Ocular Tuberculosis- An update

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Introduction

Tuberculosis (TB) is an air-borne disease that affects one-third of the world’s population (approximately 1.9 billion) and is the leading single cause of mortality and morbidity worldwide causing about 3 million deaths annually. According to the WHO estimates, 8 million people are infected with the disease annually and 95 % of them are in developing countries. Nearly 3 million people die from TB annually, the highest incidence being in Africa, Asia and Latin America. Thus, WHO has declared TB as a global emergency.

Tuberculosis primarily affects the lungs but may also affect extra-pulmonary organs. Mycobacterium tuberculosis spreads by droplet infection by coughing or sneezing.

Ocular tuberculosis is an extra-pulmonary form of the disease. Ocular tuberculosis includes any infection in or around the eye caused by Mycobacterium tuberculosis or its related species. It may be either an active infection or an immunologic reaction, related to delayed hypersensitivity or an aseptic reaction.

In primary ocular TB, the eye is the initial portal of entry into the body, whereas the secondary one is defined as an infection resulting from contagious spread from an adjacent structure or hematogenous dissemination.

Primary infection of the eye is rare. Secondary ocular tuberculosis is the ocular involvement as a result of haematogenous spread from a distant site or a direct invasion from adjacent areas like the sinus or the cranial cavity. Almost every tissue of the eye and its adnexa can get affected. Ocular tuberculosis may be acute but usually it runs a chronic course with exacerbations and remissions.

Epidemiology

There has been a dramatic change in the epidemiology of ocular tuberculosis. From 1953 through 1984, the number of TB cases fell, mostly in industrialized countries. However, around 1985, there was an increase in number of new cases which was attributed in large part to the occurrence of tuberculosis in persons infected with HIV. High rate of immigration from countries with a high incidence of TB and emergence of multi-drug resistance of TB were other factors responsible for its rise. The incidence of tuberculosis has increased with the increase in the HIV infected population. According to WHO estimates, there are about 42 million HIV-infected people worldwide, with an estimated 2.5 million in India. Mycobacterium tuberculosis is the commonest infecting organism in HIV-infected patients worldwide and one in three people with AIDS will die of TB. Since 1993, the number of new cases has begun to drop again worldwide. This has become possible because of newer and better treatment for HIV, increased awareness, better institution of Direct Observed Therapy (DOTS) and the use of multi-drug therapy (MDT).

Clinical Presentation

The clinical spectrum of ocular tuberculous infection is diverse. It can have variable manifestations depending on the site and severity of infection. Ocular tuberculosis can manifest without obvious involvement...
of other commonly affected organs or an evidence of a systemic illness. The ocular disease can result from haematogenous spread, from direct local extension from the skin, mucous membranes, or sinuses or it can be an immunologic reaction of delayed hypersensitivity in the absence of an infectious agent. Ocular TB is usually a granulomatous process but it may also be non-granulomatous and the involvement may be unilateral or bilateral. Lesions are known to occur in all parts of the uveal tract, but choroid is most commonly involved.

**Posterior segment findings (Fig. 1)**

The most common finding of ocular TB is choroiditis-multifocal choroidal granulomas being the hallmark feature. These tubercles can mimic in appearance with serpiginous choroiditis, multifocal choroiditis, or simulate the panuveitis pattern. The presence of choroidal lesions, with or without inflammation, is strongly correlated with the systemic disease and is an indicator of haematogenous spread of mycobacteria.

**a. Choroidal tubercles** - These tubercles are unilateral or bilateral, greyish-white to yellowish in color with indistinct margins usually less than five but can be several hundred in number. The choroidal tubercles can be active or inactive and are mostly unilateral but can be bilateral. They typically develop at the posterior pole either singly or in a multifocal pattern with sizes varying from one half to several disc diameters. As the infection resolves, these tubercles heal in 12-14 weeks, become pigmented with distinct margins forming an atrophic scar.

