

Fundus Changes in Millitary Tuberculosis: A Retrospective Cohort Study

Kalpna Jain, Manak Gujrani, Jaishree Murli Manohar, Jyoti Garhwal, Nilesh Gupta

Department of Ophthalmology and Chest & TB, Sardar Patel Medical College, Bikaner, Rajasthan, India

Introduction: Millitary tuberculosis occurs due to haematogenous spread of infection. It is assumed that intraocular tuberculosis is spread hematogenously from primary infection to elsewhere. The choroidal tubercles may be one of the earliest signs of millitary disease and is probably the most common form of ocular tuberculosis.

Methods: This is a retrospective observational single site study of 113 patients with millitary tuberculosis from 2001 to 2015. Fundus examination was done after full dilatation of the pupil with direct and indirect ophthalmoscope. The diagnosis of intraocular tuberculosis was presumed to be based on suggestive ocular lesion in context of evidence of systemic infection and response to antitubercular treatment.

Results: There were 77 females (68%) and 36 (32%) males. The commonest age group was 21 to 40 years as 67 (59.3%) patients belonged to this productive age group. Eighty eight (77.9%) patients were from rural areas. Fundus changes were present in 14 patients (12.39%) and these were choroidal tubercles (8.8%), papillitis (4.4%), macular edema (0.9%) and vitritis (0.9%). Choroidal tubercles were present in 10 patients. Among these, two had associated papillitis and one also had vitritis. Three patients had only papillitis and in another one, only macular edema was present. Papillitis was present in five patients in our study. HIV did not increase the incidence of ocular lesions.

Conclusion: The most common fundus changes were choroidal tubercles and optic neuropathy in our series. Early detection of these choroidal tubercles may be helpful in diagnosis as well as in treatment. The optic nerve may be involved not only by the toxic effect of anti-tubercular drug but also in the disease process itself.

Abstract

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Keywords: Choroidal tubercle, Millitary tuberculosis, Papillitis

Introduction

Tuberculosis (TB) remains the world's leading infectious cause of death and can also cause a variety of diseases in the body and the eye.¹ WHO estimate that there were 10.4 million new cases of TB in 2015, of which 1.2 million were HIV positive. About 1.4 million people who were HIV negative died from TB each year.² India is the highest TB burden country in the world. Mortality due to TB is the third leading cause of years of life lost (YLLs) in India. Tuberculosis is classed as a type of the infectious granulomas. The pathological characteristic is tissue destruction and replacement of the normal cellular structure by an overgrowth of granulomatous tissue, often in the form of tubercles. Guenea de Mussy was the first to recognize choroidal tubercles in 1830. The millitary tuberculosis (MTB) occurs due to haematogenous spread of infection. It is assumed that intraocular tuberculosis is spread hematogenously from primary infection to elsewhere, usually pulmonary. The choroidal tubercle may be one of the earliest signs of millitary disease and is probably the most common form of ocular tuberculosis. In practice, most of the cases of ocular tuberculosis are presumed to be based on suggested ocular lesion in presence of evidence of prior exposure to Mycobacterium tuberculosis and a response to antitubercular treatment (ATT).

Method

This is a retrospective observational cohort single site study of 113 patient with millitary tuberculosis from 2001

to 2015. This study is an analysis of only fundus changes in millitary tuberculosis. As the Chest and TB physician call the ophthalmologist for bedside examination of the patient, for only fundus examination.

