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CASE REPORT

# Ophthalmic Presentation of Disseminated Tuberculosis with Relapse-Immunological Profile

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**Abstract** TB as the cause of uveitis varies from 0.5 to 10.5%; low sensitivity of confirmatory laboratory investigations and inconsistency of diagnostic criteria leads to paucity of data. Diagnosis requires a high level of suspicion and is often presumptive based on indirect evidences. Interferon gamma, Interleukin-2 and Neopterin are key biomarkers in immuno-regulation of *Mycobacterium tuberculosis* infection. The relative shift from Interleukin-2 towards Interferon gamma (Interferon gamma/Interleukin-2) is more discriminatory for active tuberculosis. Protein carbonyl and Malondialdehyde, as oxidative stress markers, characterize active tuberculosis. A case of disseminated TB presenting with acute uveitis had a recurrent tubercular lymphadenitis after completing category I treatment under revised national tuberculosis control programme. The present study evaluates the potential utility of above mentioned biomarkers to predict atypical presentation in difficult cases of tuberculosis. Though tuberculous uveitis is amenable to treatment in early course of disease, the delay in diagnosis can have serious consequences for the patient.

**Keywords** Tuberculous uveitis · Disseminated tuberculosis · Biomarkers

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## Introduction

Tuberculosis (TB) remains a health problem of concern in most developing countries of the world. TB is one of the commonest systemic infections associated with uveitis and uveitis is the commonest presentation of ocular TB [1]. According to published literature; ocular involvement during TB varies from 1.4 to 16% in TB endemic population and 18% in culture-proven TB whereas uveitis due to TB ranges from 10.5% in an endemic area to 6–7% in countries with a low endemic index of TB [1, 2].

Paucibacillary forms of infection resulting into low yield of bacilli from ocular fluid and non specific ocular presentation make the diagnosis of tuberculous uveitis difficult. Besides the low positivity of conventional diagnostic methods in such cases, the yield of Mycobacterial DNA from ocular fluid has been shown to be low [3]. The probability of an immune associated ocular inflammation rather than an active infection in cases of uveitis associated with TB could explain the difficulty in bacteriological diagnosis [4]. Strong clinical suspicion along with a planned protocol with a multidisciplinary approach involving an ophthalmologist and a microbiologist is often required to diagnose these cases and initiate treatment with antitubercular drugs in addition to immunosuppressive agents [3]. Various key immune-regulatory cytokines like Interferon (IFN-γ) and Interleukin IL-2), Neopterin as a macrophage activation marker or other oxidative stress markers like protein carbonyl and malondialdehyde are suggested to be discriminatory for active TB disease and could aid in the diagnosis of TB in difficult cases. We report here a case of disseminated TB presenting with acute uveitis which recurred with tubercular lymphadenitis after complete antituberculosis treatment (ATT) category I treatment under revised national tuberculosis control programme (RNTCP).

## Case Report

A 27 years old housewife, married and mother of two kids, presented at the Ophthalmology OPD with the chief complaint of reduced vision with redness in right eye for 3 weeks. She had no history of diabetes mellitus or hypertension. She had not received BCG vaccination at birth. Her sister-in-law, a diagnosed case of TB, was a frequent visitor to her home. The patient gave no history of TB in childhood or contact with any other known case of TB. There was no history of prolonged medication for any ailment in the past.

On examination, the patient could perceive hand movement close to face in right eye. Right eye showed the presence of synechia with seclusion pupillae, keratic precipitates, an old hypopyon and posterior subcapsular cataract (Fig. 1). Patient was subjected to routine investigations including random blood sugar, complete blood counts with erythrocyte sedimentation rate (ESR) level determination, Monteux test, chest X-ray and rheumatoid arthritis (RA) factor status evaluation. Random blood sugar was in normal range. Haemoglobin level was below normal reference range for age and gender of patient. Neutrophils were marginally raised with low lymphocytes and high eosinophil count. ESR was elevated. A positive Monteux test was reported with an induration of more than 10 mm. Right lung showed patchy infiltration in upper zone suggestive of pulmonary tuberculosis on chest X-ray. RA factor was negative. Patient was referred to a physician for further management of pulmonary Koch's. ATT was started for category I treatment under the RNTCP. Meanwhile, steroids, NSAIDS, selective $\alpha_2$ receptor agonist, atropine were advised for the management of acute uveitis. On follow up visits patient reported an improvement in vision with treatment. Chest X-ray at the completion of 6 months of ATT suggested clearance of pathology, though ESR and haemoglobin persisted in the out of normal range. She was declared cured after the successful completion of 6 months of ATT.

