variety as it predominantly affects younger population with mostly bilateral lesions which are noncontiguous to optic disc. TB SLC have been defined as "single/multiple discreet yellowish-white fuzzy choroidal lesions and slightly raised edges that show wave-like progression with an active serpiginous-like edge with central healing" (Fig. 1.2). TB SLC lesions can further be *multifocal* or *placoid* [30, 46–49]. The patients with TB SLC can be differentiated from autoimmune variety of serpiginous choroiditis as eyes with TB SLC tend to show presence of vitritis, multifocality with skip lesions with or without peripheral vasculitis [30, 46].

Two different presentations of the disease are:

1. *Multifocal choroiditis*: In this phenotype of SLC, there are discrete lesions, yellowish-white in color with well-defined margins and slightly raised edges. The edges of these lesions are noncontiguous at first and progress relentlessly over a period of 1–4 weeks to a diffuse, contiguous variety, acquiring an active advancing edge [46].
2. *Plaque-like choroiditis*: This phenotype has solitary diffuse plaque-like lesion which shows amoeboid spread. These lesions have elevated active edges, while the center of the lesion heals with pigmentation [46].

TB Retinal Vasculitis (TRV)

TRV has been defined as isolated retinal vasculitis (either periphlebitis and/or arteritis) with/without occlusive disease [37, 38]. Vasculitis in patients with tuberculosis suggests an immune-mediated hypersensitivity response to the bacteria with phlebitis being an important clinical

