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Diagnosis and Management of Intraocular Tuberculosis*

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Introduction

Tuberculosis (TB) is one of the leading infectious causes of death, next to Malaria and HIV. Although the primary focus of infection is usually the lung, it can involve various organs, including the eye. The ocular tuberculosis results from the hematogenous seeding from the primary complex or the secondary lesions that may develop, where the bacilli may remain latent for years before reactivation (1). The organisms may get reactivated in the eye. By the time the ocular TB manifests, the patients may not show evidence of concurrent active systemic disease; however, uncommonly it may occur simultaneously with active pulmonary or extra pulmonary TB. According to the World Health Organization (WHO) estimates (2), about one-third of the world's population is infected with Mycobacterium tuberculosis. The infection remains latent in the immunocompetent individuals who run a 10% lifetime risk of systemic reactivation, which is alarmingly increased to 10% annual risk in the HIV infected people. Approximately 8-10 million people get TB every year (95% in the developing countries), and about 3 million deaths are reported from TB every year (3-5). Its prevalence is largely governed by poor socio-economic conditions, as evidenced by its predominance in countries of Asia, Africa and Latin America.

In the absence of any definitive diagnostic guidelines or criteria, there is no reliable data to indicate the true prevalence of tuberculosis as a cause of uveitis reported as 0.5% in USA (6), 6.31% in Italy (7), 6.9% in Japan (8) and 10.5% in Saudi Arabia (9). The prevalence rates are highly variable from 0.39 to 9.86% in the south (10), and north

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Indian uveitis clinic population respectively (11). A recent report highlighted the predominance of India as the country with largest number of presumed tubercular uveitis cases reported in the world (12).

Clinical spectrum of ocular tuberculosis

Tubercular intraocular inflammation presents with a wide spectrum of clinical manifestations including chronic, recurrent anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, or rarely endophthalmitis, panophthalmitis or neuroretinitis (13).

Anterior uveitis:

Tubercular anterior uveitis is characterized by the presence of broad based posterior synechiae and low-grade cellular reaction and flare. Though this sign is not pathognomonic of ocular tuberculosis, it is highly suggestive of tubercular etiology in patients with positive PPD skin reaction. Posterior synechiae may be complicated by pupillary block and secondary glaucoma (14, 15). Additionally, mutton fat keratic precipitates few in number often occupying inferior half of the corneal endothelium, Koeppe nodules at the pupillary border or Bussaca nodules on the surface of the iris are highly suggestive of tubercular etiology in patients with positive PPD skin reaction. Uncommonly, there may be formation of granulomas in the angle of the anterior chamber or formation of hypopyon. Chronic recurrent inflammation is complicated by the formation of cataract. If treated early and appropriately with antitubercular therapy and corticosteroids, the inflammation resolves with minimum residua. Inadequate treatment may be complicated by band shaped keratopathy and iris neovascularization.

Intermediate Uveitis:

Commonly, there is spillover of inflammatory cells into the anterior vitreous from the anterior uveitis. Inflammation of the ciliary body, beginning in the region of pars plana, simulating pars planitis may be seen as moderate to severe vitritis with or without snowballs and pars plana exudates (snow bank) (16). Peripheral vascular sheathing and cystoid macular edema are usually present. Tuberculomas may form in the ciliary body (17) that may be detectable only on ultrasonic biomicroscopic examination.

Posterior Uveitis:

Posterior segment involvement is the most common form of tubercular uveitis and choroidal tubercle is the most

characteristic clinical presentation. Choroidal tubercles are granulomas located deep in the choroid. The lesions are discrete, few in number (usually less than 5), most commonly situated in the posterior pole, grayish-white to yellowish in color and have indistinct borders. The choroidal lesions may or may not be associated with subretinal fluid. They heal with pale, atrophic, sharply demarcated borders with variable pigmentation.

Nearly 30% of the patients suffering from disseminated tuberculosis or tubercular meningitis may show tubercular granulomas (1). On fundus fluorescein angiography, they exhibit early hypofluorescence and late hyperfluorescence. Very often, retino-choroidal anastamotic vessels are apparent in the centre of the lesions.

The diagnosis is made on the basis of characteristic clinical features, demonstration of M tuberculosis from intraocular fluids, and corroborative evidence of the disease in other organs. Polymerase chain reaction for detection of the M. tuberculosis genome from ocular fluids is likely to play a major role in diagnosing intraocular tuberculosis.

