

Ocular tuberculosis: current perspectives

Faiz I Shakarchi^{1,2}

¹Ibn Al-Haetham Teaching Eye Hospital, ²Department of Ophthalmology, Medical College, Al-Mustansiriya University, Baghdad, Iraq

Abstract: The World Health Organization currently estimates that nearly two billion people, or one-third of the world's population, are infected by tuberculosis, and that roughly 10% of the infected people are symptomatic. Tuberculosis affects the lungs in 80% of patients, while in the remaining 20% the disease may affect other organs, including the eye. Uveitis can be seen concurrently with tuberculosis, but a direct association is difficult to prove. Ocular tuberculosis is usually not associated with clinical evidence of pulmonary tuberculosis, as up to 60% of extrapulmonary tuberculosis patients may not have pulmonary disease. The diagnosis of tuberculous uveitis is often problematic and in nearly all reported cases, the diagnosis was only presumptive. Tuberculous uveitis is a great mimicker of various uveitis entities and it can be considered in the differential diagnosis of any type of intraocular inflammation. It is still unknown if ocular manifestations result from a direct mycobacterium infection or hypersensitivity reaction and this is reflected on the management of tuberculous uveitis. Prevalence of tuberculosis as an etiology of uveitis may reach up to 10% in endemic areas. Tuberculous uveitis is a vision-threatening disease that inevitably leads to blindness if not properly diagnosed and treated. The aim of this review is to illustrate the various clinical features and management of presumed tuberculous uveitis. The current review focuses on the diagnostic criteria, significance of tuberculin skin test, and use of systemic corticosteroids in the management of tuberculous uveitis as recommended in recent publications.

Keywords: tuberculosis, uveitis, choroiditis, tuberculin skin test

Introduction

Tuberculosis (TB), a multisystem infectious disease caused by *Mycobacterium tuberculosis* (MTB). TB has existed since ancient times. Evidence of tuberculous pathology was present in fragments of spinal columns from Egyptian mummies. In ancient Greece, the disease was known as consumption, and was uniformly fatal. In 1882, Robert Koch discovered a staining technique to demonstrate MTB. In 1944, streptomycin was first used to treat patients with pulmonary TB.¹

TB is the leading infectious cause of morbidity and mortality worldwide. According to The World Health Organization, approximately one-third of the world's population, approximately two billion persons, are infected by TB; 10% of infected people are symptomatic and 90% have latent TB.^{2,3} Persons with latent MTB infection do not manifest symptoms of active TB and are not infectious, but they may develop clinical disease at anytime during their life.

More than 95% of new infections occur in the developing world, particularly in Africa and South Asia. There is an increasing number of TB infections in both the developing and developed world due to multidrug-resistant TB, human immunodeficiency virus (HIV), and global migration.⁴⁻⁶ Poor socioeconomic conditions, immunosuppression, and general debility are important predisposing factors irrespective of ethnic origin.⁷

Correspondence: Faiz I Shakarchi
Department of Ophthalmology,
Medical College, Al-Mustansiriya
University, Jinub street, Baghdad, Iraq
Email faizalshkr@yahoo.com

TB is a multisystem disease that primarily affects the lungs and may affect other organs including the eye. Uveitis is the most common ocular manifestation of the disease, but a direct association is difficult to prove. It is still unknown if tuberculous uveitis results from a direct mycobacterium infection or hypersensitivity reaction, and this is reflected on its management.

The aim of this review article is to illustrate the various clinical features and management of presumed tuberculous uveitis. The current review focuses on the diagnostic criteria, significance of tuberculin skin test (TST), and use of systemic corticosteroids in the management of tuberculous uveitis as recommended in recent publications.

Clinical features

MTB is an obligate aerobic bacteria, usually found in highly oxygenated tissue. TB affects the lungs in 80% of patients, while in the remaining 20% the disease may affect other organs, including the eye, in which the choroid has one of the highest oxygen tension in the body.

Ocular TB is defined as an infection by MTB in the eye, around the eye, or on its surface.¹ Ocular TB is usually not associated with clinical evidence of pulmonary TB, as up to 60% of extrapulmonary TB patients may not have pulmonary TB.⁸

Ocular TB presents a complex clinical problem due to a wide spectrum of presentations and difficulty in diagnosis.⁹ Ocular TB is either primary in which the eye is the primary port of entry of the mycobacterium into the body, or secondary as a result of seeding by hematogenous spread from a distant site. Primary disease is rare, and includes eyelid, conjunctival, corneal, and scleral lesions, while the uveal tract, retina, and optic nerve are involved in secondary disease. Inflammation of the uveal tract is the most common eye manifestation of the disease, due to its high blood supply.^{10,11}