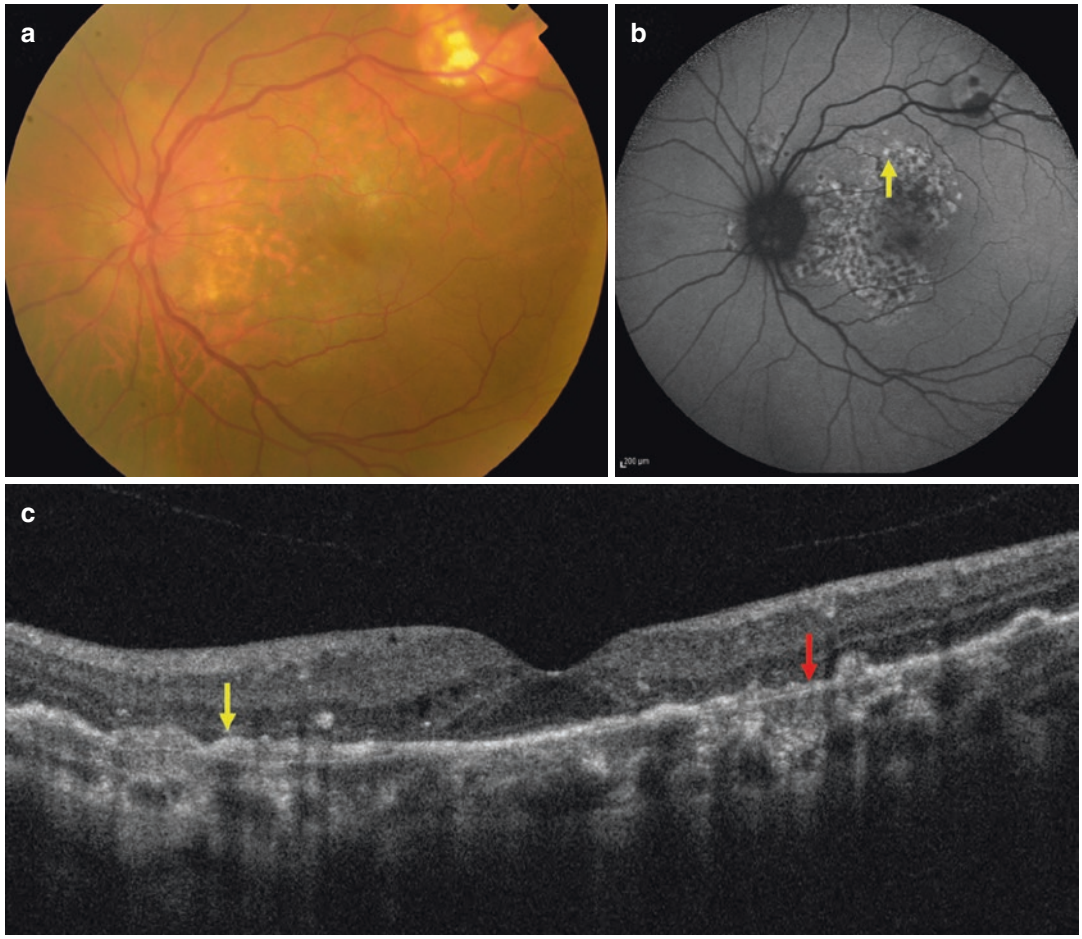

Fig. 1.2 (**a**) Fundus photography of a 28-year-old male with tubercular serpiginous-like choroiditis shows presence of yellowish-white choroiditis lesions at the posterior pole with fuzzy edges and ill-defined margins and pigmented choroidal lesions temporal to fovea. (**b**) Fundus autofluorescence (FAF) imaging of the same eye shows areas of speckled autofluorescence with hyperfluorescent edges (yellow arrow) corresponding to activity at the edges. Temporally lesions are hypo-autofluorescent (stage 4) suggestive of inactive lesions. (**c**) Swept-source OCT (SS-OCT) of the left eye passing through the fovea shows hyperreflectivity of outer retinal layers (yellow arrow) nasal to fovea. Corresponding to healed lesions, there is loss of RPE and outer retinal layers (red arrow) seen just temporal to fovea. As the edges are still active, there is a need for continued anti-tubercular therapy and systemic immunosuppression

finding. The predilection for retinal veins in tubercular retinal vasculitis and its clinical features resemble Eales' disease. Patients with active tubercular vasculitis demonstrate vitritis, neuroretinitis, perivascular cuffing by the exudates, retinal/vitreous hemorrhage, cystoid macular edema, occlusive features in the form of capillary non-perfusion of the retina, or neovascularization of the optic disc/retina [38, 50, 51]. Perivascular choroiditis lesions are quite specific indicators of TB etiology (see Fig. 1.2) [52]. The occlusive retinal vasculitis in TB tends to produce areas of capillary non-perfusion with development of neovascularization that may result in vitreous hemorrhages that may be mistaken as Eales' disease (Fig. 1.3) [53–55].

Endophthalmitis and Panophthalmitis

Rarely TB can present as acute-onset endogenous endophthalmitis with vitritis and hypopyon. It may occur due to rapid multiplication

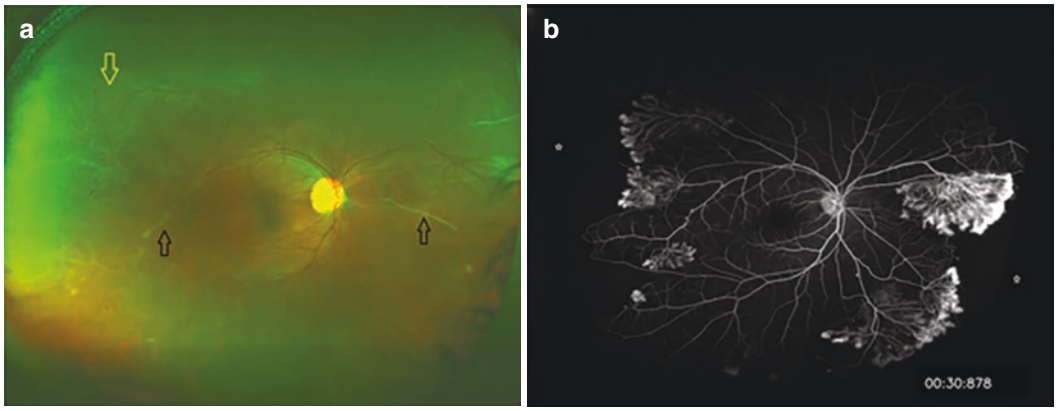

Fig. 1.3 A 30-year-old male with decreased vision in left eye for the past 1 month. Left eye had vitreous hemorrhage (not shown). (**a**) Ultrawide-field (UWF) fundus photography of the right eye showed mild vitritis with sheathing of vessels mainly veins (black arrows) and peripheral large neovascular tufts (yellow arrow). (**b**) UWF fluorescein angiography of the same eye in the late venous phase confirmed the presence of large neovascularization complexes both nasally and temporally with peripheral non-perfusion areas (white asterisk). The patient had a positive tuberculin skin test. He was started on oral corticosteroids and anti-tubercular therapy. Peripheral scatter laser of the non-perfused areas was performed

of acid-fast bacilli or in patients who receive corticosteroid therapy without concomitant antitubercular drugs [56, 57].

Tubercular Optic Neuropathy

Optic nerve involvement in TB may reflect direct infection induced by the mycobacteria or from a hypersensitivity to the infectious agent. It might manifest as neuroretinitis, papilledema, papillitis, optic neuritis, retrobulbar neuritis, or optic nerve tubercle. The neuroretinitis may result from contiguous spread of the organisms to the juxtapapillary retina from the choroid or from disseminated hematogenous spread of the TB organisms from the pulmonary or other primary infectious focus [58–60].

