

Clinical Reasoning: A 42-year-old man with sequential monocular visual loss

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SECTION 1

In April 2005, a 42-year-old African American man developed insidious, painless visual loss in the left eye which quickly progressed over several weeks.

There was no significant medical history. Family history revealed hypertension and diabetes, but no autoimmune disorders, brain tumors, or vision loss. He was a restaurant manager, smoked ½ pack of cigarettes daily, consumed alcohol rarely, and did not use illicit drugs.

He presented to another institution, where he was found to have 20/100 acuity, dyschromatopsia, and a relative afferent pupillary defect in the left eye. The left optic nerve head was mildly swollen, without hemorrhage or exudate.

Humphrey visual fields of the left eye revealed a dense superior altitudinal defect with a less prominent inferior arcuate defect. The right eye field was full.

He was thought to have idiopathic optic neuritis. He was treated briefly with oral corticosteroids, but his vision in the left eye never improved.

Questions for consideration:

1. What are the diagnostic considerations for subacute monocular visual loss in an adult?
2. What diagnostic workup would you perform?

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SECTION 2

The differential diagnosis for subacute monocular visual loss is broad. Although idiopathic demyelinating optic neuritis is a common cause, the differential also includes inflammatory and infectious conditions, compression, infiltrative or neoplastic processes, hereditary optic neuropathies, glaucoma, retinal disorders, and ischemic optic neuropathy (table 1).

Optic neuritis. Optic neuritis most often occurs between the ages of 20 to 50 and is three times more frequent in women.¹ Visual loss reaches its nadir within 7 to 10 days and begins to recover within 1 month. Retro-orbital pain, particularly with eye movements, occurs in almost all cases; it may precede the visual loss and typically persists for 1 to 2 weeks.²

Characteristic findings on examination support the diagnosis of typical optic neuritis. Visual field defects, such as diffuse field loss or central scotomas, are common. In acute optic neuritis, one-third of patients have mild optic disc swelling; the remainder have retrobulbar inflammation and the optic nerve head will appear normal.¹

Atypical features should prompt a rigorous search for other causes of monocular visual loss. These “red flags” include an unusual temporal profile (progression beyond 2 weeks, or lack of recovery within 1 month), absence of pain, an unusual scotoma (such as an altitudinal defect), or an atypical fundoscopic

examination (including a nerve that is markedly swollen or atrophic, or retinal abnormalities such as hemorrhages, inflammation, or exudates).

Other causes of optic neuropathy. Inflammatory conditions are an important cause of subacute optic neuropathy. In sarcoidosis, optic nerve involvement can be accompanied by anterior uveitis or posterior segment vitritis.³ There is progressive visual loss, which is often steroid-responsive, and significant pain is unusual. Optic neuropathy is also rarely associated with systemic lupus erythematosus and Sjögren disease.

Infectious conditions are another frequent etiology.⁴ Neuroretinitis, in which optic neuropathy coexists with peripapillary or macular exudates, may be due to cat scratch disease (*Bartonella henselae*), syphilis (*Treponema pallidum*), or Lyme disease (*Borrelia burgdorferi*). Other infectious causes include HIV and opportunistic infections, including toxoplasmosis, cytomegalovirus, and cryptococcus. Paranasal sinusitis or mucocele can lead to compressive or inflammatory optic neuropathy.

A variety of compressive mass lesions can cause a progressive optic neuropathy. Important causes include neoplasm (including optic nerve sheath or skull base meningioma, pituitary adenoma, and cranio-pharyngioma), sinus lesions, bony processes (fibrous

