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Original Research Article

# Visual loss and ocular morbidity in tubercular uveitis with systemic correlation: Analysis in a tertiary multi-speciality hospital

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## Abstract

**Background:** Tuberculosis (TB) affects all ages resulting in morbidity in multiple organ systems. This study was performed to determine pattern of posterior uveitis, incidence of visual loss, role of aqueous humour analysis in systemic tuberculosis and its correlation with ocular and laboratory investigations.
**Materials and Methods:** A retrospective study on 200 patients with systemic tuberculosis over 2 years. Laboratory workup consisted of tuberculin test, chest x-ray, polymerase chain reaction, and interferon gamma assay. Blood and ocular sample analysis with ancillary ophthalmic investigations were performed.
**Results:** Incidence of uveitis in TB was 32%, visual loss in 7% and the initial presentation in 12%. Mean age of onset was 38 years (SD+/- 5). Uveitis was due to active systemic TB in 12% and immune response in 75% which was statistically significant (p=0.02). Etiology was pulmonary TB in 21% and extrapulmonary TB in 4%. Posterior uveitis occurred in 49 patients (77%) and was the most common (p=0.01.)
Chest x-rays revealed lung infiltrates, hilar lymphadenopathy, and calcification in 15% of patients. Mantoux was positive in 72% and positive PCR in 37% and positive aqueous humour analysis PCR results ranged from 71% to 96%. Overall, systemic investigations were positive in 72% of patients. Improvement was observed within 6 months in 87% of patients. Vision improvement or complete resolution occurred in 78% with ATT and corticosteroids.
**Conclusion:** Clinical suspicion guided by combination of investigations provides accurate diagnosis. In diagnostic dilemmas, when investigations are inconclusive, PCR performed on ocular samples are reliable and confirmatory. We recommend a multidisciplinary approach in the management of tuberculosis in the active stage, during and after treatment.

**Keywords:** Posterior uveitis, Tuberculosis, Vitritis, anti-tuberculosis treatment, Vasculitis.

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## 1. Introduction

Tuberculosis (TB) is caused by the bacillus mycobacterium tuberculosis (MTB) and can affect all age groups causing extensive or localized infection.[1] It can occur secondary to pulmonary tuberculosis (PTB) or extra-pulmonary tuberculosis (EPTB). Tubercular uveitis (TU) is associated with significant visual loss and ocular morbidity, necessitating thorough systemic correlation and analysis. In a tertiary multispeciality hospital, various ocular manifestations such as granulomatous iridocyclitis, choroidal tubercles, and retinal vasculitis contribute to the complexity and severity of the condition. Effective management often requires a combination of anti-tubercular therapy (ATT) and immunomodulatory treatment to control inflammation and prevent relapses. Comprehensive evaluation and targeted treatment strategies are crucial for improving patient outcomes and preserving vision. Ocular morbidity and complications due to the chronic and recurrent nature of the disease requires immediate management to prevent visual loss which can occur during any stage of the illness.[2] Complete resolution of lesions, improvement in vision and rehabilitation are possible with early diagnosis and anti-tubercular therapy.

The incidence of TU varies between different populations. The clinical presentation can resemble other infectious, autoimmune or idiopathic uveitic entities. TU uveitis presents with a variety of ocular manifestations, including granulomatous iridocyclitis, iris/ciliary body granuloma, pars planitis, and panuveitis. Other possible

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conditions include serpiginous choroiditis, choroidal tubercles, subretinal abscess, scleritis, neuroretinitis, optic neuritis, retinitis, and retinal vasculitis. Miliary TB, a form of ETB, follows haematogenous spread with widespread lesions of greater severity due to the poor immunity in the patient.[3]

Investigations may not always be conclusive and results may be negative despite clinical resemblance to established lesions of TU. This may be due to low bacillary count or the presence of bacillus in the retinal pigment epithelium with no spill over into the blood or ocular fluids. The detection of DNA of MTB or the organism itself from ocular samples has been reported to be less than other organs. TU can be vision threatening and an early diagnosis is crucial for treatment.

This is a retrospective study, in a cohort of patients referred from the department of Infectious diseases with confirmed TB, to assess the spectrum of systemic TB associated with TU, the interplay of ocular ancillary and laboratory investigations and their effect on vision and prognosis. Determining the usefulness of polymerase chain reaction (PCR), nested (PCR) and real time PCR on aqueous humour samples was a novel approach. To our knowledge, no study so far has compared and assessed the role of ocular and systemic investigations and their effects on treatment or visual outcome in TU.

