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Intraocular manifestations of mycobacterium tuberculosis: A review of the literature☆

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ABSTRACT

Mycobacterium tuberculosis: is most commonly associated with pulmonary infection. However, tuberculosis (TB) can also affect the eye. TB can affect nearly any tissue in the eye, and a high index of suspicion is required for accurate diagnosis, as many of the intraocular manifestations of TB can mimic other, more common diseases. Correct diagnosis is critical because systemic anti-tuberculosis treatment may be required, and vision loss or even loss of the affected eye can occur without proper treatment. Thus, it is important for ophthalmologists and infectious disease specialists to work together to accurately diagnose and treat intraocular TB. This article reports the various known presentations of intraocular TB and reviews important elements of diagnosis and treatment.

Review of the literature

Background

Tuberculosis (TB) is an airborne infectious disease that most commonly affects the lungs. The causative organism is the obligate aerobic, acid-fast bacillus *Mycobacterium tuberculosis* [1–3]. There are numerous manifestations of extrapulmonary tuberculosis, many involving the eye [4]. This review will focus primarily on the intraocular forms of TB. A previous review summarized orbital TB [5].

Literature search strategy

The literature was reviewed using a PubMed search with both Medical Subject Headings (MeSH) and keywords. MeSH terms included tuberculosis, ocular tuberculosis, eye infections and visual acuity. Keywords included eye, intraocular, periocular, ocular, uveitis, sclerouveitis, panuveitis, choroiditis, retina, retinal, tuberculosis, and "ocular tuberculosis." Results were limited to available peer-reviewed, English-language journals published between 1930 and 2015. All papers were reviewed, (including single case reports), to determine if they should be referenced in this review.

Epidemiology

The Centers for Disease Control and Prevention (CDC) estimates that one third of the world's population is infected with TB, but only ten percent of infected persons develop clinical manifestations of the disease [6]. Of the ten percent with detectable disease, sixteen to twenty-seven percent have extrapulmonary TB involvement, which includes those with intraocular findings [7]. The incidence of intraocular TB has been reported to range from 1.4 to 18 percent [4, 8–13]. Age over forty, female gender, and HIV infection increase the risk of extrapulmonary TB, and individuals with HIV also have an increased risk of ocular TB [4].

Intraocular involvement

Hematogenous spread is the primary mechanism by which TB affects the eye [14–16]. However, direct local extension and hypersensitivity responses from infection elsewhere in the body can also result in intraocular findings [14]. Intraocular TB often affects the ciliary body and choroid due to the high regional oxygen tension of these tissues, and uveitis, especially posterior uveitis, is the most common form of intraocular TB [6,14,16]. Regardless of the clinical presentation, multiple recurrences of inflammation despite treatment should increase the level of suspicion for intraocular TB in a patient with TB risk factors. The wide variety of ways in which TB

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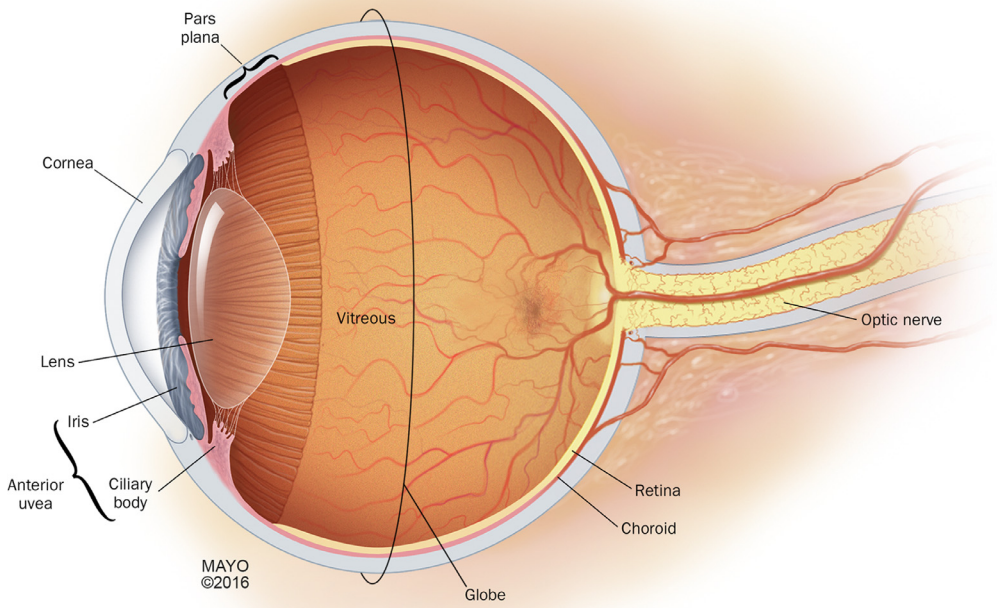

Fig. 1. Anatomical diagram of the eye. The various anatomical structures of the eye that can be affected by tuberculosis are labeled. Labels correspond to the structures listed in Table 1

Table 1
Clinical presentations of intraocular tuberculosis.