Tuberculosis of Ocular Adnexa

Mycobacteria rarely affect the scleral tissue leading to either diffuse or nodular TB scleritis. These cases are usually difficult to diagnose and need to be differentiated from autoimmune scleritis [61–63]. However, if left untreated, they may progress to cause scleral necrosis and perforation. Orbital TB may manifest as periostitis, dacryoadenitis, soft tissue tuberculoma, osteomyelitis, or a cold abscess. TB of conjunctiva is extremely rare; however, nodular inflammation phlyctenular keratoconjunctivitis may be a delayed hypersensitivity reaction to mycobacterial antigens [64].

Laboratory Testing

There has been no clear gold standard test for the diagnosis of ocular tuberculosis and thus no consensus regarding its diagnostic criteria. A definitive diagnosis would require isolation of *M. tuberculosis* in tissue or ocular fluid culture. However, due to the technical difficulty and risks of proceeding with obtaining ocular fluid, coupled with the paucibacillary nature of the disease associated with low sensitivity of culture and PCR testing, distinguishing between active TB of the eye and an immune-mediated reaction to a distant focus of infection or latent TB becomes challenging. This has led to significant heterogeneity in the approach to the diagnosis and management of intraocular tuberculosis among various referral centers in the world [65, 66].

Direct Laboratory Evidence of *M. tuberculosis* Ocular Infection

Mycobacterial culture is the gold standard for diagnosing *M. tuberculosis* infection. It allows for organism species and strain identification and susceptibility testing. On solid media, it takes 3–8 weeks for *M. tuberculosis* to grow, whereas on liquid media, growth is facilitated and can be detected within 7–21 days. Nucleic acid amplification can offer direct detection in clinical specimens and thus can provide the advantage of a more rapid diagnosis and turnaround time. Gene Xpert MTB/RIF assay is recommended by WHO for the rapid diagnosis of tuberculosis. It can detect both the presence of *M. tuberculosis* in clinical specimens and also rifampin resistance by determining the presence of rpoB gene mutations. The typical turnaround time is 2 h. Its use in diagnosing ocular tuberculosis is worth studying. In a recent study of 714 patients' samples (285 from pulmonary and 429 from extrapulmonary sources), the sensitivity and the specificity of GeneXpert MTB/RIF were almost similar in both groups (78.2% and 90.4%, and 79.3% and 90.3%, respectively) [67].

In ocular tuberculosis, confirming the diagnosis by identifying *M. tuberculosis* in an ocular specimen is usually very challenging given the relatively low sensitivity of these diagnostic tests, the paucibacillary nature of the disease, and the potential complications of the diagnostic procedure which include visual loss, retinal detachment, and infection [21]. In addition, it is uncommon to find histopathologic evidence of necrotizing granulomatous inflammation among clinical cases since this would need a fairly large ocular biopsy sample to establish a diagnosis [68, 69]. Overall, ocular TB diagnosis remains a clinical or presumptive diagnosis based on the summative results of the patient's history, physical exam findings, radiographic evidence, and other supporting lab results. Given this, there is a heterogenous approach to the diagnosis and management of ocular tuberculosis throughout the world, and no clear consensus has been reached [21].

Polymerase Chain Reaction

Polymerase chain reaction (PCR) from intraocular fluids for the diagnosis of TB has limited application in real-world scenario as only one-third of patients with suspected TBU may be positive for *Mycobacterium tuberculosis* on PCR [53, 70–72]. Moreover, there is lack of standardization of PCR. Factors affecting sensitivity and specificity include volume of sample, number of amplification targets, and DNA extraction method, with inhibitors in the fluid sample. Due to lack of sensitivity of current PCR techniques, a positive PCR may be considered reliable if the phenotype is suggestive of TB and other possible causes have been ruled out. However, negative results do not exclude TBU [72].

Ancillary Ocular Investigations

Color Photography and Ultra-Wide Field Imaging

Color fundus photography helps in accurately identifying the morphology of the IOTB lesions, and serial imaging at regular intervals aids in objective assessment of change in lesions over an extended period of time [73]. Ultra-wide field (UWF) fundus too is a useful adjunct to identify peripheral active TB vasculitis, peripheral neovascularization, and areas of non-perfusion requiring laser which might be missed on conventional imaging modalities [52].

Fundus Autofluorescence

Fundus autofluorescence (FAF) is a noninvasive imaging technique that details the health of the RPE. As RPE and choriocapillaris are the proposed major sites of involvement in TB SLC, FAF can play an important role in assessing disease activity and resolution of such lesions. Gupta et al. [74, 75] have described different stages in the resolution of SLC lesions using FAF imaging (see Fig. 1.2). The acute stage (stage 1) shows an ill-defined amorphous lesion with halo-like hyperautofluorescence and ill-defined margins. As the lesion starts healing, a thin rim of hypo-autofluo-

rescence is seen surrounding the lesion which remains predominantly hyper-autofluorescent with a stippled pattern (stage 2). With further healing, there is increasing hypo-autofluorescence in an outward-in fashion, and the lesion shows predominant hypo-autofluorescence (stage 3) on FAF imaging. The entire lesion becomes hypo-autofluorescent (stage 4) on complete resolution, and this marks the end of activity and RPE atrophy.