Till before 50 years, TB was considered as the most common cause of granulomatous uveitis, but there has been a dramatic change in the prevalence of ocular TB over the subsequent decades as many of previously unknown etiologies, such as sarcoid, toxoplasmosis, and histoplasmosis, were now recognized.¹

In recent years, there has been a renewed interest in TB stimulated by a rising incidence, the spread of the HIV pandemic and the emergence of multidrug-resistant strains.⁹

Ocular TB is still an important cause of uveitis. Prevalence of TB as an etiology of uveitis has varied from 0.5% in the USA,¹² 4% in the People's Republic of China,¹³ 6.31% in Italy,¹⁴ 6.9% in Japan,¹⁵ 9.86% in north India,¹⁶ 10.5% in Saudi Arabia,¹⁷ and 11.4% in Iraq where TB is endemic.¹⁸

Intraocular TB is a great mimicker of various uveitis entities and it can be considered in the differential diagnosis of any type of intraocular inflammation. Ocular inflammation could be unilateral or bilateral, sometimes inflammation of one eye starts months or years before the other.¹⁹ Uveitis can present as anterior, intermediate, posterior, or panuveitis.

Tuberculous anterior uveitis has an insidious onset and runs a chronic course. Anterior uveitis presents as unilateral or bilateral chronic granulomatous disease that manifests as granulomatous keratic precipitates associated sometimes with iris nodules or granulomas. Anterior uveitis is often accompanied by vitritis, and inevitably complicated by the development of posterior synechiae and cataract.^{1,20}

The vitreous may be the primary site of inflammation and presents with moderate-to-severe cellular reaction in the vitreous cavity, including snowball opacities. Intermediate uveitis is often associated with granulomatous keratic precipitates. Peripheral retinal vasculitis associated with discrete perivascular choroiditis or scars may indicate a tuberculous etiology. Cystoid macular edema, cataract, peripheral neovascularization, and vitreous hemorrhage can occur with TB intermediate uveitis.^{20,21}

Posterior uveitis is the most common presentation of intraocular TB, with lesions predominantly present in the choroid 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.^{19,22-24}

In a study from India of 158 patients with presumed intraocular TB, 66 (42%) had posterior uveitis, 57 (36%) anterior uveitis, 18 (11%) panuveitis, and the remaining 17 (11%) had intermediate uveitis.²⁵ In a study conducted in Saudi Arabia of 51 patients (73 eyes) with presumed tuberculous uveitis, 58 (79.5%) eyes had panuveitis, and 15 (20.5%) eyes had posterior uveitis at presentation. Clinical manifestations included vitritis in 52 (71.2%) eyes, macular edema in 46 (63%) eyes, retinal periphlebitis in 26 (35.6%) eyes, multifocal choroiditis in 15 (20.5%) eyes, and granulomatous anterior uveitis in 13 (17.9%) eyes.²⁶ According to a study¹⁹ conducted in Iraq that included 64 patients (126 eyes) with presumed TB uveitis; 116 eyes (92.1%) had panuveitis, six eyes (4.7%) had posterior uveitis, and four eyes (3.2%) had intermediate uveitis. Vitritis was a universal finding, while multifocal choroiditis was recorded in 104 eyes (82.5%).

The physical findings mentioned above are suggestive but nonspecific. It is still unknown if ocular manifestations result from a direct mycobacterial infection or a hypersensitivity response to mycobacteria and this is reflected on the management of TB uveitis. The choroidal nodules may suggest direct hematogenous infection while the vasculitis and choroiditis are more likely to be the result of immune hypersensitivity.^{10,22,27}

In one study, 50 patients presented with multifocal choroiditis and were treated with antituberculous therapy (ATT) without concomitant use of systemic corticosteroids. All patients treated had a favorable response, and no recurrence was recorded. These findings may indicate that ocular manifestations in these patients were probably due to direct mycobacterial invasion.¹⁹

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.¹¹ 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.²⁸ The absence of clinically evident pulmonary TB does not rule out the possibility of ocular TB, as ~60% of patients with extrapulmonary TB have no evidence of pulmonary TB and chest X-rays are normal in cases of latent TB.^{21,28,29}

In most studies, the diagnostic criteria for presumed tuberculous uveitis were: residence or migration from areas endemic in TB, previous history of contact with TB-infected patients, presence of suggestive ocular findings, exclusion of other known causes of uveitis, corroborative evidence such as a positive TST, positive interferon-gamma release assays (IGRAs), and a positive response to conventional ATT without recurrence. An extraocular evidence of TB in a patient with uveitis also aids in diagnosing intraocular TB.^{11,19,21,29} In a study that included 64 patients with presumed TB uveitis, 24 patients (37.5%) reported that they had previous contact with pulmonary TB-infected patients, sometimes that contact was several years before eye symptoms start.¹⁹

