

CASE REPORT

Ocular Tuberculosis: Unilateral, Asymmetric, and Varied in Presentation

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PUBLISHED 28 February 2025

CITATION

Lambert, LH., Deitel, CM., et al., 2025. Ocular Tuberculosis: Unilateral, Asymmetric, and Varied in presentation. Medical Research Archives, [online] 13(2). https://doi.org/10.18103/mra.v13i2.6356

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DOI

https://doi.org/10.18103/mra.v13i2.6356

ISSN

2375-1924

ABSTRACT

Tuberculosis is an infectious illness that can causes substantial morbidity and mortality globally. It is a "great masquerader," as it can affect any organ system, in a variety of manifestations. The eye is no exception. Ocular tuberculosis can affect any part of the eye: the anterior segment, posterior segment, or adnexa. A common ocular manifestation is choroiditis. However, it may also present as panuveitis, retinal vasculitis, and neuroretinitis. Involvement of the posterior segment can produce substantial inflammation, increasing the risk of damage to the neurosensory retina, optic nerve, and surrounding tissues, resulting in irreversible vision loss. Thus, it is imperative to identify ocular tuberculosis as early as possible to initiate vision-saving treatment. Here, we present two cases of tuberculous chorioretinitis that demonstrate the wide spectrum of clinical presentation of posterior segment ocular involvement and its characteristic of being asymmetric or unilateral. These cases exemplify the importance of maintaining TB on a broad differential diagnosis of ocular inflammation.

Keywords: Ocular tuberculosis; Chorioretinitis; Mycobacterium; Vitritis; Neuroretinitis

Introduction:

Tuberculosis (TB) is an infectious illness with extremely morbidity and mortality rates worldwide. hiah Mycobacterium tuberculosis is the primary cause of the illness. It belongs to the Mycobacteriaceae family alongside other pathogenic bacterial species, M. bovis and M. africanum, which also cause clinical TB infection. Nearly a third of the world's population is latently infected with TB, and more than nine million new cases are diagnosed annually. A disproportionally large disease burden is carried by developing countries, up to 95% of new cases by some estimates.¹ Reported incidence of ocular TB varies widely, based on population and diagnostic criteria. For example, ocular disease has been described in 1.4%^{2,3} to 10.5%⁴ of TB cases in high-TB incidence countries, but is less common in low-TB incidence countries. Accordingly, TB occurs in <1% of suspected infectious uveitis cases in the United States.^{5,6}

TB is an airborne communicable disease that most commonly affects the lungs. However, as a "great masquerader" it may affect any organ in a variety of ways.⁷ The eye is no exception. TB can affect any part of the eye, and may present unilaterally or with marked asymmetry. Posterior uveitis is the most common presentation of intraocular TB. Even this single umbrella category of posterior uveitis includes many choroidal manifestations: tubercles, multifocal serpiginous-like choroiditis, chorioretinitis, diffuse retinitis, neuroretinitis, occlusive vasculitis, and vitritis.^{8,9} Many of these presentations are similar to other infectious, inflammatory, and neoplastic posterior segment conditions, such as syphilis, toxoplasmosis, fungal infection, sarcoidosis, white dot syndromes, and

malignancy. Therefore, a high index of suspicion for TB is needed for any ocular inflammation.

Early diagnosis is critical, as treatment is available for ocular TB. Prompt treatment can prevent devastating destruction to vision, and potentially other organ systems, as ocular involvement may be the earliest sign of disseminated disease.⁸ Here, present two distinct cases in the United States of asymmetric ocular TB as the only manifestation of the disease.

Case presentation 1:

A 53-year-old female without a past ophthalmic history and no relevant medical history presented to the clinic for two weeks of worsening photopsias in the right eye associated with headaches. A recent evaluation by the emergency department for her symptoms resulted in a diagnosis of ocular migraines, and she was discharged with sumatriptan. However, her symptoms progressed despite this treatment and she was subsequently referred to ophthalmology. On presentation to ophthalmology, the patient denied floaters, photophobia, eye pain, or recent illness. She had no history of autoimmune disease. On evaluation, the patient's best corrected visual acuity (BCVA) was 20/20 in each eye. The ocular surface and anterior segment were normal. Fundoscopic exam of the right eye was notable for peripheral gray-white choroidal lesions superonasally and inferiorly (Figure 1A). No vitreous inflammation was evident on the exam, which was otherwise normal. Fundus autofluorescence (FAF) showed confluent hyperautofluorescence corresponding to the choroidal lesions on the exam (Figure 1B).