Fundus Fluorescein Angiography (FFA)

The active lesions in TB SLC appear hypofluorescent in the early phase and hyperfluorescent in the late phase (Fig. 1.4). Areas of resolution show

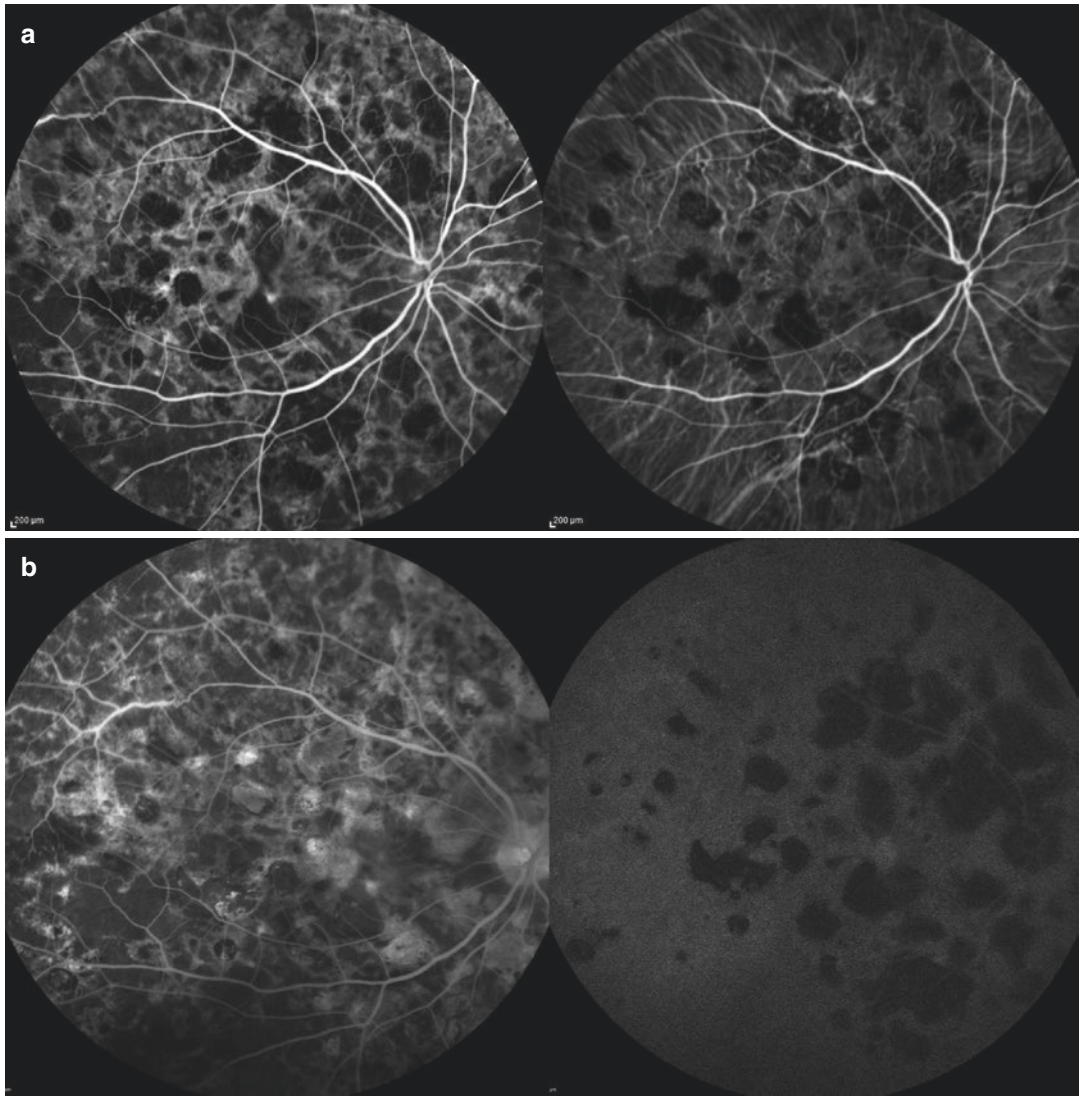

Fig. 1.4 Combined fluorescein angiography (FA) and indocyanine green angiography (ICGA) in the early (**a**) and late phase (**b**) in a young female with tubercular serpiginous-like choroiditis. The FA shows presence of early hypofluorescence and late hyperfluorescence with fuzziness of the active lesions, and transmission defects in the areas of choriocapillaris atrophy. ICGA imaging shows hypofluorescence in both early and late frames along with visible underlying choroidal vasculature in areas with choriocapillaris atrophy

transmission defects due to RPE damage and choriocapillaris atrophy. Also complications such as inflammatory choroidal neovascularization may be detected using FFA, though it may be very challenging in the absence of high index of suspicion [40, 76].

