
Diagnosis of Ocular Tuberculosis: A Role for New Testing Modalities?

██████████ Carolyn T. Bramante, BA

██████████ Elizabeth A. Talbot, MD

██████████ Sivakumar R. Rathinam, MNAMS

██████████ Rosalind Stevens, MD

██████████ Michael E. Zegans, MD

■ Clinical Features of Tuberculosis

Tuberculosis (TB) is a disease caused by the acid-fast bacillus (AFB) *Mycobacterium tuberculosis*. TB usually affects the lungs [pulmonary TB (PTB)], but it can also affect any other part of the body [extrapulmonary TB (EPTB)]. EPTB with no evidence of pulmonary involvement accounted for 21.1% of those with TB in 2005, which represents an increase from 16% in 1992.¹ The increase in the proportion of TB cases that are HIV coinfecting has contributed to this increase in EPTB.² The general symptoms of TB include weakness, weight loss, fever, and night sweats. Symptoms of PTB may also include coughing, chest pain, and hemoptysis. Symptoms of EPTB depend on the area affected.

TB is spread from person to person through the air when a person with PTB coughs, sneezes, or speaks. Persons who breathe in the air containing *M. tuberculosis* can become infected asymptotically; this is called latent TB infection (LTBI). It is estimated that one-third of the world's population has LTBI.³⁻⁵ LTBI is not contagious, but about 5% of persons with LTBI (about 100 million people) will develop TB disease in the future.⁵⁻⁷ Progression of LTBI to TB is more common among those with compromised immune systems, those who were recently infected with *M. tuberculosis*, and people with certain medical conditions. Progression of LTBI to TB can be prevented with treatment such as 9 months of isoniazid.

Typical drug sensitive PTB can be cured by taking antimycobacterial drugs for 6 months. Drug resistant forms of EPTB and PTB are harder and more expensive to treat. The World Health Organization (WHO) advocates that all TB treatment be given under Direct Observed Therapy (DOT) to ensure cure.

■ Characteristics of Ocular TB

The recognized association of TB with ocular disease dates to the 1700s, when iris lesions in TB patients were described.⁸ Recognition of choroidal tubercles in the medical literature was first noted between 1830 and 1844.⁹ The current incidence of ocular TB is uncertain.^{5,10,11} It is estimated that 1.4% of persons with PTB develop ocular manifestations^{3,10,12} but many patients with ocular TB have no evidence of PTB^{5,13–15} (Table 1).

Table 1. Selected Studies From 1998 to Present in Which There Were Data About Systemic Involvement in Ocular Tuberculosis Patients

Year	Author	Ocular TB Patients With Active Systemic TB		Ocular TB Patients With No Active Systemic TB	
		Number	Percentage	Number	Percentage
1998	Sahu et al ¹⁶	27/55	49.09	28/55	50.91
1998	Sarvananthan et al ¹⁴	0/3	0.00	3/3	100.00
2002	Morimura et al ¹³	1/10	10.00	9/10	90.00
2002	Ortega-Larrocea et al ¹¹	7/22	31.81	15/22	68.18
2003	Grosse ¹⁷	1/1	100.00	0/1	0.00
2003	Taynac et al ¹⁸	2/2	100.00	0/2	0.00
2004	Demicri et al ¹⁹	2/5	40.00	3/5	60.00
2004	Torres and Calonge ²⁰	1/1	100.00	0/1	0.00
2005	Domingues et al ²¹	1/1	100.00	0/1	0.00
2006	Babu et al ²²	15/15	100.00	0/15	0.00
2006	Kurup et al ²³	3/12	25.00	8/12	75.00
2006	Kurup and Chan ⁴	2/2	100.00	2/2	100.00
2006	Mehta ²⁴	3/3	100.00	0/3	0.00
2006	Shome et al ¹⁵	0/1	0.00	1/1	100.00
2006	Reddy et al ²⁵	1/1	100.00	0/1	0.00
2006	Varma et al ²⁶	12/12*	100.00	0/12	0.00
Total		77/146 = 52.74%		69/146 = 47.26%	

Please note that the definition of tuberculosis and ocular tuberculosis varied between these studies.

*Reports positive TST for all 12 cases, and CXR for 6: CRX was normal for 3 considered positive by TST.

Ocular *M. tuberculosis* infection is most often a result of hematogenous spread during PTB or EPTB. Infection may also occur via local spread from an active sinus or meningeal infection. Primary ocular infection in which bacilli enter the body through the conjunctiva is rare and is most likely to occur in children.^{6,27} Symptomatic disease is most commonly observed during reactivation of dormant lesions in ocular tissue rather than during the initial infection.^{6,10} Additionally, immune-mediated ocular TB can occur due to hypersensitivity to *M. tuberculosis* antigens from a distant focus (such as lungs). This hypersensitivity causes inflammation despite the absence of the bacterium in the eye.^{4,5,23,26} Phlyctenulosis, retinal vasculitis, and interstitial keratitis are examples of ocular pathology associated with *M. tuberculosis* infections believed to be hypersensitivity reactions.^{3,5,16,28}

Ocular TB is often unilateral and asymmetric.^{16,22,28} TB can cause a wide variety of ophthalmic findings, ranging from the ocular surface through the optic nerve and to the central nervous system. TB infection of the eyelid can start discretely as a minute nodule and later become lupus vulgaris (soft brownish TB nodules with ulceration and scarring), often accompanied by lymphadenopathy.⁶ After choroid involvement, anterior uveitis and sclerokeratitis are among the most common manifestations of TB in the eye.^{19,29–31} Other anterior segment presentations of TB include conjunctival granulomas, phlyctenulosis, sclerokeratitis, interstitial keratitis, anterior uveitis, and iridocyclitis.^{16,30} Subsequent calcification of granulomas can impede vision, and inflammation can cause irreversible damage to ocular tissue.⁶ Compared with adults, children and adolescents have higher rates of phlyctenular keratoconjunctivitis, which is found in 35% of children living in areas of high rates of TB.^{3,7} Anterior uveitis presents with mutton-fat keratic precipitates, photophobia, and floaters.⁵ In patients with miliary (disseminated) TB, iris nodules are often associated with anterior uveitis.⁵ Patients can also present with an intermediate uveitis pattern including “snowball” cellular aggregates and “snow banks” at the pars plana.

