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Strengths and Weaknesses of Diagnostic Tools for Tuberculous Uveitis

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Abstract

Diagnostic criteria for tuberculous uveitis encompass exclusion of other known etiologies of uveitis, suggestive clinical history and signs, supportive systemic investigations, positive response to empiric antituberculosis treatment and evidence of *Mycobacterium tuberculosis* or its DNA in ocular fluids/tissues. Recent advances in diagnostic tools for tuberculous infection, including molecular biology techniques for detection of *M. tuberculosis* DNA and interferon-gamma release assays, have improved the specificity of the diagnosis and the ability to ascertain exposure to the infectious agent. However even with such advances, establishing the diagnosis of tuberculous uveitis remains a challenging issue because each of these available investigations has its strengths and limitations and tuberculous infection can present with clinical features of any type of extraocular or intraocular inflammation. This article critically analyzes the role of these tests in supporting the diagnosis of tuberculous uveitis and proposes a practical diagnostic approach, based on a judicious combination of these tests.

Keywords

tuberculosis; uveitis; diagnosis

It is estimated that up to one-third of the human population may be infected with *Mycobacterium tuberculosis*.¹ Of these, approximately 5–10% develop primary pulmonary disease soon after exposure to the infectious agent, while the remaining individuals are able to control the spread of the mycobacteria at the primary focus (Gohn's complex). Hematogenous dissemination of the microorganism may occur causing tuberculous seeding of virtually any bodily organ, including the eye.² In the vast majority of individuals the bacilli enter a dormant state in the pulmonary or extrapulmonary lesions, evading the host immune response through various mechanisms and remaining dormant for up to several decades after primary infection. But these individuals will have a positive tuberculin test, which is clinically recognized as a sign of latent tuberculous infection.^{3–5} Under special circumstances, such as immunosuppression, these microorganisms may reactivate from this dormant state, leading to clinically apparent disease, mainly in the lungs, but also in any other organ.^{3,5} In AIDS, for instance, the annual risk of reactivation of tuberculosis is about 10%.⁶ Individuals on immunosuppressive treatment, especially antitumor necrosis factor agents, are also at increased risk of reactivation.⁷

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The diagnosis of intraocular tuberculosis has evolved from an era in which almost any granulomatous inflammation involving the eye would be considered to be of tuberculous origin⁸ to the current assumption that tuberculous etiology is an unusual cause of uveitis, with most such rare cases being presumptive, since unequivocal evidence of the infection is often unavailable.² Recently proposed guidelines for the diagnosis of tuberculous uveitis encompass exclusion of other known etiologies of uveitis, suggestive clinical history and signs, supportive investigations such as positive tuberculin skin test (TST) and chest X-ray findings, response, to empiric antituberculosis treatment and, in some, evidence of *M. tuberculosis* or its DNA in ocular fluids/tissues.² Although, TST and chest X-ray have been frequently employed to arrive at a presumptive diagnosis of ocular tuberculosis, these investigations have limitations (Table 1). Recent advances in diagnostic tools for tuberculous infection, including molecular biology techniques for detection of *M. tuberculosis* genomic DNA and interferon-gamma release assays (IGRA) have improved the specificity of the diagnosis and the ability to ascertain, previous exposure to the infectious agent.^{9–12} However even with such advances, establishing the diagnosis of tuberculous uveitis remains a challenging issue because each of these available tests has its strengths and weaknesses,^{9,10} (Table 1) and because tuberculous infection can present with clinical features of any type of extraocular or intraocular inflammation.^{2,13}

Immunological methods for the diagnosis of tuberculosis have been expanded with the advent of IGRA. In contrast to the TST, which may be relatively nonspecific, IGRAs can detect immune response to specific *M. tuberculosis* antigens and, thus, are not influenced by BCG vaccination or by atypical mycobacterial infection.^{9–11} Moreover, IGRA may be a stronger indicator of exposure to *M. tuberculosis* than the TST. However, like TST, IGRA still lack specificity in that they do not distinguish latent tuberculous infection from active disease.^{9,10,14} In addition, IGRA results may also be influenced by immunosuppressive states, and their exact role in individuals with TST anergy is still to be determined.⁹ Most cases of intraocular tuberculosis would test positive by these immunological methods, but a negative, indeterminate, or borderline result may not be enough to definitely exclude tuberculous etiology. Furthermore, the prognostic value of a positive IGRA result in a patient with latent tuberculosis is still unknown⁹ (Table 1).