TB granulomas would also block choroidal fluorescence in the early phases as it does not have its own separate vascular supply. However, in the late phases, it may become intensely hyperfluorescent due to large amount of dye accumulating in the lesion. Being an inflammatory choroidal pathology, a TB choroidal granuloma may also be associated with an exudative detachment showing late phases pooling of the dye [8, 39, 40, 60]. Tuberculomas may sometimes be associated with deep retinal and subretinal hemorrhages in which case FFA helps in ruling out development of a secondary choroidal neovascularization or a retinal angiomatous proliferation-like lesion.

UWF FFA plays a significant role in identifying peripheral vascular leakage in cases of active TB vasculitis. Moreover since TB vasculitis is occlusive in nature, it can help identify neovascularization and areas of peripheral non-perfusion which would require scatter photocoagulation [52].

Indocyanine Green Angiography

Indocyanine green angiography (ICGA) is a useful tool in detecting choriocapillaritis and presence of choriocapillaris hypoperfusion among patients with IOTB (see Fig. 1.4). Active lesions of TB SLC remain hypofluorescence from early to late phase on ICGA. Two different ICG presentations are seen with TB choroidal granuloma based upon the thickness of the lesion in the choroidal stroma. Full-thickness choroidal involvement is seen as hypofluorescence in all phases of angiography, whereas partial choroidal thickness involvement is seen as early hypofluorescence becoming iso- or hyperfluorescent in mid and later phases [77]. Other changes of tubercular uveitis include fuzzy appearance of choroidal vessels in the intermediate phase and late choroidal hyperfluorescence due to dye leakage which tends to regress following therapy [1, 8, 40, 77].

Optical Coherence Tomography (OCT)

Acute SLC lesions correspond to outer retinal layer hyper-reflectivity on OCT with involvement of RPE, photoreceptor outer segment tips, ellipsoid region, ELM, and outer nuclear layer with a minimal involvement of inner retinal layers. With onset of resolution, the hyper-reflective regions are replaced by knobby irregular elevations of outer retinal layers. With further healing of lesions, a loss of outer retinal layers with increased choroidal backscattering has been reported (see Fig. 1.2) [40, 49, 74, 78, 79].

TB granulomas are seen as lobulated and non-homogeneous on EDI-OCT. These granulomas may show increased transmission signal as compared to normal surrounding choroid. OCT can also help in differentiating choroidal tumors from inflammatory granulomas as the latter tend to have a smooth lesional surface and moderate thickness, unlike the often irregular topography and greatly increased choroidal thickness of choroidal tumors [40, 80, 81].

Recent introduction of OCT angiography (OCTA), a dye-less noninvasive technique, has furthered our capabilities to understand the pathological involvement in IOTB. OCTA was found to be effective in clearly delineating the lesion of CNV and detailing the involvement of retinochoroidal layers with branching vascular networks (Fig. 1.5) [49, 78, 82].

IFN-Gamma Release Assays (IGRA)

Other adjunctive tests include immunological tests such as the tuberculin skin test (TST) and interferon-gamma (IFN-gamma) release assay (IGRA) and chest imaging studies. The TST sensitivity for active TB is approximately 70% [83]. Its sensitivity and specificity for ocular TB range from 92% to 95% and 72% to 90%, respectively [84, 85]. False positives, however, may occur among populations that receive the BCG vaccine or those infected with certain nontuberculous mycobacterial infections that cross-react with the purified protein derivative used for the skin test.

