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Review Article

OCULAR TUBERCULOSIS: A DIAGNOSTIC CHALLENGE WITH EMPHASIS ON MICROBIOLOGIC AND CLINICAL DIAGNOSTIC METHODS

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ABSTRACT

Background: Ocular tuberculosis (OTB) represents a broad spectrum of intraocular inflammatory disorders associated with Mycobacterium tuberculosis infection or immune sensitization. Despite tuberculosis remaining a major global health concern, the diagnosis of ocular involvement continues to pose significant challenges. Ocular disease is typically paucibacillary, direct sampling of ocular tissues is invasive and often unrewarding, and immunologic tests detect prior exposure rather than active intraocular infection. Consequently, most cases are classified as presumed or probable rather than microbiologically confirmed. This diagnostic ambiguity carries important clinical implications, including the risks of unnecessary antitubercular therapy (ATT) versus delayed treatment with irreversible visual loss. This narrative review synthesizes contemporary understanding of OTB diagnosis, with particular emphasis on microbiologic and molecular diagnostics, while integrating clinical diagnostic methods, imaging, and consensus-based frameworks. We highlight key diagnostic challenges encountered in routine practice, discuss the interpretation of laboratory results in light of ocular phenotype and epidemiologic risk, and review emerging diagnostic approaches. A balanced, phenotype-driven strategy combining clinical judgment, targeted microbiology, and multidisciplinary collaboration is emphasized.

Materials and Methods: This is a narrative review carried out, over a period of six months. Data was retrieved from articles and studies available online on PubMed, Google scholar and various websites. Last 10 year data was collected and reviewed.

Results: The results are tabulated in the article which rely on microbiologicak test, immunological test, and clinical presentation.

Conclusion: Ocular tuberculosis remains one of the most challenging diagnoses where microbiologic confirmation is uncommon, and no single test reliably establishes disease. Advances in molecular diagnostics and biomarker research may reduce uncertainty. Consensus-based frameworks and multidisciplinary collaboration provide valuable guidance, but clinical judgment remains central.

Keywords: Ocular tuberculosis; tubercular uveitis; microbiologic diagnosis; clinical diagnosis; PCR; Xpert MTB/RIF; IGRA; paradoxical reaction.

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide, with extrapulmonary TB accounting for a substantial proportion of cases. Ocular tuberculosis, although relatively uncommon compared with pulmonary disease, is clinically significant because it can cause recurrent inflammation, structural damage, and permanent

visual impairment. Importantly, ocular involvement may precede systemic manifestations or represent the only site of disease.

Unlike pulmonary TB, where sputum microscopy and molecular testing often establish the diagnosis, ocular TB is rarely microbiologically proven. Most patients present with non-specific intraocular inflammation, and the organism is seldom isolated from ocular tissues. As a result, OTB is widely regarded as a clinical diagnosis supported by indirect evidence, rather than a condition confirmed by a single definitive test. This concept is reflected in the British Thoracic Society (BTS) clinical statement, which explicitly acknowledges the inherent diagnostic uncertainty in OTB and recommends a structured, multidisciplinary approach to management.[1]

Recent international efforts, including the Collaborative Ocular Tuberculosis Study (COTS) and the Standardization of Uveitis Nomenclature (SUN) Working Group, have attempted to standardize diagnostic criteria and treatment thresholds. Nevertheless, substantial variability persists in real-world practice, particularly in regions with differing TB prevalence.

Pathogenesis and Its Diagnostic Implications

Two principal, non–mutually exclusive mechanisms are thought to underlie ocular tuberculosis:

1. Direct intraocular infection, in which viable M. tuberculosis organisms infect ocular tissues such as the choroid, retina, or optic nerve.
2. Immune-mediated ocular inflammation, in which sensitization to mycobacterial antigens triggers a delayed hypersensitivity response without active bacillary replication in the eye.

From a diagnostic standpoint, this dual-pathogenesis model is central to understanding why microbiologic confirmation is so difficult. Direct infection is typically characterized by a very low bacillary burden, while immune-mediated disease may occur in the complete absence of organisms within ocular tissues. Both scenarios lead to low sensitivity of conventional microbiologic tests, even when advanced molecular techniques are employed.[2]

Clinical Diagnostic Methods: Phenotype Recognition and Bedside Assessment

Ocular Phenotypes and Diagnostic Probability

In the absence of a definitive test, clinical phenotype recognition forms the foundation of OTB diagnosis. Certain patterns of uveitis have been consistently associated with TB and therefore carry a higher pre-test probability:

- Serpiginous-like (multifocal) choroiditis
- Choroidal granuloma or tuberculoma
- Occlusive retinal vasculitis (including Eales-like disease)
- Granulomatous anterior uveitis with iris nodules
- Posterior uveitis or panuveitis with multifocal choroidal lesions

Conversely, isolated non-granulomatous anterior uveitis, mild intermediate uveitis, or uveitis with a well-established alternative etiology (e.g., HLA-B27 disease) carries a lower probability of TB association.[3-5]

Clinical diagnostic accuracy improves when ocular findings are interpreted alongside epidemiologic risk factors, including residence in or travel to endemic regions, prior TB exposure, previous TB treatment, and immunosuppression.

