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Research Article

OCULAR TUBERCULOSIS

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A R T I C L E I N F O

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A B S T R A C T

Tuberculosis is a very common disease in India. Ocular tuberculosis is an extrapulmonary mycobacterial infection with varied manifestations. In recent years, ocular involvement due to TB has re-emerged. The most common manifestation of ocular tuberculosis in patients with pulmonary tuberculosis is choroiditis. Retinal periphlebitis is rarely caused by direct invasion of the retina by tubercle bacilli. Retinal tuberculosis is usually, but not always, secondary to an underlying choroiditis. The lack of any uniform diagnostic criteria for intraocular tuberculosis, in either immunocompetent or immunocompromised individuals, has contributed to the confusion regarding diagnosis and management. . It is imperative for physicians to consider this diagnosis in their differential, as ocular tuberculosis can present in a fashion similar to that of more common conditions causing ocular inflammation. Techniques such as ultra-wide field fundus photography, fluorescein and indocyanine green angiography, optical coherence tomography and most recently, optical coherence tomography angiography, provide valuable information regarding the disease progression and severity. This review article focuses on the clinical characteristics and diagnostic modalities useful in the diagnosis of intraocular TB. Specifically, IFN-gamma Release Assays (IGRAs) and polymerase chain reactions are discussed. The use of corticosteroids along with anti-tuberculous medications and potential side-effects are discussed.

INTRODUCTION

Ocular Tuberculosis

Tuberculosis (TB) is a chronic infection caused by *Mycobacterium tuberculosis* (MTB) that is characterized by the formation of necrotizing granulomas[1]. Ocular TB is defined as an infection by MTB in the eye, around the eye, or on its surface[2]. The diagnosis of ocular TB poses two major challenges to treating physicians: multiple clinical manifestations of the disease that overlap with other forms of uveitis, and absence ofdefinitive diagnosis based on detection of thepathogen in majority of cases.Despite these challenges, there have been advances in understanding of clinical manifestations and diagnostic criteria for ocular TB in the last two decades.

Epidemiology and Pathogenesis

The World Health Organization has declared tuberculosis a global Emergency[3-5]. In 2012, there were 8.6 million new TB cases and 1.3 million TB deaths, worldwide [6]. In addition, one-third of the world population is infected with latent Mycobacterium tuberculosis infection.

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About 5–10 % of such infected persons are known to develop active TB disease at some time in their lives[7]. The epidemiology of tuberculosis in developing countries has been impacted by the onset of the human immunodeficiency virus(HIV) epidemic, as tuberculosis is the most common opportunistic infection[8]. Majority of reports on ocular TB during the last two decades have been from high-endemic countries like India and other Asian countries, where it accounted from 0.6 to 20 % of all uveitis cases[9-10] .

Criteria for establishing a diagnosis of ocular TB are not well established and, therefore, the epidemiology of ocular TB is less certain than for TB. Lack of clear diagnostic criteria may also explain the variation of the reported incidence of ocular TB over time and geography. The regions most plagued by TB are also least equipped to screen thoroughly for ocular involvement, potentially resulting in underdetection of ocular manifestations[11,12,13]

Tuberculosis is essentially a communicable infection caused by inhalation of aerosolized droplets carrying the mycobacteria. The identification of M. tuberculosis in enucleated eyes and amplification of mycobacterial DNA from ocular fluid samples suggest that this condition results from an inflammatory response to the bacteria in ocular tissues[14,15]

It has been suggested that mycobacteria remainsequestered in the RPE in a dormant form for long periods and on their activation they lead to recurrent inflammation[16]. Most recently,

it has been shown that RPE cells are better able tocontrol growth of M. tuberculosis than macrophages, which helps them survive longer in thepresence of infection [17].

Clinical Features

MTB is an obligate aerobic bacteria, usually found in highly oxygenated tissue.In the eye, choroid which has one of the highest oxygen tension harbours the bacteria.