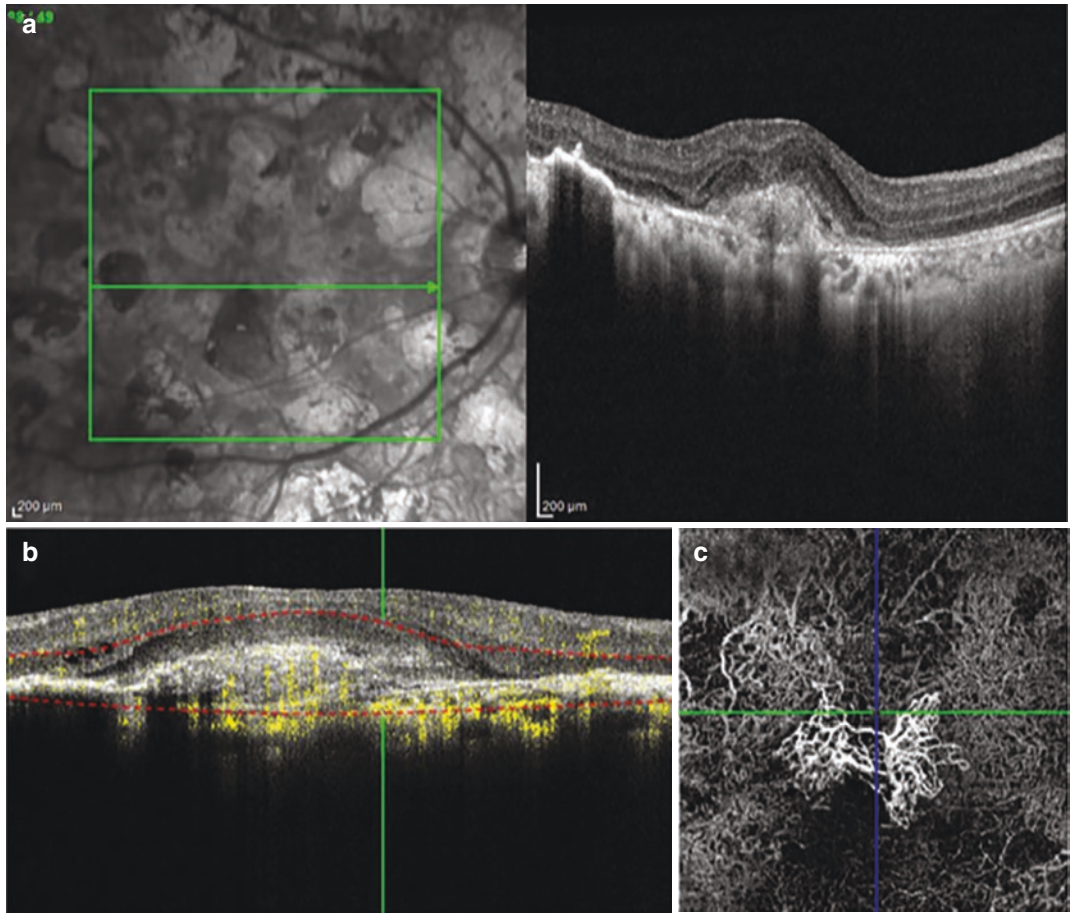

Fig. 1.5 Optical coherence tomography (OCT) and OCT angiography (OCTA) in a young male with healed tubercular serpiginous-like choroiditis. The OCT imaging shows presence of subretinal hyper-reflective material (SHRM) with streak of subretinal fluid indicating presence of choroidal neovascularization (**a**). The cross-sectional B-scan image obtained using OCTA confirms the presence of active CNV with flow signals (**b**). The en face OCTA scan shows an exuberant type 2 CNV (**c**)

Specificity for diagnosing tuberculosis infection is increased through the use of IGRAs: QuantiFERON TB-Gold (QFN-TB) and T-SPOT-TB. QFN-TB measures the amount of IFN-gamma produced by an individual's T cells when incubated for 24 hours with specific *M. tuberculosis* antigens such as ESAT6 and CFP10. The IFN gamma concentration is determined using optical density. T-SPOT-TB determines the amount of peripheral blood T cells secreting IFN-gamma represented by the number of spot footprints using the ELISpot technique. The antigens used by IGRA are specific to *M. tuberculosis* (ESAT6, CFP10, and TB7.7), and specificity in populations at low risk for latent TB infection ranges from 92% to 97% [83]. Sensitivity of IGRAs is fairly similar to TST for diagnosing active TB (76%) and latent TB. In a retrospective review of 82 cases of presumed ocular TB which described anti-tuberculosis treatment (ATT) response and association with QFN-TB, steroid use did not have a significant association with QFN-TB values and did not appear to affect QFT-TB accuracy [85].

Although IGRA is recognized to have a higher specificity than TST for the diagnosis of active or latent tuberculosis, there are also certain pitfalls with its use. Its positive predictive value is lower

in populations that have a lower pretest probability [86, 87]. Some studies propose a higher cutoff value to increase the likelihood of a positive response to ATT [88].

It is important to consider other potential etiologies for uveitis and exclude these prior to making a diagnosis of ocular tuberculosis, even among those who have a positive IGRA result. The differential diagnoses include sarcoidosis, Behcet's, syphilis, and toxoplasmosis. For instance, in one study 25% of patients with uveitis and a positive QuantiFERON were found to have other causes [89]. Another study showed 37 out of 80 were found to have an alternative etiology, most cases secondary to intraocular sarcoidosis. IGRA should be checked selectively and only in those individuals who have a good pretest probability of TB infection such as those with a history of TB exposures or those with an idiopathic chronic inflammation that have had a suboptimal response to immunosuppression [9].

In a prospective cohort study of patients with clinical ocular signs of TB-associated uveitis (TAU), TST (72%) was found to be more sensitive than TSpot (36%), but TSpot (75%) was more specific than TST (51%). It was found however that if patients were positive for both TST and TSpot, they were 2.16 times more likely to have TAU. The authors thus recommended using both tests in addition to the presence of clinical ocular signs in diagnosing TB uveitis [90].