Six months later, patient presented to her treating physician with a painless swelling in left upper cervical region. She also observed similar ocular symptoms that she had experienced in past. She reported blurring of vision, photophobia and redness in right eye. Fine needle aspiration cytology (FNAC) was advised for enlarged lymph node. FNAC revealed a tubercular abscess with the presence of granulomas, necrosis and acid fast bacilli. Lymph node aspirate was also subjected to Ziehl–Neelsen (ZN) staining and culture on Löwenstein–Jensen (LJ) medium for isolation of *Mycobacterium tuberculosis*, both of which were positive. The immunological profile of the patient was assessed. Serum levels of IFN-γ, Neopterin, Protein carbonyl and Malondialdehyde were raised and, along with a ratio of IFN- γ and IL-2, were above the best cut-off values obtained by receiver-operating-characteristic curve (ROC) analysis for serum levels of individual biomarker among the clinically diagnosed cases of extrapulmonary tuberculosis and age and sex matched healthy controls (Table 1 and Fig. 2). She was referred to directly observed treatment, short-course (DOTS) centre and integrated counselling and testing centre (ICTC). She tested non reactive for HIV. She was classified as a recurrent case of extrapulmonary tuberculosis and ATT was started under category II treatment under RNTCP. She gave a history of strict compliance with treatment throughout the period. Her cervical lymph node swelling subsided within few weeks of starting the treatment. Her ocular symptoms also improved with the medications prescribed for acute uveitis and simultaneous ATT. As of now, she has been declared cured of TB, but has been told to stay cautious for any worsening