Tissue	Possible presentations
Anterior uvea/ Pars plana	Granulomatous anterior uveitis Iris nodules Iris atrophy Intermediate uveitis
Lens	Cataract
Choroid	Tubercles Tuberculomas Abscesses Choroiditis
Retina	Macular edema Intra- or preretinal hemorrhage Retinitis Vasculitis Neovascularization Neuroretinitis Eales disease
Optic nerve	Optic neuritis Retrobulbar neuritis Papillitis Papilledema Tubercles
Globe	Panuveitis Endophthalmitis Panophthalmitis Globe rupture

can affect the intraocular tissues are described below and summarized in Table 1 with a corresponding diagram outlining the relevant structures of the eye in Fig. 1.

Anterior uveitis

TB can cause a granulomatous uveitis with iris and angle granulomas, mutton-fat keratic precipitates, posterior synechiae, and occasionally hypopyon [17–20]. A pigmented hypopyon, iris nodules, and iris atrophy have also been reported [14,21,22]. Cataract can develop as a result of ongoing inflammation and steroid treatment, and extensive synechiae can lead to angle closure glaucoma [14]. Of patients with TB-related uveitis, anterior uveitis has been reported in 12 to 36 percent of the cases; these patients are more likely to have broad-based posterior synechiae and less likely to have filiform synechiae than patients with uveitis unrelated to TB [6,23,24].

Posterior and panuveitis

Panuveitis has been reported in 11 to 20 percent of patients with TB uveitis (Fig. 2), whereas posterior uveitis accounts for 35 to 42 percent of intraocular TB [6,23]. Multifocal choroiditis is the most common manifestation of posterior segment involvement (Fig. 3) [6,14,15,23]. Retinitis usually occurs in the setting of concomitant choroiditis rather than as an isolated syndrome [6]. TB-associated posterior uveitis can also take the form of serpiginous-like choroiditis (Figs. 4 and 5), which is hypothesized to be a hypersensitivity reaction that progresses relentlessly despite steroid treatment. [6,25]. Serpinginous-like choroiditis may be an important marker for TB even in patients residing in non-endemic regions [26,27]. In contrast to classic serpiginous choroiditis, the lesions in TB-associated serpiginous-like choroiditis are more pigmented, more likely to be multifocal, and often arise outside the peripapillary region [28]. However, both TB-associated choroiditis and true serpiginous choroiditis can be difficult to treat. Patients with serpiginous-like choroiditis are typically from TB-endemic regions and/or of Asian Indian ethnicity [29]. In one report, serpiginous-like choroiditis was found in 21.5 percent of patients with TB uveitis in Tunisia, North Africa, and another report found that patients with TB-associated uveitis are more likely to have serpiginous choroiditis than patients with uveitis unrelated to TB [23,24]. Since chorioretinal inflammation may breach Bruchs