The inclusion criteria were chest x-ray showing millitary mottling and response to anti tubercular treatment. The exclusion criteria were patients had corneal opacity, cataract and other ocular diseases, and systemic diseases like sarcoidosis, brucellosis, silicosis, metastatic diseases. We analyzed information regarding age, gender, socio-economic condition, history of contact and BCG vaccination. Complete systemic evaluation, investigations like chest x-ray (CXR), Ultrasonography abdomen, erythrocyte sedimentation rate, mantoux test and sputum for Acid Fast Bacilli had done. Computerized tomography scan and tests for HIV were done in selected cases where they were required. The diagnosis of millitary tuberculosis was done on the basis of specific X-ray finding like millitary mottling of lung field, constitutional symptoms, respiratory symptoms, involvement of other organ and response to ATT. The ocular lesions diagnosed as in course of suspicion of millitary tuberculosis. Fundus examination done after full dilatation of pupil with direct and indirect ophthalmoscope. The case records had only fundus examination as chest and TB physician needs to support their diagnosis. The diagnosis of intraocular tuberculosis was presumed to be based on suggestive ocular lesion in context of evidence of systemic infection. The ATT started when patient confirmed as a millitary tuberculosis.

After starting the ATT ocular and other systemic lesion of millitary tuberculosis resolved.

Results

The record of 113 patients was analyzed who came in Chest & TB hospital of tertiary care centre from February 2001 to August 2015. There were 77 females (68%) and 36 (32%) males. This is probably because females are the neglected part of Indian society. 67 (59.3%) patients belonged to age group 21 to 40 year. 88 (78%) patients were from rural areas where their socio-economic condition was not so good. (Table 1)

In all the patients CXR showed milliary mottling (Figure 1), 61 patients showed hepatomegaly, splenomegaly, lymphadenopathy, pleural effusion or ascites. (Table 2) Elisa for HIV was positive in two patients for whom fundus was normal. Fundus changes were present in 14 patients (12.4%) and these were choroidal tubercles (8.8%) (Figure 2), papillitis (4.4%) (Figure 3), macular edema (0.9%) and vitritis (0.9%). Choroidal tubercles were present in 10 patients and all were females. Among these two had associated papillitis and one also had vitritis (Figure 4). Three patients had only papillitis and in another one only macular edema was present. Edema of either disc or macula more common in male. (Table 3) Papillitis was present in five patients in our study so, Choroidal tubercles and papillitis both were common.

The statistical analysis was done using the SPSS software version 15. The association between age group and fundus changes was analyzed using the Chi square test and statistically not significant.

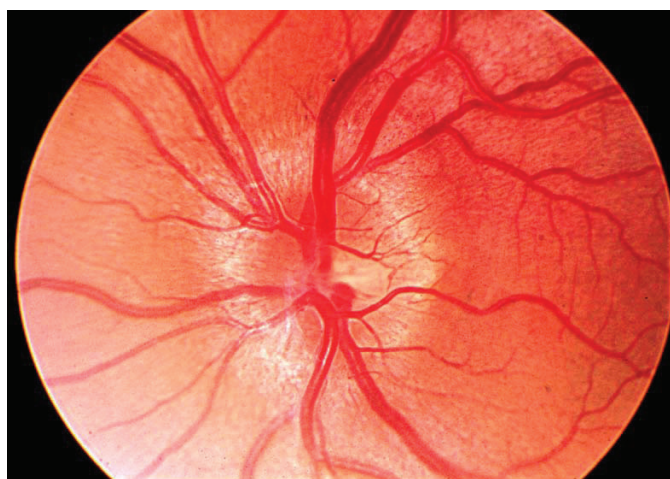


Figure 3: Papillitis

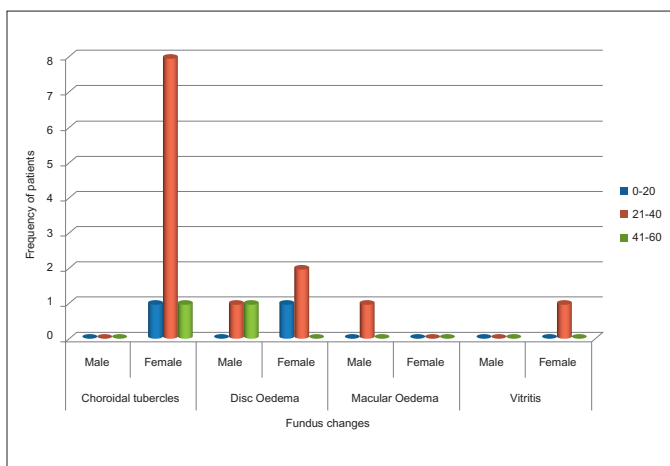


Figure 4: Fundus changes in study Cohort (n=113)