Tuberculin skin testing

The TST or the Mantoux test has been used for several decades to detect latent TB. The standard test consists of an intradermal injection of five units of purified protein derivative. An induration of 10 mm or more after 48–72 hours is

considered positive. However, in patients with HIV infection and those who are immunosuppressed, an induration of 5–10 mm is taken as positive. An induration of less than 5 mm is considered to be a negative result. The disease may be associated with false-negative reaction, especially in elderly people, the malnourished, and the immunosuppressed.⁹

False-positive TST can occur in exposure to nontuberculous mycobacteria³⁰ and some patients have already received Bacille Calmette–Guerin (BCG), but the effect of BCG on TST declines over the first 7 years after vaccination and strongly positive TST is unlikely to be due to prior BCG vaccination.³¹ TST can give false-positive result in patients with exaggerated skin hypersensitivity like in Behçet's disease, as it may act as a pathergy test.¹⁹

Guidelines for interpreting of TST vary in different countries where different strengths are used. The predictive value varies depending on the incidence of TB in the population and local BCG vaccination policy. In the USA, the routine use of TB skin testing in patients with uveitis is considered unhelpful,³² whereas in India it is considered mandatory.³³ A previous study conducted in Iraq, showed a high sensitivity and specificity of strongly positive TST (more than 14 mm area of induration/necrosis) for ocular TB in the Iraqi population.¹⁸

Interferon-gamma release assay

IGRA is based on gamma interferon production by T cells sensitized to specific antigens, which are specific to MTB and therefore not influenced by BCG and most nontuberculous bacteria. These tests include QuantiFERON-TB Gold In-Tube (QFT; Cellestis Inc., Carnegie, VIC, Australia) and ELISpotPLUS (T-SPOT.TB, Oxford Immunotec, Oxford, UK). The IGRA is approved by the US Food and Drug Administration and many other countries. The T-SPOT.TB test is approved in Europe, it is an enzyme-linked immunospot (ELISpot) assay-based test.^{34–36}

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.³⁹

Molecular techniques

Polymerase chain reaction techniques were used for the detection of MTB in aqueous and vitreous samples from

patients with presumed tuberculous uveitis. Detection of antibodies against purified cord factor, the most antigenic and abundant cell wall component of MTB, can provide strong evidence of the infection.⁴⁰ However, the sensitivity was reported to be low, as many ocular manifestations may represent a delayed hypersensitivity reaction rather than a direct mycobacterial infection, making the analysis of a fluid sample from the eye less sensitive.^{11,24,41}

Treatment

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.³³ This is reflected in the absence of information on ocular TB management in any of the TB guidelines of the UK, USA, or Canada.⁴²

According to the recommendations of the American Thoracic Society, the Centers for Disease Control and Prevention and the Infectious Diseases Society of America for pulmonary and extrapulmonary TB, four drugs (isoniazid 5 mg/kg/day, rifampicin 450 mg/day if body weight is <50 kg and 600 mg if the weight is >50 kg, ethambutol 15 mg/kg/day, and pyrazinamide 25–30 mg/kg/day) are prescribed initially for 8 weeks, followed by two drugs (rifampicin and isoniazid) for at least another 18 weeks.⁴³

The use of oral steroids in patients with presumed tuberculous uveitis is clearly a confounding issue.³³ Patients treated only with systemic corticosteroids showed worsening or recurrence of the inflammation.^{23,44} Several studies reported a favorable response to ATT when administered concomitantly with systemic corticosteroids in patients with presumed tuberculous uveitis.^{23,25,44} Oral prednisone can be used in the treatment of ocular TB, in order to control the coexisting inflammatory reaction, and reduce macular edema.⁴⁵ It might be desirable diagnostically to delay steroid treatment in order to assess the response to ATT, this must be balanced against the risk of loss of sight.⁹

In a previous study that included 64 patients (126 eyes) with presumed TB uveitis, 50 patients (100 eyes) were treated with ATT drugs only, while systemic corticosteroids (oral prednisone) were added in 14 patients (26 eyes) to decrease macular edema and macular scarring.¹⁹ All patients treated with ATT drugs only had favorable response and no recurrence was recorded for more than 6 months after completion of treatment. Use of ATT in these patients could help by killing the intraocular microorganisms; thus eliminating the antigen load, the recurrences, and the resultant hypersensitivity inflammation.⁴¹ Probably, in eyes with presumed TB uveitis, oral prednisone can be added with ATT, only when

lesions are involving or threatening the macula in order to decrease macular scarring.

Secondary cataract in eyes with TB uveitis can be safely managed, after controlling of the inflammation, by phacoemulsification with intraocular lens implantation.¹⁹

Disclosure

The author reports no conflicts of interest in this work.

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