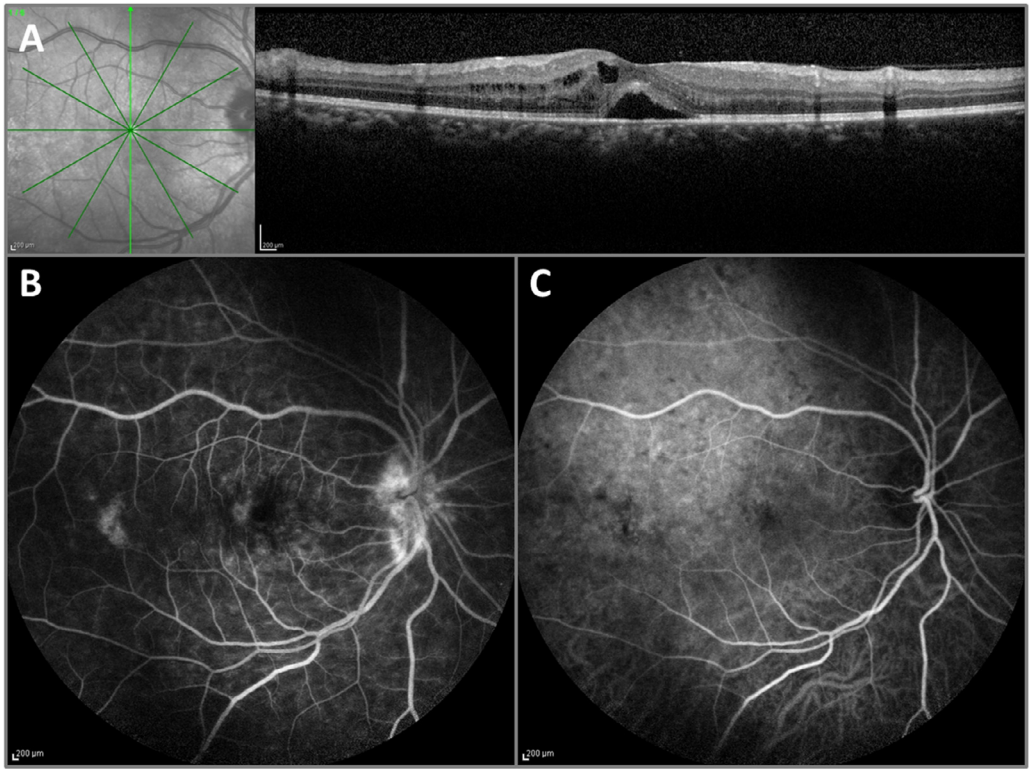

Fig. 2. Panuveitis secondary to tuberculosis. Optical coherence tomography of the right eye (A) reveals subfoveal fluid with intraretinal cysts and diffuse thickening. There is mild diffuse macular leakage on fluorescein angiography (B) with more distinct areas of leakage in the central and temporal macula. Indocyanine green demonstrates a vague area of hypercyanescence in the superior macula (C). The left eye looked similar.

membrane, all types of chorioretinal scars should be monitored for the development of neovascularization [14].

Tubercles, tuberculomas, and subretinal abscesses

Another manifestation of TB-associated posterior uveitis is the tubercle, which is a small nodule that is usually located in the posterior pole. Tubercles may be unilateral or bilateral, typically lack associated vitreitis, and are usually multifocal in miliary TB [14,30]. Tubercles are strongly associated with meningitis [31].

Large choroidal tuberculomas measuring up to 14 mm are encountered less commonly [32,33]. Tuberculomas are yellow subretinal masses that mimic tumors and often have associated exudative retinal detachments [6]. They can occur in immunocompetent patients, those with disseminated TB, and those with central nervous system TB [34–38].

Sub-retinal abscesses occur as a result of liquefaction necrosis in caseating granulomas and can develop in patients with disseminated TB [14,39]. Vitreitis and retinal hemorrhages can also be associated with these abscesses [6].

Endophthalmitis and panophthalmitis

If sub-retinal abscesses go untreated, they can rupture and result in endophthalmitis [15,40,41]. TB endophthalmitis is exceedingly rare, with only 18 cases published worldwide [42]. Panophthalmitis, which includes scleral involvement, can also occur, leading to globe rupture or scleral calcification in advanced cases [14,43].

Retinal vasculitis and other retinovasculopathies

Retinal vasculitis, which is more common with TB-associated intraocular inflammation than non-TB associated uveitis, typically presents as a periphlebitis and very rarely involves the arterioles in intraocular TB [24,44]. Periphlebitis is typically accompanied by vitreitis and is the second most common presentation of intraocular TB [45]. In a patient with TB risk factors, TB should be highly suspected in the setting of exudative hemorrhagic periphlebitis [46] Ischemic central retinal vein occlusion has also been reported in the setting of retinal vasculitis due to TB [47].

Eales disease, first described by Henry Eales in 1882, is characterized by peripheral capillary nonperfusion, neovascularization, recurrent vitreous hemorrhages, periphlebitis, and intraocular fibrovascular proliferation in a quiet eye (Fig. 6). This entity typically affects otherwise healthy men in their third to fourth decade of life from TB-endemic countries. Associated systemic symptoms have been reported to include epistaxis, peripheral circulation disorders, headache, and constipation [48–50]. *M. tuberculosis* DNA has been detected in patients with Eales disease, but it remains unclear whether or not TB is directly causative of this entity, or if it is a separate retinal hypersensitivity reaction [19,46,51–53].

Neuroretinitis and optic neuropathy

Neuroretinitis typically occurs secondary to choroidal spread of a peripapillary infection [6], whereas optic nerve infiltration and subsequent optic neuropathy can occur secondary to hematogenous spread or choroidal extension [15]. Optic neuropathy can also be the result of a hypersensitivity response without direct infection of the nerve [14]. Manifestations of TB optic nerve involvement can also include papillitis, papilledema, optic neuritis, retrobulbar optic neuritis, and optic nerve tubercles [51,54,55].

Immunocompromised patients

Ocular involvement of TB is both more common and more severe in immunocompromised patients. There have been reports of extensive choroidal infiltrates and nodules, severe vitreitis, endophthalmitis, choroidal tuberculomas, choroiditis, chorioretinitis, and bilateral optic neuritis in the immunocompromised with TB [56–61].