Figure 1. Presentation of Case #1. (A) Color fundus photograph showing multiple gray-white peripheral choroidal lesions of the right eye, inferior and superonasal to the optic disc. The vitreous is clear, and the optic disc and vessels are normal. (B) Fundus autofluorescence highlights the choroidal lesions as hyper-autofluorescent.

At presentation, the differential diagnosis included various infectious and inflammatory etiologies: syphilis, tuberculosis, sarcoidosis, white dot syndromes (e.g. multiple evanescent white dot syndrome (MEWDS) was highest on the differential given the unilateral presentation, but others include acute posterior multifocal placoid pigment epitheliopathy (APMPEE), multifocal choroiditis, and panuveitis (MCP), punctate inner choroidopathy (PIC), and birdshot chorioretinopathy). A laboratory evaluation was performed and notable for a positive interferon gamma release assay (IGRA), indicating the presence of tuberculosis infection. Subsequent exams were notable for the progression of ocular symptoms and headache, corresponding to an increase number of lesions on exam (Figure 2). The left eye remained normal. Evaluation by the Infectious Disease service concluded her only risk factor was that she grew up in the Philippines. Further testing included chest imaging and a lumbar puncture, which was negative for pulmonary and central nervous system involvement, respectively. Treatment was initiated with a regimen of rifapentine, isoniazid, pyrazinamide, and ethambutol

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(RIPE). The patient's symptoms resolved within two weeks of starting RIPE therapy, and her exam returned to baseline (Figure 3A and 3B). The patient remained symptom-free, and her exam remained normal following the completion of RIPE therapy a year following completion of treatment.



Figure 2. Subsequent exam upon progression of ocular symptoms and headache, prior to treatment, demonstrated increased number of choroidal lesions on color fundus photograph (A) and autofluorescence (B).



Figure 3. After initiation of treatment, choroidal lesions resolved, as demonstrated on color fundus photograph (A) and autofluorescence (B).

Case presentation 2:

A 64-year-old female with diabetes and hypertension presented to the clinic complaining of two weeks of left eye pain, redness, and worsening vision. The patient's ocular history was notable for idiopathic polypoidal choroidal vasculopathy (IPCV) complicated by macular hemorrhage in the left eye, successfully treated with pneumatic displacement and intravitreal injection of antivascular endothelial growth factor (anti-VEGF) and tissue plasminogen activator (tPA). She presented for a routine appointment for continued intravitreal anti-VEGF injections. BCVA in the affected eye following the macular hemorrhage was 20/70. At the time of her routine injection appointment, she had reported two weeks of worsening left eye pain, redness, and decreased vision. The BCVA of the left eye was 20/80, and she had severe anterior chamber inflammation with 270 degrees of posterior synechiae. Posteriorly, exam was notable for vitreous inflammation, exudative retinal detachment, and new gray-white choroidal lesions in the posterior pole (Figure 4 A-C).

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Figure 4. Presentation of Case #2. (A, B) Color fundus photographs of the left eye with vitreous haze, a temporal exudative retinal detachment (asterisks), and new gray-white choroidal lesions (arrowheads). (C) Optical coherence tomography (OCT) with a large central pigment epithelial detachment (stable from prior exams given the recent diagnosis of IPCV complicated by a macular hemorrhage) and new subretinal fluid.

The patient was started on oral and topical steroids with a resultant improvement of the exudative detachment, and her BCVA improved to 20/60. Despite this, the previously noted gray-white choroidal lesions increased (Figure 5). Fluorescein angiography was relatively unremarkable, without vasculitis or optic disc inflammation (Figure 6). A laboratory evaluation revealed positive IGRA, confirming tuberculosis infection. The patient urgently returned for a sudden change in vision and new photopsias, after two weeks of significant improvement on oral and topical steroids and cycloplegia. Her BCVA worsened to 20/100, and the exam showed increased number of choroidal lesions, new small retinal holes, and a new rhegmatogenous retinal detachment (Figure 7).



Figure 5. After initiation of oral and topical steroids, exudative retinal detachment (asterisks) improved, but macular choroidal lesions (arrowheads) increased in number and size, demonstrated on color fundus photographs (A, B). The large central pigment epithelial detachment remained stable, though with improvement of the adjacent subretinal fluid, on OCT (C).