Table 1 Differential diagnosis for subacute monocular visual loss

Condition	Types	Characteristic features
Optic neuritis	Idiopathic optic neuritis, multiple sclerosis	Retro-orbital pain; visual recovery starts within 1 month; normal-appearing optic nerve or mild disc swelling
Ischemic optic neuropathy	Arteritis, nonarteritic ischemic optic neuropathy	Typically no pain; disc swelling with nerve fiber layer hemorrhages
Inflammatory optic neuropathy	Sarcoidosis, systemic lupus erythematosus, Sjögren syndrome	Anterior uveitis or posterior segment vitritis
Infectious optic neuropathy	Paranasal sinusitis, cat scratch disease (<i>Bartonella henselae</i>), syphilis (<i>Treponema pallidum</i>), Lyme disease (<i>Borrelia burgdorferi</i>), toxoplasmosis, cytomegalovirus, cryptococcus	Neuroretinitis (optic disc swelling and retinal exudates)
Compression	Paranasal mucocele, meningioma (optic nerve sheath or skull base), bony compression (fibrous dysplasia), enlarged extraocular muscles, aneurysms	Optic disc swelling in intraorbital compression; atrophy in intracranial or intracranial compression; optic nerve head shunt vessels in chronic compression
Neoplasm	Optic nerve glioma, optic nerve glioblastoma multiforme, lymphoma, leukemia, carcinomatous meningitis, metastasis	Slowly progressive visual loss
Hereditary	Leber hereditary optic neuropathy	Circumpapillary telangiectatic microangiopathy, nerve fiber layer pseudoedema
Glaucomatous	Chronic glaucoma, acute angle closure glaucoma	Elevated intraocular pressure and optic disc cupping in chronic glaucoma; excruciating pain and scleral injection in acute angle closure glaucoma
Retinal	Chronic serous chorioretinopathy (CSR), retinal artery occlusion (RAO), retinal vein occlusion (RVO), acute idiopathic blind spot enlargement syndrome (AIBSE)	Macular serous detachment (CSR), retinal whitening (RAO), retinal hemorrhage and engorged veins (RVO), peripapillary pigmentary changes (AIBSE)

Table 2 Diagnostic testing considerations

Imaging	MRI brain and orbits, optical coherence tomography, fluorescein angiography
Serologies	NMO-IgG, RPR, titers for Lyme, toxoplasmosis, <i>Bartonella henselae</i> , West Nile virus (WNV), HIV, herpes simplex virus (HSV), angiotensin converting enzyme, antinuclear antibodies, SS-a, SS-b; lumbar puncture for cell counts, protein, glucose, oligoclonal bands, and PCR for Lyme, HSV, WNV
Genetic testing	Leber hereditary optic neuropathy mitochondrial DNA testing
Electrophysiology	Visual evoked potentials, electroretinogram

dysplasia), enlarged extraocular muscles, or aneurysms. Primary neoplasms include benign optic nerve glioma in children, and rarely malignant glioblastoma in adults. Other neoplastic conditions include lymphoma, leukemia, carcinomatous meningitis, and optic nerve metastasis.

Among the hereditary causes, Leber hereditary optic neuropathy is most common.⁵ It often becomes bilateral and the visual impairment is usually severe. There is maternal inheritance, with variable penetrance within families. The condition arises from mitochondrial DNA mutations that impair cellular energy stores. Most cases affect men, but the reasons for this gender asymmetry are unclear. The absence of pain in Leber hereditary optic neuropathy can serve as an important distinguishing feature. Findings on examination may include circumpapillary telangiectatic microangiopathy and pseudoedema of the nerve fiber layer.

Glaucomatous optic neuropathy is typically easily distinguished from optic neuritis, since it occurs in the setting of elevated intraocular pressure and optic disc cupping. However, angle closure glaucoma may present with painful acute visual loss, resembling the features of optic neuritis. Distinguishing characteristics include the severity of pain (which can be excruciating) and a red eye with an enlarged, nonreactive pupil.

A number of retinal conditions may present with symptoms similar to optic neuritis. These patients will often describe metamorphopsia (distorted or bent images) or photopsia (sparkles of light). Furthermore, there are often distinctive retinal findings. In acute idiopathic blind spot enlargement syndrome, examination reveals peripapillary pigmentary changes without disc swelling. Central serous chorioretinopathy, which predominantly affects young men with a type A personality, presents with acute, painless visual loss due to macular retinal detachment. The hallmark of retinal artery occlusion is retinal whitening, and that of retinal vein occlusion is retinal hemorrhage and engorgement of retinal veins.