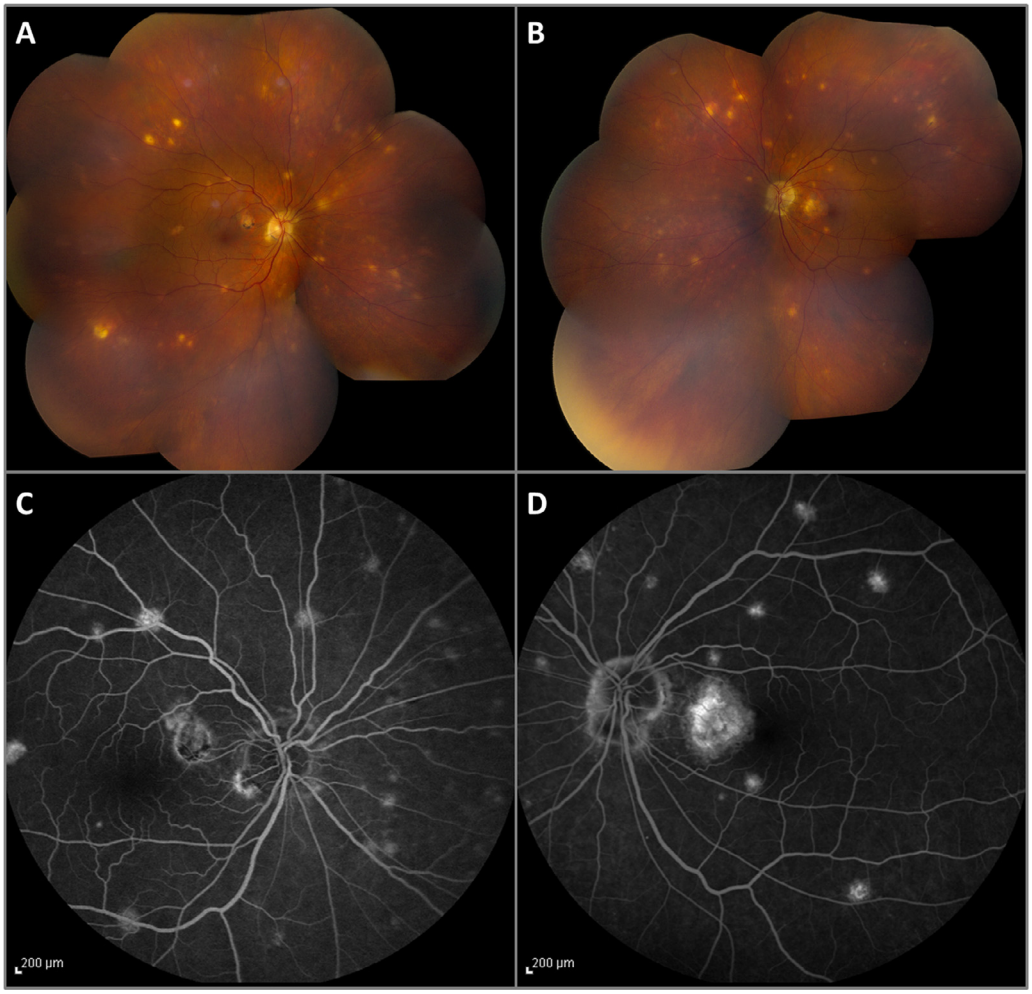

Fig. 3. Multifocal choroiditis secondary to tuberculosis. Montage color fundus photos of the right and left eyes (A and B) demonstrate multifocal punched out lesions in both eyes. The lesions are hyperfluorescent on mid-phase fluorescein angiography (C and D). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Immune recovery uveitis occurs in HIV positive patients with TB who have reconstitution of the immune system after starting antiretroviral therapy [46]. The findings in immune recovery uveitis can vary widely and include anterior uveitis, hypopyon, vitreitis, papillitis, panuveitis, retinal or optic disc neovascularization, retinal detachment, cystoid macular edema, epiretinal membrane formation, vitreomacular traction, and macular hole [62]. One reported case was so severe that it resulted in globe rupture [63]. It should be noted that immune recovery uveitis can also occur in treated HIV patients who do not have TB.

Ophthalmic imaging characteristics of intraocular TB

Fluorescein and indocyanine green angiography

On fluorescein angiography, active choroidal tubercles show early hypofluorescence and later hyperfluorescence [6]. Tuberculomas show early hyperfluorescence with late pooling in areas of exudative retinal detachment [6]. Serpiginous-like choroiditis demonstrates early hypofluorescence with late hyperfluorescence and leakage of the active borders of the lesion [15]. Inactive serpiginous-like choroiditis lesions have staining borders and less hyperfluorescent centers. Retinal vasculitis from TB will demonstrate leakage surrounding the involved vessels as well as peripheral capillary nonperfusion [6]. Indocyanine green angiography of choroidal lesions demonstrates early hypocyanescence followed by late hypercyanescence surrounding a central zone of hypocyanescence [15].