Figure 6. Fluorescein angiography (montage of late images) revealed mild focal staining of choroidal lesions and blockage centrally in the area of prior macular hemorrhage. No evidence of vasculitis or optic nerve involvement.



Figure 7. After two weeks of steroids and cycloplegia, color fundus photograph shows an increased number of choroidal lesions and a new rhegmatagenous component to the retinal detachment inferiorly (A), and OCT demonstrates corresponding subretinal and intraretinal fluid (B).

Infectious Disease specialists evaluated the patient. This patient too was from the Philippines, which was the only identified risk factor. No pulmonary or other extrapulmonary involvement was present. RIPE therapy was initiated before ophthalmic surgical intervention. Subsequently, the patient underwent repair of the complex retinal detachment with combined cataract extraction and retinal detachment repair with a silicone oil tamponade. Following surgery and RIPE therapy, the patient's visual acuity remained stable at 20/200, and her retina remained flat with a resolution of the choroidal lesions (Figure 8). The patient's silicone oil tamponade was removed three months after she completed her course of RIPE therapy, and her BCVA improved to 20/100 (Figure 9).



Figure 8. After initiation of RIPE therapy and surgical repair of the retinal detachment with silicone oil tamponade, color fundus photograph reveals improvement of choroidal lesions (A), though some remain present superiorly. (Large reflection centrally is from silicone oil; it does not represent pathology). OCT confirms resolution of subretinal fluid, with small persistent outer retinal changes (B), which are expected post retinal detachment and IPCV.



Figure 9. After completion of RIPE therapy and removal of silicone oil, color fundus photograph reveals continued resolution of choroidal lesions, flat retina, and central pigmentary changes (A). OCT shows corresponding persistent outer retinal changes (B). Pigmentary and outer retinal changes are expected post-retinal detachment and IPCV.

Discussion:

While TB most commonly affects the lungs, extrapulmonary disease is common. In the US in 2019, 30% of patients diagnosed with TB had extrapulmonary disease including two thirds without pulmonary involvement.¹⁰ Ocular disease has been described in as many as 10.5% of TB cases in high-TB incidence countries, and may be the earliest sign of disseminated disease.^{4,8} The incidence of ocular TB among patients presenting with uveitis is high in high-TB incidence countries, but occurs in <1% of suspected infectious uveitis cases in the US.^{5,6}

Filardo et al published epidemiology of ocular TB in the United States between 1993-2019.11 This article found that in the US, ocular TB is found most commonly, and about in equal rates in Asians, Blacks, and Latinos, at 25%, 28%, and 29%, respectively. Ocular TB occurs more commonly in those born outside of the US (65%), compared to those born in the US (35%). The vast majority of ocular TB cases (93%) do not have concomitant pulmonary disease. Finally, 52% of ocular TB cases had no epidemiologic risk factors (e.g. known prior untreated latent TB infection, homelessness, correctional or long-term facility resident, contact with TB-infected person within two years, and occupation as a healthcare worker). Our two patients with ocular TB therefore represent a rare disease in the US. However, as Asians born outside of the US without pulmonary involvement or epidemiologic risk factors, they both represent the most common epidemiologic categories of ocular TB in the US.

Ocular transmission can occur in three ways: primary ocular TB occurs as the primary site of inoculation, and is characteristic of disease on the ocular surface. Secondary ocular TB occurs via hematogenous spread from a distant infectious focus, and is characteristic of uveal disease. Finally, a hypersensitivity reaction occurs when the immune system reacts to tuberculosis bacteria elsewhere, resulting in ocular inflammation.¹²

Any ocular structure may be affected by tuberculosis, even without pulmonary involvement. Furthermore, ocular infection can present unilaterally or with marked asymmetry. Some examples of relatively superficial manifestations, though not an exhaustive list, include: on the eyelid as an abscess, chronic blepharitis, atypical chalazion, or reddish-brown nodules that blanch to an "apple jelly" color with pressure; on the ocular surface and anterior segment as a mucopurulent conjunctivitis with lymphadenopathy, a phlyctenule regional (an inflammatory nodule at the junction of the cornea and sclera), infectious keratitis, interstitial keratitis (inflammation within the cornea stroma), infectious scleritis, or anterior uveitis.^{8,12} These presentations are more straightforward to diagnose as tissue is easily accessible for biopsy and culture. Orbital disease can also occur, but is uncommon.¹³

Uveitis, and particularly posterior uveitis, is the most common presentation of intraocular TB. This category includes a wide array of presentations affecting the vitreous, retina, retinal vasculature, choroid, and optic disc.^{8,12} Of these, the choroid is most often affected, which is thought to result from the bacteria's predilection for highly oxygenated tissue.^{14,15} Indeed, our patients presented with choroidal tubercles. In the first case, these were isolated. In the second, they were accompanied by vitritis and retinal detachment, though this was in the setting of prior retinal disease (IPCV).

