Clinical Reasoning: A woman with monocular vision loss

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Section 1

A 48-year-old woman presented to her primary care physician (PCP) with right eye vision loss. She began noticing changes in her vision earlier in the year while at work. Over the ensuing months, her vision progressively declined such that she was no longer able to read with the right eye but could appreciate movement. Her past medical history included iron deficiency anemia for which she received iron infusions, depression, and anxiety. She denied fevers, sweats, chills, anorexia, weight loss, cough, shortness of breath, swollen lymph nodes, or any other systemic symptoms. She had traveled to Mexico, South America, the Caribbean, and Europe. She never had penetrating trauma to the head, although she did have a concussion as a toddler. She had spent time in Arizona and in the northern United States/southern Canada. She has several pets including dogs, small mammals, and birds; none was ill. She had no history of diabetes, immunosuppression, or HIV.

Question for consideration:

1. What is the differential diagnosis for progressive monocular vision loss?

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Figure 1 Initial MRI brain with contrast and follow-up optical coherence tomography (OCT)

(A) Coronal (right) and axial (left) T1 postcontrast MRI of the brain at time of initial presentation. The extraaxial, contrast-enhancing lesion is indicated by the red arrows. (B) OCT of the retinal nerve fiber layer (RNFL). The OCT tomogram shows the different layers of the retina. The RNFL lies between the red and cyan lines. The color diagram illustrates how the RNFL thickness compares that of age- and sex-matched controls (green, normal; yellow, borderline thin; red, abnormal thin). Note the thinning of the RNFL in the temporal field of the right eye. INF = inferior; NAS = nasal; SUP = superior; TMP = temporal. (C) OCT of the ganglion cell layer (GCL). The GCL lies between cyan and purple lines on the tomogram. The GCL thickness segregation map shows the average GCL thickness (in black) in each quadrant. Clinically, the volume number (vol [mm³] red number) is more frequently used. The total average volume number (in the upper left corner of the GCL thickness map) is normally ~1.00. Here, there is diffuse thinning of the GCL in the right eye indicating prior optic nerve damage from compression.

Section 2

The clinical presentation of progressive, subacute unilateral visual loss, particularly in a young patient, is typically due to either a retinopathy or optic neuropathy. Differentiating between the 2 clinically is difficult but necessary, as it affects the patient's diagnostic evaluation, treatment, and prognosis. On the one hand, diseases of the retina typically cause photopsias (flashing lights), metamorphopsias (visual distortion), or night blindness. On the other hand, optic neuropathies are often associated with dyschromatopsia (i.e., abnormal color testing), optic disc edema, or pallor, and, in the setting of optic neuritis, pain. On examination, optic neuropathies can result in a relative afferent pupillary defect (RAPD), but this can also be seen with severe retinopathies.

The patient's PCP ordered a MRI brain and orbits with contrast, which revealed an extraaxial, contrast-enhancing right orbital apex mass (figure 1A). No parenchymal or meningeal enhancement was noted. The patient was referred to neurosurgery and underwent biopsy of the mass. Pathology revealed granulomatous inflammation with focal necrosis (figure 2A). Immunohistochemical staining for *Mycobacterium* spp. showed equivocal staining (figure 2B), and histochemical stains for acid-fast bacilli (i.e., Ziehl-Neelsen), fungi, and bacteria were negative. This raised the possibility of a mycobacterial infection, with other infectious and noninfectious causes of granulomatous inflammation remaining in the differential. Mycobacterial sequencing of the tissue block was also negative. Because of limited tissue sample, a mycobacterial culture was not performed. Additional infectious assays, including histoplasma serology, coccidioides serology, Quantiferon gold, HIV, erythrocyte sedimentation rate, and C-reactive protein were either negative or within normal limits.

Postresection, the patient was treated with a short, 10-day taper of dexamethasone. After resection of the mass, the patient reported initial improvement in visual acuity in the right eye. However, over the course of weeks, her vision again declined. She was seen in the neuro-ophthalmology clinic, where examination demonstrated 20/60 visual acuity with a small central island of spared vision, severe dyschromatopsia, and a RAPD in the right eye. On fundoscopic examination, temporal pallor was noted in the optic disc OD.

Figure 2 Initial biopsy of apical orbital mass and follow-up fine needle aspirate of FDG-avid lymph node

(A) Biopsy of the right extraaxial, apical orbital mass reveals caseating granulomatous inflammation, concerning for mycobacterial infection. (B) Immunohistochemical staining for *Mycobacterium* spp. demonstrates equivocal staining. (C) Fine needle aspirate of peribronchial lymph node reveals noncaseating granulomatous disease. (D) Whole body PET reveals multiple FDG-avid lesions.

Optical coherence tomography (OCT) of the right eye revealed thinning of the retinal nerve fiber layer (RNFL) temporally (figure 1C), as well as diffuse thinning of the ganglion cell layer (GCL) (figure 1B). Her left eye examination was normal, and the rest of her neurologic examination was unremarkable.

Questions for consideration:

1. Are the examination findings and OCT consistent with the imaging findings?
2. Based on the pathologic findings, would you pursue empiric treatment or take further steps to establish a diagnosis?

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Section 3

The findings of a RAPD, optic disc pallor, loss of color vision, and an unremarkable retinal examination all suggest an optic neuropathy. OCT further supports this conclusion. Temporal thinning of the RNFL in the right eye indicates loss of the RNFL from compression of the optic nerve. Diffuse thinning of the GCL is due to retrograde damage to the ganglion cell bodies from axonal compression. In a disease process primarily affecting the retina, pathologic changes will either be visible on fundoscopic examination or OCT will disclose abnormalities specific to the retinal pigment epithelium and photoreceptor layers in the outer retina.