Clinically, choroiditis appears to involve the inner choroid and RPE. An evidence of the mycobacterium being present within the RPE has been recently reported (18). The AFB were detected within the necrotic RPE cells. Microdissection of RPE and real-time PCR later confirmed Mycobacterium tuberculosis. Even though retina and uvea were involved (panuveitis), these findings suggest preferential localization of *M.tuberculosis* in the RPE in panuveitis, or even multifocal or serpiginous-like choroiditis resulting from TB. Since the RPE shares several functions with alveolar macrophages (which engulf the mycobacteria in pulmonary TB), the authors hypothesized that (1) bacteria noted in the RPE may represent the phagocytosed bacteria, (2) the bacteria thrive in the RPE by avoiding phagolysosome fusion, and (3) recurrences in tubercular choroiditis could result from reactivation of sequestered organisms in the RP.

Clinical characteristics of tubercular Retinal Vasculitis:

Inflammation of retinal vessels is a known association of systemic tuberculosis. Patients with retinal vasculitis are subjected to extensive but unrewarding systemic workup. Active vasculitis is seen as severe perivascular cuffing with infiltrates, usually accompanied by moderate vitritis. Tubercular retinal vasculitis causes extensive peripheral capillary non-

perfusion. Anterior segment inflammation is uncommon with tubercular vasculitis. These eyes frequently develop optic disc or retinal neovascularization and require scatter laser photocoagulation. In the past these eyes were often labeled as suffering from Eales' disease of unknown etiology. Tubercular retinal vasculitis is commonly associated with focal choroiditis lesions that are typically observed under the retinal vessels.

For the first time, we characterized the clinical characteristics of PCR-positive tubercular retinal vasculitis, so as to determine the clinical presentation, associated systemic features, management, and course of this form of vasculitis (19).

The clinical records of 13 patients seen between 1997 and 1999 with the diagnosis of PCR-positive tubercular retinal vasculitis from the aqueous or vitreous humor were reviewed. All received antituberculosis therapy with or without concomitant corticosteroids. There were 9 (69.2%) male and 4 (30.7%) female patients with a median age of 20 years. The disease was bilateral in seven. The most consistent finding was the presence of vitritis in all the eyes followed by vitreous snowball opacities in 17 eyes (89.4%), neovascularization in 11 eyes (57.8%), retinal hemorrhages in 10 eyes (52.6%), neuroretinitis in 10 eyes (52.6%), focal choroiditis in 9 eyes (47.3%), vitreous/preretinal hemorrhage in 5 eyes (26.3%) and serous retinal detachment in 3 eyes (15.7%). Over a median follow-up of 12 months, all showed resolution of vasculitis with no recurrences (19).

Tubercular posterior scleritis:

Scleritis is an uncommon ocular inflammatory disorder most often associated with systemic inflammatory diseases of autoimmune origin. Some cases of anterior scleritis may be caused by microbial infection. Posterior scleritis is predominantly idiopathic or autoimmune or when infective, is an extension of anterior scleritis. Infective isolated posterior scleritis is rare. Although anterior scleritis due to Mycobacterium tuberculosis had been reported in literature, isolated posterior scleritis in a patient of systemic tuberculosis had not been recognized. We reported a case of isolated posterior scleritis associated with histopathologically documented systemic tuberculosis, a hitherto unreported association. The patient responded well to a combination of oral corticosteroids with antituberculosis therapy (20).

Presumed Tubercular Serpiginous like Choroiditis:

While Choroiditis, choroidal tubercles and tuberculomas are well known ocular manifestations of systemic tuberculosis, choroidal tuberculosis may present as multifocal progressive or diffuse choroiditis resembling serpiginous choroiditis especially in people of Asian-Indian origin. We reported first time the occurrence of serpiginous like choroiditis of presumed tubercular origin, which we believe, is the commonest cause of posterior uveitis in India (21).

Serpiginous like choroiditis may present different morphological patterns: (a) Multifocal discrete lesions may be the initial presentation which show a wavelike progression and eventually becoming confluent. These lesions begin as yellowish-white, well-defined round lesions, ¼ to 1 DD in size with raised edges. On fundus fluorescein angiography, the lesions show hypo fluorescence in the early frames of fluorecein angiograms and hyper fluorescence in the late frames. (b) Occasionally the lesions may manifest as diffuse, larger, yellowish-white, plaque-like lesion. The active edges are elevated, the center of the lesion is flat and shows pigmentary changes, indicating the process of healing. The fundus fluorescein angiography shows mixed fluorescence in the central areas indicating healing/ healed lesions while the advancing edge show characteristic initial hypofluorescence and late hyperfluorescence. (c) However, the patients may show a mixed pattern, with discrete lesions in one eye and diffuse, plaque-like lesion in the opposite eye.