A classic and visually devastating manifestation of posterior uveitic TB is serpiginous-like choroiditis. It is distinct from idiopathic serpiginous choroiditis, as lesions in the latter usually extend from the optic nerve to macula, whereas in 85% of serpiginous-like choroiditis the lesions are not contiguous with the optic disc.^{16,17} This distinction is paramount, as disease associated with TB may be treatable, while the idiopathic form is not and carries a poor visual prognosis.

The gold standard for diagnosis is identification of Mycobacterium species in culture. Such studies can be particularly difficult in cases of ocular tuberculosis, as obtaining tissue samples for culture is invasive. PCR of ocular fluid is a newer alternative to cultures.^{18,19} Often, presumed ocular TB is the working diagnosis when the clinical picture is right: risk factor history, ocular findings, chest radiography results, and the Mantoux tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA). Negative testing does not rule out ocular tuberculosis.²⁰⁻²²

If tissue can be obtained, bacteriological staining techniques can be diagnostic. Ziehl-Neelson acid-fast stained bacilli and/or caseous necrosis with epithelioid cells and Langerhans giant cells suggest ocular tuberculosis. Bacteria in multinucleated giant cells are inconsistently detected by histologic staining.^{23,24} Thus, the results are highly variable, and biopsies can be unreliable. A biopsy may be taken for histopathologic analysis in rare external disease or anterior segment involvement cases. However, intraocular tissue biopsy can be risky and impractical.

Treatment of tuberculosis is the similar, whether the eye or lungs are affected. Ocular tuberculosis is treated with a multidrug regimen of antitubercular antibiotics (e.g. RIPE therapy), and steroid medication is frequently necessary. Multidrug resistant TB must be approached with different treatment, and indeed represents a significant global public health and safety concern, that is beyond the scope of this discussion.^{25,26} In rare instances, administration of ethambutol may cause optic neuropathy, which resolves with discontinuation of the drug. Nonetheless, high-risk patients, such as those taking ethambutol at a high dose or for an extended period or those with impaired renal function, should undergo regular visual examination.^{27,28} Treatment can halt the progression, and often reverse, much of the visual morbidity caused by TB, as was seen in our cases.

Conclusion:

Ocular TB is an infection by Mycobacterium, that can occur with or without pulmonary involvement. Disease manifestation is varied and often asymmetric between the eyes. Involvement of the posterior segment can be particularly damaging to vision. TB must be on the broad differential for inflammation in any ocular tissue. Early diagnosis is important, as treatment exists, and ocular TB may be the earliest sign of disseminated disease. Therefore, treatment may save vision and improve the prognosis of other potentially affected organs.

Conflict of Interest Disclosures:

The authors have no conflicts of interest to declare.

Disclosures:

The authors report having no proprietary or commercial interest in any materials discussed in this letter. The views expressed in this correspondence are those of the author(s) and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government. This work was prepared as part of our official duties. Title 17 U.S.C. 105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 U.S.C. 101 defines a United States Government work as a work prepared by a military service member or employee of the United States Government as part of that person's official duties.

Funding Statement: None declared.

Clinical Trial Registration: Not applicable.

Institutional Review Board (Human Subjects): Not applicable.

Institutional Animal Care and Use Committee (IACUC): Not applicable.

Acknowledgements:

The authors thank the hospital corpsmen and support staff of Naval Medical Center San Diego for the care of the patients. We thank the patients for granting permission to publish this information.

Author Contributions:

All authors contributed to the writing of the manuscript. Dr. Lambert (LT, MC, USN), Dr. Powell (CDR, MC, USN), and Dr. Choi (LT, MC, USN) wrote the original manuscript. Dr. Deitel (LT, MC, USN) and Dr. Powell (CDR, MC, USN) revised it.

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