Anthony Amoroso and Ajit P. Limaye, Section Editors

In the Eye of the Beholder: A Conjunctival Lesion in a Woman With Acute Myelogenous Leukemia

Figure 1. Physical exam on presentation was notable for an elevated white nummular lesion on the nasal conjunctiva with surrounding conjunctival injection and diffuse chemosis with conjunctival infiltrates. Her right eye was normal on exam (A). Enlarged image of affected eye (B).

QUESTION

A woman in her mid-forties presented to the Emergency Department with worsening left eye erythema and swelling despite topical antibiotics and steroids. She had been diagnosed with acute myelogenous leukemia (AML) and started on chemotherapy 24 months prior. Seven months prior to her current presentation, she developed *Fusarium solani* sinusitis that was resected and treated with liposomal amphotericin B, voriconazole, and terbinafine with negative repeat endoscopic exams. She underwent matched related donor peripheral blood stem cell transplant 4 months prior to presentation with no evidence of residual disease on repeat bone marrow biopsy. Three months prior to presentation, she was treated for cytomegalovirus viremia (serum cytomegalovirus [CMV] 2300 IU/mL) with valganciclovir and for gastrointestinal graft versus host disease (GVHD) with a steroid taper. Two months prior to presentation, she was treated for methicillin-sensitive staphylococcus aureus (MSSA) preseptal cellulitis based on

culture from eye discharge. She also had multiple episodes of bilateral chalazia and hordeola during this time. She previously worked as a nurse in the Philippines. She never smoked, drank alcohol, or used illicit drugs. She had no animal, water, or soil exposures. She had not traveled internationally in over 10 years and never lived in the Southwest or Midwest United States. She received the BCG tuberculosis vaccine as a child. Quantiferon testing after starting chemotherapy was positive, but treatment of latent tuberculosis was deferred given the above infections. She denied fevers, chills, headache, floaters, double vision, or eye pain. She endorsed decreased visual acuity. Physical exam revealed a 3 mm × 5 mm elevated white nummular conjunctival lesion with surrounding injection and chemosis (Figure 1). The cornea was clear; the anterior chamber was deep and quiet; the iris, lens, and vitreous were normal. On fundoscopic exam the macula, vessels, choroid, and retina were normal. Visual acuity was 20/40 and 20/20 in the affected and contralateral eyes, respectively. She endorsed mild tenderness with palpation

Figure 2. CT maxillofacial with contrast revealed enhancement of the anterior periorbital soft tissue, adjacent fat stranding, and preseptal edema without evidence of post-septal or sinus involvement. Abbreviation: CT, computed tomography.

over the left maxillary sinus. There were no rashes, mucosal lesions, or lymphadenopathy. Her pulmonary, cardiac, abdominal, neurologic, and musculoskeletal exams were benign. Laboratory testing revealed an absolute neutrophil count of 1500 cells/uL, absolute lymphocyte count of 420 cells/uL, voriconazole level of 2.7 mcg/mL, normal liver enzymes and creatinine, and plasma CMV PCR 0 IU/mL. Maxillofacial

computed tomography imaging revealed uncomplicated left orbital preseptal cellulitis (Figure 2). Histopathological examination of the conjunctival nodule demonstrated hemorrhagic and partially necrotic tissue with extensive nongranulomatous lymphohistiocytic and neutrophilic inflammation. The specimen was also sent for culture.

What is your diagnosis?

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Diagnosis: *Mycobacterium tuberculosis* infiltration of the conjunctiva

The initial differential diagnosis included bacterial periorbital cellulitis, fungal infection (including extension of prior *Fusarium* sinusitis), ocular acute myeloid leukemia, graft-versus-host disease, or trauma. No organisms grew from routine bacterial and fungal cultures of the conjunctival nodule. However, acid-fast bacilli (AFB) culture and pathology revealed AFB by Ziehl-Neelsen and Fite stains with associated necrosis and lymphohistiocytic inflammation (Figure 3). Polymerase chain reaction (PCR) confirmed a diagnosis of ocular tuberculosis. The isolate was susceptible to the medications in RIPE (rifamycin, isoniazid, pyrazinamide, and ethambutol), her

initial treatment regimen. Chest, abdominal, and pelvic computed tomography imaging revealed no pulmonary or other extrapulmonary involvement. With no evidence of pulmonary, oral, or laryngeal tuberculosis, and no eye drainage, no special infection control measures were implemented [1, 2].