The most common sign of ocular TB is a choroidal mass, followed by choroiditis (Fig. 1).^{5,10,14,16,19,22,25,26,28–30,32} This is likely caused by the extensive blood supply to the choroid which makes it susceptible to hematogenous spread of *M. tuberculosis*. Hematogenous dissemination is the assumed etiology of tuberculous choroidal granulomas, but more widespread inflammation in choroiditis and vasculitis is likely due to hypersensitivity.²⁶ Indocyanine green angiography can be useful in determining the extent of choroidal involvement.¹⁸ Although this method is highly sensitive in detecting choroidal lesions, it is not specific to mycobacterial etiologies.¹⁸ Massaro and other authors²⁹ note that choroidal tubercles can arise early in the progression of TB and may be an important early indicator of hematogenous *M. tuberculosis* before the development of symptomatic TB.³² Massaro highlighted 2 autopsy

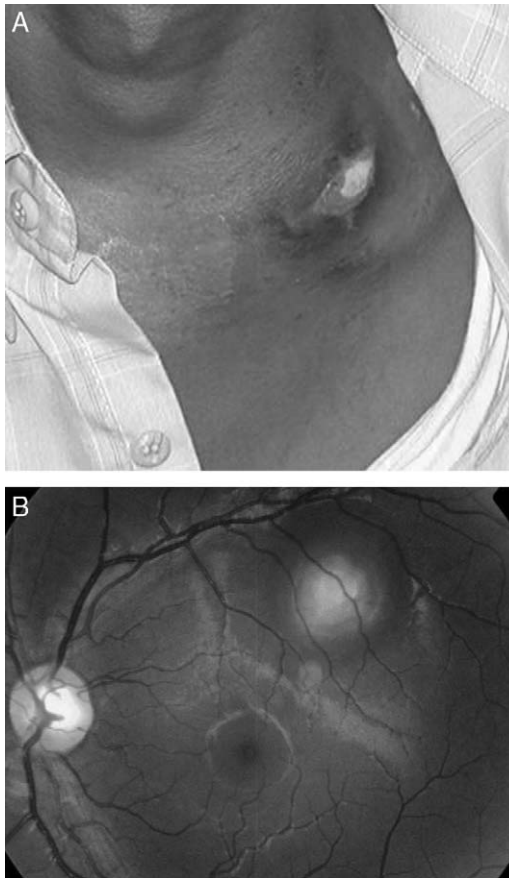


Figure 1. *A, Scrofula. B, Accompanying choroidal granuloma. (Photographs courtesy of Dr S.R. Rathinam.)*

studies of miliary TB in 1946, each showing that only one-fourth of the patients had been correctly diagnosed with TB before death.^{29,33}

In addition to choroiditis, neuroretinitis and retinal vasculitis are common posterior segment manifestations.¹⁰ A rare case of cystoid macular edema as the only ocular presentation of TB was reported in 2004.²⁰ Vitritis, geographic chorioretinitis, papillitis, subretinal abscess, tuberculoma, panophthalmitis, and endophthalmitis have also been described in TB patients.^{5,10,19,22} Finally, TB can involve the orbit in the form of granulomatous inflammation and fibrosis, potentially accompanied by osteomyelitis and endophthalmitis.¹⁵ Patients with these features commonly present with proptosis and sinus discharge.¹⁵

Eales disease is an idiopathic retinal vasculitis sometimes accompanied by vitreous hemorrhage (Fig. 2). Eales disease has been postulated to represent a manifestation of TB because it tends to be more common in

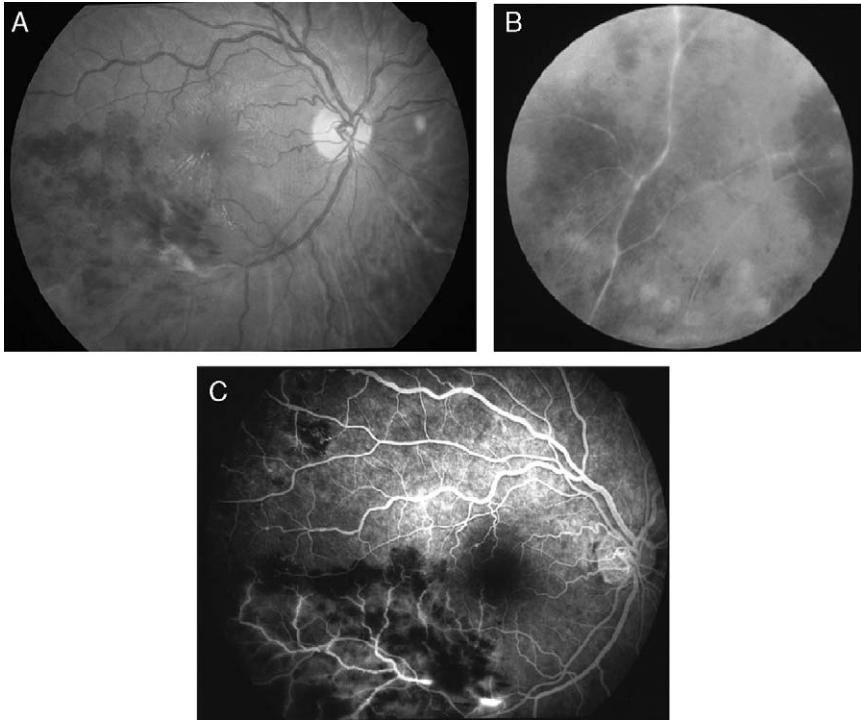


Figure 2. Eales disease. *A*, Multifocal areas of periphlebitis with associated intraretinal flame-shaped hemorrhages, secondary lipid maculopathy, and subtle choroidal folds within the papillomacular bundle are present. *B*, Peripheral vaso-occlusive arterial inflammation coexistent with venous involvement and secondary intraretinal hemorrhage in the same patient. Late neovascularization with vitreous hemorrhage is a common sequelae (not shown). *C*, Fluorescein angiography demonstrates staining of venous walls and blockage of background fluorescence by intraretinal blood. (Photographs courtesy of Dr R. Stevens).