Multimodal Imaging as a Clinical Diagnostic Tool

Although imaging cannot confirm TB etiology, it plays a critical role in clinical diagnosis and disease monitoring. Fundus fluorescein angiography (FA) is essential for identifying occlusive vasculitis and areas of ischemia, while indocyanine green angiography (ICGA) highlights choroidal involvement and occult lesions. Fundus autofluorescence (FAF) is particularly useful in serpiginous-like choroiditis, demonstrating active and healed lesions with characteristic patterns.[6]

Optical coherence tomography (OCT) and OCT angiography provide high-resolution assessment of retinal and choriocapillaris involvement, enabling detection of complications such as macular edema, choroidal neovascularization, and ischemia. These imaging modalities contribute to phenotype classification and objective monitoring but must be interpreted cautiously, as similar patterns can occur in non-tubercular inflammatory conditions.

Microbiologic and Molecular Diagnostic Methods

1. Smear Microscopy and Culture

Demonstration of M. tuberculosis by acid-fast staining or culture from ocular tissue or fluid remains the diagnostic gold standard. However, due to low organism load and limited sample volume, smear microscopy is almost invariably negative. Culture, while highly specific, is slow and has low sensitivity, with positive results reported mainly in cases with choroidal granulomas or subretinal abscesses.[7]

Consequently, microbiologic confirmation using conventional methods is achieved in only a small minority of suspected cases.

2. Polymerase Chain Reaction (PCR)

PCR-based assays have become central to microbiologic evaluation in suspected OTB. Detection of mycobacterial DNA from aqueous or vitreous samples allows diagnosis from minimal tissue volumes. Multitarget PCR assays targeting IS6110, MPB64, and other genomic regions appear to improve diagnostic yield.[8]

However, PCR positivity does not necessarily indicate viable organisms, and false-negative results remain common. Variability in assay design, laboratory expertise, and contamination control further complicates interpretation. PCR results must therefore be integrated with clinical and radiologic findings rather than used in isolation.

3. Xpert MTB/RIF and Rapid NAATs

The Xpert MTB/RIF assay (GeneXpert) is a cartridge-based nucleic acid amplification test that detects M. tuberculosis DNA and rifampicin resistance within hours. Although validated primarily for pulmonary and extrapulmonary TB, several studies have demonstrated its utility in selected cases of posterior uveitis and choroiditis.[9]

While specificity is high, sensitivity remains modest, reflecting the paucibacillary nature of ocular disease. Nevertheless, GeneXpert offers practical advantages, including rapid turnaround and resistance detection, and is increasingly considered when ocular sampling is undertaken in severe or atypical cases.

Immunologic Tests: Clinical Utility and Pitfalls

Tuberculin skin testing (TST) and interferon-γ release assays (IGRAs) detect immune sensitization to TB antigens rather than active disease. Their main value lies in corroborating clinical suspicion in patients with compatible ocular phenotypes.

However, in endemic regions, high background positivity limits specificity, while immunosuppression may yield false-negative results. World Health Organization guidance emphasizes that these tests identify TB infection, not active disease, and should not be used in isolation to justify ATT.[10,11]

Diagnostic Challenges in Routine Clinical Practice

Several factors complicate the diagnosis of OTB in real-world settings:

- Overlap with mimicking diseases, including sarcoidosis, syphilis, Behçet disease, viral uveitis, and intraocular lymphoma.
- Limited access to ocular microbiology, particularly in low-resource settings.
- Risk of overdiagnosis in endemic regions, where positive IGRA or TST results may be incidental.
- Risk of underdiagnosis in low-burden regions, where TB may not be initially considered.
- Impact of prior corticosteroid therapy, which can suppress microbiologic yield and alter clinical appearance.[12-14]

These challenges underscore the need for a structured diagnostic approach and careful exclusion of close mimics before labeling a case as presumed OTB.

Paradoxical Reactions and Therapeutic Response

Paradoxical worsening of ocular inflammation after initiation of ATT is a well-recognized phenomenon. Such reactions are thought to result from immune-mediated responses to mycobacterial antigen release rather than treatment failure. Clinically, this may manifest as worsening vitritis, enlargement of choroidal lesions, or new inflammatory foci.[15]

Recognition of paradoxical reactions is critical, as misinterpretation may lead to premature discontinuation of ATT or unnecessary diagnostic escalation.