Chest Imaging

Most patients with tuberculous uveitis do not have associated extraocular manifestations. Majority of the time, especially in non-endemic regions, chest imaging is negative for signs of tuberculous involvement.

In a study of patients presenting with uveitis of unknown cause in South Africa, CXRs were normal/indeterminate in 88 out of 104 patients. Abnormal CXRs were present in 5 of 34 cases of IOTB (14.7%) versus 62.5% (5 of 8 cases) of intraocular sarcoidosis (IOS). CXR had a sensitivity of 14.7% and a specificity of 94.3% for intraocular TB compared with a sensitivity of 62.5% and specificity of 96.9% for IOS. The overall diagnostic accuracy of CXR was only 54.5% for IOTB, whereas it was higher at 79.9% for IOS [91].

Treatment of Intraocular Tuberculosis

There is little evidence available in the literature to help guide the management of ocular tuberculosis. Majority of studies are retrospective, and there are no randomized controlled trials to compare treatment outcomes. Thus, various referral centers in the world have attempted at least to develop a pathway or standardization of care for individuals who present with uveitis of unknown etiology that have had a suboptimal response to standard therapy [23, 92].

Several studies have described successful outcomes starting empiric ATT in presumed ocular tuberculosis [93–96]. In a retrospective study of 48 patients in the UK with presumed TB uveitis and positive IGRA, 6 months of ATT was given with complete resolution in 60% [93]. In a tertiary uveitis clinic in New Zealand, 30 patients with presumed TB uveitis were treated with 6–12 months of ATT, and 67% went into remission for at least 12 months [95]. Disappearance of ocular inflammation and response to ATT have likewise been reported in 60–70% of patients after ATT [31, 88]. A prospective case study of 96 patients presenting with ocular inflammation to an ophthalmology clinic in France described the outcome of 25 patients with positive QuantiFERON-TB Gold who were treated with 6 months ATT (6 of 25 with accompanying systemic steroids). The median QuantiFERON-TB Gold value was significantly higher in the patient group with a successful treatment response (7.67 IU/mL [0.46 to 33.37]) versus the group that did not improve (1.22 IU/mL [0.61 to 4.4]). The authors suggested considering a higher cutoff QuantiFERON-TB Gold value (>2 IU/mL) in helping identify patients who would more likely benefit from ATT [88].

Management of Intraocular Inflammation

The goal of therapy in TBU is to control current episode of inflammation to prevent any damage to intraocular structures and to prevent recurrences over a long-term follow-up. Intraocular inflammation is mainly controlled by the use of corticosteroids [46]. Systemic immunosuppressive agents may be considered when inflammation is not controlled by steroids. However, systemic corticosteroid or other immunosuppressive therapy should not be prescribed alone, and specific therapy in the form of ATT needs to be added for two reasons: (1) addition of ATT has shown to reduce recurrences over long-term follow-up by more than 80% [90, 97]. A report by the Collaborative Ocular TB Study (COTS) group on long-term follow-up of more than 24 months of treatment with ATT indicated that more than 75% of these patients are able to achieve cure [98]. (2) Treatment with systemic corticosteroids and immunosuppressive therapy in patients with latent TB may cause a flare-up of systemic TB by activating a latent infection [10, 48, 73, 97].

Tuberculosis screening should be performed ideally before immunosuppression is started among those patients who have had uveitis of unknown etiology that have not responded to conventional treatment and those with ocular findings suggestive of ocular tuberculosis [23]. Evaluation includes a combination of obtaining a clinical history, chest imaging, immunological testing, and sputum collection (if indicated) and, if feasible, obtaining an ocular specimen for mycobacterial culture or acid-fast bacilli PCR. HIV screening should be performed in all patients with presumed ocular TB. If workup is not definitive for a diagnosis of ocular tuberculosis but the clinical features point to active TB, a presumptive diagnosis can be made and initiation of an anti-tuberculosis regimen considered. Among clinical features, choroidal granulomas, occlusive retinal vasculitis, and multifocal serpiginoid choroiditis have been found to be most strongly predictive of ocular TB [99, 100]. Among these in particular, choroidal granulomas should raise a high index of suspicion especially since the inability to recognize it could lead to severe complications [101]. Lastly, ophthalmologists should also consider involving infectious disease in evaluating patients who continue to have a nondiagnostic workup. Reviewing with an infectious disease consultant the need for further CT chest imaging or PET scan may be of benefit in some situations [102].

