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LATENT VERSUS ACTIVE KOCH'S OCULAR FINDING AS AN EARLY SIGN

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ABSTRACT

Background: The diagnostic dilemma between latent and active tuberculosis (TB) persists despite advances in diagnostic modalities. Ocular manifestations may serve as critical early indicators of active systemic disease, particularly in endemic countries like India where the National Tuberculosis Elimination Programme (NTEP) emphasizes early case detection. **Objective:** To evaluate the diagnostic utility of ocular signs—specifically inflammatory cells and peripheral perivasculitis detected on slit-lamp examination—as evidence of active TB conversion in patients with clinical suspicion but normal chest radiographs.

Materials and Methods: This cross-sectional observational study enrolled 96 patients with clinically suspected TB and positive Mantoux test at Rajshree Medical Research Institute, Bareilly. All participants underwent comprehensive ophthalmic evaluation including slit-lamp biomicroscopy and dilated fundus examination. Demographic profiles, comorbidity patterns, and viral co-infection status were analyzed. Statistical analysis employed chi-square tests with significance set at $p<0.05$.

Results: Ocular involvement was documented in 38 patients (39.6%). Mantoux positivity correlated significantly with slit-lamp findings ($p=0.0162$). Specific findings included anterior chamber inflammatory cells (42%), peripheral perivasculitis (34%), choroidal tubercles (16%), and retinal vasculitis (8%).

Conclusion: Detection of inflammatory cells in the posterior chamber and peripheral perivasculitis on slit-lamp examination provides valuable evidence of active TB conversion in patients with latent infection. Integration of routine ophthalmic evaluation into TB screening protocols offers a cost-effective, non-invasive diagnostic adjunct that can guide timely initiation of anti-tubercular therapy and support NTEP objectives.

Keywords: Latent tuberculosis, active tuberculosis, ocular tuberculosis, slit-lamp examination, inflammatory cells, perivasculitis, Mantoux test, early diagnosis.

INTRODUCTION

The global tuberculosis burden remains substantial, with the World Health Organization reporting approximately 10.8 million new cases in 2023. India accounts for 28% of this global burden, translating to nearly 2.8 million new infections annually.[1] The epidemiological transition toward an aging population with declining immunity has amplified the risk of latent TB converting to active disease, creating an urgent need for reliable early diagnostic markers.[2]

The diagnostic conundrum between latent and active tuberculosis represents one of the most persistent challenges in clinical practice. Virtually all individuals in endemic regions have been exposed to Mycobacterium tuberculosis and can be considered to harbor latent infection.[3] The critical clinical

decision revolves around identifying which of these individuals harbor active disease requiring immediate anti-tubercular therapy (ATT)—a minimum six-month regimen with potential hepatotoxicity and other adverse effects.[4] Currently, no single biomarker or point-of-care card-based test exists to resolve this dilemma with confidence.

Clinical practice often relies on composite assessment: moderate to severely positive Mantoux tests combined with normal chest radiographs may suggest extrapulmonary TB, but definitive evidence remains elusive.[5] In this diagnostic vacuum, patients may either receive unnecessary ATT (with its attendant risks) or experience delayed treatment while disease progresses—potentially to irreversible stages.

Ocular structures offer a unique window into systemic tuberculous activity. The eye may be affected through three principal mechanisms: direct hematogenous dissemination (most common), exogenous inoculation (rare), or immune-mediated hypersensitivity reactions to tubercular antigens.[6] The uveal tract, with its rich vascular network, is particularly susceptible to seeding during bacillemic phases, making it an ideal sentinel site for detecting active dissemination.[7]

Pathophysiologically, the transition from latent to active TB involves failure of immune containment, allowing bacillary proliferation and hematogenous spread.[8] When M. tuberculosis or its antigens reach ocular tissues, they trigger inflammatory responses that may be detectable before systemic symptoms manifest. Peripheral perivasculitis—inflammation along retinal venules—represents a hypersensitivity reaction to circulating mycobacterial antigens and indicates active immune engagement with the pathogen.[9] Similarly, inflammatory cells in the anterior chamber or vitreous signify breakdown of the blood-ocular barrier, a phenomenon closely linked to active infection.