The clinical profile of nonarteritic ischemic optic neuropathy may occasionally overlap the findings of optic neuritis.⁶ Features that favor ischemic optic

neuropathy in the appropriate clinical setting include nerve fiber hemorrhages, altitudinal visual field loss, moderate to severe disc edema, and the absence of pain. Vascular risk factors such as age, hypertension, diabetes, or hyperlipidemia are often present. Moreover, most patients with nonarteritic ischemic optic neuropathy have the anatomic predisposition of a small cup to disc ratio.

Diagnostic workup. Once the differential diagnosis has been narrowed on the basis of the clinical history and physical examination, an appropriate diagnostic workup is imperative to confirming the correct diagnosis (table 2).

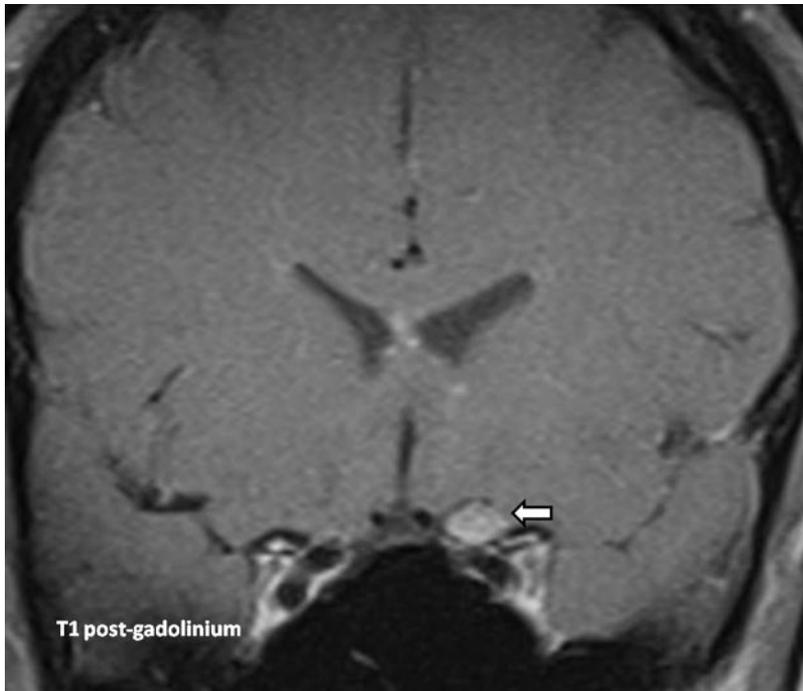
All patients with typical optic neuritis should undergo brain MRI to assess the risk of multiple sclerosis. MRI of the orbits may confirm optic nerve enhancement in the majority of patients with optic neuritis and may be helpful to exclude alternative causes of optic neuropathy.¹ Testing for NMO-IgG (neuromyelitis optica anti-aquaporin-4 antibody) is useful in patients with recurrent, bilateral, or severe optic neuritis, especially in patients with longitudinally extensive transverse myelitis.

In the routine case of optic neuritis, serologic tests are of limited diagnostic value. However, in patients with atypical or systemic features, serum testing may be considered for syphilis, Lyme disease, toxoplasmosis, cat scratch fever, West Nile virus, HIV infection, and herpesvirus infection, as well as serum angiotensin converting enzyme level, antinuclear antibodies, and Sjögren antibodies. In cases of suspected inflammatory or infectious optic neuropathy, lumbar puncture is necessary.

Genetic testing for Leber optic neuropathy is useful in patients with painless visual loss that is severe or bilateral, particularly if they are young men.

Visual evoked potentials are not routinely used in the diagnosis of demyelinating optic neuritis, although the finding of a P100 response with prolonged latency provides evidence for optic nerve demyelination. Testing may be helpful when there is a question of retinal disease vs optic neuritis or when subclinical optic neuritis is suspected.