The uniqueness of this study is that the correlation of TB with ocular and systemic investigations has never been studied on the Indian population. Based on our data the inferences and highlights are as follows

1. Uveitis may be the initial manifestation of both active and latent TB
2. Complications of uveitis cause visual loss in pulmonary and extrapulmonary TB
3. Aqueous humour analysis by PCR is a reliable investigation in diagnostic dilemmas
4. Uveitis occurs in extrapulmonary TB (miliary, abdominal and bone tuberculosis)
5. Uveitis is more common in pulmonary than in extrapulmonary TB

## 2. Materials and Methods

This study was performed over a 2year period after obtaining approval from the Institutional Ethics Committee (IEC-NI/09/DEC/13/34) and informed consent from each patient.

### *2.1. Diagnostic criteria for reproducibility*

Patients were grouped based on the Standardised uveitis classification (SUN) classification. Group A consisted of patients who were suspected to have ocular TB based on clinical features such as granulomatous anterior uveitis, vitritis, chorioretinitis, retinal vasculitis or granuloma. Group B consisted of patients with at least one positive investigation such as tuberculin test, immunological (interferon gamma release assay) or radiological evidence and group C was patients with positive ocular investigations such as intraocular fluid analysis or histopathologic evidence. Criterion A was mandatory along with B or/and C.

A 2-step reduction in anterior chamber reaction/ vitritis from the first visit to 1 month after treatment, refinement of borders of chorioretinitis, resolution of macular oedema and increase of visual acuity were considered indicators of improvement.

The outcome was to be analysed based on variables such as severity of inflammation and response to treatment. Those who required ATT in isolation or in combination with corticosteroids and the utility of systemic and ocular investigations were compared.

### *2.2. Subjects*

Case records of 200 patients with history of TB were retrieved and analysed. Those with a minimum follow-up for 6 months were included in the study. Patients with uveitis due to other infections and autoimmune diseases were excluded from our study. Ophthalmic evaluation comprised of assessment of visual acuity, refraction, tonometry for checking intraocular pressure, slit lamp examination, direct and indirect ophthalmoscopy. Ancillary ophthalmic investigations performed were fundus photography, B scan ultrasonography,[4] fundus fluorescein angiography, optical coherence tomography and perimetry to assess visual fields. Laboratory tests such as total blood counts, Purified protein derivative test (Mantoux test), chest imaging by x-ray or high-resolution computed tomography (HRCT), polymerase chain reaction and quantiferon TB gold test were performed. During every follow-up visit, ophthalmic examination and physician review was performed and the response to treatment with details of improvement were recorded. This cohort study was performed in liason with the departments of general medicine and infectious diseases.

### *2.3. Ocular investigations*

Ancillary ophthalmic investigations were performed to delineate extent of the lesion and to assess the activity. Fundus fluorescein angiography (FFA) helped to identify staining, pooling and leakage of the dye based on hyper or hypofluorescent images.[5] Optical coherence tomography (OCT) provides for retinal image acquisition using non-invasive methods helps to identify anatomical abnormalities in the retina and the choroid.[6] B scan ultrasound was performed in opaque media to detect vitreous haemorrhage, tumours and retinal detachment. PCR analysis of the aqueous humour sample was performed on a subset of patients. Aqueous humour was obtained by anterior chamber (AC) paracentesis under topical anaesthesia.[7] RT PCR and nested PCR were performed on aqueous humour when diagnosis was inconclusive or in recalcitrant uveitis to identify MTB DNA.[8]

*2.4. Laboratory tests and systemic investigations*

Total blood counts, ESR, mantoux test, chest imaging, and interferon gamma release assay were performed on all patients.[9]

We considered decrease in anterior chamber/ vitreous inflammation, organizing of borders of the lesion and improvement in visual acuity as indicators of response to treatment.

In our study cohort, all patients were treated with a standard ATT regimen consisting isoniazid, ethambutol, pyrazinamide and rifampicin for 2 months during the acute stage and isoniazid and rifampicin for 6 months. Corticosteroids was administered after starting ATT to prevent inflammation related scarring.

*2.5. Statistical analysis*

Data from the results of examination, investigations, treatment and outcome were analysed. Pearson's chi-square test was used in the statistical analysis of categorical variables.