Table 1: Demographics of study Cohort (n=113)

Age Group	Rural		Urban	
	Male	Female	Male	Female
0-20	4	7	1	4
21-40	17	38	3	9
41-60	7	7	3	2
61-80	0	8	1	2

Table 2: Ultrasonographic findings in different age groups

Age Group	Hepeto-megaly	Spleno-megaly	Lymphadenopathy or Lymph node enlargement	Ascites
0-20	6	0	2	1
21-40	26	10	0	4
41-60	6	0	2	1
61-80	1	0	1	1
Total	39	10	5	7



Figure 1: CXR showing milliary mottling

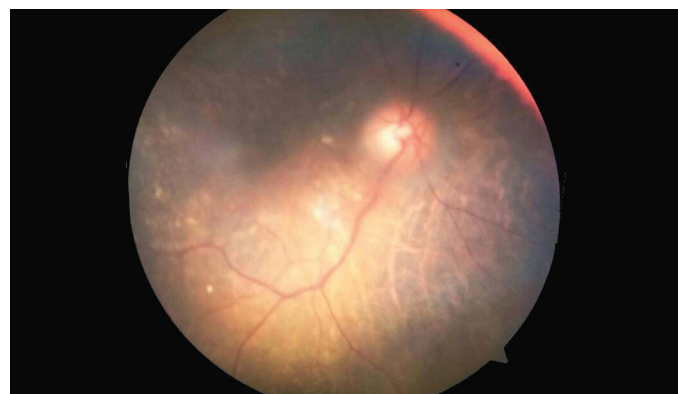


Figure 2: Choroidal tubercles

Table 3: Table showing Fundus changes in study Cohort (n=113)

Age Group	Choroidal tubercles		Disc Oedema		Macular Oedema		Vitritis	
	Male	Female	Male	Female	Male	Female	Male	Female
0-20	0	1	0	1	0	0	0	0
21-40	0	8	1	2	1	0	0	1
41-60	0	1	1	0	0	0	0	0
Total	0	10	2	3	1	0	0	1

Discussion

Milliary tuberculosis (MTB) is a form disseminated tuberculosis (DTB), which have tiny discrete foci usually the size of millet seed (1-2 mm) more or less uniformly distributed in the lungs and other viscera.

The numbers of TB cases worldwide correspond with socio-economic condition; the higher incidences are seen in the countries of Africa, Asia and Latin America. Ocular tuberculosis is considered rare yet its incidence varies widely across time, patient population and geography. In 1967, Donahue reported 1.46% incidence of tuberculosis in 10524 patients in a sanatorium.³ The epidemiology of milliary tuberculosis has changed dramatically over time.

Milliary tuberculosis is both a radiological and pathological term used to describe hematogenous dissemination of *M. tuberculosis*. Radiologically the term milliary refers to pattern often seen on chest radiography, which is described as resembling millet seeds. Not all patients with disseminated disease have pulmonary involvement; however, dissemination can occur during primary infection, after reactivation of a latent focus or reinfection. During primary infection, a small number of tubercle bacilli gain access to the circulation through the lymphatics and disseminate into visceral sites which have rich vascular supply and good oxygenation such as liver, spleen, bone marrow, brain and uveal tissue. Later in life, reactivation of these latent foci, caseation and erosion into blood vessels can result in hematogenous embolism and development of MTB. Symptoms often progress over a period of 1 to 4 months before diagnosis. Fever, anorexia and weight loss occur in most patients. Respiratory symptoms (cough and dyspnea) occur in about half of patients with milliary disease, but haemoptysis is quite rare. Many other symptoms may appear, headache is particularly important because it may reflect co-existing tubercular meningitis. Organomegaly is also a frequent physical finding. Choroidal tubercles are less common but they are diagnostically useful, if present. Laboratory findings are often nonspecific. MTB continues to be a diagnostic problem even in areas which are endemic to tuberculosis and clinical suspicion is very high.