Anterior Uveitis

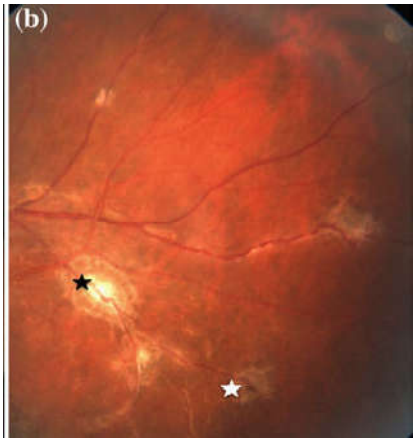
Tuberculosis typically causes granulomatous anterior uveitis, with or without mutton-fat keratic precipitates, broad posterior synechiae, iris Nodules (Koeppe and Busacca) and iris or angle granulomas. It has an insidious onset, unilateral or bilateral and runs a chronic course[18-20]. Administration of anti-TB treatment helps in reducing the number ofrecurrences in these eyes.[21]

Intermediate Uveitis

TB can account for nearly half the cases of intermediate uveitis in high-endemic countries[22]. It presents as chronic, low-grade inflammation associated with vitritis, and 'snowballs'in vitreous cavity. 'Snow-banking' is less commonly seen. Long-standing disease may lead to cystoid macular edema, complicated cataract, elevated intraocular pressure, epiretinal membrane, and peripheral retinal neovascularization

Posterior uveatis

Tuberculosis commonly presents in the posterior segment as focal, multifocal or serpiginous choroiditis, solitary or multiple choroidal nodules (tubercles), choroidal granuloma (tuberculoma), neuroretinitis, subretinal abscess, endophthalmitis, panophthalmitis, and retinal vasculitis, which is frequently ischemic in nature and may lead to proliferative vascular retinopathy with recurrent vitreous hemorrhage, rubeosis iridis, and neovascular glaucoma[23-26]



Fundus photograph of inferotemporal quadrant of left eye showing active (black asterix) and healed (white asterix) choroiditis patches along blood vessels

Choroidal tubercles are the most recognized manifestation of intraocular tuberculosis and result from hematogenous spread of the mycobacteria when a caseous pulmonary lesion erodes blood vessels/ lymphatics.[27]

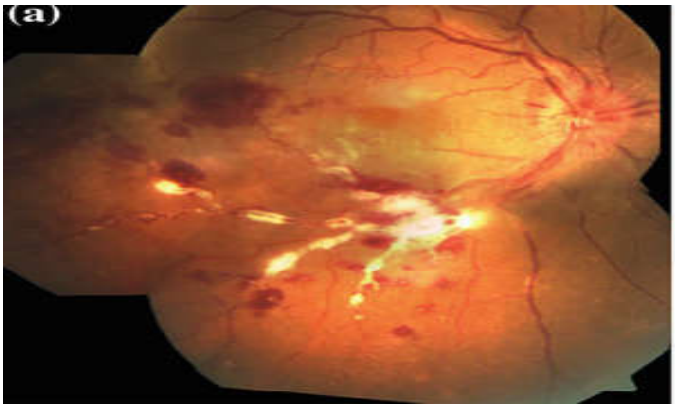
Tuberculomas vary between 4 and 14 mm in size with exudative retinal detachment.[27] On ultrasonography, these lesions are solid, elevated masses with moderate to low internal reflectivity.[27]

Subretinal Abscess

These are large yellowish subretinal lesions that occur due to liquefaction of caseous material inlarge tuberculous granulomas. They usuallyrespond well to antituberculous therapy (ATT), healing with atrophy and variable pigmentation.

Retinal Vasculitis

Tubercular retinal vasculitis typically involvesthe retinal veins.