Figure 1 Coronal T1-enhanced MRI revealing left optic nerve enlargement and enhancement (arrow)



An electroretinogram may be helpful in patients with suspected retinal dystrophy, paraneoplastic retinopathy, retinal artery occlusion, or a retinal inflammatory process. Likewise, fluorescein angiography may also confirm retinal inflammatory or ischemic processes. Optical coherence tomography (OCT) is usually normal in acute optic neuritis, but may be helpful in distinguishing some retinal conditions.

Clinical course. An MRI of the brain was obtained at the initial presentation. It revealed an enlarged and enhancing left optic nerve, and was thought to be consistent with the presumed diagnosis of optic neuritis (figure 1).

In September 2005 (6 months after the initial presentation), the vision in the left eye had progressed to no light perception. A follow-up MRI re-

vealed increased left optic nerve enlargement, with extension into the chiasm and pathologic enhancement. At another institution, a presumptive diagnosis of a left optic nerve glioma was made on the basis of clinical and radiographic progression. Neither biopsy nor resection was considered feasible due to chiasmatic involvement, and he was treated empirically with proton beam therapy (50 Gy equivalent, January 2006–March 2006) and temozolomide (March 2006–May 2007). He tolerated the therapy well, but there was no clinical improvement. Serial MRIs demonstrated stability of the left optic nerve lesion, with resolution of enhancement.

In May 2007 (25 months after the initial symptoms), he presented to our institution and reported 2 weeks of painless vision loss in the previously unaffected right eye. He perceived cloudiness over the entire visual field. The left eye remained no light perception. Associated symptoms included mild headache, fatigue, decreased appetite, mildly impaired concentration, and frequent epistaxis. He denied weakness, numbness, dysarthria, fevers, rash, arthralgia, or cough.

Medical examination, including detailed skin examination, was normal. Mental status was normal. He had no light perception in the left eye and 20/30 acuity in the right eye which did not improve with pinhole. He saw 10/10 color plates with the right eye. There was a large left relative afferent pupillary defect. He had small arcuate field defects in the right eye visual field. There was optic nerve pallor bilaterally (left greater than right). There was no uveitis. There was a mild comitant exotropia, with full ocular ductions, and normal saccades and pursuit. There was no ptosis or nystagmus. The remainder of the neurologic examination was normal.

Questions for consideration:

1. What are the diagnostic considerations for bilateral sequential monocular visual loss?
2. What diagnostic workup would you pursue?

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Figure 2 Coronal T1-enhanced MRI demonstrating right optic nerve enlargement and enhancement



SECTION 3

The differential diagnosis for bilateral sequential monocular visual loss includes many of the causes described above, including inflammatory, neoplastic, and infectious etiologies.⁷ Sarcoidosis, for example, may affect additional sites in the nervous system, including the contralateral optic nerve. In cases of treated neoplastic optic neuropathy, the distinction between radiation optic neuropathy and tumor recurrence can sometimes be challenging. Radiation optic neuropathy is suggested by exposure (to 50 Gy), characteristic 18 to 36 month lag time to symptoms, and radiation changes in proximal tissues. Bilateral visual loss in a patient with known or suspected cancer raises the possibility of a paraneoplastic

retinopathy or, less commonly, optic neuropathy. In paraneoplastic optic neuropathy, there is often evidence of other neurologic dysfunction, and the antibody most commonly identified is directed toward collapsing response mediated protein (CRMP 5). The asymmetric and sequential visual loss of our patient coupled with the enlarged, enhancing optic nerves make other conditions such as toxic/nutritional optic neuropathy or hereditary optic neuropathy unlikely.