A diagnosis of ocular tuberculosis most often involves the uveal tract, either as chronic anterior uveitis or as disseminated choroiditis. Tubercular uveitis is classically a chronic granulomatous uveitis. Choroid is most commonly involved in MTB. Choroidal tubercles and tuberculomas are its most common manifestation. The choroid has greater chances of infection than the other parts of eye because of its

rich vascular supply and abundance of reticuloendothelial cells. Multifocal choroidal tubercles are the most characteristic clinical feature of MTB and provide evidence that intraocular tuberculosis develop from hematogenous spread of tubercular bacilli from pulmonary or other sites.⁴⁻⁷

The tubercles may be unilateral or bilateral, greyish white or yellowish in colour, discrete with indistinct border lying deep in the choroid and 0.5 mm to 3 mm in diameter. Usually they are multiple and less than 5 in number and may be accompanied by hemorrhage or overlying serous detachment. Usually involve posterior pole but can be seen in the midperiphery as well. The choroidal tubercles heal over 12 to 14 weeks with pale atrophic, sharply demarcated area with variable pigmentation. Histologically the choroidal tubercles are similar to the tubercles elsewhere in the body.⁸⁻¹⁰

On fluorescein angiography, the lesions are hypoflorescent in the die transit and become hyperflorescent in late frames. Ocular tuberculosis may present as solitary elevated mass like lesion (tuberculoma) measuring from 4-14 mm. The lesion results from progressive caseation and multiplication of bacilli and tissue destruction. Large tuberculoma may present as yellowish subretinal mass with exudative retinal detachment and may lead to subretinal abscess, breaking into the vitreous cavity or even ocular perforation.^{10,11} Ocular tuberculosis may present as multifocal progressive choroiditis resembling serpiginous choroiditis.¹²

Tuberculosis of retina is most commonly caused by extension from choroid but may also be caused by hematogenous spread. Retinal lesions are either focal tubercles or diffuse retinitis. There may be vitreous opacification, grey white retinal lesion or retinal vasculitis. Eales disease is a form of retinal vasculitis. In 1990 P.H. Rosen et al found in twelve patients of intraocular tuberculosis, nine patients showed florid ischaemic retinal vasculitis and a marked tendency to neovascularization. Two patients developed choroidal tubercles and iris nodules were observed in association with anterior uveitis in the remaining patient.¹³ Tubercular optic neuropathy may manifest as optic nerve tubercle, papillitis, papilloedema, optic neuritis, neuroretinitis or optochiasmatic arachnoiditis. Tuberculous meningitis may cause raised intracranial pressure, optic neuritis or optic atrophy. It may be due to tuberculous meningitis or retinal periphlebitis. In tubercular meningitis there is extension of tuberculous inflammation from the meninges to the sheath of optic nerve. In the absence of identifiable intracranial involvement optic nerve may be involved. The possible mechanism is infectious optic neuritis. Macular edema and optic disc edema may be seen.¹⁴ Retinal periphlebitis occasionally may cause central retinal vein occlusion. Tubercles are found along the pial coat & may even present in intraseptal pial extension into the nerve substance, necrosis and caseation follows with complete local destruction of the nerve substance and finally optic atrophy occurs.