settings with a high rate of TB. However, data regarding its association with TB has been inconsistent. A prospective study of 1005 TB patients in 1986 found no cases of Eales disease.¹² On the other hand, between 1992 and 1998, Indian researchers tested epiretinal membrane samples from well-documented Eales disease patients by nested polymerase chain reaction (PCR).³⁴ Nearly half (47.8%) of patients with Eales disease had *M. tuberculosis* detected, whereas only 11% of the non-Eales controls from the same population tested positive.³⁴ In a later study in 2002, 20.8% of Eales disease patients and only 4.2% of the controls tested positive for *M. tuberculosis* by PCR of vitreous fluid.³⁵ Difficulty in diagnosis is compounded by the fact that both Eales disease and TB often occur in the same populations—as many as 0.74% of ophthalmic patients in India, where much of the population has LTBI, have Eales disease.^{12,34,35}

■ Epidemiology of TB and Ocular TB

According to the WHO 2006 Global TB Report [http://www.who.int/tb/publications/global_report/2006/results/en/index.html], the number of TB cases was stable or falling in 5 of 6 WHO regions, but growing in Africa where the TB epidemic is still driven by the spread of HIV. Overall incidence rates have been increasing for most of the period since 1990 in African countries with low and high rates of HIV infection, and in Eastern Europe. In the United States in 2005, 14,097 TB cases (a rate of 4.8 cases per 100,000 persons) were reported. This represents a 3.8% decline in the rate from 2004. The 2005 TB rate was the lowest recorded since national reporting began in 1953 [CDC website: <http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/TBTrends.htm>].

Criteria for establishing a diagnosis of ocular TB are not well established and, therefore, the epidemiology of ocular TB is less certain than for TB. Lack of clear diagnostic criteria may also explain the variation of the reported incidence of ocular TB over time and geography. The regions most plagued by TB are also least equipped to screen thoroughly for ocular involvement, potentially resulting in underdetection of ocular manifestations.^{6,19,30} In 1964, DeVoe and Locatcher-Khorazo³⁶ noted that the Institute of Ophthalmology at Presbyterian Hospital in New York City reported only 4 cases of ocular TB in 140,000 routine ophthalmic examinations over 30 years (0.003%). In 1967, at a TB sanatorium in the United States, 1.46% of patients with active TB were identified as having ocular manifestations, as discussed in Thompson's 2005 review.³² By contrast, in Spain in 1997, 100 persons with TB were chosen at random and examinations revealed 18% had ophthalmic manifestations, and 11 of the 18 were HIV+.³⁷ In Malawi, Africa in 2002, 2.8% of TB patients, 94% of whom were coinfecting with HIV, had choroidal granulomas suggestive of ocular TB.³⁸ In a recent retrospective study from India, 15 (<2%) of 766 HIV-infected patients who presented with ophthalmic complaints were found to have ocular TB, all of whom were also said to have concurrent PTB, although diagnostic criteria were not clearly described for either ocular or PTB.²² We summarize this data in Table 2.

The proportion of uveitis attributed to TB has been particularly variable over the last several decades. In 1944, the Wilmer Eye Institute ascribed 79% of uveitis cases to TB.⁴⁰ Ten years later, concomitant with an increased awareness of brucellosis, toxoplasmosis, and sarcoidosis, and stricter criteria for the diagnosis of ocular TB, only 22% of uveitis was attributed to TB.⁴⁰ Variable rates of uveitis attributable to TB have been reported: 0.6% of uveitis patients in Boston from 1982 to 1992; 10.5% in Saudi Arabia from 1995 to 2000; and 7.9% in Japan in 2000.^{13,41,42} A uveitis clinic in Southern India reported 0.39% of its cases were caused by TB from 1992 to 1994.⁴³ According to a study in

Table 2. Selected Studies in Which Rates of Ocular Involvement Were Reported Among Patients With Tuberculosis

Year	Author	Percent of TB Patients With Ocular TB	
		Number	Percentage
1964	Massaro et al ²⁹	4/7	57.14
1967	Donahue ³²	154/10,524	1.46
1996	Biswas and Badrinath ¹²	14/1005	1.39
1997	Bouza et al ³⁷	18/100	18.00
2002	Beare et al ³⁸	3/109	2.02
2004	Mehta ²⁸	6/24	2.92
2005	Mehta and Gilada ³⁹	4/17	23.50
Total		203/11,784 = 1.72%	
Total without Donahue*		49/1262 = 3.88%	

Please note that the definition of tuberculosis and ocular tuberculosis varied between these studies.

*We were interested in the average without data from the Donahue study because of the large number of patients in that study.

Northern India, 9.8% of uveitis cases at a referral eye clinic were caused by TB from 1996 to 2001.⁴⁴ During that same time period, 5.6% of uveitis cases at the Aravind Eye Hospital in Madurai, Tamilnadu, India were caused by TB.⁴⁵ In the United States, the decrease in the proportion of uveitis attributed to TB may reflect improved diagnostic capacity and the overall decrease in the incidence of TB.⁴⁶

Patients receiving immunosuppressive therapy are at particular risk for reactivation of LTBI in the eye and elsewhere. A 4-fold increase in TB was noted among rheumatoid arthritis patients who had received infliximab over those who had not.⁴⁷ Recent clinical trials done on patients receiving infliximab and adalimumab showed that prescreening for LTBI resulted in up to 85% fewer cases of reactivated TB.⁴⁷⁻⁴⁹ Ophthalmologists should apply equal rigor in screening for undiagnosed LTBI when considering immunosuppression in patients with presumed autoimmune ocular disease. Both the possibility of TB masquerading as an autoimmune process or an unrelated LTBI should be explored before the initiation of immunomodulatory therapy. Ophthalmologists confronted with a patient with an autoimmune eye disease requiring immunosuppression or a possible presentation of ocular TB should assess the potential for risk factors for LTBI. According to the CDC, these factors include recent travel to and immigration from regions where TB is endemic; work in healthcare; infection with HIV; work and residence in high-risk congregate housing; low income and access to medical care; intravenous drug use; and

previous tests consistent with LTBI.⁵⁰ Screening strategies for diagnosis of LTBI are discussed later in this text.