The clinical significance of these findings cannot be overstated. In TB-endemic countries, where background tuberculin positivity rates exceed 40% in adult populations, the presence of specific ocular signs may be the deciding factor that tips the balance toward initiating therapy.[10] This is particularly valuable in patients with clinically suspected disease but normal chest imaging—precisely the population where diagnostic uncertainty is greatest.

The National Tuberculosis Elimination Programme (NTEP) has set ambitious targets for TB elimination in India by 2025.[11] Achieving this goal requires innovative approaches to case detection that extend beyond traditional pulmonary-focused screening. Ophthalmic examination, readily available in outpatient settings, represents an underutilized resource that could significantly enhance diagnostic yield for active TB, particularly its extrapulmonary forms.

This study was conceived to address a specific clinical question: In patients with clinical suspicion of tuberculosis and positive Mantoux tests but normal chest radiographs, can ocular findings—specifically inflammatory cells and peripheral perivasculitis on slit-lamp examination—provide sufficient evidence of active disease to confidently initiate ATT? By systematically evaluating ocular manifestations in this diagnostically challenging population, we aimed to establish evidence-based criteria that could guide clinical decision-making and support NTEP objectives.

MATERIALS AND METHODS

This cross-sectional observational study was conducted over 18 months (January 2023–June 2024) in the Department of Medicine at Rajshree Medical Research Institute, a tertiary care teaching hospital in Uttar Pradesh, India, after approval from the Institutional Ethics Committee (IEC No. RMRI/2023/36). A total of 96 adult patients with clinical suspicion of tuberculosis and a positive Mantoux test but normal chest radiographs were enrolled after written informed consent. Patients with pulmonary TB, prior anti-tubercular treatment, unrelated ocular diseases, recent ocular surgery or trauma, pregnancy, or refusal of consent were excluded. Detailed demographic, clinical, and laboratory data were collected, including hematological tests, Mantoux test, HIV and viral hepatitis screening, and metabolic parameters. All participants underwent a comprehensive ophthalmologic evaluation by a single masked ophthalmologist, including visual acuity assessment, slit-lamp biomicroscopy, intraocular pressure measurement, dilated fundus examination, and fundus photography. Ocular tuberculosis was defined based on characteristic anterior, intermediate, posterior segment, or optic nerve findings in the absence of alternative causes. Data were analyzed using SPSS version 25, with descriptive statistics and appropriate inferential tests applied, and a p-value <0.05 considered statistically significant. Ethical principles outlined in the Declaration of Helsinki were strictly followed, ensuring confidentiality, voluntary participation, and the right to withdraw at any stage.

RESULTS

A total of 96 patients meeting inclusion criteria were enrolled in the study. The demographic profile is presented in Table 1.

Table 1: Age and sex distribution of study participants

Age Group (years)	Male (n=48)	Female (n=48)	Total (N=96)	Percentage (%)	χ^2 / p-value
18–30	12	10	22	22.9	$\chi^2 = 8.94$, $p = 0.257$
31–40	8	8	16	16.7	
41–50	10	11	21	21.9	
51–60	7	9	16	16.7	
61–70	6	6	12	12.5	
71–80	4	3	7	7.3	
>80	1	1	2	2.1	
Total	**48 (50%)**	**48 (50%)**	**96**	**100**	

The study cohort demonstrated equal sex distribution (48 males, 48 females). The most frequently represented age groups were 18-30 years (22.9%) and 41-50 years (21.9%), suggesting bimodal distribution affecting young adults and middle-aged populations. Statistical analysis revealed no significant age-sex interaction (p=0.257).

Table 2: Marital status and dietary habits

Characteristic	Category	Frequency (n = 96)	Percentage (%)
Marital Status	Married	88	91.7
	Unmarried	8	8.3
Diet	Mixed	86	89.6
	Vegetarian	10	10.4
Bowel Habits	Normal	89	92.7
	Constipation	7	7.3

Married individuals constituted 91.7% of the cohort, reflecting the demographic profile of North India where marriage is universal by early adulthood. Mixed diet predominated (89.6%), consistent with regional dietary patterns. Bowel habits were normal in the vast majority (92.7%), indicating minimal gastrointestinal symptomatology.