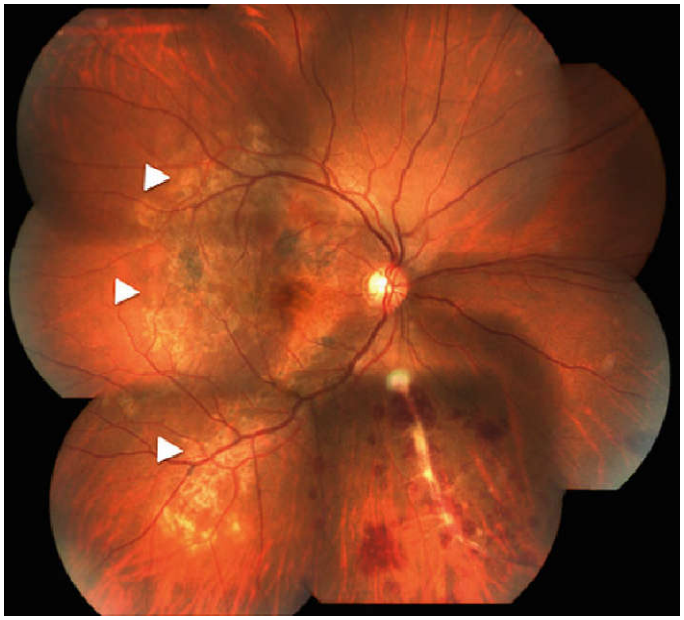


Fundus photograph of right eye showing retinal periphlebitis associated with massive perivascular exudation, in the inferotemporal quadrant. Retinal hemorrhages and macular edema are also seen

Infectious Multifocal Serpiginoid Choroiditis (MSC)

This is a chronic recurrent inflammation of the retinal pigment epithelium and inner choroid that shows central healing and active margins progressing in an ameboid fashion. Three patterns have been described: multifocal lesions that progress to confluent, diffuse choroiditis, lesions that are diffuse at presentation and a mixed variety (between opposite eyes[28].

The following characteristics distinguish MSC from classical serpiginous choroiditis:endemic population/travel to endemic area, multifocality, presence of vitritis, lesions originatingat macular, dense pigmentation at centerof lesions, and immunological/radiological evidenceof systemic TB [29]. On fundus fluorescein angiography, the active edge is initially hypofluorescent which shows late hyperfluorescence.



Fundus photograph of right eye showing multifocal serpiginoid choroiditis (arrowheads) associated with retinal vasculitis and hemorrhages along inferonasal quadrant.

Tubercular Optic Neuritis

These may range from papillitis and neuroretinitis to optic nerve granuloma [30]. They are usually associated with some form of uveitis.Most cases recover well after appropriate therapy.

Endophthalmitis and Panophthalmitis

Intense inflammatory response in intraocular TB may result in destruction of ocular tissues with a resultant clinical picture of endophthalmitis or rarely panophthalmitis.These present acutely with hypopyon and dense vitritis. Subretinal or choroidal abscess can be present that may burst into the vitreous cavity.

Diagnosis

The diagnosis of ocular TB is often problematic due to a wide spectrum of presentations and it is impractical to take uveal biopsy for culture and direct histopathological examination to provide definitive proof of ocular infection.[31] In nearly all reported cases, the diagnosis of ocular TB was only presumptive.Most patients with ocular involvement have no history of pulmonary or other systemic forms.[32]

Ocular Imaging

Although ocular TB is a clinical diagnosis in the majority of patients, imaging studies is helpful in assessing disease activity, and evaluating associated complications of intraocular inflammation.

Fundus Photography

Serial fundus photography can be very useful indocumenting disease progression as well as identifying small lesions that may be missed onroutine examination.

Fluorescein Angiography

It is most useful in patients with retinal vasculitis in demonstrating areas of capillary non-perfusion and associated neovascularization[33]. It can also help in the diagnosis choroidal neovascularmembranes that may complicate MSC.

Fundus Autofluorescence

It has emerged as a quick imaging tool formonitoring the course of MFC lesions [34]. Typically, acute lesions show an ill-defined halo of hyperautofluorescence. With healing, a dark outer rim of hypoautofluorescence appears, that progressively increases to occupy the entire lesion.

Optical Coherence Tomography (OCT)

It also shows characteristic changes in MFClesions [35]. In spectral-domain optical coherence tomography (OCT), acute lesions show hyperreflective areas in outer retina and RPE with no back-scattering from inner choroid. OCT is also useful in documenting macular pathology like cystoid macular edema and epiretinal membranes.

Ultrasonography and UltrasoundBiomicroscopy

In hazy media, ultrasonography can help in differentiating tuberculomas and subretinal abscesses (moderate to low internal reflectivity) from intraocular tumors, while ultrasound biomicroscopycan help in studying the pars plana forciliary body atrophy or presence of a granuloma

Immunological Tests

Two tests are available for immunological diagnosis of mycobacterial infection: the purified protein derivative (PPD) or Mantoux skin test, and the interferon-gamma release assays (IGRA).As per the Centers for Disease Control and Prevention, the sensitivity of IGRA is 'statistically similar to that of PPD for detecting infectionin persons with untreated culture-confirmed TB' [36]. Importantly, neither test can distinguish between active and latent TB.