Clinical course. The patient was admitted for evaluation and treatment of right eye visual loss. Laboratory evaluation revealed a negative or normal metabolic profile, cell counts, erythrocyte sedimentation rate (2 mm/hour), c-reactive protein, angiotensin converting enzyme level (34 units/L), antinuclear antibodies, ANCA, SSA/B, serum protein electrophoresis, thyroid stimulating hormone, and B12 level. The spinal fluid showed 1 wbc/mm³, 0 rbc/mm³, 42 mg/dL protein, 60 mg/dL glucose, no oligoclonal bands, and negative cytology.

MRI of the brain and orbits revealed enlargement and enhancement of the right optic nerve (figure 2). No additional lesions were identified in the brain.

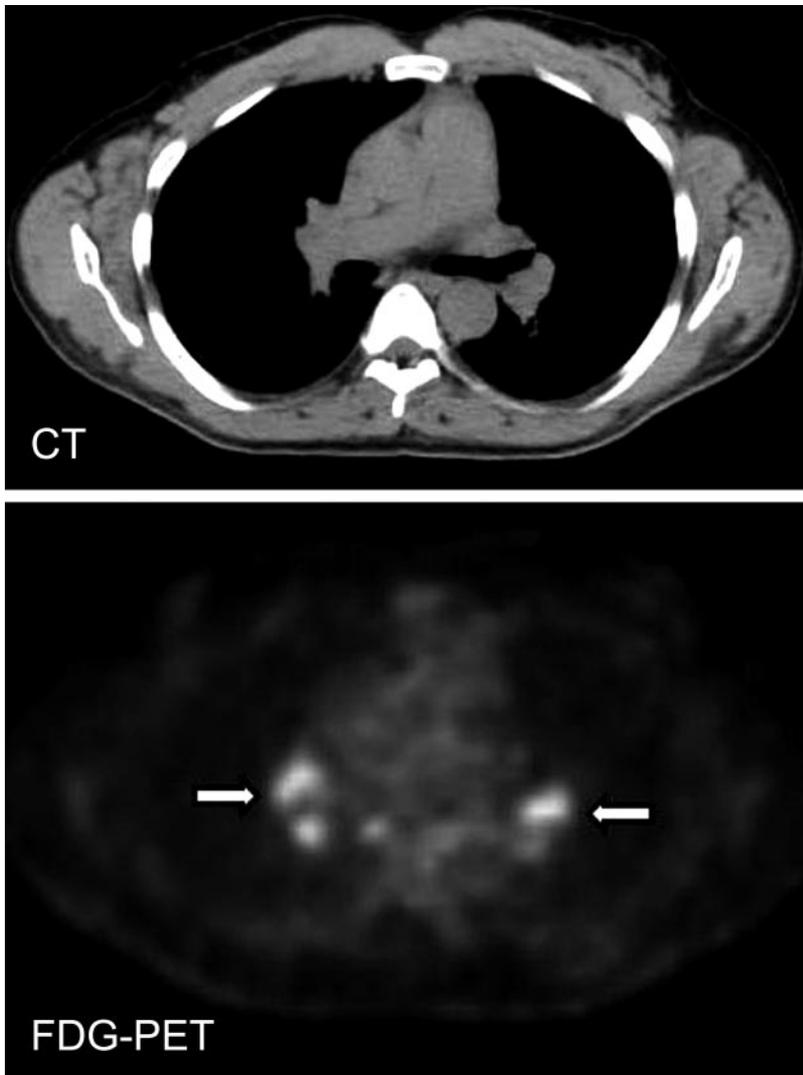
CT scan of the chest and abdomen were essentially normal, without evidence of malignancy or hilar adenopathy (figure 3). PET scan revealed mildly hypermetabolic lymph nodes in the bilateral hila (maximum SUV 3.4–4.2) and mediastinum (maximum SUV 1.5–3.5), inguinal lymph nodes (maximum SUV 1.6–1.7), and prostate (figure 3). There were no hypermetabolic regions in the head or neck, including the optic nerve.

Questions for consideration:

1. On the basis of these results, what additional tests will likely yield the diagnosis?
2. What is the prognosis and optimal treatment of this condition?