A less common type is seen as a reactivation at the edge of an old scar of serpiginous like choroiditis. Unlike the autoimmune serpiginous choroiditis, tubercular serpiginous like choroiditis is seen at a younger age, and is accompanied by mild vitritis and is bilateral in majority. These lesions heal with exuberant pigmentary changes unlike the autoimmune variety that is seen in middle or old age and the lesions heal with choroidal atrophy and minimum pigmentation. It is important to recognize these presentations because these eyes show good response to systemic antituberculosis chemotherapy.

In a retrospective, noncomparative, interventional case series, eleven eyes in seven consecutive patients with a diagnosis of choroidal tuberculosis simulating serpiginous choroiditis were studied between 1997 and 2000.

There were five men and two women ranging in age from 17 to 32 years. Clinical presentations included three morphologic variants: multifocal progressive choroiditis showing wavelike progression to confluent, diffuse, lesions resembling serpiginous choroiditis (three eyes); diffuse choroiditis characterized by diffuse plaque like choroiditis with an amoeboid pattern suggestive of serpiginous choroiditis at initial presentation (four eyes); and mixed variety where opposite eyes had mixed features (four eyes). All patients had strongly positive Mantoux skin test results and positive chest radiograph results. The PCR results from aqueous and vitreous humor in four samples was positive for Mycobacterium tuberculosis; one had sputum positive for acid-fast bacilli, whereas two had histopathologic evidence of tuberculosis from cervical or parahillar lymph nodes. Treatment was associated with resolution of choroidal lesions and visual improvement. Final visual acuity of 20/30 or better was achieved in five eyes. Subsequent to our report, this manifestation of ocular tuberculosis has been recognized in different parts of the world.

Successful management of tubercular subretinal granulomas

Very large granulomas are usually solitary and may appear like a subretinal abscess and invariably accompanied by extensive exudative retinal detachment (22). The subretinal abscess is seen as a yellowish, solitary, elevated subretinal mass-like lesion. It develops as a result of progressive, liquefied caseation necrosis with rapid multiplication of bacilli and tissue destruction.

Tubercular subretinal granulomas are amenable to medical management provided an early diagnosis is made and treatment is initiated promptly. We reported successful management of 12 eyes of 11 patients (seven males and four women with median age of 30.5 years) with tubercular subretinal granulomas who were treated with four-drug anti-tubercular chemotherapy with concomitant corticosteroids. Two patients underwent pars plana vitrectomy. Ten eyes responded well to medical management and a final visual acuity of 20/80 or better was achieved in eight of them. The eyes subjected to pars plana vitrectomy had a relatively worse outcome. We concluded that once the diagnosis of presumed or confirmed tuberculosis is established, surgical intervention should be avoided (22).

We also reported simultaneous choroidal tuberculoma and epididymo-orchitis caused by *Mycobacterium tuberculosis*. DNA products from

vitreous and epididymal fluid matched with IS 6110 sequence of *M. tuberculosis.* Choroidal granuloma and epididymitis responded to antitubercular therapy (23).

Diagnosis of intraocular tuberculosis

The definitive diagnosis of introcular tuberculosis is based on demonstration of acid-fast bacilli on direct smear examination or growth of *M Tuberculosis* from ocular or tissue specimens. Whereas periocular tissues such as lid, conjunctiva or sclera are amenable to biopsy and histopathological diagnosis, intraocular inflammation involving the uveal tissues, vitreous and retina poses considerable difficulty in obtaining microbiologic or histopathologic evidence, and is a major challenge to an ophthalmologist. In the absence of the above, however, the diagnosis remains presumptive based only on corroborative evidence such as positive tuberculin skin test, healed lesions on chest x-ray, or associated systemic TB. The absence of clinically evident pulmonary TB does not rule out the possibility of ocular TB, as about 60% of patients with extrapulmonary TB have no evidence of pulmonary TB (24). Latent TB is diagnosed when person is infected with *Mycobacterium tuberculosis* but does not have active tuberculosis disease.