The major challenge, however, in possible tubercular uveitis is defining the indications for initiating ATT as this decision is based on institutional and country practices and very often requires involvement of infectious disease specialists who may not be convinced to initiate ATT only for ocular disease in the absence of any direct evidence of infection. The COTS Consensus group tried to define the indications of initiating ATT. The experts took into consideration the phenotype, endemicity, immunological tests (TST skin test and QuantiFERON TB Gold ®), and radiologic evidence that mostly shows evidence of past exposure to TB in the form of calcified hilar nodes and not active disease. There was consensus to treat any form of TB choroiditis if any one of immunological and one radiologic test was positive. For phenotypes like TB SLC and tuberculomas, even one immunologic test alone without any radiologic evidence was considered sufficient for initiating ATT [103]. However, for phenotypes like TAU, the experts felt the need to treat only if disease was recurrent. Experts agreed on initiating ATT in TIU and active TRV only when one immunologic along with radiologic test was positive [104].

Anti-tuberculosis Treatment

ATT for ocular tuberculosis is similar to the treatment regimen for pulmonary tuberculosis, i.e., four drugs consisting of rifampin, isoniazid, pyrazinamide, and ethambutol for 8 weeks followed

by isoniazid and rifampin for 4–10 months [103–105]. Some experts recommend co-management with infectious disease for assistance with antibiotic treatment and addressing potential side effects [21]. Ethambutol can lead to optic neuropathy, and monitoring for toxicity at follow-up every 2 months is recommended [23]. Ethambutol should be discontinued as soon as signs of ocular signs or symptoms of optic neuropathy appear (decreased visual acuity or abnormal ocular testing). Moxifloxacin has been used as an alternative to ethambutol, but there are experts who feel that the risk for ethambutol toxicity is relatively low and does not justify modifying the standard treatment regimen [93].

The duration of antibiotic treatment ranges from 6 to 9 months. There is no consensus regarding the optimal duration of ATT although there are some who recommend at least 9 months of treatment or longer. A higher success rate was found among patients with presumed ocular TB who received ATT for 9 months or longer, whereas poorer outcomes were associated with those on immunosuppression [106]. In a case-control study done by Ang et al., an 11-fold reduction in the likelihood of recurrence was noted among those patients with uveitis and latent TB treated with >9 months of ATT [90].

Paradoxical Worsening of IOTB

Paradoxical worsening of the disease also known as ocular Jarisch-Herxheimer reaction is an entity described in a subset of patients with extrapulmonary TB. It is the continued progression of the disease seen in patients who have been started on ATT. This has been postulated to be due to release of antigens from the dying bacilli. These patients require an increased dose of systemic steroids/immunosuppressive therapy to prevent damage to ocular tissues due to excessive release of inflammatory mediators. It is important for clinicians to be aware of this phenomenon and continue patients on ATT despite initial worsening as it can help in decreasing recurrences in long-term follow-up [41, 48]. Intravitreal injections of methotrexate or dexamethasone implant, too, have been reported to manage paradoxical worsening (Fig. 1.6) [107–109]; however, the expert committee could not reach any consensus on local therapy, and thus these are left to discretion of treating physicians [103].

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections may be used to treat complications of IOTB such as inflammatory choroidal neovascularization or macular edema [42, 60].

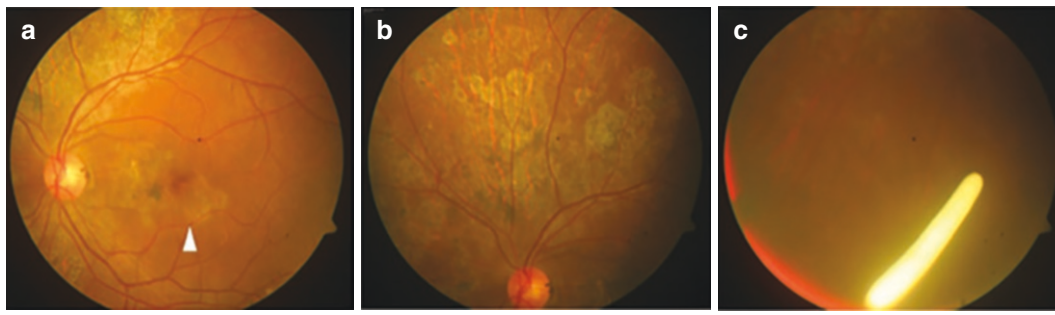

Fig. 1.6 The figure shows a patient with tubercular serpiginous-like choroiditis treated with intravitreal dexamethasone implant (along with anti-tubercular therapy). The fundus photographs with macula in the center (**a**) show active lesions involving the posterior pole (white arrowhead). The superior retina shows healed inactive lesions (**b**). The intravitreal dexamethasone implant injection is seen in the inferior vitreous cavity (**c**)

Conclusion

It is important to have a high index of suspicion based on the history and phenotype. The patients with characteristic phenotype and corroborative evidence of TB may be initiated ATT. That helps in reducing the recurrence.

Compliance with Ethical Requirements The authors declare that they have no conflicts of interest.

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