Diagnostic Frameworks and Consensus Guidance

To reduce variability in diagnosis and management, several structured frameworks have been proposed. The BTS clinical statement emphasizes multidisciplinary evaluation, while COTS guidelines provide phenotype-specific recommendations for initiating ATT. The SUN Working Group classification criteria offer standardized definitions primarily for research but also inform clinical thinking.[1,3,4]

Most frameworks categorize cases as:

- Proven OTB: microbiologic confirmation from ocular tissue or fluid.
- Probable/presumed OTB: compatible phenotype with supportive immunologic or systemic evidence, after exclusion of close mimics.

Emerging and Future Diagnostic Approaches

Newer diagnostic strategies include targeted next-generation sequencing for mycobacterial DNA and host-based biomarkers such as cytokine profiles and transcriptomic signatures. These approaches aim to improve sensitivity and distinguish TB-driven inflammation from non-specific uveitis but remain investigational in ophthalmology.[16,17]

MATERIALS AND METHODS

This study was conducted as a narrative review carried out, over a period of six months to explore and analyze the evolving microbiological, immunological and molecular tests available to diagnose ocular tuberculosis. The study was conducted in the Department of Microbiology, of a Central Govt. Institute in collaboration with a private eye center in New Delhi. Data was retrieved from articles and studies available online on PubMed, Google scholar and various Govt. And Institutional websites using the Key words. Last 10 year data was collected and reviewed.

RESULTS

The results are tabulated as Table 1 and Table 2 in the article which rely on microbiological test, immunological test, and clinical presentation.

The correlation between the clinical presentation and the tests to be opted

that can guide towards reaching a diagnosis have been tabulated for ease.

I was seen that Tuberculin skin test, IGRA, Chest X Ray, HRCT, AFB Smear, Multi targeted PCR all can be used judiciously to diagnose Ocular Tuberculosis.

Table 1: Diagnostic Tests Used in Ocular Tuberculosis: Clinical Question Addressed, Utility, and Key Limitations

Test / Modality	Primary Clinical Question Answered	Best Use Scenario	Strengths	Key Limitations / Pitfalls	Management	Key References
Tuberculin Skin Test (TST)	Has the patient been sensitized to TB antigens?	Initial corroborative test in compatible ocular phenotype	Widely available; inexpensive	False positives in endemic regions and BCG vaccination; false negatives with immunosuppression	Supportive only; never diagnostic in isolation	WHO; BTS; COTS,[1,3,10,11]
Interferon-γ Release Assay (IGRA)	Evidence of TB infection independent of BCG	Preferred in BCG-vaccinated or low-endemic settings	Higher specificity than TST	Cannot distinguish latent vs active disease; false negatives with steroids	Adds weight to presumptive diagnosis; negative does not exclude OTB	WHO; BTS; SUN,[1,4,10,11]
Chest X-ray	Evidence of prior or active pulmonary TB	Baseline evaluation in all suspected OTB	Simple; accessible	Often normal in extrapulmonary TB	Abnormality increases confidence; prompts TB referral	BTS; WHO,[1,10]
Chest CT (HRCT)	Occult pulmonary/mediastinal disease	High suspicion with normal X-ray	Higher sensitivity for healed or active lesions	Incidental inactive lesions common	Strengthens case for ATT in high-probability phenotype	BTS; COTS,[1,3]
AFB smear (ocular fluid)	Are bacilli directly visible?	Rare; selected severe posterior disease	Highly specific if positive	Extremely low sensitivity	Positive = proven OTB	BTS; microbiology reviews,[1,7]
Mycobacterial culture (ocular fluid/tissue)	Are viable organisms present?	Choroidal granuloma, subretinal abscess	Gold standard; resistance testing	Low yield; long turnaround	Confirms diagnosis; guides therapy	BTS; StatPearls,[1,2]
Conventional PCR (single target)	Is mycobacterial DNA detectable?	Posterior uveitis with high suspicion	Rapid; small sample volume	Variable sensitivity; target dependent	Supports ATT when phenotype is compatible	PCR reviews; SUN,[4,8]
Multi target PCR	Improved DNA detection probability	Centers with validated assays	Higher sensitivity than single-target PCR	Inter-lab variability	Strong supportive evidence if positive	Theranostics review; AAO abstracts,[8,17]
Xpert MTB/RIF (GeneXpert)	MTB DNA and rifampicin resistance	Severe posterior disease; prior TB	High specificity; rapid resistance data	Limited sensitivity; sample-volume dependent	Strong indication for ATT; guides drug choice	Lancet Infect Dis; WHO,[9,10]
Fundus Fluorescein Angiography (FA)	Is there occlusive vasculitis/ischemia?	Retinal vasculitis, Eales-like disease	Defines severity and ischemic burden	Non-specific etiology	Phenotype classification and urgency assessment	BTS; Eales reviews,[1,5]
Indocyanine Green Angiography (ICGA)	Occult choroidal involvement?	Choroiditis, serpiginous-like lesions	Sensitive for choroidal disease	Limited availability	Supports TB-associated phenotype	COTS; imaging reviews,[3,6]
Fundus Autofluorescence (FAF)	Are lesions active or healed?	Serpiginous-like choroiditis	Non-invasive activity tracking	Not pathognomonic	Monitoring response rather than diagnosis	Imaging reviews; COTS,[3,6]
Optical Coherence Tomography (OCT)	Structural retinal/choroidal damage	All posterior disease	Objective; repeatable	Etiology cannot be determined	Monitoring complications and response	SUN; imaging literature,[4,6]
Syphilis serology (VDRL/TPHA)	Is this a treatable infectious mimic?	Mandatory uveitis work-up	High sensitivity for ocular syphilis	None significant	Must be negative before presumed OTB	BTS; uveitis guidelines, [1,12]
Sarcoidosis screen (ACE ± imaging)	Alternative granulomatous disease?	Granulomatous uveitis	Identifies major mimic	Low specificity	Prevents misdiagnosis	BTS; SUN,[1,4]