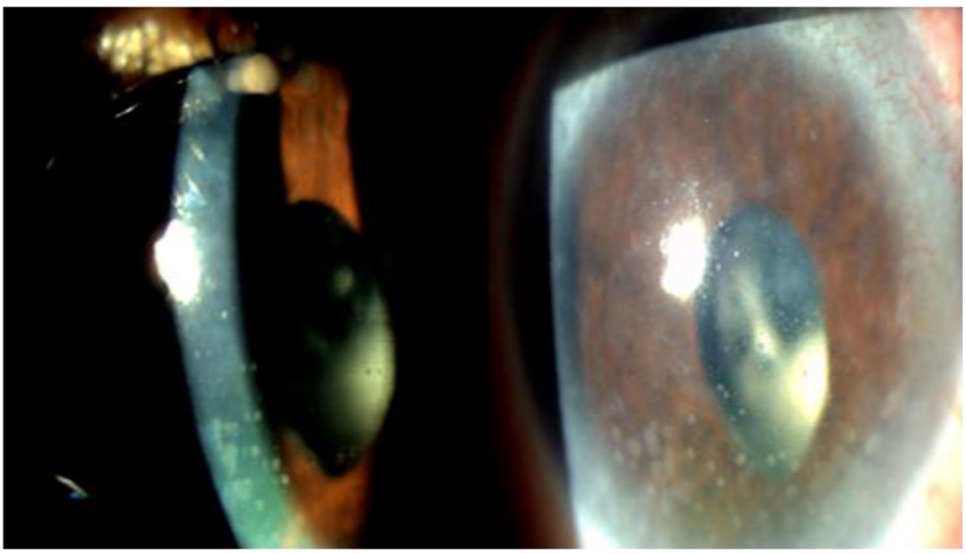

**Fig. 1** Keratic precipitates: anterior uveitis

**Table 1** Comparison of immunological biomarkers in the case under study with EPTB cases and healthy controls

| Biomarker | Serum levels in case | Median serum levels among EPTB cases | Median serum levels among healthy controls | *p* value |
|---|---|---|---|---|
| IFN-γ (pg/ml) | 24.17 | 24.98 (9.96–226.87) | 3.93 (0.31–14.73) | < 0.001 |
| IL-2 (pg/ml) | 10.93 | 8.34 (3.64–14.51) | 7.86 (2.87–18.04) | 0.93 |
| IFN-γ/IL-2 | 2.21 | 3.22 (2.07–56.12) | 0.52 (0.05–1.54) | < 0.001 |
| Neopterin (nmol/L) | 8.1 | 21.6 (4.2–111.0) | 4.20 (0.7–16.8) | < 0.001 |
| MDA (nmol/ml) | 5.05 | 7.31 (1.32–22.82) | 2.20 (0.78–5.78) | < 0.001 |
| Protein carbonyl assay (pg/ml) | 548.7 | 660.6 (325.2–1502.8) | 298.1 (208–526.8) | < 0.001 |

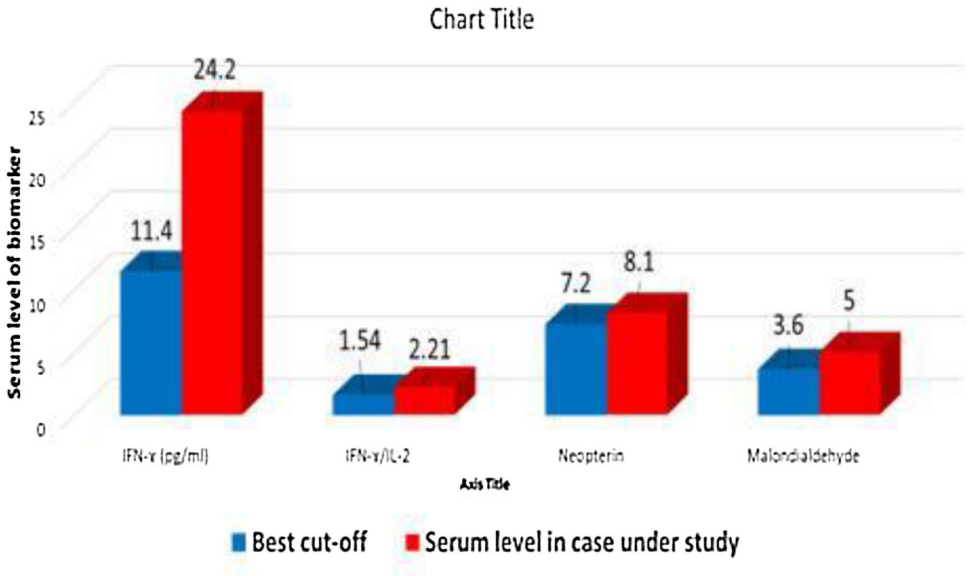


**Fig. 2** Comparison of immunological biomarkers in case under study with ROC curve analysis for extrapulmonary tuberculosis cases

of ocular symptoms and immediately seek medical help without any delay. Her vision in right eye persists to be below normal.

## Discussion

Ocular form of extrapulmonary TB is important and can sometimes be the presenting feature [1]. Several researchers have been attempting to identify predictive or correlating factors for diagnosis but have failed; predominantly due to the protean clinical presentation, lower numbers of patients, variable durations of follow up done in such cases and lack of any gold standard diagnostic test. Since conventional bacteriological methods of diagnosis are almost negative in such cases, our report highlights importance of prompt clinical suspicion and justifies need for a standardized diagnostic workup along with details of possible TB contact and concomitant screening tests for diagnosis of other forms of TB.

Besides lack of standardization of diagnostic protocol, decision to initiate ATT too lacks uniformity varying due to personal preference or professional experience of the treating physician. A study found history of contact, latent TB, systemic TB, and abnormal chest X ray findings to be associated with a diagnosis of tuberculous uveitis, whereas ESR, C-reactive protein (CRP), and ocular findings were not predictive for the same [2]. Same study also reported 70% patients reporting improvement in ocular finding with initiation of ATT and that there was considerably more improvement with a combined treatment of steroid and ATT as compared to ATT alone. Our case too responded to a combined treatment of ATT and steroids both at the time of initial infection as well as during relapse [2]. In a recent Indian case series of tubercular uveitis with ocular manifestation as first presentation 100% of patients were positive for Mantoux test and 73% of them had induration between 11 and 15 mm similar to ours [5]. A negative Quantiferon Gold test has been reported to be used as an adjunct before initiation of steroids in uveitic patients

particularly in an endemic country like India [1]. A recurrence of 6.66% as been reported in uveitis and was later treated with Category 2 of ATT after being completely treated with Category 1 of ATT as seen in our case [5].

