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*The biggest disease today is not leprosy or tuberculosis, but rather the feeling of being unwanted.*

*Mother Teresa*

## Summary

Tuberculosis (TB) is a major infectious disease that primarily affects the lungs. Extrapulmonary organs, including the eyes, might be involved. Ocular TB represents an extrapulmonary spread of TB. The clinical spectrum of ocular TB is variable. It may affect the ocular adnexa with or without intraocular involvement. A high index of suspicion is needed to establish the diagnosis of ocular TB. The definitive diagnosis of TB of the eye can be established through isolation of the *Mycobacterium tuberculosis* bacilli in ocular tissue samples by microscopic examination or culture on specific media. Recently, evidence and experience-based guidelines for treating tubercular uveitis were proposed. This

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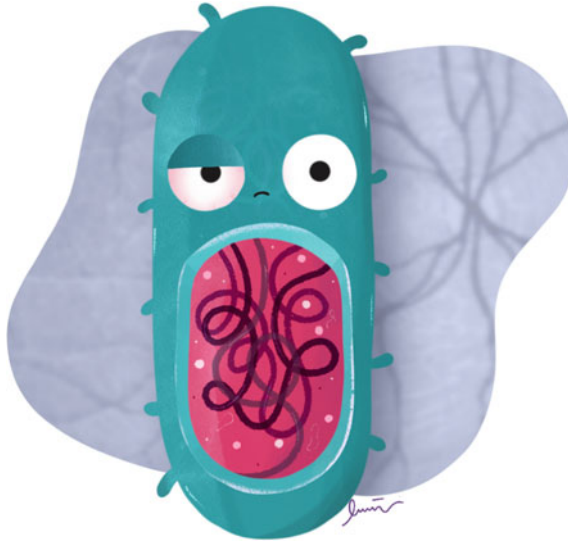
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chapter reviews the ocular manifestations of TB and the recent guidelines for managing TB uveitis established by The Collaborative Ocular Tuberculosis Study group.

### Graphical Abstract



Ocular tuberculosis

### Keywords

Extrapulmonary • Inflammation • *Mycobacterium tuberculosis* • Ocular tuberculosis • Tuberculosis

## 1 Introduction

Tuberculosis (TB) is a major infectious disease that primarily affects the lungs. Extrapulmonary organs, including the eyes, might be involved [1]. Extrapulmonary TB (EPTB) accounts for up to 20% of the health burden of TB and increases to 50% in patients with concomitant HIV infection [2, 3]. Ocular TB represents extrapulmonary dissemination of *Mycobacterium tuberculosis* (*M. tb*). Ocular involvement may present clinically with the pulmonary disease; however, it was found that about 92% of patients with tubercular ocular involvement show no associated pulmonary TB (PTB) [3].

The clinical spectrum of the lesions seen in the eye in patients with TB is variable. It may be unilateral or bilateral. Involvement of the eye may result from active mycobacterial infection or immunologic response.

Tubercular infection may reach the eye through different routes, including [4]:

- hematogenous spread involving mainly the uveal tract due to its high vascularity;
- primary exogenous ocular infection may occur in the lids, conjunctiva, cornea, sclera, lacrimal gland, and lacrimal sac; and
- secondary ocular infection may occur via direct extension from adjacent tissues.

## 2 Tubercular External Eye Disease

Table 1 provides a summary of these diseases.

**Table 1** Tubercular external eye disease

Structure	Clinical findings
Eyelid	Chronic blepharitis Localized nodule Recurrent chalazia Ulcerated skin nodules Cicatricial eyelid changes Lupus vulgaris Cold abscess
Conjunctival involvement	Conjunctivitis Conjunctival nodular lesions Tuberculomas Conjunctival ulceration Phlyctenulosis
Orbit	Tuberculous periostitis Bony destruction Orbital granuloma Cold abscess Orbital apex syndrome Lacrimal gland granuloma Lacrimal gland abscess Tuberculous dacryoadenitis Lacrimal sac granuloma
Cornea	Interstitial keratitis Disciform keratitis Corneal erosions
Sclera and episcleral	Anterior scleritis Posterior scleritis Nodular episcleritis

## 2.1 Eyelid

Tubercular involvement of the eyelid is rare to present an isolated ocular finding. It may display a clinical picture of chronic blepharitis or a localized nodule that mimics a chalazion [4]. The skin of the lids may also show cutaneous TB, which may present in different ways, including recurrent chalazia, subepithelial nodules, ulcerated skin nodules, plaques, and cicatricial eyelid disease [5, 6]. Lupus vulgaris is a common form of cutaneous TB, which may affect the skin of the lids [4]. TB of the lids may also present in the form of an acute abscess or in the form of soft fluctuant mass without acute inflammation [4].