Table 2: Diagnostic Yield and Relative Utility of Investigations Across Common Ocular Tuberculosis Phenotypes

Ocular Phenotype	Most Informative Tests	Relative Microbiologic Yield	Common Diagnostic Pitfalls	Evidence Level / Key References
Serpiginous-like choroiditis	IGRA/TST, Chest CT, FAF, ICGA; Vitreous PCR/Xpert in selected cases	Low–moderate (PCR positive in minority)	Confusion with classic autoimmune serpiginous choroiditis; false-negative PCR	COTS consensus; SUN criteria; PCR studies,[3,4,8,9]
Choroidal granuloma / tuberculoma	Chest imaging, IGRA/TST; Aqueous/vitreous PCR; Rarely culture	Moderate–highest among phenotypes	Misdiagnosis as sarcoid or neoplasm; biopsy often avoided	BTS statement; StatPearls; microbiology reviews,[1,2,7]
Occlusive retinal vasculitis (Eales-like disease)	FA, IGRA/TST, Chest imaging; PCR rarely contributory	Very low	Over-reliance on positive IGRA in endemic regions; missing Behçet disease	BTS; Eales reviews; COTS,[1,3,5]
Granulomatous anterior uveitis with iris nodules	Slit-lamp exam, IGRA/TST, Chest imaging; Aqueous PCR (selected)	Low	More commonly sarcoidosis or herpetic uveitis	SUN criteria; BTS; clinical reviews,[1,4,12]
Intermediate uveitis (TB-associated)	IGRA/TST, Chest imaging; limited role for ocular sampling	Very low	Coincidental latent TB infection	COTS; Stat Pearls,[2,3]
Posterior uveitis / panuveitis (multifocal)	IGRA/TST, Chest CT; Vitreous PCR/Xpert	Low–moderate	Viral retinitis and lymphoma masquerade	PCR/Xpert series; BTS,[1,8,9]
Subretinal abscess (rare)	Vitreous/subretinal aspirate for PCR, culture, Xpert	Highest (relative)	Delay in sampling leads to loss of yield	Case series; microbiologic reports,[7,9]
Optic nerve involvement	MRI, Chest imaging, IGRA/TST	Very low	Demyelination or sarcoidosis more likely	BTS; neuro-ophthalmic reviews,[1,12]
Immunosuppressed patients (any phenotype)	IGRA + imaging; early PCR/Xpert if sampling planned	Variable, often lower than expected	False-negative IGRA; atypical presentations	WHO; BTS; clinical series,[1,10,11]

CONCLUSION

Ocular tuberculosis remains one of the most challenging diagnoses in uveitis practice. Microbiologic confirmation is uncommon, and no single test reliably establishes disease. Optimal diagnosis requires careful integration of clinical phenotype, imaging, epidemiologic context, immunologic testing, and selective use of molecular microbiology. Consensus-based frameworks and multidisciplinary collaboration provide valuable guidance, but clinical judgment remains central. Advances in molecular diagnostics and biomarker research may ultimately reduce uncertainty, but until then, a balanced, evidence-weighted approach is essential to preserve vision while minimizing unnecessary treatment.

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