HIV and TB promote each other's virulence. Persons living with HIV are more likely to progress from LTBI to TB, to have atypical presentations including EPTB, and to be more difficult to diagnose. For these reasons, TB is a leading cause of death of HIV patients worldwide. Active TB has been associated with an increase in viral load and decrease in CD4 lymphocytes.⁶ Africa's TB incidence has tripled in concert with rising levels of HIV, and HIV is considered the primary reason for the increase in TB in the United States in the 1990s.^{30,51} Five percent of immunocompetent persons infected with TB advance immediately to active disease, compared with 40% of HIV-positive patients.^{2,5} Similarly, EPTB, which is associated with disseminated disease, affects 21% of immunocompetent TB patients and over 50% of those who are HIV-positive.^{1,52,53}

The implications for ocular TB in the presence of HIV infection are less clear. A large study in Chennai, India from 1993 to 2005 found the incidence of ocular TB in HIV patients to be 1.95%.²² A study from the same population reported that 1.39% of patients with active PTB and EPTB had ocular TB, suggesting that the HIV coinfection does not dramatically increase the rate of ocular TB.¹² The relatively high prevalence of EPTB and disseminated TB in HIV patients does not seem to be reflected in increased cases of ocular TB.^{2,22} Like non-HIV patients, among HIV-infected patients with ocular TB in these studies, choroidal granulomas were the most common presentation. However, there was a relatively high rate of panophthalmitis due to TB compared with data from immunocompetent individuals.²²

■ Challenges Toward the Diagnosis of Ocular TB

The diagnosis of ocular TB is important because prompt treatment may improve the individual patient's outcome. Delayed diagnosis can lead to pain, vision loss, and systemic complications of the infection. Diagnosis is also important from a public health perspective because identification and treatment of coexisting PTB may prevent TB transmission to others. Unfortunately, there is no pathognomonic ophthalmic finding for ocular TB. Ocular TB is difficult to diagnosis due to its similarity to other causes of uveitis, the invasiveness of obtaining tissue samples, and limitations of available diagnostic tests. Clinician suspicion is an imperative first step toward the correct diagnosis.^{3-6,17,19,23,26,30,36}

■ Diagnostic Tests for TB

The diagnosis of ocular TB is most certain if *M. tuberculosis* is cultured from the eye. This is rarely possible, either because of

difficulties in acquiring a specimen or unavailability of mycobacterial culture facilities. Histologic examination of an ocular biopsy specimen can be suggestive of the diagnosis. Although not necessary for the diagnosis, caseating granulomas are a sensitive finding of the histology of *M. tuberculosis* infection.^{4,6,10}

In a patient with consistent ocular features, but without microbiologic confirmation from the eye, the diagnosis of TB from another anatomic site can be helpful. The first step in the investigation for evidence of TB is a thorough history and physical examination. The characteristics and availability of TB diagnostic technology (varies substantially worldwide) are described in several recent reviews.^{54,55}

The WHO recommends sputum microscopic examination to establish the diagnosis of PTB because the method detects the most infectious TB cases, it is highly specific, inexpensive, and widely established.⁵⁶ However, it is difficult to maintain capacity and expertise for reliable sputum microscopy, it requires repeat patient visits and is insensitive (35% to 70%; requiring 5000 to 10,000 bacteria/mL of sputum) especially in HIV patients, children, and EP disease.⁵⁷ AFB smear is also unable to distinguish among mycobacterial species, and between drug-resistant and drug-sensitive *M. tuberculosis*.

In settings with mycobacterial culture capacity, sputum, blood, cerebrospinal fluid, lymph node, or any other site implicated as infected by physical examination should be cultured if AFB sputum smear is negative. Sputum culture detects 80% of TB cases with >98% specificity, is more sensitive than smear (requires 10 to 100 bacteria/mL of sputum), allows species identification, and allows drug susceptibility testing.^{58–60} Limitations include that culturing is slow (2 to 6 wk); and that it requires specialized personnel, equipment, water, and electricity.

Radiography can suggest active or remote PTB, which in turn can support a diagnosis of ocular TB. Advantages of radiography include convenience, routine availability in developed country settings, and high sensitivity in HIV-negative patients. The results may also be relevant in diagnosing sarcoidosis that is often a possibility when a diagnosis of ocular TB is being considered. Limitations of radiology as a method to diagnosis TB are that it is nonspecific and especially unreliable for HIV-infected person. In resource-limited settings, it is considered expensive, and has limited availability at point-of-care clinics because it requires specialized equipment and a power source.^{55,61}

Nucleic acid amplification (NAA) methods may represent a significant improvement for TB diagnosis. Parts of the *M. tuberculosis* genome are amplified and bound to a signal-generating probe to allow detection. Tests based on NAA are rapid and usually highly specific for *M. tuberculosis* (close to 100%), with excellent sensitivity (>95% in smear-positive, 60% to 70% in smear-negative sputum specimens).^{62–64}

Limitations of NAA tests include cost and complexity. Currently, NAA tests are used primarily for confirmation of smear positive results or for primary case finding in combination with other methods. Because of their price and complexity, the use of these methods is still limited to developed countries.⁵⁵

Ocular samples have also been analyzed using NAA tests in a number of studies.^{11,34,65–69} The probes used often differ between clinical sites as does the criteria for interpretation, depending on the population tested. For instance, in the study of Eales disease discussed earlier, although 47.8% of patients with Eales disease had *M. tuberculosis* detected by PCR in their epiretinal membranes, 11% of the non-Eales control patients from the same population tested positive.³⁴ Although supportive of the association between Eales and TB, this study also reveals the high background rate of TB detectable by PCR in ocular specimens from a population of patients presumed not to have TB-related ocular disease. The rate of PCR-positive tests for *M. tuberculosis* among patients with Eales and controls was lower, 20.8% and 4.2%, respectively, in a 2002 study which examined vitreous samples rather than epiretinal membranes.³⁵ These different rates of positive PCR tests among Eales patients and controls suggest that the ability to detect DNA from *M. tuberculosis* in Eales and perhaps other forms of ocular TB may depend of the ocular tissue sampled.

Reliable, serologic tests for TB diagnosis have been a goal for TB control for many years. There are many theoretic advantages, but field testing of this technology has repeatedly shown poor sensitivity and inability to distinguish between TB, *Bacillus Calmette-Guérin* (BCG), LTBI, and nontuberculous mycobacteria.⁵⁵

Mycobacteriophage assay is a method that uses viruses that infect mycobacteria to demonstrate the presence of *M. tuberculosis*.⁷⁰ This technology is not yet widely available.