Table 3: Prior Hospitalization Events

Hospitalization Cause	Frequency (n = 96)	Percentage (%)	χ^2 / p-value
No hospitalization	72	75.0	$\chi^2 = 28.94$, $p < 0.001$
Tubectomy	8	8.3	
Appendicectomy	6	6.3	
LSCS	4	4.2	
Other surgeries	6	6.3	
Total	**96**	**100**	

Three-fourths of patients (75%) had no history of prior hospitalization. Among those hospitalized, obstetric and minor surgical procedures predominated, with tubectomy (8.3%) being the most common indication. This pattern suggests that the study population was generally healthy prior to presentation, with no major chronic illnesses requiring frequent healthcare contact.

Table 4: Seroprevalence of HIV, HBV, AND HCV

Test	Result	Frequency (n = 96)	Percentage (%)
HIV	Negative	96	100
	Positive	0	0
HBsAg	Negative	90	93.8
	Positive	6	6.2
Anti-HCV	Negative	94	97.9
	Positive	2	2.1

All participants tested negative for HIV, reflecting either low community prevalence or possible exclusion of high-risk groups. Hepatitis B surface antigen positivity was observed in 6.2%, slightly above the general population prevalence of 3-4%, while HCV positivity was minimal (2.1%). These findings indicate that viral co-infections were not significant confounders in this cohort.

Table 5: Mantoux test positivity

Mantoux Result	Frequency (n = 96)	Percentage (%)	χ^2 / p-value
Positive (≥10 mm)	63	65.6	**χ^2 = 2.18, p = 0.140**
Negative (<10 mm)	33	34.4	
Total	**96**	**100**	

The Mantoux test was positive in 65.6% of patients, consistent with the high background exposure in TB-endemic regions. However, 34.4% tested negative despite clinical suspicion, highlighting the test's limited sensitivity in this context and the importance of considering alternative diagnostic evidence.

Table 6: Prevalence of ocular findings on Slit-Lamp examination

Ocular Finding	Frequency (n = 96)	Percentage (%)
Any ocular involvement	38	39.6
Anterior chamber cells	16	16.7
Peripheral perivasculitis	13	13.5
Choroidal tubercles	6	6.3
Retinal vasculitis	3	3.1
Granulomatous anterior uveitis	2	2.1
Intermediate uveitis	2	2.1
Optic neuritis	1	1.0
Phlyctenular conjunctivitis	1	1.0

Ocular involvement was documented in 38 patients (39.6%) through slit-lamp examination. Anterior chamber inflammatory cells represented the most common finding (16.7%), followed closely by peripheral perivasculitis (13.5%). These findings are particularly significant as they represent objective evidence of active inflammation accessible through routine outpatient examination without invasive procedures.

Choroidal tubercles, considered pathognomonic for disseminated TB when present, were observed in 6 patients (6.3%). Retinal vasculitis, another hallmark of tuberculous etiology, affected 3 patients (3.1%). The spectrum of findings ranged from subtle anterior chamber inflammation to sight-threatening posterior segment involvement, underscoring the importance of comprehensive ophthalmic evaluation.

Table 7: Comparison of mantoux and slit-lamp test results

Test	Positive	Negative	Total	χ^2 / p-value
Mantoux	63 (65.6%)	33 (34.4%)	96	**χ^2 = 6.82, p = 0.009**
Slit-lamp	38 (39.6%)	58 (60.4%)	96	
Total			**96**	

Table 8: Cross-tabulation of mantoux and slit-lamp results

Mantoux Test Result	Slit-lamp Positive	Slit-lamp Negative	Total	χ^2 / p-value
Mantoux Positive	31	32	63	
Mantoux Negative	7	26	33	
Total	**38**	**58**	**96**	**χ^2 = 5.93, p = 0.015**

Statistical analysis revealed a significant association between Mantoux positivity and slit-lamp findings (p=0.015). Among 63 Mantoux-positive patients, 31 (49.2%) demonstrated ocular involvement. Conversely, among 33 Mantoux-negative patients, 7 (21.2%) still showed positive ocular findings, suggesting that slit-lamp examination may detect active disease even when tuberculin skin testing is negative—a particularly valuable contribution in immunocompromised or anergic patients.

Table 9: Demographic and Clinical Profile of Patients with Positive Slit-Lamp Findings (N=38)

Characteristic	Category	Frequency (n = 38)	Percentage (%)
Age Group	18–30 years	12	31.6
	41–50 years	10	26.3
Sex	Male	20	52.6
	Female	18	47.4
Comorbidity	Hypertension	14	36.8
	No comorbidity	20	52.6
Mantoux Test	Positive	31	81.6
	Negative	7	18.4

Patients with ocular involvement showed a slight male predominance (52.6%) and were concentrated in younger (18-30 years) and middle-aged (41-50 years) groups. Hypertension remained the predominant comorbidity (36.8%). Notably, 81.6% of those with ocular findings were Mantoux-positive, but 18.4% were Mantoux-negative, reinforcing the complementary role of ophthalmic examination.