Although approximately one-third of the world's population is infected with tuberculosis, only 10% of those develop clinical disease. Of this subset, only 20% have extrapulmonary manifestations, and fewer develop ocular disease [3–5]. The prevalence of ocular tuberculosis is difficult to ascertain due to the lack of uniformity in diagnostic criteria and the wide spectrum of disease manifestations [6–9]. Diagnosis is frequently presumptive based on tuberculin skin testing or quantiferon

Figure 3. Hematoxylin and eosin-stained sections of the conjunctival lesion: *A*, Low power magnification revealed a fragment of conjunctiva with associated fresh hemorrhage and extensive subepithelial non-granulomatous inflammation (epithelium designated with *). *B*, The inflammation appeared as a mixed infiltrate composed of lymphocytes, histiocytes, and neutrophils. *C*, Areas of necrosis were also noted (designated with **). High power magnification of a Fite stain revealed eosinophilic mycobacterial filamentous bacilli. *Mycobacterium tuberculosis* complex DNA was detected with a 16S rRNA gene primer.

assay, concurrent radiographic evidence of pulmonary granulomas, ocular findings on exam, and response to antituberculosis medications [6–9].

Primary ocular disease is uncommon and can affect the eyelid, cornea, conjunctiva, and/or sclera, as the eye is the primary portal of entry [6]. Notably, tuberculosis in the eyelid can manifest as chronic blepharitis or nodules resembling chalazia, similar to the eyelid nodules noted in our patient [7]. More commonly, secondary ocular tuberculosis, in which the mycobacteria infect the eye via hematogenous dissemination, affects the uvea due to high oxygen tension. Uveitis can be complicated by granulomatous precipitates, vitritis, retinitis, abscesses, or optic neuritis. Ocular symptoms can also occur secondary to antigenic mimicry or a hypersensitivity reaction in the setting of tuberculosis infection in a remote site [5, 8]. Many patients have no personal history of prior tuberculosis [5].

No strict consensus guides antituberculous therapy or duration [5]. The Center for Disease Control and Prevention recommends a standard 4-drug RIPE regimen. Most experts treat for at least 6 months [4, 5, 10]. The role of systemic corticosteroids remains controversial as studies have shown varying outcomes [5, 6, 11]. Ophthalmic side effects of antituberculosis therapy can be of particular concern when treating ocular tuberculosis though the antibiotics tend to be well tolerated. Routine ophthalmic follow-up is recommended [7, 12]. Treatment outcomes are heterogeneous, but visual acuity and inflammation improve in most patients (24–100%) [5, 11, 13, 14].

As no nonmycobacterial organisms were isolated, our patient received RIPE therapy alone. Rifabutin was used to limit drug interactions, valganciclovir was stopped as plasma cytomegalovirus (CMV) PCR was 0 IU/mL, and dose adjustments were made to other medications. Repeat retinal imaging after 1 week of antituberculosis therapy revealed an asymptomatic choroidal lesion in the ipsilateral eye (Figure 4). Fundus fluorescein angiography showed vascular permeability in the lesion suggestive of a tuberculosis granuloma.

Medication side effects and infectious complications plagued our patient's course. She developed transaminitis with initial RIPE treatment. Pyrazinamide and isoniazid were stopped, and levofloxacin was added. As plasma CMV viremia returned, she resumed valganciclovir, leading to neutropenia (requiring granulocyte-colony stimulating factor) and neutropenic fevers (requiring broad-spectrum antibiotics). New pulmonary nodules prompted treatment with liposomal amphotericin B, complicated by acute kidney injury. Ultimately, she completed an 8-week course of 3–4 drugs; she remains on rifabutin and levofloxacin for a total course of 9 months. Ongoing nausea, diarrhea, and fluctuating renal and liver function have necessitated close monitoring of drug doses and levels. Initially worsening with tuberculosis treatment, her visual symptoms and exam

Figure 4. Retinal imaging of the left eye with a pale choroidal lesion (arrow) superior and temporal to the macula. Fundus fluorescein angiography showed vascular permeability in the lesion suggestive of inflammation.

have improved somewhat though decreased visual acuity and conjunctival inflammation remain.

Notes

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