Other novel technologies for TB diagnosis include those that are based on detection of mycobacterial antigens. For example, during TB disease, *M. tuberculosis* cells are lysed by the host immune system, metabolized, and DNA and carbohydrate antigens such as lipoarabinomannan are released into the blood, filtered by the kidneys, and can be detected in the urine. Preliminary studies to detect lipoarabinomannan and the transrenal DNA in the urine are so far promising, PCR has been used and shown good sensitivity in preliminary studies.^{71–75} Larger studies under field conditions among TB suspects are needed. Advantages of these approaches include ease of specimen collection, less generation of infectious aerosols during collection compared with sputum, and because tests are based on the detection of antigen, performance is not limited by the status of the immune system of the patient.

■ Diagnosis of LTBI

In highly TB endemic settings where most of the population has evidence of LTBI, the diagnosis of ocular TB is not meaningfully influenced by confirmation of LTBI. However, in settings where TB is less common (such as the United States and Western Europe), the diagnosis of ocular TB may be considered more likely by diagnosis of LTBI. There are 2 tests that can be used to detect LTBI. The Mantoux tuberculin skin test (TST) is performed by injecting a small amount of fluid containing antigens of *M. tuberculosis* (called tuberculin) into the skin in the lower part of the arm. A person given the TST must return within 48 to 72 hours to have a trained health care worker look for a reaction on the arm.

A second type of test to detect LTBI is the interferon gamma release assays (IGRAs). These are blood tests that measure how the patient's immune system reacts to *M. tuberculosis*. The QuantiFERON-TB Gold test (QFT-G) is an IGRA, which is approved in the United States for immunocompetent persons. The T Spot TB Test is an IGRA that is widely used elsewhere in the world and is under consideration for licensure in the United States. A positive TST or IGRA only indicates that a person has LTBI. It does not tell whether or not the person has TB disease. Other tests, such as a chest x-ray and a sample of sputum, are needed to see whether the person has PTB disease.

BCG is a TB vaccine that contains a strain of the closely related bacteria, *Mycobacterium bovis*. BCG is used in many countries, but it is not generally recommended in the United States. BCG vaccination does not completely prevent people from getting TB. It may also cause a false-positive TST. To detect LTBI in persons who have been vaccinated with BCG, the IGRAs are preferred to the TST because of less cross-reaction to the BCG.

The T SPOT-TB (Oxford Immunotec, Oxford, UK) has been shown to give very high sensitivity (97%) in active TB⁷⁶ and has been used in a number of contact tracing situations where it has shown high correlation to the amount of exposure.^{77,78} The QuantiFERON-Gold (Cellestis Limited, Victoria, Australia) has demonstrated a specificity of 98.1% among 216 BCG-vaccinated Japanese nursing students who were entering their training and considered at low risk for LTBI. A sensitivity of 89.0% was reported in 118 patients with culture-confirmed TB.⁷⁹ In another study, QFT-G was compared with TST by using 2 tuberculin units of RT-23. In a group of 99 healthy, BCG-vaccinated medical students in Korea, the specificity of QFT-G was 96%, compared with 49% for the TST. Among 54 patients with PTB disease, the sensitivity of the QFT-G was 81%, compared with 78% for the TST.⁸⁰ QFT-G and the TST were compared in an unselected population of 318 hospitalized patients.⁸¹ QFT-G had greater sensitivity for TB disease (67%) than did

TST (33%), but indeterminate QFT-G responses were common (21%) among patients with negative TST results, the majority of whom were thought to be immunocompromised or immunosuppressed.⁸²

The sensitivity of these tests is reduced during active TB and during any immunocompromised state, whether by medication, overwhelming TB infections (such as miliary TB), comorbid illness, or HIV. The utility of these tests in ocular TB is uncertain and stems from our lack of understanding as to whether ocular TB represents active TB similar to other well-described forms of EPT. Studies from 1996 to 2006, which we reviewed, indicate that approximately 52% of these cases of ocular TB were associated with active TB elsewhere (Table 1). If ocular TB is a form of active TB, a positive TST or IGRA may be helpful if positive in establishing TB exposure, but there may also be reduced sensitivity of these tests as there is in other forms of active TB. Alternatively, if ocular TB is not associated with a generalized reduction in the maintenance of immune-mediated TB latency, responses to TST and IRGA may be normal and possibly enhanced during active ocular TB. If this is the case, a negative or minimally reactive TST or IRGA may be very helpful in ruling out ocular TB whereas an enhanced response may be helpful in establishing the proper diagnosis. In practice, many clinicians working in populations with a high prevalence of TB use a robust response to TST to support the diagnosis of ocular TB in patients with characteristic clinical findings. However, in a report of 1005 patients with active TB, there was no statistically significant association of a positive Mantoux test and ocular TB.¹² The results may have been different in patients without evidence of active PTB or EPTB, but more study is warranted to explore these competing hypotheses and to understand the value of these tests in patients with presumed ocular TB (Tables 1, 2).

■ Suggested Diagnostic Approach for Ocular TB

Testing for TB by ophthalmologists usually occurs in response to 2 clinical situations: (1) screening of patients for LTBI who are candidates for immunosuppressive therapy, but are not suspected of having ocular TB and (2) screening of patients suspected of having ocular TB.

(1) Testing to exclude LTBI begins with an appropriate history for risk factors for TB. In a patient from a population with a low incidence of TB and no additional personal risk factors for TB, a TST or IGRA should be ordered. If this is negative no further work up is necessary. Many uveitis specialists routinely order chest x-rays when evaluating patients because of their value in both TB and sarcoidosis. If the TST or IGRA suggest LTBI, a chest x-ray should be obtained and if the chest x-ray reveals findings consistent with TB, a sputum sample should be obtained for smear and culture. At this point in the evaluation, consultation with an infectious disease specialist is usually warranted.