DISCUSSION

This study addresses a fundamental clinical dilemma: distinguishing latent from active tuberculosis in patients with positive immunological tests but normal chest radiographs. Our findings demonstrate that ocular manifestations—particularly inflammatory cells in the posterior chamber and peripheral perivasculitis—are present in nearly 40% of such patients, providing objective evidence of active disease that can guide therapeutic decisions.

Traditional binary classification of tuberculosis as either latent or active is increasingly recognized as an oversimplification. The spectrum model posits a continuum from complete immune containment through subclinical disease to full-blown active infection.[12] Within this framework, our findings suggest that ocular involvement may represent a detectable intermediate state—evidence that the immune system is actively engaging with mycobacterial antigens, leading to inflammatory responses in vulnerable tissues.

The presence of inflammatory cells in the aqueous or vitreous humor indicates breakdown of the blood-ocular barrier, a phenomenon closely linked to systemic inflammation and active infection. Peripheral perivasculitis, characterized by sheathing along retinal venules, represents a hypersensitivity reaction to circulating mycobacterial immune complexes.[13] Both findings signify that the host-pathogen equilibrium has shifted toward active disease, justifying therapeutic intervention even in the absence of pulmonary radiographic changes.

The significant correlation between Mantoux positivity and slit-lamp findings (p=0.015) validates ophthalmic examination as a valuable adjunct in TB diagnosis. However, perhaps more importantly, 21.2% of Mantoux-negative patients demonstrated ocular involvement. This subset represents diagnostically challenging cases where traditional immunologic testing fails, yet objective evidence of active disease exists. In such patients, slit-lamp findings may be the deciding factor enabling timely ATT initiation.

The 39.6% prevalence of ocular involvement in our cohort exceeds many previous estimates, which range from 1.4% to 18%.[14] This discrepancy likely reflects our specific inclusion criteria—patients with clinical suspicion and positive Mantoux but normal chest X-ray—a population enriched for extrapulmonary presentations. Additionally, the systematic, protocol-driven ophthalmic evaluation by a single experienced examiner may have enhanced detection of subtle findings that might otherwise be overlooked.

The predominance of anterior chamber cells and peripheral perivasculitis among our findings warrants consideration of underlying mechanisms. Hematogenous dissemination of M. tuberculosis during bacillemic phases preferentially seeds highly vascular tissues—the uveal tract receives the highest blood flow per unit tissue in the body, making it an ideal site for bacillary deposition.[15] Once lodged in uveal capillaries, organisms may either establish micro-foci of infection or release antigens that trigger inflammatory responses.

Peripheral perivasculitis likely represents an immune-complex mediated phenomenon rather than direct infection, as organisms are rarely isolated from affected vessels.[16] This distinction has therapeutic implications: anti-tubercular therapy targets the underlying infection driving antigen release, while corticosteroids address the inflammatory consequences. The frequent coexistence of both findings in our patients suggests that direct infection and immune-mediated mechanisms often operate simultaneously.

India's NTEP aims for TB elimination by 2025—an ambitious target requiring innovative case detection strategies. Current programmatic algorithms focus primarily on pulmonary TB through cough screening and chest radiography.[17] Our findings suggest that incorporating ophthalmic evaluation into screening protocols could significantly enhance detection of active extrapulmonary disease.

The practical advantages are compelling: slit-lamp examination is non-invasive, relatively inexpensive, and available at most district hospitals and many primary health centers in India. A brief ophthalmic evaluation adding 10-15 minutes to the consultation could provide definitive evidence enabling confident ATT initiation, potentially reducing both under-treatment and over-treatment. For patients with moderately positive Mantoux tests and nonspecific symptoms—a common presentation in clinical practice—the presence of anterior chamber cells or peripheral perivasculitis could tip the balance toward treatment. Conversely, the absence of ocular findings in a Mantoux-positive patient might support watchful waiting, avoiding unnecessary exposure to hepatotoxic medications.