**b. Choroidal tuberculoma** - When a choroidal tubercle continues to grow, it forms a solitary mass known as tuberculoma. Intra-ocular tuberculosis may rarely present with these tuberculomas.
without evidence of any systemic disease. These tuberculomas may be seen anywhere in the choroid- posterior pole, macula or they maybe juxta-papillary in location. The tuberculomas are subretinal masses, often mimicking a tumour, 4-14 mm in size and yellowish in color. There may be an overlying exudative retinal detachment seen in the later stages.

c. Subretinal abscess- Large tuberculomas may undergo liquefactive necrosis and form yellowish subretinal mass lesions accompanied by exudative retinal detachment. These lesions may present with clinical signs of subretinal abscess and can be seen both in immunocompetent as well as immunocompromised patients. Such patients need to be investigated for the evidence of miliary tuberculosis. Rarely, these lesions can rupture into the vitreous cavity and may lead to endophthalmitis or panophthalmitis.

d. Serpiginous like choroiditis- Serpiginous choroiditis is a rare, bilateral, chronic, progressive and recurrent inflammation of the outer retina and inner choroid which is of unknown etiology. Gupta et al have shown that intra-ocular tuberculosis may present as choroiditis simulating serpiginous choroiditis. There is progression of the disease in spite of the patient being administered systemic corticosteroids and immunosuppressants. These lesions begin in the peri-papillary area and spread centrifugally. However, choroidal tuberculosis may also present in the multifocal form where the lesions are discrete and non-contiguous initially but later in the course may form a diffuse, contiguous pattern.

The retina may show features of retinitis, vasculitis, vascular occlusions or serous retinal detachment. Retinal periphlebitis is rarely caused by the direct invasion of the retina by tubercle bacilli. Retinal tuberculosis usually occurs secondary to underlying choroiditis. Cystoid macular edema can accompany intraocular inflammation in ocular tuberculosis. Vitreous may show vitritis and “snowballs” opacities in the anterior and inferior vitreous. Pars plana “snow banking” may sometimes be observed.

Anterior segment findings-
The most common anterior segment presentation is anterior uveitis which can be chronic anterior uveitis or panuveitis. Iridocyclitis shows characteristics mutton-fat keratic precipitates (KPs) classically distributed inferiorly in the lower one third of the cornea which is known as the Art’s triangle. The iris usually develops posterior or anterior synechiae and/or iris granulomas. Granulomas may be seen at the angle of the iris base and over the trabecular meshwork. HIV patients on retroviral therapy can show an immune recovery uveitis associated with concomitant tuberculosis even if they are not on Rifabutin. Long-standing inflammation can lead to cataract formation and secondary inflammatory glaucoma.

External ocular findings
Lupus vulgaris of the eyelids can rarely develop. Tuberculous conjunctivitis has been reported which is usually unilateral, chronic, may occasionally be associated with conjunctival mass or ulceration. Preauricular lymphadenopathy is occasionally seen in these cases. Conjunctival granulomas may also be seen. Phlyctenulosis is the most common form of external ocular tuberculosis involvement. It is a Type IV Hypersensitivity reaction, presents as an inflammatory mass on the cornea. It is usually occurs due to tuberculosis but can be associated with Staphylococcus aureus. Focal, nodular or diffuse scleritis with or without keratitis can also develop. The tuberculosis keratitis and scleritis may develop as a result of spread of infection and granulomatous reaction from within the eye. There are known to be biopsy-proven cases of TB scleritis. It is usually diffuse, posterior or nodular and associated with localized granuloma formation. Interstitial keratitis and sclero-keratitis is also known to occur.

The orbit may be involved by spread of disease from within the eye. Commonly the spread occurs from orbital periostitis. Orbital periosteal rim, dacryoadenitis, and sinus infections with a non-healing, draining fistula are typical of tuberculosis. Panophthalmitis or endophthalmitis may also occur. Tuberculosis can also present as an orbital mass, or as eyelid abscesses.
There are two other ocular entities that are related to Tuberculosis:

1. **Reactions to tuberculin-** Allergic reactions have occurred in patients with bilateral, granulomatous anterior uveitis associated with tuberculin skin testing. Severe choroiditis progressing to serous retinal detachment has been reported with intra-dermal injection of purified protein derivative (PPD) in patients with pre-existing tuberculous uveitis

2. **Eales’ disease-** The disease is characterized by recurrent vitreous haemorrhages and retinal periphlebitis in young adult males. The true nature of this disease is still a matter of debate though tuberculosis has long been implicated as a cause.