If the sputum is positive, antituberculosis therapy (ATT) should be initiated and the patient reported to the health department. If the sputum is negative, consideration should be given to a trial of ATT for culture-negative TB. In this scenario, the new IGRAs may be helpful in streamlining the evaluation of patients as they are simpler than skin testing in that they do not require patient follow up. A small study, 12 patients, compared TST to IGRA, QuantiFERON-TB test, for screening ophthalmology patients before immunosuppressive therapy and found similar results between the 2 methodologies.²³ It should be noted that this study used a first generation IGRA. More recently developed IGRA tests, as discussed previously, seem to be more specific than TST in patients previously vaccinated with BCG.²³

In a patient from a population with a high incidence of TB, exposure can be assumed and the history should be focused more on eliciting symptoms of active TB. In a patient without symptoms of TB, a TST or IGRA may be helpful in this diagnosing LTBI, but as stated earlier both are unreliable in active TB. Many physicians proceed directly to a chest x-ray when screening patients with significant risk factors for LTBI before immunosuppression. If chest x-ray is negative, immunosuppression is given. If it is positive or there are other signs or symptoms of TB, the patient is referred to an infectious disease specialist for evaluation before initiating immunosuppression.

(2) The diagnosis of ocular TB depends on several lines of evidence. First, the patient must have a characteristic lesion. Although ocular TB should be at least fleetingly considered in all cases of uveitis and retinal vasculitis, choroidal granulomas should raise particular concern for the possibility of ocular TB, as should granulomatous uveitis unresponsive to steroid treatment. Second, exposure to TB has to be established. In patients from populations in which there is a high incidence of TB, this can be taken for granted. In patients from populations with a low incidence of TB, evidence of LTBI can be established as described above. However, it must be kept in mind that TST and IGRA may be unreliable in patients with active TB. Thus, negative testing for LTBI does not exclude the possibility of ocular TB. Third, evidence of active TB should be pursued. In some cases, patients will have obvious findings such as active pulmonary disease or lymph nodes. However, in other cases, the findings will be more subtle. In these cases a chest x-ray is warranted. If this shows evidence of TB, the sputum should be evaluated. If the sputum shows evidence of TB, then ATT should be started and the health department notified. In patients with a positive chest x-ray but negative sputum, consideration should be given to an empiric trial of ATT to see if there is improvement in the ocular findings during the course of this treatment. This empiric trial, also known as the Schlaegel test, was traditionally a course of INH for 3 weeks while monitoring for a clinical response to treatment.⁸³ In the era of drug resistant TB, many

ophthalmologists advocate a similar trial, but employ 3 or 4 drugs with activity against *M. tuberculosis*. A therapeutic response to ATT is taken as evidence of ocular TB and treatment is continued.

In sum, the diagnosis of ocular TB remains a challenge. Prospective studies with strict criteria for the diagnosis of TB and ocular TB are necessary to better define the incidence of ocular TB. Although new testing methodologies for TB are promising, the utility of these has yet to be established in patients with ocular TB and thus research on their application to ocular TB is also warranted. Finally in cases in which uncertainty about TB remains, biopsy of the eye for culture, histologic examination, and/or NAA testing may be useful to establish the diagnosis of ocular TB.

■ References

1. CDC. *Tuberculosis Cases and Percentages by Pulmonary and Extrapulmonary Disease*. Atlanta, GA: States, US Department of Health and Human Services, CDC; 2005.
2. Maniar JK, Kamath RR, Mandalia S, et al. HIV and tuberculosis: partners in crime. *Indian J Dermatol Venereol Leprol*. 2006;72:276–282.
3. Chuka-Okosa CM. Tuberculosis and the eye. *Nigerian J Clin Pract*. 2006;9:68–70.
4. Kurup SK, Chan CC. Mycobacterium-related ocular inflammatory disease: diagnosis and management. *Ann Acad Med Singapore*. 2006;35:203–209.
5. Tabbara KF. Ocular tuberculosis: anterior segment. *Int Ophthalmol Clin*. 2005;45:57–69.
6. Deschenes J, Wade NK, Lalonde R. Tuberculosis and atypical Mycobacteria. In: Tasman W, Jaeger E, eds. *Duane's Ophthalmology*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2006.
7. Helm CJ, Holland GN. Ocular tuberculosis. *Surv Ophthalmol*. 1993;38:229–256.
8. Maitre-Jan A. Traite des maladies des yeux. 1711, Troyes. 456. In: Helm CJ, Holland GN, Ocular tuberculosis. *Surv Ophthalmol*. 1993;38:229–256.
9. Wecker LV. Die Erkrankungen des Uvealtractus und des Glaskorpers. Tuberkeln der Choroidea. Chloroiditis tuberculosi, in Graefe A, Saemisch T, eds. *Handbuch der Gesamten Augenheilkunde*. 1874;4:642–648. In: Helm CJ, Holland GN. Ocular tuberculosis. *Surv Ophthalmol*. 1993;38:229–256.
10. Gupta A, Gupta V. Tubercular posterior uveitis. *Int Ophthalmol Clin*. 2005;45:71–78.
11. Ortega-Larrocea G, Bobadilla-del-Valle M, Ponce-de-Leon A, et al. Nested polymerase chain reaction for *Mycobacterium tuberculosis* DNA detection in aqueous and vitreous of patients with uveitis. *Arch Med Res*. 2003;34:116–119.
12. Biswas J, Badrinath SS. Ocular morbidity in patients with active systemic tuberculosis. *Int Ophthalmol*. 1996;19:293–298.
13. Morimura Y, Okada AA, Kawahara S, et al. Tuberculin skin testing in uveitis patients and treatment of presumed intraocular tuberculosis in Japan. *Ophthalmology*. 2002;109:851–857.
14. Sarvananthan N, Wiselka M, Bibby K. Intraocular tuberculosis without detectable systemic infection. *Arch Ophthalmol*. 1998;116:1386–1388.
15. Shome D, Honavar S, Vemuganti G, et al. Orbital tuberculosis manifesting with endophthalmos and causing a diagnostic dilemma. *Ophthalm Plast Reconstr Surg*. 2006;22:219–221.
16. Sahu GN, Mishra N, Bhutia RC, et al. Manifestations in ocular tuberculosis. Ahmedabad: National Conference on Tuberculosis and Chest Diseases. *Ind J Tub*. 1998;45:153–154.
17. Kuruvilla A. Correspondence: ocular tuberculosis. *Lancet*. 2003;361:260–261.