Optical coherence tomography

Optical coherence tomography (OCT) may be helpful in detecting and quantifying macular edema and other pathology such as chorioretinal lesions [14]. While a significant degree of intraocular inflammation could result in decreased image resolution, the OCT may still provide valuable information when clinical examination by slit lamp and ophthalmoscopy is very difficult [64].

Fundus autofluorescence

Fundus autofluorescence can be particularly useful in cases of serpiginous-like choroiditis [65]. Serpiginous-like choroiditis progresses from an ill-defined area of hyperautofluorescence in the acute stage, to a well-defined hypoautofluorescent halo surrounding an area of hyperautofluorescence in the subacute stage, and finally a uniformly hypoautofluorescent lesion after resolution [65].

Ocular ultrasound

B-scan ultrasonography is also useful when severe inflammation or cataract limits the view of the fundus. While mass-like tuberculomas can mimic tumors, A-scan shows low to medium internal reflectivity, which may help differentiate the tuberculoma from other entities [3,15].

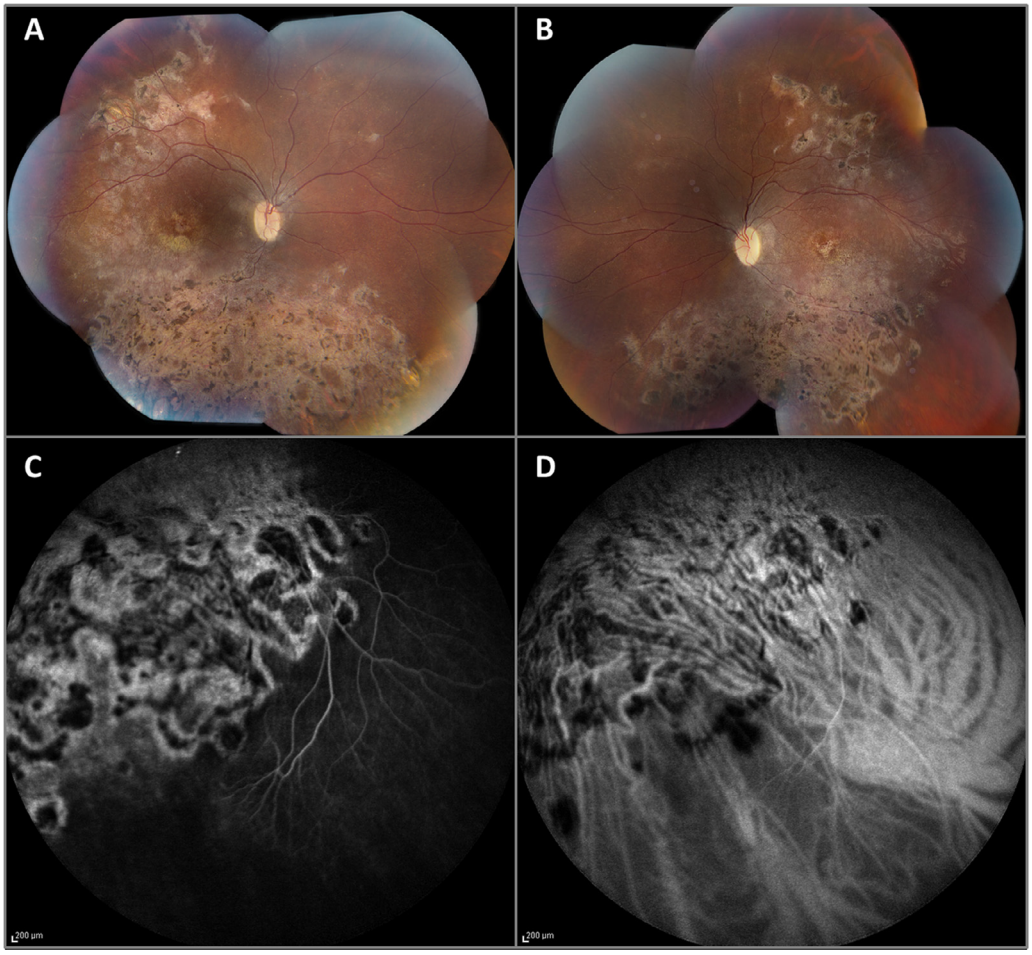

Fig. 4. Serpiginous-like choroiditis secondary to tuberculosis. Montage color fundus photos of the right and left eyes (A and B) demonstrate extensive retinal pigment epithelial changes, atrophy, and scarring in both eyes. The lesions are hypofluorescent centrally with hyperfluorescent borders which do not leak on fluorescein angiography (C). The lesions are hypocyanescent on indocyanine green (D). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Diagnosis

The myriad of intraocular TB manifestations can mimic other diseases, making diagnosis challenging. Delays in diagnosis of intraocular TB can lead to permanent vision loss and even loss of the affected eye(s) [66]. Without microbiologic confirmation, which can be challenging to obtain, a diagnosis of intraocular TB may be empiric; therefore it is necessary to maintain a high index of suspicion aided by a targeted review of systems and directed laboratory testing [14,67,68]. Response to anti-tuberculosis treatment (ATT) may be the only definitive evidence of intraocular TB, but patients should not be committed to long courses of systemic ATT without first undergoing a thorough evaluation to rule out other entities such as syphilis and toxoplasmosis that may have similar findings [6,69].