IGRAs such as T-SPOT.TB (Oxford Immunotec) and QFT (Cellestis Inc.) are more specific and sensitive than TST in detecting active pulmonary TB infections.[37] However, they are less sensitive for diagnosing latent TB infections.[38] T-SPOT.TB is more specific for diagnosing TB-associated uveitis, and serves as a better diagnostic tool if used in conjunction with the TST.[39] The accuracy of diagnosing TB uveitis increases when both tests are used in combination with suggestive clinical signs

Radiological Tests

Routine chest radiography can reveal evidence of healed or active pulmonaryTB anywhere in the lungfields. High resolution computed tomography (HRCT) of thorax may have increased sensitivity for the detection of pulmonary or mediastinal TB[40]. Recently, positron emission tomography (PET)/CTscan has been used to demonstrate metabolic activity in mediastinal lymph nodes that were not detected on CT scan of thorax.

Definitive Evidence of M. Tuberculosis in ocular tissues

PCR-based assays have recently emerged as a promising approach for definitive diagnosis of ocularTB in large number of cases[41].

New innovations like multi-target PCR (multiple gene targets includingIS6110, MPB64 and Protein B) have helped in achieving greater than 70 % positivity rates in clinicallysuspected cases of ocular TB [42].

Differential Diagnosis of Ocular Tuberculosis[27]

Infectious Disorders	Noninfectious Disorders
Syphilis	Sarcoidosis
Toxoplasmosis	Behçet's disease
Toxocariasis	Metastasis
Candidiasis	Tumors
Brucellosis	Autoimmune vasculitis
Leprosy	
Nocardiasis	
Coccidiomycosis	
Leptospirosis	
Cat scratch disease	
Lyme disease	

Treatment

The majority of cases of ocular TB are diagnosed on the basis of clinical signs, ancillary tests (immunological and radiological), and exclusion of other uveitic entities. The diagnosis of ocular TB is presumptive, and it is unknown if ocular manifestations result from a delayed hypersensitivity reaction or due to the infectious agent.[43]

A multiple drug regimen is recommended to avoid resistance. Systemic corticosteroids together with multidrug anti-TB treatment may limit damage to ocular tissues. ATT should be given for aminimum of 6 months in total-2 months offour-drug therapy (isoniazid 5 mg/kg daily, rifampicin 450 mg daily, pyrazinamide 30 mg/kgdaily and ethambutol 15 mg/kg daily) followed bya 4-month continuation phase of isoniazid and rifampicin.. Systemic issues that arise are primarily from thedrug related hepatotoxicity. Ocular toxicities include optic neuropathy (ethambutol, especiallyif used >15 mg/day for >2 months, and rarely, isoniazid) and anterioruveitis (rifabutin). Concomitant corticosteroid therapy is vital to controlthe inflammatory tissue damage caused by delayed type hypersensitivity to M. tuberculosis.

CONCLUSION

Tuberculosis is the leading infectious cause of morbidity and mortality worldwide. Although ocular complications are less common than systemic involvement but still well recognized. Intraocular inflammation includes mutton- fat keratic precipitates, iris granulomas, posterior synechiae, vitritis, vasculitis, retinal ischemia, macular edema choroidal tubercles, retinal involvement, endophthalmitis, and panophthalmitis, of these presentations the most common clinical findings of intraocular TB are solitary or multiple choroidal nodules, choroiditis and retinal vasculitis . There are no specific findings for ocular TB, culture or direct histopathological examination of the infected tissue can provide definitive proof of ocular infection but is often impractical given the risks of intraocular biopsy, particularly in the setting of active inflammation. The widely accepted approach to the diagnosis of ocular TB is based on the clinical findings consistent with TB, positive tuberculin skin testing, and absence of any other systemic disease to account for ocular signs. Diagnosing ocular TB is especially important, as TB is one of the few causes of uveitis with a definitive effective treatment and where the standard treatment of uveitis with steroids in the absence of anti-TB treatment could by sight or life threatening. Patients should be treated for active tuberculosis with 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 6–9 months. Patients should be reviewed at the end of the initiation phase (two months) and at the end of the overall treatment (6–9 months).

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