Radiological methods for the diagnosis of tuberculosis usually target the chest because the lungs are the main site of tuberculous involvement, whether in primary infection, persistence or reactivation of the dormant microbes, or even reinfection.¹⁵ Recent evidence has shown that primary and reactivation tuberculosis share similar radiological findings.^{16,17} In immunosuppressed individuals radiological findings are more often atypical, with a higher prevalence of miliary disease, pleural effusions, and lymphadenopathy.¹⁷ The latter is usually a prominent feature in the pediatric age group.¹⁵ Nevertheless, many (if not most) cases of tuberculous uveitis show no evidence of concomitant active lung involvement.¹⁸ Moreover, radiologic evidence of postinflammatory lesions such as hilar lymphadenopathy and parenchymal scarring may not be specific of tuberculosis.¹⁹ Furthermore, the pulmonary changes are not detected in many patients with extrapulmonary tuberculosis, including those with tuberculous uveitis.¹⁸ Although less sensitive, plain chest radiographs are still recommended in the initial workup of patients with possible tuberculosis.^{9,15} Computer-assisted tomography, which may help delineate concomitant hilar, parenchymal, or pleural disease, can be an effective diagnostic method, especially when plain chest radiographs are normal or inconclusive¹⁵ in highly suspected cases (Table 1). However, the cost of computer-assisted tomography and the increased exposure to radiation may preclude its use for routine investigation of all suspected cases.²⁰

Traditional bacteriological diagnosis has relied on detection of acid-fast bacilli (AFB), usually after Ziehl-Neelsen or auramine-rhodamine staining of body fluids and tissue

sections. Despite the low sensitivity of microscopic examination of stained smears for AFB detection (e.g., >5,000 bacilli/mL are required for sputum), up to half of all cases of active pulmonary tuberculosis may present positive sputum⁹ even though results of the chest radiographs are normal.²¹ For other fluids, such as aqueous humor or vitreous, however, the likelihood of detecting AFB is even lower.² Culture is regarded as the gold-standard for the diagnosis of tuberculosis;⁹ but it is more laborious and may not be widely available. Additionally, return of culture results may take as much as 6–8 weeks. Costly semi-automated and automated systems with liquid media may allow a shortening of this time to less than 2 weeks.⁹ By detecting viable mycobacteria, culture systems also allow testing for antibiotic resistance (Table 1).

Nucleic acid amplification tests (NAAT), of which the most important is the polymerase chain reaction (PCR), have emerged as powerful tools for rapid detection of the mycobacterial genome in clinical and research specimens.^{9,22} In addition to detecting *M. tuberculosis* DNA in active lesions, PCR may also disclose the presence of DNA from possibly dormant mycobacteria in normal tissues of latently infected individuals.^{23,24} Results for several in-house and some commercially available PCR assays for *M. tuberculosis* indicate high specificity and variable sensitivity, depending on the clinical setting and the tested specimens.^{9,22} Real-time or quantitative PCR (qPCR) has additional advantages, allowing the fast detection and quantification of mycobacterial load in the tested specimen, with a minimized risk of carryover and cross-contamination.²² Aqueous humor, vitreous, or subretinal fluid and even tissue specimens have been used, for PCR testing of *M. tuberculosis* DNA, with promising results.^{2,25,26} However, comparative studies with the gold standard (culture) are still lacking and may be difficult to accomplish, considering the small volume of ocular samples (Table 1). The use of these increasingly more sensitive NAAT, particularly qPCR, for ocular specimens should help elucidate some therapeutic and prognostic aspects of *M. tuberculosis*-associated intraocular inflammation.

While histopathologic examination of tissue sections may be useful, it is not often a first-line diagnostic resource. Evidence of necrotizing granulomatous inflammation may support a diagnosis of tuberculosis.^{25,27} But when no AFB is seen, the diagnosis cannot be confirmed unless the results of other methods, such as culture or NAAT, are positive.^{18,28} Of note, other infectious (bacterial, fungal, viral, or parasitic) or noninfectious entities may lead to necrotizing granulomatous inflammation, which can be confounded with that associated with tuberculosis (Table 1).

A better understanding of the strengths and weaknesses of diagnostic tests for tuberculosis may help develop a more logical approach to the dilemma of intraocular inflammation of possible tuberculous etiology. A judicious combination of the above-mentioned diagnostic techniques for each individual setting is warranted and may allow better diagnosis and selection of those patients who would most benefit from empiric antituberculous treatment. Since tuberculostatic drugs are associated with significant side effects,²⁹ their prudent use is essential. Taking into consideration such limitations, we propose a practical approach to the diagnosis and treatment of patients with presumed or definite tubercular intraocular infections (Figure 1). This approach is primarily recommended for uveitis patients in regions that are not endemic for tuberculosis, but might be applicable to endemic regions as well.

