Clinical Reasoning:

A 57-year-old man with unilateral anosmia, papilledema, and meningismus

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SECTION 1

A 57-year-old previously healthy man was referred to our clinic for bilateral vision loss.

Six weeks before presentation, the patient developed central graying of vision in his right eye that progressed to blindness over a week. Over the next several weeks, the same occurred in the left eye. There was retro-orbital pain and a new holocephalic headache that was worse in the mornings. He reported lancinating pain down his neck, left arm, back, and left leg with neck movement. An outside ophthalmologist noted bilateral optic disc edema and referred him to our clinic.

The patient was employed as a prison guard. Screening for tuberculosis exposure with purified protein derivative testing was negative for at least the last 5 years. He neither drank alcohol nor smoked. His

mother had died of a brain tumor in her 70s. He denied fever, chills, cough/dyspnea, epistaxis, recent illness, bowel or bladder dysfunction, hematuria, and any history of neurologic issues. He was current on preventative cancer screening.

On examination, the patient had normal vital signs, left-sided anosmia, and a relative afferent pupillary defect (RAPD) on the right with bilateral disc edema. Visual acuity was finger counting at 1 foot OD and 4 feet OS with a large central scotoma in each eye. He had mild nuchal rigidity. The remaining examination was normal.

Questions for consideration:

1. What is the localization?
2. What is the differential diagnosis and what are the next steps in the diagnostic evaluation?

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SECTION 2

The clinical findings are referable to the left orbito-frontal groove (left anosmia), bilateral optic nerves, right > left (vision loss with right RAPD), cranial meninges (headache), and cervical meninges (nuchal rigidity/Lhermitte). The absence of long track findings makes intraparenchymal cord pathology unlikely. Taken together, a meningeal process is most likely. In approaching the differential diagnosis, the left olfactory deficit should be considered part of the same process, particularly given its unilaterality.

The time course (subacute, progressive) suggests malignancy, immune disease, or insidious infection. The differential diagnosis includes malignancy (neoplastic meningitis, lymphoma, esthesioneuroblastoma), immune-mediated illness (neurosarcoidosis, neuromyelitis optica, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides such as granulomatosis with polyangiitis), and indolent infection (tuberculous meningitis, cryptococcal meningitis, histoplasmosis, blastomycosis). The next steps in the diagnostic evaluation include contrasted MRI brain/orbits and cervical spine, serum laboratory studies, and CSF analysis.

Contrasted brain/orbit MRI with fat suppression and cervical MRI demonstrated a left olfactory groove homogenously contrast-enhancing mass, bilateral optic disc edema with an enhancing right optic nerve head, longitudinally extensive perineural enhancement of both optic nerves sparing the optic chiasm, and meningeal enhancement along the ventral pons and surrounding the cervical spinal cord (figure 1). Complete blood count, metabolic panel, sedimentation rate, and C-reactive protein were normal. Lumbar puncture demonstrated elevated opening pressure at 31 cm H₂O, 28 nucleated cells/μL (79% lymphocytes), hypoglycorrhachia with glucose 27 mg/dL, and elevated protein at 162 mg/dL. Infectious studies, including syphilis, mycobacterial, and fungal testing, were sent. Serum and CSF angiotensin-converting enzyme (ACE) levels were normal. Serum aquaporin-4 antibody was sent. CSF cytology and flow cytometry were nondiagnostic. HIV testing was negative.

Questions for consideration:

1. What is unique about the patient's optic neuritis?
2. What is the differential for this unusual finding?

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Figure 1 Brain, orbit, and cervical spine MRI with contrast

(A) Axial postcontrast T1-weighted fat saturated MRI reveals a homogenously enhancing anterior cranial fossa mass (arrow), optic disc edema with enhancing right optic nerve head (arrowhead), and perineural enhancement of both optic nerves (brackets). (B) Sagittal postcontrast T1-weighted fat saturated MRI demonstrates abnormal leptomeningeal enhancement along the ventral pons (arrow) and surface of the spinal cord (arrowheads). (C) Coronal postcontrast T1-weighted fat saturated MRI shows enhancement along the optic nerve sheath comprising the pia mater (arrow), subarachnoid space filled with CSF (hypointense ring), arachnoid, and dura mater (arrowhead). The homogenously enhancing anterior cranial fossa mass is again seen.

SECTION 3

MRI demonstrated optic perineuritis, wherein the optic nerve sheath is affected with relative sparing of the nerve fibers themselves (figure 1). The clinical presentation is indistinguishable from other causes of optic neuritis but the diagnostic considerations are unique. An idiopathic (primary) form of optic perineuritis has been reported that appears to respond to steroids, but recognition of identifiable etiologies is critical for appropriate management.¹

Secondary causes of optic perineuritis include neoplastic meningitis, neurosarcoidosis, granulomatosis with polyangiitis and other ANCA-associated vascu-

litides, Behçet, immunoglobulin G4-related disease, Crohn disease, syphilis, and other infectious causes of meningitis (especially opportunistic infections). Fungi that can infect immunocompetent hosts include *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*. ANCA testing was negative.

Question for consideration:

1. What imaging and laboratory features can be used to distinguish among the most likely remaining diagnoses and what further investigations should be conducted?

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SECTION 4

The most challenging diagnoses to differentiate in this case are neoplastic meningitis, neurosarcoidosis, and fungal or mycobacterial infection. MRI and laboratory studies, when diagnostic, may spare the patient from biopsy.

Neurosarcoidosis, neoplastic (specifically lung and breast carcinomas and lymphomas), fungal, and mycobacterial meningitides share similar imaging features of pial–arachnoid enhancement, which is often nodular, with a penchant for affecting the basilar cisterns and fourth ventricle. For this reason, they are generally indistinguishable on imaging studies.