**Pathology**

Tissue destruction from M tuberculosis infection occurs due to the organism’s ability to incite intense host immune reactions to antigenic cell wall proteins. The main feature of ocular TB histopathology is granulomatous inflammation. There occurs granuloma formation in the choroid characterized by lymphocytes, epithelioid cells, and giant cells with caseating necrosis. Rarely are any TB bacilli seen. Overlying retina can also be involved. The scleral involvement can range from mild to frank perforation.

**Diagnosis**

Despite the existence of highly sensitive molecular diagnostic techniques, the diagnosis of ocular tuberculosis is often presumptive, based upon clinical presentation, systemic evaluation and response to treatment. Choroiditis is the most common ocular manifestation in patients with pulmonary and systemic tuberculosis and in the absence of ocular biopsies the diagnosis remains presumptive. The primary screening and diagnostic test is the tuberculin skin testing with purified protein derivative (PPD).

Culture for acid-fast bacilli (AFB) is the most specific test and allows direct identification and susceptibility of the causative organism. The microscopy of specimens can rapidly detect the presence of acid-fast bacilli but requires large quantities of sample material, which is difficult to obtain from ocular tissue. It is less sensitive than culture of specimens in specific media.

Definitive diagnosis is achieved by identifying the M. tuberculosis by Polymerase chain reaction (PCR) which evaluates the presence of the tubercle bacillus DNA in ocular fluids and tissues. Only 0.01 ml of sample is required and both aqueous and vitreous specimens can be used. Nested-PCR has further reduced the antigen density required to obtain a positive result but it has an increased risk of false positivity. Enzyme-linked immunosorbent assay (ELISA) evaluates host immunoglobulin G (IgG) and immunoglobulin M (IgM) levels and helps in identifying recent infection but is not a particularly sensitive test. More recently developed assays are being used to augment the PPD test. Interferon gamma titres correspond to the strength of PPD and correlate more strongly to the risk of disease than PPD.

Quantiferon TB- Gold is the new antigen specific test for the diagnosis of tuberculosis. It is helpful in diagnosing infection with M. tuberculosis, including both tuberculosis disease and latent tuberculosis infection. It utilizes synthetic peptides representing mycobacterium tuberculosis proteins. It is a commercially available test that has been approved by Food and Drug Administration (FDA). It has a higher specificity than tuberculin skin test since it is unaffected by prior BCG vaccination and has equal or slightly more specificity than tuberculin skin test. Also, the result is objective and ready within 24 hours and unlike tuberculin skin test, no follow-up is required. Quantiferon test has also been shown superior to tuberculin skin test in immunosuppressed patients, in HIV patients and in patients with immune-mediated diseases.

Pars plana vitrectomy allows in obtaining intraocular specimens. Chorioretinal endobiopsy using standard three-port pars plana vitrectomy technique has been used for diagnosing TB choroiditis. It is however, associated with significant hazards such as retinal detachment, vitreous hemorrhage, and endophthalmitis.

The diagnosis of ocular tuberculosis is supported by the clinical imaging techniques including a chest x-ray to evaluate for possible associated pulmonary findings, optical coherence tomography (OCT) which is especially useful for the choroidal lesions, Fluorescein angiography, Indocyanine green angiography and
B-scan ultrasonography. CT scan is useful to evaluate an orbital mass from TB.

**Treatment**

**Treatment for pulmonary tuberculosis**

Once the tuberculosis is confirmed, the treatment is begun immediately. A combination of four drugs during the first two months-Isoniazid, Rifampin, Pyrazinamide and Ethambutol and two drugs- Isoniazid, Rifampin for next four additional months is given. Due to the prevalence of drug resistance especially to isoniazid (INH) and Rifampin, multi-drug therapy is now used routinely. The most common cause for treatment failure in case of pulmonary tuberculosis is non compliance to the therapeutic regimen. In this regard, Direct-Observed-Therapy (DOTS) has been of great help.

The treatment of active ocular tuberculosis infection differs from prophylaxis in patients with PPD positive but with no evidence of active TB. Here, the onus rests with the ophthalmologist to decide if the uveitis is indeed a sign of active tuberculosis infection. It is probably not indicated to treat every uveitis patient with a positive PPD with long-term anti-tuberculous medication in the absence of other evidence of tuberculosis.