A high clinical suspicion index along with time-honored and judicious use of lab tests is crucial to prevent ocular morbidity in cases of tubercular uveitis especially in an endemic country and BCG-vaccinated population. An innocuous ocular manifestation may sometimes be an early indication of hematogenous dissemination of tuberculosis and thus guide the treating physician to make a diagnosis of systemic TB [6]. Though ocular manifestation in tuberculosis is less common than systemic complications, these are well recognized. A case of rapid relapse of chorioretinitis while on ATT leading to blindness and loss of one eye has been reported from same area as ours [7]. Another recent literature from India reports bilateral squint with iritis, corneal opacity, festooned pupil with posterior synechiae and cataract in a disseminated case of ocular TB similar to ours [8]. The possibility of intraocular inflammation following *M. tuberculosis* infection in our patient is further strengthened by raised serum levels above the best cut-off values of IFN-γ, Neopterin, Protein carbonyl and Malondialdehyde. Biomarkers in the aqueous humor could be a potential alternative for diagnosing a condition that may otherwise be thought to be idiopathic in uveitis [4]. Several cytokine profiles have been reportedly associated with uveitis of specific etiologies [9]. Due to the difficulty in achieving microbiological evidence, usually a good response to treatment or supportive evidences as mentioned above may help in a provisional diagnosis.

Ocular TB is one of the complex but well recognized extra pulmonary form with diverse ocular manifestations often without signs of any systemic illness. Our case highlights the fact that whereas ocular examination should be a routine in suspected or proven TB, TB should be a differential diagnosis in all cases of uveitis. Treating Ophthalmologists need to be more aware and familiar with the disease pattern and lines of anti tubercular treatment as they are more likely to encounter drug resistant forms of TB.

**Compliance with ethical standards**

**Conflict of interest** None

## References


1. Sudharshan S, Ganesh SK, Balu G, Mahalakshmi B, Therese LK, Madhavan HN, et al. Utility of QuantiFERON®-TB Gold test in diagnosis and management of suspected tubercular uveitis in India. Int Ophthalmol. 2012;32(3):217–23.
2. Vos AG, Wassenberg MW, de Hoog J, Oosterheert JJ. Diagnosis and treatment of tuberculous uveitis in a low endemic setting. Int J Infect Dis. 2013;17(11):e993–9.
3. Yeh S, Sen HN, Colyer M, Zapor M, Wroblewski K. Update on ocular tuberculosis. Curr Opin Ophthalmol. 2012;23:551–6.
4. Ang M, Cheung G, Vania M, Chen J, Yang H, Li J, et al. Aqueous cytokine and chemokine analysis in uveitis associated with tuberculosis. Mol Vis. 2012;18:565–73.
5. Shah JS, Shetty N, Shah SKD, Shah NKS. Tubercular uveitis with ocular manifestation as the first presentation of tuberculosis: a case series. J Clin Diagn Res. 2016;10(3):NR01–3.
6. Alami S, El Merrouni M, Oudbib E, Abdellah A, Berraho F. Systemic tuberculosis revealed by ophthalmic manifestations. J Med Surg Res. 2015;2(2):161–2. Available at: http://revues.imist.ma/index.php?journal=JMSR&page=article&op=view&path%5B%5D=3298. Accessed 18 Dec 2017.
7. Agarwal M, Jha V, Biswas J. Rapidly blinding posterior tubercular uveitis. J Ophthalmic Inflammation Infect. 2014;4:13.
8. Islam Md F, Mukherjee D, Kundu R, Niyogi PC, Das J. A case of disseminated tuberculosis with ocular involvement. Nitte J Univ Health Sci. 2015; 5(1): ISSN 2249-7110.
9. Curnow SJ, Falciani F, Durrani OM, Cheung CM, Ross EJ, Wloka K, et al. Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. Invest Ophthalmol Vis Sci. 2005;46:4251–9.