## 2.2 Conjunctiva

TB of the conjunctiva may present as conjunctivitis, conjunctival nodular lesions, polyps, tuberculomas, conjunctival granuloma with ulceration or phlyctenulosis [1, 5]. Although the conjunctiva is more commonly involved in association with systemic disease, isolated involvement of the conjunctiva may occur [5]. Patients may complain of redness, ocular pain, mucopurulent discharge, and/or lid swelling [4].

## 2.3 Orbit

Tubercular involvement of the orbit is a rare form of EPTB [1]. It may present as proptosis secondary to mass effect or in the form of diplopia resulting from involvement of the extraocular muscles or the cranial nerves [7]. Other presenting features may include pain, headache, lid swelling, decreased vision, visual field abnormalities, chemosis, and epiphora [4]. The mycobacteria may reach the orbit via the hematogenous route or by direct spread from the surrounding paranasal sinuses.

Orbital TB may present as tuberculous periostitis, bony destruction, orbital granuloma, cold abscess, and orbital apex syndrome [4, 5]. The affection of the lacrimal system can be in the form of lacrimal gland granuloma, lacrimal gland abscess, tuberculous dacryoadenitis, nasolacrimal duct involvement, and/or lacrimal sac granuloma [4, 5].

## 2.4 Cornea

Patients with tubercular corneal involvement may complain of photophobia, ocular pain, tearing, and blepharospasm [8]. Tubercular corneal involvement may be in the form of corneal erosions, interstitial keratitis, disciform keratitis, or phlyctenular keratoconjunctivitis [9, 10]. The corneal findings are manifestations of mycobacterial infection or represent an immunologic response to the mycobacterial antigen

[11]. The keratitis may be associated with scleritis and uveitis [12]. Sclerokeratitis is more common than isolated keratitis.

## 2.5 Sclera and Episclera

TB of the sclera may occur in the form of anterior scleritis and, less commonly, posterior scleritis [13]. Tuberculous anterior scleritis may be nodular or diffuse. The severely inflamed sclera may undergo necrosis and may perforate [14]. Tuberculoma or infective posterior scleritis may rarely occur in patients with ocular tuberculosis [13, 15]. TB can also cause nodular episcleritis [16].

## 3 Tubercular Uveitis

Ocular involvement in patients with TB most often manifests as uveitis [17, 18]. Tubercular uveitis may be the initial presentation of TB infection [19] (Table 2).

### 3.1 Tubercular Anterior Uveitis

The term tubercular anterior uveitis (TAU) was used by the COTS group to describe the inflammation limited to the anterior segment (inflammation mainly involves the iris and the ciliary body) [20, 21]. Tubercular anterior uveitis may be unilateral or bilateral, acute or chronic, granulomatous or non-granulomatous (less frequently) [8]. The granulomatous form of tuberculous anterior uveitis manifests by features such as mutton-fat keratic precipitates and nodular iris granulomas (Koeppel and Busacca nodules), and anterior chamber angle nodules [8]. Broad-based posterior synechiae may lead to iris bombe [22]. Non-granulomatous uveitis may also occur in the form of iritis or iridocyclitis in patients with TB, usually presenting with fine white keratic precipitates and inflammatory cells with no accompanying iris nodules [1, 8]. Cyclitis is frequently seen and may be

**Table 2** Tubercular uveitis

Structure	Clinical findings
Iris and ciliary body	Anterior uveitis
Pars plana and vitreous	Intermediate uveitis
Retina and/or the choroid	Tubercular serpiginous-like choroiditis Tubercular multifocal choroiditis Orbital granuloma Tubercular focal choroiditis Tuberculoma
Anterior chamber, vitreous, and retina/choroid	Panuveitis

associated with necrosis and calcification, leading to caseating granuloma [8]. Pigmented hypopyon, anterior pupillary membrane, and cataracts may also develop in patients with tubercular anterior uveitis [1, 7, 8].