Mantoux skin test

A Mantoux skin test involves the intradermal injection of a purified protein derivative followed by examination for cutaneous induration 48 to 72 hours after the injection [70]. A positive result is caused by a delayed-type hypersensitivity reaction and is defined as 1) induration measuring greater than 5 mm in HIV-positive patients; 2) induration greater than 10 mm in high-risk persons, including healthcare workers, nursing home patients, and those living in endemic areas; 3) induration greater than 15 mm in all other patients [6]. Cutaneous hypersensitivity has been shown to correlate directly with ocular hypersensitivity in rabbits, indicating this test may be useful in diagnosing ocular disease [71]. Unfortunately, Mantoux test interpretation is subjective, and the test has low sensitivity and specificity [6]. Anergy to the protein can lead to false negative results, especially in immunocompromised patients [6]. False positive reactions may be encountered in patients who have been exposed to different species of mycobacteria, those who have received multiple Mantoux tests in the past, or those who have previously received Bacillus Calmette-Guerin (BCG) vaccinations [6,14,72]. However, induration greater than 10 mm should not be attributed to prior BCG vaccination according to the United States Preventative Services Task Force [73].

Interferon gamma testing

The QuantiFERON TB-Gold test (QFTG: Qiagen, Germantown, Maryland, USA) is a blood test designed to specifically detect TB. One advantage over the Mantoux test is the fact that the QuantiFERON blood test does not require a return office visit for interpretation [74]. The blood test quantifies interferon gamma release by using *M. tuberculosis* antigens to stimulate sensitized T cells from TB-infected patients. Theoretically this test should not yield false positive results due to exposure to other mycobacteria or prior BCG vaccination [74,75]. However, the false positive rate has been reported to be as high as 41% in healthcare workers and 80.5% in HIV-positive patients at low risk for TB [76–79]. Nevertheless, while the QuantiFERON test may have the most utility in