Analysis was done using Stata version 8.0: StataCorpLLC, College Station, TX. Inferences of P value of equal to or less than 0.05 was considered statistically significant.

## 3. Results

Case records of a cohort of 250 patients with a diagnosis of TB (pulmonary and extra pulmonary) were analysed retrospectively.

The incidence of uveitis in TB was seen in 78 of 200 patients (42%) and visual loss was the most common presentation (27%). Among this cohort, TU was due to active systemic TB in 12% and due to an immune response in 75% with statistical significance of p=0.02. The percentage of uveitis in PTB was 21% and ETB was 4% (**Table 1**). Uveitis was the initial manifestation of systemic TB in 12% of patients. In those with EPTB, miliary TB (12%) was most common followed by CNS, bone or abdominal TB.

Mean age of onset was 38 years (SD+/- 5) and the percentage of males and females affected was 62% and 38% respectively. TB uveitis was more commonly bilateral (75%). Anatomically, posterior uveitis was the most common; seen in 49 patients (77%) with p=0.01, followed by anterior uveitis 8 patients (11%), intermediate uveitis in 5 patients (8%) and panuveitis in 2 patients (5%).

In patients with anterior uveitis, bilateral granulomatous iridocyclitis with iris nodules and broad based posterior synechiae was the most frequent presentation. Complicated cataract occurred in 27% of these patients.

Among those with PU the clinical signs were active multifocal choroiditis in 45%, vasculitis in 26%, choroidal tuberculoma in 3% and subretinal abscess in 3% (**Figure 1**), (**Table 2**).

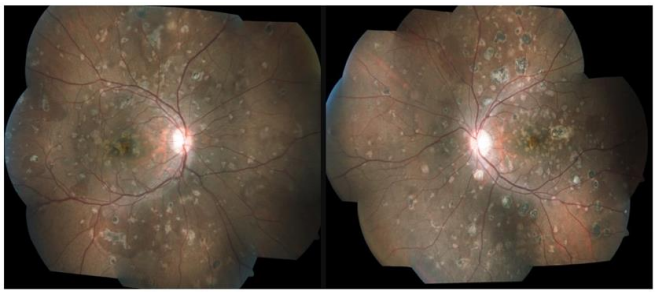
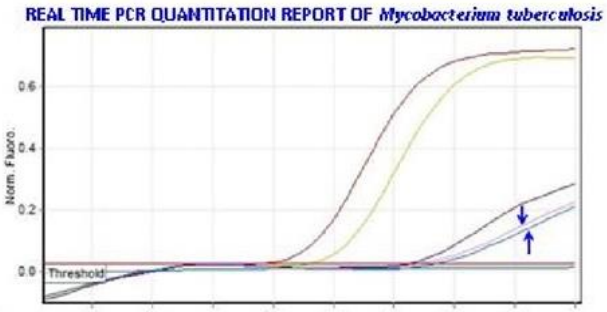


**Figure 1:** Both eyes showing extensive tubercular multifocal choroiditis

Severe visual loss was due to complicated cataract, band shaped keratopathy, cystoid macular edema (CME), secondary glaucoma, choroidal neovascular membranes and macular scarring. Blindness was due to reversible causes in 72%.

Chest x-ray showed lung infiltrates, hilar lymphadenopathy and calcification in 15% of patients. Mantoux test reaction was seen as induration which was strongly positive in 12% and weakly positive in 60%. Blood results showed positive PCR in 37% and aqueous humour analysis revealed positive PCR in 71%, nested PCR in 83% and RTPCR in 96% (**Figure 2**) of patients. QFT-G was positive in 54%, collectively, systemic investigations such as chest x-ray, Mantoux test and those performed on blood samples such as PCR and QFT were positive in 72% of patients. In inconclusive patients, nested PCR and/or RT-PCR were done on aqueous humour samples and were diagnostic in 21%.




| Colour | Name | Type | Ct | Given Conc (copies/ml) | Calc Conc (copies/ml) | % Var |
|---|---|---|---|---|---|---|
| | S1 | Standard | 19.06 | 25,000,000 | 24,970,236 | 0.1% |
| | S2 | Standard | 23.13 | 2,500,000 | 2,504,471 | 0.2% |
| | S4 | Standard | 31.29 | 25,000 | 24,985 | 0.1% |
| | VRF 1406/13 10 | Unknown | 32.22 | | 14,781 | |
| | VRF 1406/13 15 | Unknown | 33.46 | | 7,364 | |
| | NC | NTC | | | | |

**Figure 2:** Positive real time- PCR in aqueous sample of the patient

Improvement was seen in 3 months in 12% and 6 months in 87%. ATT was the only mode of treatment in 81% and ATT along with corticosteroids in 19%. Resolution was achieved with topical corticosteroids in anterior uveitis and subtenon injections in intermediate uveitis. Improvement in vision and complete resolution occurred in 78% and worsening was seen in 12%.