### 3.2 Tubercular Intermediate Uveitis

Tubercular intermediate uveitis (TIU) was defined by the COTS group as the inflammation which mainly involves the vitreous [20, 21]. TIU has non-specific features. It may present with features of simulating pars planitis and other forms of intermediate uveitis. Patients usually present with a blurring of vision and floaters. The ocular signs include mild chronic uveitis with vitritis, snowballs, snow banking, and peripheral vascular sheathing [23–25].

### 3.3 Tubercular Posterior Uveitis

Tubercular posterior uveitis (TPU) was defined by the COTS group as the inflammation which involves the retina with or without the involvement of the choroid [20, 21]. Posterior segment involvement is frequent in patients with ocular TB. The most commonly encountered sign of tubercular involvement of the posterior segment is multifocal choroiditis [26]. There are four distinct clinical forms of tubercular choroiditis (TBC) as defined by the COTS study group [20]:

- i. tubercular serpiginous-like choroiditis (TB SLC): The lesions involving the choroid may be single or multiple. The lesions are discreet fuzzy, and the edges are slightly raised. The lesions progress by a wave-like pattern. It is characterized by an active serpiginous-like edge and central healing;
- ii. tubercular multifocal choroiditis (TMC): This pattern may simulate other types of choroiditis such as acute posterior multifocal placoid pigment epitheliopathy and idiopathic multifocal choroiditis. Choroidal tubercles were included under tubercular multifocal choroiditis;
- iii. tubercular focal choroiditis (TFC): This pattern occurs in the form of unifocal choroiditis lesions which do not show features of tubercular serpiginous-like choroiditis;
- iv. tuberculoma: The lesions may be single or multiple in the form of yellowish subretinal lesions. The lesions possess indistinct borders and surrounding exudates. Tubercular subretinal abscesses are included under this category.

### 3.4 Tubercular Panuveitis

Tubercular panuveitis (TBP) uveitis was defined by the COTS group as the inflammation involving the whole uveal tissues, including the anterior chamber, vitreous, and retina/choroid [20, 21].

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### 3.5 Tubercular Retinal Vasculitis (TRV)

Patients with ocular TB may present with isolated retinal vasculitis. The vasculitis may affect either arteries or veins and might be occlusive [20]. The veins are more commonly affected than the arteries in patients with tubercular retinal vasculitis [27]. Eales disease is not the same as tubercular retinal vasculitis and should not be used to describe such cases [20, 21]. The characteristic features include vitritis, retinal hemorrhages, neovascularization, perivascular cuffing with dense exudates, and neuroretinitis [7]. Tubercular retinal vasculitis is most commonly occlusive. This may predispose to variable sequelae, including branch retinal vein occlusion, branch and/or central retinal artery occlusion with subsequent extensive peripheral capillary nonperfusion, retinal neovascularization, optic disc neovascularization, bleeding into the vitreous, and subsequent retinal traction detachment [8]. Iris neovascularization may develop with subsequent neovascular glaucoma [8].

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## 4 Optic Nerve Involvement

Infection may reach the optic nerve by either contiguous spread of infection from the choroid or by hematogenous spread from PTB [1, 7]. Clinical presentation may be in the form of papillitis, retrobulbar neuritis, compressive optic neuropathy, ischemic optic neuropathy, optic nerve tubercle, optic atrophy, papilledema, and optochiasmatic arachnoiditis [28].

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## 5 Endophthalmitis and Panophthalmitis

Endophthalmitis and panophthalmitis have been rarely reported in patients with ocular TB [29–31]. It may result from hematogenous spread, untreated choroidal or subretinal abscesses, and less commonly following cataract surgery.