18. Taynac E, Akova Y, Yilmaz G. Indocyanine green angiography in ocular tuberculosis. *Ocul Immunol Inflamm.* 2004;12:317–322.
19. Demicri H, Shields CL, Shields JA, et al. Ocular tuberculosis masquerading as ocular tumors. *Surv Ophthalmol.* 2004;49:78–88.
20. Torres RM, Calonge M. Macular edema as the only ocular finding of tuberculosis. *Am J Ophthalmol.* 2004;138:1048–1049.
21. Domingues MF, Palmares J, Reis J, et al. Presumed bilateral multifocal tuberculous choroiditis in an HIV-negative patient with disseminated tuberculosis. *Jpn J Ophthalmol.* 2005;49:334–336.
22. Babu S, Kumarasamy N, Therese L, et al. Ocular tuberculosis in acquired immunodeficiency syndrome. *Am J Ophthalmol.* 2006;142:413–418.
23. Kurup SK, Buggage RR, Clarke GL, et al. Gamma interferon assay as an alternative to PPD skin testing in selected patients with granulomatous intraocular inflammatory disease. *Can J Ophthalmol.* 2006;41:737–740.
24. Mehta S. Fundus fluorescein angiography of choroidal tubercles: case reports and review of literature. *Indian J Ophthalmol.* 2006;54:273–275.
25. Reddy S, Roe R, Cunningham ET Jr, et al. Diagnostic and therapeutic challenges. *Retina.* 2006;26:954–959.
26. Varma D, Anand S, Reddy AR, et al. Tuberculosis: an under-diagnosed aetiological agent in uveitis with an effective treatment. *Eye.* 2006;20:1068–1073.
27. Whitford J, Hansman D. Primary tuberculosis of the conjunctiva. *Med J Aust.* 1977;1:486–487.
28. Mehta S. Ocular lesions in acute disseminated tuberculosis. *Ocul Immunol Inflamm.* 2004;12:311–315.
29. Massaro D, Katz S, Sachs M. Choroidal tubercles: a clue to hematogenous tuberculosis. *Ann Intern Med.* 1964;60:231–241.
30. Mistr SK, Chavis PS, Scales D. Tuberculosis, in eMedicine Specialties, Sheppard JD, et al. eds., 2006.
31. Cunningham ET, Rathinam SR. TB or not TB? The perennial question. *Br J Ophthalmol.* 2001;85:127–128.
32. Thompson MJ, Albert DM. Ocular tuberculosis. *Arch Ophthalmol.* 2005;123:844–849.
33. Chapman CB, Whorton CM. Acute generalized miliary tuberculosis in adults. *N Engl J Med.* 1946;235:239–248.
34. Madhavan HN, Therese KL, Gunisha P, et al. Polymerase chain reaction for detection of *Mycobacterium tuberculosis* in epiretinal membrane in Eales' disease. *Invest Ophthalmol Vis Sci.* 2000;41:822–825.
35. Madhavan HN, Therese KL, Doraiswamy K. Further investigations on the association of *Mycobacterium tuberculosis* with Eales' Disease. *Indian J Ophthalmol.* 2002;50:35–39.
36. DeVoe A, Locatcher-Khorazo D. The external manifestations of ocular tuberculosis. *Tr Am Ophth Soc.* 1964;62:204–211.
37. Bouza E, Merino P, Munoz P, et al. Ocular tuberculosis. A prospective study in a general hospital. *Medicine (Baltimore).* 1997;76:53–61.
38. Beare NA, Kublin JG, Lewis DK, et al. Ocular disease in patients with tuberculosis and HIV presenting with fever in Africa. *Br J Ophthalmol.* 2002;86:1076–1079.
39. Mehta S, Gilada IS. Ocular tuberculosis in acquired immune deficiency syndrome (AIDS). *Ocul Immunol Inflamm.* 2005;13:87–89.
40. Woods AC. *Endogenous Inflammations of the Uveal Tract.* Baltimore, Maryland: Williams and Wilkins Company; 1961.
41. Islam SM, Tabbara KF. Causes of uveitis at The Eye Center in Saudi Arabia: a retrospective review. *Ophthalmic Epidemiol.* 2002;9:239–249.
42. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol.* 1996;114:593–599.

43. Biswas J, Narain S, Das D, et al. Pattern of uveitis in a referral uveitis clinic in India. *Int Ophthalmol*. 1996;20:223–228.
44. Singh R, Gupta V, Gupta A. Pattern of uveitis in a referral eye clinic in north India. *Indian J Ophthalmol*. 2004;52:121–125.
45. Rathinam SR, Namperumalsamy P. Global variation and pattern changes in epidemiology of uveitis. *Ind J Ophthalmol*. 2007;55:173–183.
46. CDC. *Prevention and Control of Tuberculosis in the US Communities with at-risk minority populations: recommendations of the Advisory Council for the Elimination of Tuberculosis, United States, in MMWR*. Atlanta, GA: US Department of Health and Human Services, CDC; 1992.
47. Bresnihan B, Cunnane G. Infection complications associated with the use of biologic agents. *Rheum Dis Clin North Am*. 2003;29:185–202.
48. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest*. 2005;127:1064–1071.
49. Winthrop K. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol*. 2006;2:602–610.
50. CDC. *Epidemiology; Risk Groups, in Core Curriculum on Tuberculosis*. Atlanta, GA: US Department of Health and Human Services, CDC; 2000.
51. Dunn J, Helm C, Davidson P. Ocular manifestations of tuberculosis. In: Holland GN, Pepose JS, Wilhelmus KR, eds. *Ocular Infection and Immunity*. Mosby: Hanover, MD; 1996:1405–1420.
52. Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res*. 2004;120:316–353.
53. Sharma SK, Mohan A, Kadhivaran T. HIV-TB co-infection: epidemiology, diagnosis & management. *Indian J Med Res*. 2005;121:550–567.
54. Perkins M, O'Brien R. New diagnostics for tuberculosis: Essential elements for global control and elimination. In: Raviglione MC, ed. *Tuberculosis: A Comprehensive, International Approach*. New York: Informa Health Care; 2006.
55. WHO. *Diagnostics for Tuberculosis: Global Demand and Market Potential in UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FINN)*. Geneva, Switzerland: World Health Organization; 2006.
56. WHO. *Treatment of Tuberculosis: Guidelines for National Programmes*. W.C.T. 313 ed. 3rd ed. Geneva, Switzerland: World Health Organization; 2003:1–107.
57. WHO. *Laboratory Services in Tuberculosis Control Part II: Microscopy*. Geneva, Switzerland: World Health Organization; 1998.
58. Idigoras P, Beristain X, Iturzaeta A, et al. Comparison of the automated nonradiometric Bactec MGIT 960 system with Lowenstein-Jensen, Coletsos, and Middlebrook 7H11 solid media for recovery of mycobacteria. *Eur J Clin Microbiol Infect Dis*. 2000;19:350–354.
59. Lee JJ, Suo J, Lin CB, et al. Comparative evaluation of the BACTEC MGIT 960 system with solid medium for isolation of mycobacteria. *Int J Tuberc Lung Dis*. 2003;7:569–574.
60. Roggenkamp A, Hornef MW, Masch A, et al. Comparison of MB/BacT and BACTEC 460 TB systems for recovery of mycobacteria in a routine diagnostic laboratory. *J Clin Microbiol*. 1999;37:3711–3712.
61. Nakamura K, Ohmi A, Kurihara T, et al. Studies on the diagnostic value of 70 mm radiophotograms by mirror camera and the reading ability of physicians. *Kekkaku*. 1970;45:121–128.
62. Abe C, Hirano K, Wada M, et al. Detection of *Mycobacterium tuberculosis* in clinical specimens by polymerase chain reaction and Gen-Probe Amplified *Mycobacterium tuberculosis* Direct Test. *J Clin Microbiol*. 1993;31:3270–3274.