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Figure 3 Normal CT scan of the chest, axial slice (top), and increased hilar uptake on PET indicating increased metabolism (arrows)



SECTION 4

Tissue diagnosis was sought to confirm the etiology of the patient's vision loss because serology, CSF analysis, and imaging studies were largely unrevealing. The left optic nerve was selected because of the longstanding no light perception vision and the high signal abnormality on MRI.

Optic nerve sections showed severe atrophy and gliosis with virtually no axonal elements (figure 4, top left and top middle panels). There were very few inflammatory cells and no granulomas. Glial fibrillary acid protein immunohistochemical stains were diffusely positive, without demonstration of piloid morphology characteristic of glioma (top right panel). Ki67 stain did not show increased proliferation. Hemosiderin deposition was present, likely secondary to radiation and chemotherapy exposure. The previous diagnosis of an optic nerve glioma could not be confirmed.

Findings at PET scanning, including hypermetabolic mediastinal lymph nodes, presented a second-

ary site amenable to tissue sampling. Transbronchial biopsy was performed and showed several well-formed, noncaseating granulomas comprised of clusters of epithelioid macrophages and multinucleated giant cells (figure 4, bottom panels). Grocott and acid fast stains were negative for fungal and acid fast organisms. Noncaseating granulomas, in the absence of an infectious etiology, support the diagnosis of sarcoidosis.

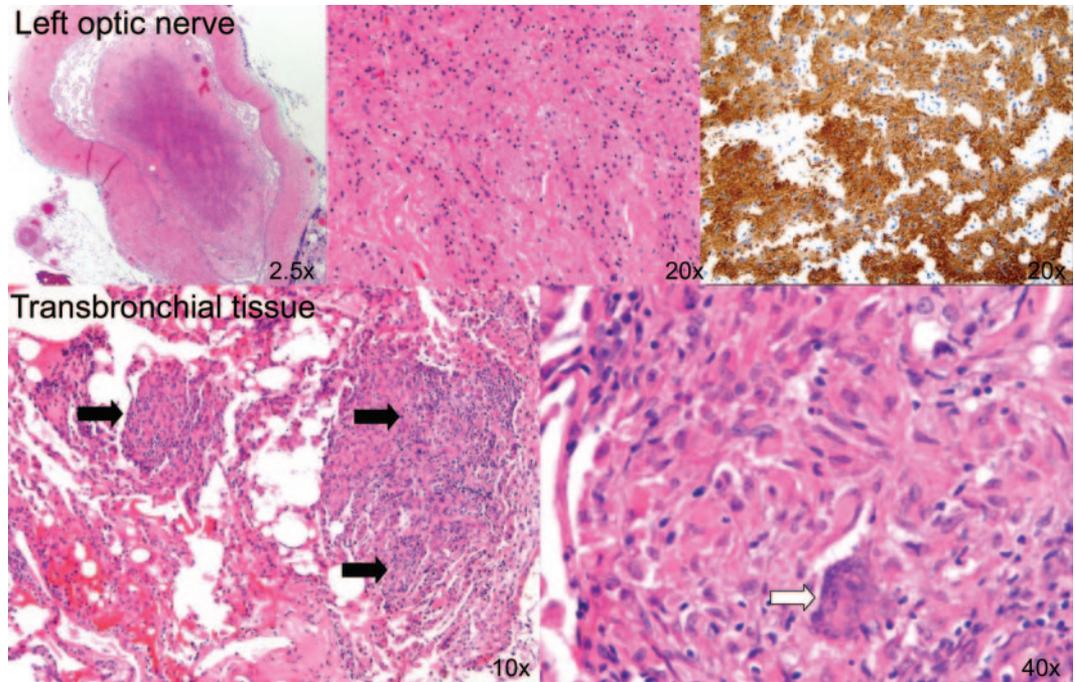
DISCUSSION Sarcoidosis is an uncommon disease characterized by granulomatous inflammation, likely caused by both genetic and environmental factors.⁸ While the lung and skin are most commonly affected, approximately 5% of patients will have neurologic involvement. Neurosarcoidosis has tremendous clinical heterogeneity, which poses diagnostic and therapeutic challenges.³ The most commonly affected sites are the leptomeninges and cranial nerves, with a predilection for the facial and optic nerves. Involvement of brain and spinal cord parenchyma, pituitary gland, peripheral nerves, and muscle also occurs.