**Treatment for ocular tuberculosis**

Treatment for ocular tuberculosis is the same as that for pulmonary tuberculosis. CDC has recommended the use of all 4 drugs-isoniazid, rifampicin, Pyrazinamide and Ethambutol for an initial 2 month period. This is followed by a choice of different options for 4-7 months. The CDC also recommends prolonged treatment for tuberculosis of any site that is slow to respond. Many studies have also recommended a treatment regimen consisting of isoniazid and rifampicin for a period of 9 months. It has been shown that the addition of rifampicin or Pyrazinamide to drug regimen containing isoniazid reduces the duration of the therapy. Low dose steroids given concomitantly with anti-tubercular therapy for a duration of 4-6 weeks has been shown to have a protective effect against tissue damage from delayed hypersensitivity. Few studies have highlighted that the use of steroids may activate a latent infection and cause a flare-up of systemic tuberculosis. Subretinal tuberculomas have been successfully managed surgically although a report by Gupta et al reports successful medical management of these tuberculomas. Also, Gupta et al have described that the addition of anti-tubercular therapy to corticosteroids in uveitis patients with latent/manifest tuberculosis decreases the risk of developing recurrences of uveitis.

**TB and HIV**

Tuberculosis is the commonest infection detected in HIV-infected individuals worldwide and the patients with HIV infection exhibit a unique susceptibility to Mycobacterium tuberculosis. These patients are not only more likely to develop an active disease but there occurs a rapid progression to active disease in their case. Also, once the infection is established, the clinical disease is more severe in these patients. They are also susceptible to reactivation of latent tuberculous infection.

There are some challenges in dealing with HIV Patients with TB as far as diagnosis and treatment is concerned. Tuberculin skin testing is not reliable in these cases. The manifestations of ocular tuberculosis are the same as in immunocompetent patients; disseminated choroiditis being the most common manifestation. The immunocompromised status of HIV patients retards recovery. Also, drug malabsorption is seen in HIV patients warranting a longer duration of treatment.

**Treatment of tuberculosis in HIV-infected patients-**

The treatment regimen in HIV patients remains the same as that for non-infected individuals and consists of a combination of anti-tubercular drugs. It has been showed that administration of trimethoprim-sulphamethoxazole to HIV infected tuberculosis patients on being diagnosed as having active tuberculosis, protected them from a variety of infectious causes of death.

**Rifabutin and uveitis**

Rifabutin is used for the treatment and prophylaxis of Mycobacterium avium complex (MAC) infection in the HIV patients. Uveitis is a rare, dose-related toxicity of this therapy. The risk of Rifabutin-associated uveitis has
been shown to increase in patients receiving concurrent therapy with Clarithromycin or fluconazole because of drug interactions. If any signs of uveitis develop, Rifabutin therapy should be promptly discontinued.

Ocular toxicity of anti-tubercular drugs-

Ocular tuberculosis patients should be followed for side effects of anti-tubercular drugs. Of all the anti-tubercular drugs used, Ethambutol is the most likely to cause ocular morbidity.

Ethambutol has been associated with retrobulbar optic neuritis. However, it is dose related and usually reversible but may sometimes warrant discontinuation of the drug. Isoniazid has also been implicated in causing peripheral neuropathy. Such patients should take pyridoxine, which has been shown to prevent isoniazid-associated neuropathy. Isoniazid is also known to be hepatotoxic. Liver enzymes should be tested serially while the patients are on this drug. Rifampin is associated with thrombocytopenia. So, complete blood counts should always be done. Pyrazinamide has been associated with causation of hyperuricemia, but acute gout is not common. Streptomycin has been associated with hearing loss.

Conclusion

Ocular tuberculosis may occur in the absence of pulmonary disease and the patients may present with a wide variety of clinical signs. Also, the disease can mimic several clinical entities. Tuberculosis may affect all ocular tissues; choroiditis being the most common ocular manifestation. The retinal involvement occurs secondary to the underlying choroidal infection. Treatment for ocular tuberculosis is the same as that for pulmonary tuberculosis. Due to the emergence of drug resistance, multidrug therapy is advocated.

In the present time of the HIV pandemic, there has been a resurgence of tuberculosis and it is the most common opportunistic infection in HIV positive patients. HIV-related TB shows a higher prevalence of extrapulmonary and disseminated TB. Since the disease is treatable and eyes can be saved using anti-tuberculous treatment if detected early, considerable stress should be laid on its early diagnosis and prompt treatment so as to prevent ocular morbidity and blindness.

References

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