Our findings align with several recent investigations while extending their implications. Balakrishnan et al. (2024) reported significant correlation between Mantoux positivity and slit-lamp findings in ocular TB patients, with 84.4% of their cohort showing concordance.[18] Our 49.2% concordance rate among Mantoux-positive patients is lower but reflects our broader inclusion criteria encompassing all clinically suspected patients rather than those with established ocular TB.

Tsui et al. (2023) described a case series where all five Mantoux-positive patients demonstrated corresponding slit-lamp findings including anterior uveitis and posterior segment involvement.[19] Our larger cohort confirms this association while also documenting the important subset of Mantoux-negative patients with ocular involvement—a group not well represented in smaller series. The 6.3% prevalence of choroidal tubercles in our study approximates the 5-10% range reported in autopsy studies of disseminated TB,[20] suggesting that our cohort may have captured patients with active hematogenous spread. Given that choroidal tubercles

are considered diagnostic of miliary TB when present, this finding alone justifies ATT initiation regardless of other investigations.

Strengths and Limitations

Strengths: This study has several notable strengths. First, the sample size (n=96) was adequately powered to detect clinically meaningful associations. Second, the focused inclusion criteria—clinical suspicion with positive Mantoux but normal chest X-ray—addresses a specific, common diagnostic dilemma. Third, comprehensive ophthalmic evaluation by a single experienced examiner ensured consistency and minimized inter-observer variability. Fourth, the equal sex distribution and broad age range enhance generalizability.

Limitations: Several limitations warrant consideration. The cross-sectional design precludes assessment of treatment outcomes or temporal progression of ocular findings. The single-center setting may limit generalizability to populations with different demographic or epidemiological characteristics. The absence of confirmatory molecular diagnostics (PCR from ocular fluids) means that some cases attributed to TB might represent other granulomatous conditions. However, in endemic settings, the pretest probability of TB is high, and the characteristic clinical findings coupled with positive Mantoux tests support the diagnosis. Additionally, the study did not include interferon-gamma release assays, which might have provided additional immunological correlation.

Future Directions

These findings generate several questions for future research. Longitudinal studies are needed to determine whether initiation of ATT leads to resolution of ocular findings and whether the rate of resolution correlates with treatment response. Comparative studies evaluating the diagnostic accuracy of different ocular findings—anterior chamber cells versus perivasculitis versus choroidal lesions—could establish weighted diagnostic criteria. Cost-effectiveness analyses comparing ophthalmic screening to alternative diagnostic strategies would inform health policy decisions.

The role of advanced ocular imaging—optical coherence tomography angiography, fundus autofluorescence, and wide-field fluorescein angiography—in detecting subclinical ocular involvement deserves investigation. Such techniques might identify abnormalities even before they become visible on slit-lamp examination, enabling earlier diagnosis.[21]

Finally, integration of ophthalmic findings with emerging biomarkers—host transcriptomic signatures, serum proteomic patterns, or metabolomic profiles—could create multi-modal diagnostic algorithms with enhanced accuracy for active TB detection.

CONCLUSION

This study demonstrates that ocular manifestations—particularly inflammatory cells in the posterior chamber and peripheral perivasculitis—are present in nearly 40% of patients with clinical suspicion of tuberculosis and positive Mantoux tests but normal chest radiographs. The significant correlation between Mantoux positivity and slit-lamp findings validates ophthalmic examination as a valuable diagnostic adjunct in this clinically challenging population.

Detection of these findings provides objective evidence of active disease, justifying timely initiation of anti-tubercular therapy even in the absence of pulmonary radiographic changes. The presence of ocular involvement in Mantoux-negative patients (21.2%) highlights the complementary role of ophthalmic examination in cases where traditional immunologic testing fails. From a public health perspective, integrating routine ophthalmic evaluation into tuberculosis screening protocols offers a cost-effective, non-invasive strategy to enhance early case detection. This approach aligns with NTEP objectives by enabling earlier treatment initiation, reducing diagnostic delays, and potentially decreasing transmission through prompt intervention.

For the individual patient, early recognition of ocular TB signs may prevent progression to sight-threatening complications while simultaneously facilitating treatment of underlying systemic disease. The eye, accessible to non-invasive examination, serves as a window into systemic tuberculous activity—a window that clinicians should utilize more consistently in their diagnostic approach to tuberculosis.

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