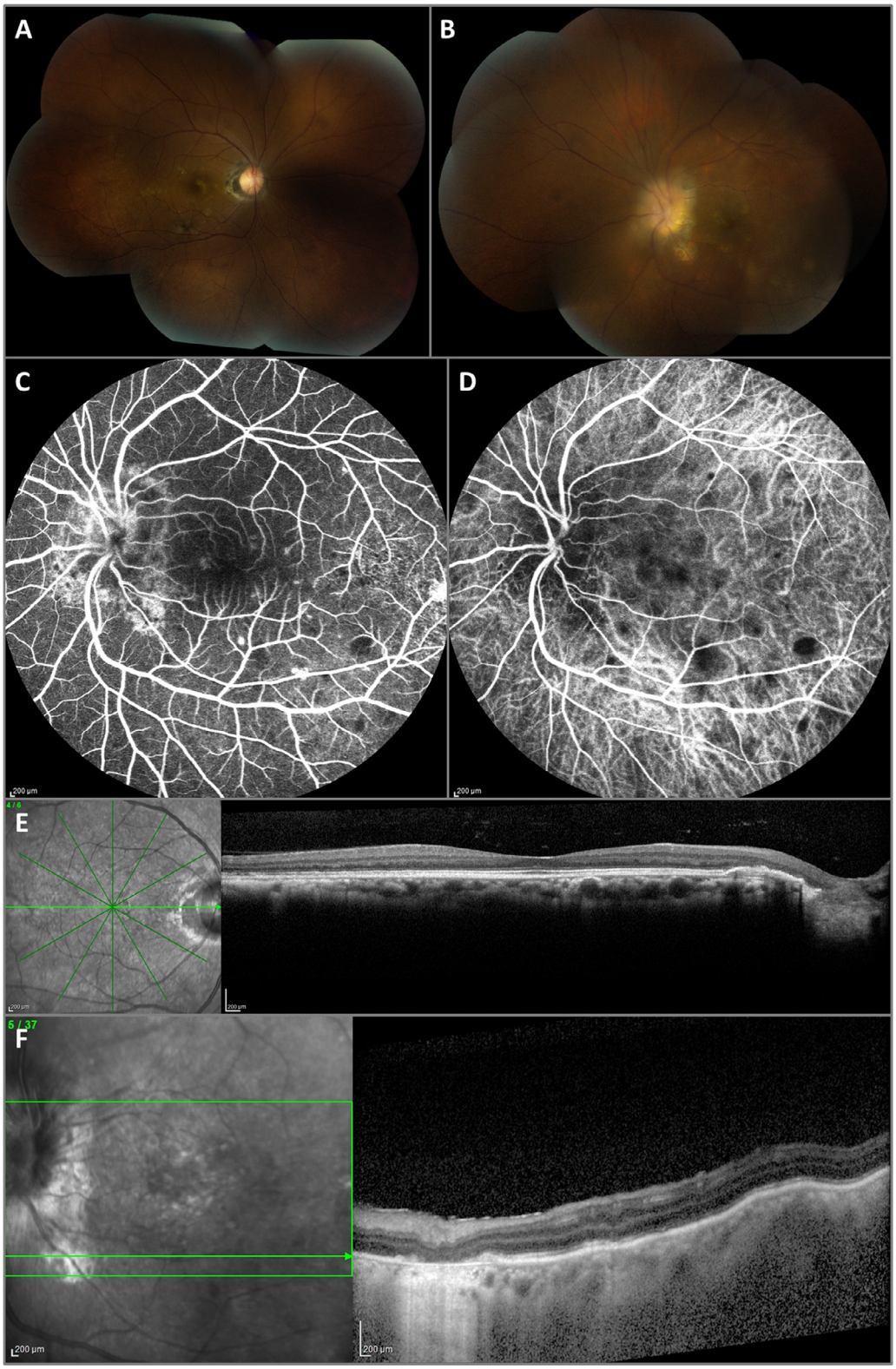

Fig. 5. Serpiginous-like choroiditis secondary to tuberculosis. Montage color fundus photos of the right and left eyes (A and B) demonstrate multiple white, irregular lesions and mottling of the retinal pigment epithelium in both eyes as well as a peripapillary serpiginous-like lesion in the left eye. The lesions are hyperfluorescent on fluorescein angiography (C) and hypocyanescent on indocyanine green (D) as shown for the left eye. Optical coherence tomography reveals macular thinning with ratty outer segment changes in the right eye (E); the left eye has an epiretinal membrane with peripapillary subretinal material corresponding to a fibrotic scar as well as elevation of the inferotemporal macula due to a large choroidal lesion (F). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

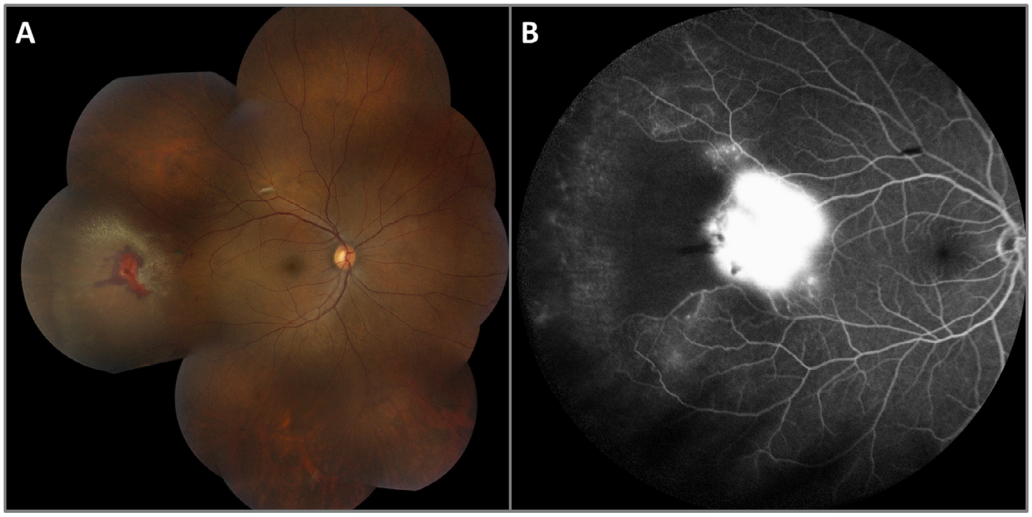

Fig. 6. Eales disease. Montage color fundus photo of the right eye (A) reveals a temporal frond of neovascularization in a patient with a positive Mantoux skin test. The corresponding fluorescein angiogram (B) shows leakage from the area of neovascularization with adjacent peripheral capillary nonperfusion. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patients who have been vaccinated with BCG or for those who are unlikely to return for skin test reading, the CDC recommends the QuantiFERON test as a screening tool that may be used in place of a Mantoux skin test in all situations were a Mantoux test would be recommended [80].

Chest x-ray and computerized tomography

Chest x-ray or computerized tomography of the chest demonstrating cavities, consolidation, or lymph node enlargement can provide supporting evidence for TB [9]. Any positive chest imaging finding should prompt sputum evaluation to distinguish between healed TB lesions and active disease [81]. Ocular TB can occur in the absence of pulmonary TB, so a normal chest radiograph does not exclude the diagnosis of intraocular TB [3,82].