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FIGURE 1.

Suggested diagnostic approach to cases of possible tuberculosis uveitis. TST, tuberculin skin test; IGRA, interferon-gamma release assay; CT, computer-assisted tomography; Tb, tuberculosis. *Anti-Tb treatment for 8 weeks; presumed and definite Tb require treatment ≥ 6 months.

TABLE 1

Advantages and disadvantages of main diagnostic tests for tuberculous uveitis

Type		Principle	Main advantages	Main disadvantages
Immunologic	Tuberculin skin test (Mantoux test, PPD test)	Tests skin hypersensitivity for mycobacterial antigens (PPD)	Low cost and wide availability. Fair marker of cell-mediated immune response to <i>Mycobacterium</i> sp. Specificity may increase with larger induration reactions	Not specific for <i>M. tuberculosis</i> . Does not distinguish latent infection from disease. May be positive with BCG vaccination/exposure to atypical mycobacteria. May be negative in immunosuppressed states/children/ extrapulmonary or miliary tuberculosis. Difficulties in test administration and interpretation may lead to false results
	Interferon- γ release assays (QuantiferON TB Gold or In-Tube and T-SPOT.TB)	Tests interferon- γ release after <i>in vitro</i> stimulation of patients' lymphocytes with <i>M. tuberculosis</i> specific antigens	More specific marker of <i>M. tuberculosis</i> infection/previous exposure. Not influenced by BCG vaccination or exposure to atypical mycobacteria. Not as subject to biases and errors of placement and reading as the TST	Higher cost. Not widely available. Possibly more sensitive to detect latent infection than TST but does not distinguish it from disease. May be negative or indeterminate in immunosuppressed states. Problems in collecting or transporting blood specimen may decrease the accuracy
Radiologic	Plain chest radiograph (chest X-ray)	Looks for evidence of pulmonary involvement, either active or healed (postinflammatory)	Low cost and wide availability. Useful when a suggestive pattern is found (e.g., upper lobe infiltrates and cavitation, Gohn's focus, miliary disease)	Not specific for tuberculosis. Other infectious/granulomatous/lymphoproliferative/occupational disorders may lead to similar patterns. Low sensitivity, especially for detection of lymphadenopathy. A normal result does not exclude ocular tuberculosis
	Chest computer-assisted tomography	Looks for evidence of pulmonary involvement, either active or healed (postinflammatory)	More sensitive than chest radiograph. Modality of choice for detection of lymphadenopathy and for tuberculomas. Useful when a suggestive pattern is found	Higher cost and greater radiation exposure than chest X-ray. Not specific for tuberculosis. A normal result does not exclude ocular tuberculosis
Bacteriologic	Smear	Identify the presence of stained acid-fast bacilli in various clinical samples	Rapid and widely-available method. Useful especially in specimens with large bacillary load	Low sensitivity (e.g., for sputum, detection threshold is >5,000 bacilli/mL). Other acid-fast organisms are also identified through this method
	Culture	Detects growth of <i>M. tuberculosis</i> after seeding of clinical samples in culture media	Gold standard. Unequivocal proof of microorganism viability. Allows identification and drug sensitivity testing	Expensive and cumbersome. May not be widely available. Results may take up to 6–8 weeks in solid media
Molecular	Nucleic acid amplification tests	Detects presence of <i>M. tuberculosis</i> genomic DNA in clinical samples after amplification (e.g., various PCR techniques)	High specificity. Better sensitivity than microscopy. Fast results. Allows identification and investigation of genetic resistance patterns	Higher cost and limited availability. Variable sensitivity. Inferior sensitivity for nonrespiratory specimens (not established for ocular samples). Does not allow ruling out tuberculous

Type		Principle	Main advantages	Main disadvantages
Histologic	Histopathology	Stained tissue sections with evidence of granulomatous inflammation (especially with caseous necrosis) support the diagnosis. Finding of AFB in this setting is diagnostic	Allows the observation of the extent of tissue damage	etiology. Detects only DNA (more prone to contamination and microorganisms may not be viable or may be dormant) Risks related to invasive procedure to obtain tissue specimen. Other microorganisms/noninfectious entities may also lead to granulomatous inflammation. Low sensitivity for AFB detection

Abbreviations: PPD=purified protein derivative; BCG=bacille Calmette-Guérin; PCR=polymerase chain reaction; AFB = acid-fast bacilli.