In a study conducted in Busan, Korea in 1973 the common finding in fundi of tubercular children were small tubercles and pale optic disc.¹⁵ A prospective study from Spain reported in 1997, examined 100 randomly chosen patients with proven systemic tuberculosis and found ocular involvement in 18 patients (18.1%). Almost all patients had

choroiditis and other ocular lesions including papillitis, retinitis, vitritis, vasculitis, dacryoadenitis, scleritis and milliary disease was a clear predisposing factor.¹⁶ In Malawi, South Africa 2.8% incidence of choroidal granuloma reported in a prospective study in 2002.¹⁷ In Saudi Arabia 10.5% uveitis cases in tuberculosis patient of a referral centre from 1995-2000.¹⁸ In Spain 2002, Tenorio et al reported in 28 patients of milliary tuberculosis, 18% having ocular lesions.¹⁹ In Brazil (2003), Mendes Gustavo Federici et al reported 5.5% incidence of posterior lesions in patients with tuberculosis while in milliary T.B. 66% patients having posterior lesions.²⁰ In a study conducted in Mumbai, India in 2004, 10 patients of milliary tuberculosis, six of which (60%) showed evidence of ocular involvement and in these (60%) about 5 patients (85%) had choroidal tubercles and one (16%) had retinal vasculitis.²¹ In 2008, AL-Mezaine HS et al shows that vitritis (71.2%), Macular edema (63%), retinal periphlebitis (35.6%). Multifocal choroiditis (20%) and granulomatous uveitis were clinical manifestation of possible ocular tuberculosis patients.²² A study done in China in 2014 by Mao Y et al showed multifocal choroiditis, retinal vasculitis and choroidal granuloma in chronic posterior uveitis patients.²³ The study done by Mehta S shows that 89% of ocular T.B. patient shows choroidal tubercle and 10.9% have choroiretinitis, 2.8% had disc edema.²⁴ In our study 12.39% patients showed evidence of ocular involvement. In these patients 8.8% had choroidal tubercles, 4.4% had papillitis, 0.9% had vitritis and macular edema present in 0.9%. HIV does not increase the incidence of ocular lesions. Choroidal tubercles can strongly correlate with systemic disease and be an indicator of hematogenous spread of mycobacteria. Papillitis is also common in our series. Detection of M. tuberculosis in the lesion by histological methods or by culture using Lowenstein-Jensen media^{25,26} is the gold standard for tuberculosis. In most of the cases of ocular tuberculosis, culture and biopsy of involved tissue for confirmatory diagnosis is not practical. Aqueous and vitrous samples generally fail to yield positive bacterial culture. In view of the risk involved in applying the standard diagnostic technique to the eye, help of indirect evidences is taken to reach a diagnosis so that the diagnosis is best termed as presumed ocular tuberculosis. Evidence of systemic tuberculosis affecting lung or other organ, sputum smear and culture, PPD test²⁷, chest X-ray, detection of mycobacterial DNA through PCR²⁸ is helpful but does not prove that tuberculosis is the cause of ocular findings. The exact duration of treatment and end point for stopping treatment is not known. Primary treatment should always be systemic. Systemic treatment with multidrug regimen is preferred for at least 6 months to 15 months because pulmonary infection or other foci of infection may be present. Response to treatment becomes evident within 2 to 4 weeks. Concomitant use of steroid is controversial. Low dose steroid for 4-6 weeks may limit damage to ocular tissue from delayed hypersensitivity but steroid is useful in tubercular meningitis and pericarditis. There may be a role of laser therapy as an adjuvant after diagnosis is established and response to chemotherapy is confirmed. Balashevich in 1984 reported that argon laser photocoagulation of tuberculous

choroiretinitis lesions near the fovea result in better visual acuity than conventional treatment.²⁹

Conclusion

Extra pulmonary tuberculosis including tuberculosis of the eye is common in underdeveloped and developing countries. MTB continues to be a diagnostic problem even in tubercular endemic areas and clinical suspicion is very high. The most common fundus change in milliary tuberculosis is choroidal tubercles. Optic neuropathy is also common in our series. Early detection of these choroidal tubercles may be helpful in diagnosis as well as in treatment. Optic nerve may be involved not only in the toxic effect of anti-tubercular drug but also in the disease process itself.

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Address for correspondence

Kalpna Jain MS

Professor,

Department of Ophthalmology

S.P. Medical College, Bikaner-334003,

Rajasthan, India

Email id: kalpnajain134@gmail.com



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