The CSF profile is not appreciably different among neurosarcoidosis, neoplastic and fungal/mycobacterial meningitis, and elevated opening pressure can be seen in all 3 conditions. Neoplastic, fungal, and mycobacterial meningitides all typically demonstrate moderate pleocytosis (~ 5 – 200 cells/ μ L), most often lymphocyte-predominant, elevated protein, and may have hypoglycorrhachia (e.g., CSF/serum glucose ratio <0.6 is seen in 30% of neoplastic cases).² There is no specific laboratory test for sarcoidosis. CSF ACE levels are both insensitive and nonspecific for neurosarcoidosis.³ Elevated immunoglobulin G index and oligoclonal bands reflect intrathecal immune activation and are seen in 43% and 34% of neurosarcoidosis cases, respectively.³ These are also expected in infectious meningitis but are not typical of neoplastic meningitis.

Given the overlapping clinical, radiologic, and CSF profiles, more focused laboratory testing is generally required. The specificity of CSF cytologic examination for malignant cells is very high, but the sensitivity is between 70% and 95%, with the higher sensitivities achieved after a second or third examination.⁴ To minimize false-negatives, at least 10 mL CSF should be specifically sent for cytology and should be processed promptly.⁴ CSF flow cytometry is useful for identifying lymphomatous/leukemic meningitis.

Testing CSF, urine, and serum for the presence of fungal antigens or antibodies may expedite diagnosis of fungal meningitis due to dimorphic fungi. Fungal cultures, acid-fast bacillus smear, and mycobacterial cultures are valuable, but may take weeks to confirm a diagnosis.⁵ Histoplasmosis and blastomycosis antigen detection in the urine and CSF is highly sensitive and specific.⁵ Coccidioides may produce peripheral or CSF eosinophilia, which is relatively unusual in other fungal meningitides, and serology and antigen testing may confirm the diagnosis.⁵ India ink staining is inexpensive, but has largely been replaced by cryptococcal antigen testing of CSF, which is highly sensitive and specific.⁶ Suspicion for tuberculous meningitis is

increased when there is evidence of exposure (a positive PPD or interferon- γ release assay), and in this setting additional testing such as CSF mycobacterial PCR or adenosine deaminase testing may be indicated.⁷

Findings on chest CT may suggest cancer, sarcoidosis, histoplasmosis, or tuberculosis. Our patient had normal CT chest, abdomen, and pelvis. After infectious evaluation returned negative, he was treated with 1,000 mg IV methylprednisolone daily for possible immune-mediated illness (neurosarcoidosis, in particular). He continued to progress steadily despite glucocorticoids, however. In the absence of a secure diagnosis, biopsy of the orbitofrontal mass was pursued. This revealed adenocarcinoma with signet rings (figure 2). Body PET did not reveal a primary source of his cancer and he was diagnosed with intestinal type sinonasal adenocarcinoma (ITSA). Palliative whole-brain irradiation was given and he was discharged to home hospice with his family. He died within a month of presentation to our clinic.

DISCUSSION Roughly 5% of patients with malignancy are diagnosed with neoplastic meningitis, although an additional 20% or more are found at autopsy.² Malignant cells reach the meninges through several mechanisms, including direct extension, migration along the epineurium of peripheral or cranial nerves (as in our case), and arterial or venous metastasis.

The most common solid tumors responsible for neoplastic meningitis include breast ($\sim 43\%$), lung

Figure 2 Histopathology of the olfactory groove biopsy

High-power hematoxylin & eosin-stained section of the olfactory groove biopsy specimen reveals infiltrative tumor cells with signet ring features. The malignant cells were immunoreactive for CDX-2 and cytokeratins including CK-7 (focally), CK-20, and CK-AE1/AE3 (not shown). Scale bar = 100 μ m.

(~29%), gastrointestinal (~7%), and melanoma (~6%).² The most common sites include the base of the brain and the dorsal spinal cord, especially the cauda equina, possibly related to slow flow of CSF through these areas. The majority of patients have evidence of active systemic malignancy, but ~5% of patients present with neoplastic meningitis. The median survival in one cohort was 2.3 months for patients with neoplastic meningitis from solid tumors, and 4.7 months for those with hematopoietic malignancies.⁸

ITSA is a rare epithelial cell tumor of the nasal cavity and paranasal sinuses with a male to female ratio of 21:1.⁹ ITSA is associated with wood or leather dust exposure (our patient reported no exposure), but typically develops decades after exposure. The most common symptoms include nasal obstruction, epistaxis, visible tumor, rhinorrhea, and pain, but most patients are asymptomatic until metastasis. A diagnostic delay of 6–8 months from symptom onset is common. The prognosis is poor, with 5- and 10-year mortality of 44% and 53%, respectively. The worst prognosis is seen with spread to the brain, orbit, dura, or sphenoid sinuses, with almost no patients surviving 5 years.⁹ The cervical lymph nodes are the most common site of metastasis (3%–33%), while retropharyngeal lymph node and other distant metastases are rare (5%–10%).⁹ Treatment consists of surgical resection when possible, usually followed by radiation. Resection with wide margins is often impossible, and local recurrence is common. There are no standardized options for chemotherapy and no phase III clinical trials have been conducted; therefore, treatment is based on case reports and case series.

AUTHOR CONTRIBUTIONS

Michael J. Bradshaw: treating physician, chart and literature review, manuscript design/drafting, critical analysis/editing of manuscript. Karen C. Bloch: critical analysis/editing of manuscript, infectious review. L. Taylor Davis: treating physician, neuroradiology review. Laura D. Craig-Owens: Pathology slides and comments. Kim Ely: Pathology slides and comments. Reid Longmuir: treating physician, critical analysis/editing of manuscript.

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