Tuberculin skin test: Popularly known as the Mantoux test since 1910, was the classic diagnostic tool for latent TB infection (LTBI) until recently (25). 0.1 ml of 5 tuberculin units of purified protein derivative (PPD) is injected intradermally. A person who has been exposed to the bacteria is expected to mount an immune response in the skin. The reaction is read 48-72 hours after inoculation by measuring the diameter of induration (palpable raised hardened area) across the forearm in millimeters. It is this indurated response to the intradermal injection of proteins from the cell wall of the tubercle bacillus that represents the type IV immune response characterizing delayed-type hypersensitivity (DTH). An induration of more than 10 mm is considered positive, indicating tuberculosis infection (26).

Role of polymerase chain reaction in diagnosis of tubercular uveitis:

The granulomatous uveitis, multifocal choroiditis and periphlebitis have been suspected to be of tubercular origin but no definitive reports about detection of etiological agents were documented in the literature. Conventional bacteriological methods are generally not helpful in diagnosing ocular tuberculosis due to difficulty with

potential morbidity associated with obtaining the biopsy material from the eye. Thus, the diagnosis of ocular tuberculosis is most often presumptive. We evaluated the role of polymerase chain reaction (PCR) for detection of Mycobacterium tuberculosis in the aqueous humor samples obtained from eyes with active uveitis. Aqueous samples from 53 patients having cellular reaction in the anterior chamber along with any one or more of the following: 1) active vasculitis; 2) anterior vitreous cells; 3) snowball opacities; 4) snow banking in the pars plana; 5) retinochoroiditis were withdrawn by anterior chamber paracentesis and subjected to PCR. Seventeen samples from patients with definite clinical diagnosis other than tuberculosis formed a disease control group. Fifteen aqueous samples obtained from healthy subjects undergoing routine cataract surgery served as healthy controls. PCR was performed using primers capable of amplifying a 150 bp segment from a conserved repetitive sequence in the genome of M. tuberculosis. Twenty out of the 53 samples (37.7%) in the study group were positive whereas only one sample out of 17 in the disease control group (5.7%) showed a weakly positive band. No sample from the healthy control group showed a positive PCR.

Our study showed that PCR can be effectively used for the diagnosis of intraocular tuberculosis in the presence of uveitis (27).

Further, forty-five patients were divided into three groups, Group I included 17 patients of presumed intraocular tuberculosis, group II had 13 disease controls and group III had 15 normal controls. Patients with positive PCR were offered antituberculosis chemotherapy and followed up for a minimum of 18 months.Ten patients in group I, 3 in group II and none in group III were positive for *Mycobacterium tuberculosis* by PCR. Ten patients with positive PCR for *Mycobacterium tuberculosis* (8 in group I and 2 in group II) were treated with antituberculosis chemotherapy and all showed resolution of inflammation without any recurrence over 18 months of follow-up. Two PCR positive patients treated with steroids alone, however, did not show complete resolution and had recurrent attacks These results suggested that anti tuberculosis treatment in PCR positive patients led to resolution of inflammation and elimination of recurrences, most likely by eliminating *Mycobacterium tuberculosis* from the intra ocular tissues (28).

Role of anti tubercular treatment in uveitis associated with latent/manifest tuberculosis:

Attempts have been made in the past to diagnose and treat ocular TB by eliciting therapeutic response to single anti-tubercular agent (29). Beneficial effects of anti-tubercular therapy in proven cases of intraocular TB have been documented in various reports (30-33). To assess the role of anti-tubercular therapy in uveitis with latent/manifest tuberculosis (TB), 360 patients with active uveitis were studied in a retrospective, interventional case series. These patients showed evidence of active uveitis i.e., cellular reaction in the anterior chamber with or without keratic precipitates, and/or active vitreous inflammation, retinal vasculitis, choroiditis or neuroretinitis; with a documented positive tuberculin skin test (10 mm of induration or more) at 48-72 hours. All known causes of infectious uveitis except TB and known non-infectious uveitic syndromes were ruled out. All patients had at least one year of follow-up from the initiation of treatment. Two hundred and sixteen of these 360 patients received 4-drug anti-tubercular therapy and corticosteroids (group A) and 144 patients (group B) received corticosteroids alone. The main outcome measure was recurrence of inflammation after minimum 6 months of initiating treatment in each group. Recurrences reduced significantly ($p<0.001$) in group A (15.74%) as compared to group B (46.53%) over a median follow-up of 24 and 31 months, respectively. The patients treated with anti-tubercular therapy with corticosteroids had decreased risk of developing recurrence of uveitis by approximately two-thirds as compared to those treated with corticosteroids alone. We concluded that addition of anti-tubercular therapy to corticosteroids in uveitis patients with latent/manifest TB led to significant reduction in recurrences of uveitis (34).

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