**Table 1:** Type of systemic tuberculosis in TB uveitis

| Spectrum of Tubercular Uveitis | Number of patients |
|---|---|
| Pulmonary Tuberculosis | 21% |
| Extrapulmonary Tuberculosis | 4% |
| Miliary Tuberculosis | 12% |
| Tuberculosis of Bone | 2% |
| Abdominal Tuberculosis | 2% |
| Cervical Node Tuberculosis | 1% |
| Tuberculosis of Spine | 1% |
| Tuberculosis of pleura | 1% |
| Breast Abscess | 1% |

**Table 1** highlights that while pulmonary TB is the most common systemic form associated with tubercular uveitis, other extrapulmonary manifestations, including disseminated and localized forms, can also lead to eye involvement, albeit at much lower rates.

**Table 2** illustrates that tubercular uveitis predominantly presents as multifocal choroiditis and vasculitis, affecting the posterior segment of the eye. Other types like acute anterior uveitis, intermediate uveitis, subretinal abscess, choroidal tuberculoma, and panuveitis are less common, highlighting a variety of ocular manifestations with differing severities and areas of involvement.

**Table 2:** Distribution and pattern of the types of uveitis

| Type of Uveitis | Number of patients in % |
|---|---|
| Multifocal choroiditis | 45% |
| Vasculitis | 26% |
| Acute anterior uveitis | 8% |
| Subretinal Abscess | 3% |
| Intermediate uveitis and vitritis | 8% |
| Choroidal tuberculoma | 3% |
| Panuveitis | 2% |

**Table 3:** Predictive values for each test in isolation

| | HRCT | QFTG | PCR | RT PCR |
|---|---|---|---|---|
| Sensitivity | 94% | 89% | 91% | 97% |
| Specificity | 86% | 83% | 71% | 99% |
| Positive predictive value | 91% | 86% | 81% | 99% |
| Negative predictive value | 71% | 23% | 69% | 21% |

**Table 3** shows that RT PCR is the most sensitive and specific test with the highest PPV, making it an excellent confirmatory test for TB. HRCT has a strong balance of sensitivity, specificity, and PPV, making it a reliable diagnostic tool. PCR performs well but has lower specificity, and QFTG has a reasonable balance but notably low NPV, indicating limitations in ruling out TB based on a negative result.

**Table 4:** Disease characteristics based on Mantoux test

| Disease | Findings | Mantoux test less than 10mm | Mantoux test more than 10mm | Mantoux test more than 15 mm | p value |
|---|---|---|---|---|---|
| Eye involved | Unilateral | 11 | 4 | 3 | 0.243 |
| | Bilateral | 9 | 6 | 7 | |
| Involvement of macula | Yes | 8 | 6 | 8 | 0.471 |
| | No | 12 | 8 | 2 | |
| Favourable structural/ anatomical outcome | Yes | 25 | 5 | 1 | 0.544 |
| | No | 15 | 12 | 5 | |
| Favourable functional outcome | Yes | 11 | 10 | 0 | 0.239 |
| | No | 4 | 4 | 9 | |

**Table 4** displays disease characteristics in patients based on Mantoux test results. The Mantoux test measures the immune response to TB antigens, and its results are categorized by induration size: less than 10mm, more than 10mm, and more than 15mm. The table also shows the distribution of these results in relation to eye involvement, macular involvement, structural/anatomical outcomes, and functional outcomes, along with associated p-values.