63. Clarridge JE III, Shawar RM, Shinnick TM, et al. Large-scale use of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in a routine mycobacteriology laboratory. *J Clin Microbiol.* 1993;31:2049–2056.
64. Wobeser WL, Krajden M, Conly J, et al. Evaluation of Roche Amplicor PCR assay for *Mycobacterium tuberculosis*. *J Clin Microbiol.* 1996;34:134–139.
65. Bodaghi B, LeHoang P. Ocular manifestations of systemic disease. *Curr Opin Ophthalmol.* 2000;11:443–448.
66. Bodaghi B, LeHoang P. Testing ocular fluids in uveitis. *Ophthalmol Clin North Am.* 2002;15:271–279.
67. Chakravorty S, Tyagi JS. Novel multipurpose methodology for detection of mycobacteria in pulmonary and extrapulmonary specimens by smear microscopy, culture, and PCR. *J Clin Microbiol.* 2005;43:2697–2702.
68. Negi SS, Anand R, Basir SF, et al. Protein antigen b (Pab) based PCR test in diagnosis of pulmonary and extra-pulmonary tuberculosis. *Indian J Med Res.* 2006;124: 81–88.
69. Therese KL, Jayanthi U, Madhavan HN. Application of nested polymerase chain reaction (nPCR) using MPB 64 gene primers to detect *Mycobacterium tuberculosis* DNA in clinical specimens from extrapulmonary tuberculosis patients. *Indian J Med Res.* 2005;122:165–170.
70. Albert H, Heydenrych A, Brookes R, et al. Performance of a rapid phage-based test, FASTPlaqueTB, to diagnose pulmonary tuberculosis from sputum specimens in South Africa. *Int J Tuberc Lung Dis.* 2002;6:529–537.
71. Boehme C, Molokova E, Minja F, et al. Detection of mycobacterial lipoarabinomannan with an antigen-capture ELISA in unprocessed urine of Tanzanian patients with suspected tuberculosis. *Trans R Soc Trop Med Hyg.* 2005;99:893–900.
72. Kafwabulula M, Ahmed K, Nagatake T, et al. Evaluation of PCR-based methods for the diagnosis of tuberculosis by identification of mycobacterial DNA in urine samples. *Int J Tuberc Lung Dis.* 2002;6:732–737.
73. Sechi LA, Pinna MP, Sanna A, et al. Detection of *Mycobacterium tuberculosis* by PCR analysis of urine and other clinical samples from AIDS and non-HIV-infected patients. *Mol Cell Probes.* 1997;11:281–285.
74. Tessema TA, Hamasur B, Bjun G, et al. Diagnostic evaluation of urinary lipoarabinomannan at an Ethiopian tuberculosis centre. *Scand J Infect Dis.* 2001;33: 279–284.
75. Torrea G, Van de Perre P, Ouedraogo M, et al. PCR-based detection of the *Mycobacterium tuberculosis* complex in urine of HIV-infected and uninfected pulmonary and extrapulmonary tuberculosis patients in Burkina Faso. *J Med Microbiol.* 2005;54(Pt 1):39–44.
76. Meier T, Eulenbruch HP, Wrighton-Smith P, et al. Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice. *Eur J Clin Microbiol Infect Dis.* 2005;24:529–536.
77. Richeldi L, Ewer K, Losi M, et al. T cell-based tracking of multidrug resistant tuberculosis infection after brief exposure. *Am J Respir Crit Care Med.* 2004;170: 288–295.
78. Zellweger JP, Zellweger A, Ansermet S, et al. Contact tracing using a new T-cell-based test: better correlation with tuberculosis exposure than the tuberculin skin test. *Int J Tuberc Lung Dis.* 2005;9:1242–1247.
79. Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. *Am J Respir Crit Care Med.* 2004; 170:59–64.
80. Kang YA, Lee HW, Yoon HI, et al. Discrepancy between the tuberculin skin test and the whole-blood interferon γ assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. *JAMA.* 2005;293:2756–2761.

81. Ferrara G, Losi M, Meacci M, et al. Routine hospital use of a new commercial whole blood interferon-gamma assay for the diagnosis of tuberculosis infection. *Am J Respir Crit Care Med.* 2005;172:631–635.
82. CDC. *Guidelines of Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States*, in MMWR. Atlanta, GA: US Department of Health and Human Services, CDC; 2005.
83. Abrams J, Schlaegel TF Jr. The role of the isoniazid therapeutic test in tuberculous uveitis. *Am J Ophthalmol.* 1982;94:511–515.