Definitive diagnosis of neurosarcoidosis requires pathologic demonstration of noncaseating epithelioid cell granulomas, an inflammatory neurologic lesion on imaging or CSF analysis, and exclusion of other etiologies. Because there is frequently no neurologic lesion amenable to biopsy, a common alternative strategy is to demonstrate systemic sarcoidosis by biopsy of another organ and to imply the diagnosis of neurosarcoidosis. Potential biopsy sites can be identified by clinical examination or PET, gallium, or MRI scans that screen for clinical or subclinical inflammation. If positive tissue pathology is not available, diagnostic support can be provided by typical systemic symptoms, typical pulmonary radiographic findings and lymphocyte subpopulation ratios in bronchoalveolar lavage fluid.⁹ Unfortunately many of these tests are characterized by poor sensitivity and specificity. A variety of diagnostic algorithms using this ancillary data have been proposed, but none have come into widespread use. Therefore, when there is high clinical suspicion, unrevealing studies should not dissuade the practitioner from the diagnosis.

Once a diagnosis of neurosarcoidosis has been made consideration should be given to screening for subclinical involvement of other organs. An initial screening workup should include chest x-ray, pulmonary function tests, complete blood count, creatinine, BUN, calcium, liver enzymes, urinalysis, ECG, ophthalmologic examination, tuberculin skin test, and additional testing guided by abnormalities detected on history and physical examination.⁹

Neurosarcoidosis often requires aggressive treatment focused on controlling symptoms and reducing inflammation. Symptomatic therapy in neurosarcoidosis may

Figure 4 Pathology



Sections from the left optic nerve were stained with hematoxylin-eosin (H-E) (top left and top middle panels) and for glial fibrillary acid protein (top right panel). There is severe atrophy of the nerve (top left) with gliosis of the substance of the nerve (top middle and top right). Sections from the transbronchial biopsy stained with H-E (bottom panels) show noncaseating granulomas (black arrows) with multinucleated giant cells (white arrow).

include antiepileptic agents, pain medication, hormonal replacement therapy, and surgical treatment of hydrocephalus. Disease-controlling therapies aim to blunt the autoimmune response and decrease pathologic inflammation. The mainstay of therapy is high-dose oral corticosteroids for 6–8 weeks, with a preceding pulse of IV corticosteroids if needed. The clinical response should guide a reduction or escalation of therapy. Escalating therapeutic options include steroid-sparing cytotoxic agents, such as methotrexate, azathioprine, cyclophosphamide, and mycophenolate.¹⁰ Other therapies that may have a role include cytokine modulators such as infliximab or thalidomide and antimicrobial agents such as chloroquine or minocycline. Radiotherapy is reserved as a third line therapeutic option. Unfortunately there are no prospective trials to guide the optimal treatment regimen for neurosarcoidosis. Therapy selection is based on comorbidities, expected toxicities, and physician experience. Chronic management should focus on continued escalation or reduction in therapy as guided by progression or remission of symptoms, imaging, and laboratory data. Therefore frequent surveillance is imperative. This should be coupled with appropriate monitoring for therapeutic toxicity.

Clinical course. The patient was treated with high-dose IV methylprednisolone for 5 days, followed by a prolonged taper of oral prednisone. Visual acuity in his right eye normalized. Four months later, while on

a tapering dose of prednisone, the patient experienced recurrent right eye visual loss. This prompted the addition of mycophenolate mofetil to the treatment regimen. On combination therapy, the patient's vision stabilized, allowing further tapering of the oral prednisone.

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