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## 6 Diagnosis and Management

The clinician should keep a high index of suspicion to establish the diagnosis of ocular TB because of the smoldering chronic course and variable clinical manifestations. The correct diagnosis of ocular TB requires isolation of the *mycobacterial* bacilli in ocular tissue samples by microscopic examination or culture on specific media [4]. However, demonstration of acid-fast bacilli with Ziehl–Neelsen stain or detection of the organism by culture usually has a low yield. This low yield could be explained in part by the low volume of the obtained sample, the paucibacillary nature of ocular TB, and the proposed role of immune-mediated

mechanisms in the development of ocular inflammation [32]. Demonstration of necrotizing granulomatous inflammation in an ocular biopsy from orbital and eyelid lesions may be helpful in the diagnosis; however, large sample size is needed to help in the diagnosis of tubercular ocular involvement [4, 32].

Detection of mycobacterial DNA by polymerase chain reaction (PCR) has been employed in the diagnosis of tubercular eye disease [33]. However, PCR cannot be used as a gold standard for the diagnosis of ocular TB because of the wide variations of the test [33]. Furthermore, PCR is unable to distinguish active from latent infection [32].

Interferon- $\gamma$ -release assay (IGRA) and the tuberculin skin test are the two immunological tests most commonly used in the diagnosis of ocular TB. Both tests cannot distinguish between active disease and latent infection [33].

Radiological tests, including chest X-ray and computed tomography (CT) of the chest, are used to image the most common primary TB infection site. Radiological findings include hilar lymphadenopathy, parenchymal scarring, and pleural disease [32].

Tabbara proposed guidelines for the diagnosis of ocular TB. They include a combination of clinical ocular findings suggestive of TB, including chorioretinitis and anterior granulomatous uveitis, positive purified protein derivative, positive therapeutic response to antitubercular therapy within four weeks, and exclusion of other causes of uveitis [34].

The COTS group developed experience and evidence-based therapeutic guidelines for the treatment of tubercular uveitis (TBU) [35]. Experts agreed to start ATT in the following conditions in the presence of positive results for either of the immunologic tests together with radiological evidence suggestive of past tubercular infection [35]:

- recurrent episodes of tubercular anterior uveitis
- cases of tubercular intermediate uveitis
- cases of tubercular posterior uveitis
- cases of active tubercular retinal vasculitis.

In cases with the first episode of tubercular anterior uveitis and patients with inactive tubercular retinal vasculitis, it was agreed to start antitubercular medications only when both immunological tests and radiological tests were positive [35].

In cases of tubercular choroiditis, it was agreed to start antitubercular medications in the presence of positive results for any one of the immunologic tests together with radiologic features suggestive of TB [36].

In cases of tuberculoma and tubercular serpiginous-like choroiditis, positive results from even one positive immunologic test were considered sufficient to recommend ATT, even in the absence of features suggestive of TB by radiology [36].

Anti-TB therapy was defined by the COTS group as multidrug therapy, which includes four drugs, namely rifampicin, isoniazid, ethambutol, and pyrazinamide. The administration of these drugs should comply with the health strategy of each



country [35, 36]. The use of systemic steroids in patients with ocular TB is controversial. It is advised to delay initiation of systemic steroids until after initiation of ATT in patients with tubercular uveitis unless there is a high risk of severe inflammation with subsequent damage to the ocular tissues [37]. Hamade and colleagues found that early administration of steroids without ATT in patients with tubercular ocular involvement may lead to poor visual outcomes compared to patients who were not given steroids prior to presentation [38].

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## 7 Conclusion

In conclusion, the clinical diagnosis of ocular TB is a challenging issue as the clinical manifestations are not specific. Further studies are needed to establish accurate criteria for the diagnosis and management of ocular TB.

### Core Messages

- The clinical spectrum of ocular TB is variable.
- The definitive diagnosis of ocular TB requires isolation of the *M. tb* bacilli.
- Treatment of ocular TB depends on a combination of clinical findings, immunological tests, and chest imaging.
- Future studies are needed to determine the specific indications, doses, and duration of anti-TB medications.

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**Khalid F. Tabbara** was the Founding Editor and former Editor-in-Chief of the Saudi Journal of Ophthalmology (SJO), the official journal of the Saudi Ophthalmological Society. Dr. Tabbara received the Senior Honor Award from the American Academy of Ophthalmology (AAO). Dr. Tabbara is the author of hundreds of scientific publications. Dr. Tabbara is currently active in residents teaching, research, continuing medical education, and clinical ophthalmology.