Acid-fast bacteria and histology

The diagnosis of intraocular TB can be proven if acid-fast bacteria are demonstrated via microscopy or Lowenstein-Jensen media culture of intraocular fluids or tissue; however, the yield of this diagnostic test is typically low due to a paucity of organisms [14,15]. Necrotizing granulomas with positively staining acid-fast bacilli by Ziehl-Neelsen stain are also compatible with TB [9].

Polymerase chain reaction

Polymerase chain reaction (PCR) amplification of mycobacterial DNA can be utilized in the evaluation of suspected intraocular TB, as the ocular specimen volume or size is often too small to detect the mycobacterium by microscopy or culture [83,84]. PCR has the potential to be an important tool in the diagnosis of intraocular TB, and has proven useful in vitreous samples from patients with serpiginous-like choroiditis [83,85,86]. However, testing of aqueous and vitreous humor may be falsely negative due to a relative paucity of organisms in TB-associated uveitis [87]. Therefore, while it can be useful, positive *M. tuberculosis* PCR is not required to make the diagnosis of intraocular TB [15,88,89].

Treatment

Medical treatment

Because systemic treatment is required to treat ocular TB, patients should be co-managed by an ophthalmologist and an infectious disease specialist. Medical ATT for ocular TB utilizes the same quadruple-drug regimen used to treat pulmonary TB. The CDC-recommended regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol for a total of 2 months, followed by an additional 4 to 7 months of dual therapy with isoniazid and rifampin [90]. Extended courses of therapy may be necessary due to multidrug resistance and/or the typically slow and sometimes relapsing nature of ocular TB [14,66]. Rifabutin, fluoroquinolones, interferon gamma, and linezolid may be utilized in cases of multi-drug resistance or patient intolerance to any of the four recommended agents [6]. Infectious disease specialists may choose to treat latent TB with isoniazid and/or rifampin rather than quadruple therapy, although it has become increasingly common to conclude that intraocular TB requires quadruple drug therapy [90]. Pyridoxine (vitamin B6) supplementation is necessary for patients taking isoniazid in order to prevent peripheral neuropathy [91].

Ocular side effects of medical therapy

A baseline eye exam must be performed prior to starting ATT, and patients should be monitored for medication side effects, which can sometimes be confused with worsening ocular TB [6]. Isoniazid and ethambutol can cause optic neuropathy, which presents as decreased visual acuity, decreased color vision, or cecocentral scotomas [92]. Ethambutol can also cause optic neuritis characterized by red-green dyschromatopsia and disc edema, which can lead to optic atrophy [6]. The offending medication should be promptly discontinued at the first sign of vision-threatening side effects, as these symptoms may be reversible, with vision often returning to normal 10 to 15 weeks after drug cessation [6]. Vitamin B12 can also occasionally help vision recovery, but in some cases vision loss may be permanent [6]. Rifabutin can cause anterior, intermediate, or panuveitis that is typically treatable with corticosteroids but may also necessitate discontinuation of the medication [3].

Use of steroids

While choroidal tubercles and tuberculomas often respond well to ATT alone, many other intraocular manifestations of TB require corticosteroids plus ATT to prevent damage to the ocular tissues secondary to the inflammatory response [15,93]. Corticosteroid treatment can be critical for certain manifestations of ocular TB, such as choroiditis, which can actually undergo paradoxical worsening upon initiation of ATT [6]. Topical and locally injected

corticosteroids are important in the management of anterior and intermediate uveitis, and systemic forms are an important component in retinal vasculitis treatment [3,6,17]. It is critical, however, that corticosteroids are never used in the absence of ATT, as this not only leads to more frequent recurrences of ocular inflammatory symptoms but can also cause significant worsening and potentially dissemination of the infection [6,94].

Surgical treatment

Typically, ocular TB can be managed with medical therapy alone. However, in cases where retinal neovascularization develops, laser photocoagulation may be necessary to treat areas of retinal capillary nonperfusion and decrease the stimulation of neovascular growth [6]. Pars plana vitrectomy has also been reported as an adjunctive therapy for TB endophthalmitis, and full thickness eye wall resection with pars plana vitrectomy has been used to treat a tuberculous granuloma [42,95].

Occasionally, patients may also require cataract surgery; however, this procedure should be postponed until all intraocular inflammation has been completely controlled for at least 3 months [14]. Elective surgical procedures such as cataract surgery should be delayed even longer in young or noncompliant patients and in those with severe ocular damage from intraocular TB [14].

Conclusion

Intraocular TB is a difficult diagnosis, as it can mimic many other more common etiologies of intraocular inflammation or uveitis. A high index of suspicion for TB and cooperation with infectious disease specialists are paramount, because timely diagnosis and treatment may prevent irreversible vision loss [96].

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