At this point in the patient's clinical course, the etiology of the mass causing the optic neuropathy remained uncertain. The initial pathology was concerning for mycobacterial infection but ancillary testing, including mycobacterial sequencing of the tissue sample, was negative, and mycobacterial cultures (the diagnostic gold standard) were not obtained. While epithelioid granulomas with focal necrosis were observed on the biopsy, there was still a concern for other inflammatory granulomatous disease processes, like sarcoidosis. Clarification of the diagnosis prior to initiating therapy was crucial given that incorrect therapy would not arrest her progressive vision loss and had the potential to worsen the underlying condition (i.e., initiating immunosuppression in the setting of an active mycobacterial infection).

Given the lack of diagnostic clarity, antimicrobial treatment was not initiated. A CT of the chest, abdomen, and pelvis was performed, which showed numerous enlarged lymph nodes. A follow-up whole body fluorodeoxyglucose PET (FDG-PET) was pursued, revealing FDG-avid lymphadenopathy in the lower neck, chest, and abdomen, splenomegaly with diffuse increased FDG uptake, heterogeneous increased FDG uptake throughout the liver, multifocal FDG-avid osseous lesions, and multiple FDG-avid pulmonary nodules (figure 2D). Endobronchial ultrasound-guided fine needle aspiration of a peribronchial lymph node was performed. Cytology showed numerous granulomas, compatible with sarcoidosis (figure 2C). Treatment with high-dose corticosteroids and methotrexate was initiated. The clinical deficits were stable at time of follow-up.

Discussion

Sarcoidosis is an idiopathic granulomatous inflammatory disorder known to affect multiple organ systems including the lungs, heart, skin, CNS, and eyes. Classically, sarcoidosis is characterized histologically by noncaseating granulomas in affected tissues. However, sarcoidosis can be associated with focal necrotizing, caseating granulomas; some studies estimate that between 1.6% and 4% of pulmonary sarcoidosis is associated with necrotizing granulomas.^{1,2} This variant of sarcoidosis, known as necrotizing sarcoid granuloma (NSG), is an uncommon condition that primarily involves

the lung, though there are case reports of systemic NSG as well.¹ Often associated with vasculitis, it is unclear whether NSG represents a necrotizing angiitis with a sarcoid reaction or sarcoidosis with necrosis of the granulomas and vessels.³

The nervous system is affected in 5%–13% of cases of sarcoidosis, with the most common CNS manifestations being cranial neuropathy (23%–73%), optic neuropathy (3%–38%), neuroendocrine/hypothalamic dysfunction (2%–26%), seizures (0%–22%), meningitis (8%–40%), and myelopathy (0%–28%).^{4,5} Sarcoidosis can also affect the peripheral nervous system and cause either a myopathy or peripheral neuropathy.⁴ Neurosarcoidosis is the presenting symptom in sarcoidosis in approximately 31% of patients and 50%–70% of these patients progress to develop other systemic manifestations of sarcoidosis.⁶ Given how frequently systemic sarcoidosis is associated with neurosarcoidosis, current consensus guidelines recommend whole body FDG-PET or gallium-67 imaging to identify systemic disease burden and identify an amenable site for biopsy.⁷

Unlike other granulomatous disorders, the antigen that drives the immune response in sarcoidosis is unknown. Multiple potential driving antigens for sarcoidosis have been proposed, both infectious and noninfectious, without any definitive evidence of causality.⁸ Mycobacteria, both tubercular and nontubercular species, have long been suspected to be the cause of sarcoidosis and there are several lines of evidence in support of this hypothesis. Mycobacterial DNA has been detected in the granulomas of sarcoid patients. The mycobacterial protein, catalase-peroxidase (mKatG), has also been detected in sarcoid granulomas using mass spectrometry.⁸ *Propionibacterium acnes*, a commensal cutaneous bacterium, is another organism that has been implicated in sarcoidosis. The organism can induce a granulomatous response in some experimental models and can be directly cultured from sarcoid granulomas; however, given how ubiquitous the organism is, it is unclear whether the organism is truly pathogenic or just a contaminant.⁸ A number of viruses including human herpesviruses⁸ have also been proposed to cause sarcoidosis; however, to date there is no evidence that viruses can drive a granulomatous immune response.

While no randomized control trials have been performed, the first-line therapy for neurosarcoidosis is corticosteroids. Because of the side effects of long-term high-dose steroid treatment, it is recommended that low-dose oral steroid be used in combination with intermittent high-dose IV steroids.⁹ In approximately 2/3 of cases, corticosteroids are sufficient for disease control. In cases of steroid-refractory neurosarcoidosis, a number of alternative immunosuppressive treatments can be used, including azathioprine, methotrexate, cyclosporine, and cyclophosphamide.⁹ Finally, there are a number of case reports that suggest TNF- α inhibitor treatment can be an effective second-line agent in the treatment of steroid refractory neurosarcoidosis.¹⁰

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Disclosure

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Appendix Authors

Name	Location	Contribution
Husain Danish, MD	Brigham and Women's Hospital	Drafted the manuscript for intellectual content
Tatiana Bakaeva, MD, PhD	Massachusetts Eye and Ear Institute	Revised the manuscript for intellectual content
Isaac Solomon, MD, PhD	Brigham and Women's Hospital	Revised the manuscript for intellectual content, prepared pathology images

Appendix (continued)

Name	Location	Contribution
Sashank Prasad, MD	Brigham and Women's Hospital	Revised the manuscript for intellectual content

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