## 4. Discussion

This study aims to identify the various clinical manifestations of TU and the cause of visual loss in these patients. TU can occur due to invasion by active bacilli or due to hypersensitivity as an immune response to tubercular antigens. Latent TB refers to an exposure to the bacillus that has occurred without resulting in a clinically active disease.[10]

The modalities used for investigations, therapy and their prognosis have been described in association with systemic TB.[11] In our study, latent type was a more frequent cause of uveitis than the active type which is consistent with recent reports.[12] Uveitis has been described as an isolated presenting feature in extra pulmonary TB.[13]

Among our patients, the most common association was miliary tuberculosis followed by abdominal and bone tuberculosis all of whom presented with systemic and ocular features. Multifocal distribution of choroidal lesions with retinal vasculitis was the most frequent presentation in our patients. Scleritis and scleral abscess was probably due to an immune reaction. The most common complications were CME, CNVM and were associated with good prognosis in the early stages. Patients in the third and fourth decades of life had better response to ATT and those in the sixth decade had quicker onset of complications. Based on our study, ocular ancillary and systemic investigations when performed in combination provided most information. In active infection the bacillus may be detected by culture while PCR detects the DNA of MTB. The purified protein derivative test has an unreliable predictive value and the test result is dependent on the amount of exposure to MTB bacilli, the immunity of the patient and previous vaccination with BCG.[14] A positive result means that an infection with MTB has occurred but a clinically apparent disease may not be present.

X-ray was positive in only few patients with ocular TB but in those with a negative X-ray, HRCT still detected signs that could not be visualised otherwise. The importance of ocular investigations has been described in several studies on the subject.[15] High resolution CT of the chest helps to detect features such as lymphadenopathy, pulmonary infiltrates, cavitation, consolidation and pleural effusion during primary active and healed stages.

Positive serology with PCR on aqueous humour sample detected TB in few patients when all other tests were negative. PCR is useful to diagnose infectious causes of uveitis by amplification of small samples of DNA with fewer false positive results when performed on intraocular sample, the sensitivity, specificity, positive predictive value and negative predictive value of PCR analysis was 90.2%, 93.9%, 93.9% and 90.2% respectively.[16] RT-PCR provides quantitative analysis of MTB genome.[17] Treatment with ATT is recommended based on RT-PCR and nested PCR which target specific genes such as MPB64 and IS6110 primers in the detection of MTB.[18]

Treatment has to address both the tubercular infection and the inflammation. In our study cohort, 73% improved, 12 maintained and 7 worsened after therapy with ATT and corticosteroids. We did not see recurrences in our patients. Rao et al have reported that MTB bacilli reside in retinal pigment epithelial cells and thus reactivation and recurrences can occur several years later.[19]

In inconclusive scenarios where clinical suspicions remain high, we recommend the use of aqueous humour analysis for the precise identification of the TB antigen.

Ocular inflammation and uveitis can be the first presentation of both PTB and ETB. Patients with choroidal involvement and associated vitreous haze have a higher risk of treatment failure. The severity of TU is proportional to the bacterial load, virulence of the microbe and the immune status of the host. Ophthalmic involvement in TB indicates extrapulmonary infection. Pulmonary TB is thought to occur in 80% of patients while it is extrapulmonary in the remaining 20% and in these patients the eye is an important area that is affected.[20] The visual prognosis is good and incidence of treatment failure rate is low in patients with TB uveitis who were treated with ATT in early stages of the disease.[21]

The likelihood of detection of an underlying tubercular etiology increases with a combination of laboratory and ocular ancillary investigations both from ocular and blood samples.

An infectious etiology is more common in posterior uveitis and it may be the first sign of an underlying systemic infection which has not evolved completely. Hence a liaison is essential between the ophthalmologist and infectious disease specialist. We recommend that an ophthalmic screening should be made a part of routine work up when TB is suspected or confirmed. A 9–12-month course of ATT is associated with total resolution and good prognosis in patients with tubercular uveitis. Limitation of this study is that it contains data from a single hospital.

## 5. Conclusion

Ophthalmic evaluation should be incorporated as a practice during treatment of TB. We recommend a multidisciplinary team approach which involves a physician, infectious diseases specialist, pulmonologist and an ophthalmologist for the work up in both pulmonary and extrapulmonary TB.

The authors declare that they have no conflict of interest to share.

## 6. Source of Funding

None.

## 7. Conflict of Interest

None.

## 8. Ethical

Ethical Committee No.: IEC-NI/09/DEC/13/34.

## 9. Highlights

1. Tubercular uveitis can occur due to both active or latent TB.
2. Uveitis in TB can be due to a hypersensitivity to the DNA of mycobacterium tuberculosis.
3. Choroidal and vitreous involvement have the highest risk of treatment failure.
4. PCR on ocular fluids is conclusive when other systemic investigations are negative.
5. Aqueous humour analysis by RTPCR and nested PCR can determine tubercular etiology.

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