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Stalking the Diagnosis

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A 22-year-old man presented with progressive neurologic decline. A year prior, he had experienced painless vision loss of the left followed by the right eye. Over the next 4-6 months, he developed diffuse numbness, limb stiffness, whole body weakness, and urinary incontinence. Additional symptoms included a 15-pound weight loss during the previous year, disorientation, and progressive inability to care for himself.

He was from Pakistan and had moved to Central California 3 months prior to symptom onset. He had worked as a delivery driver. He did not smoke tobacco, drink alcohol, or use any recreational drugs. His family history was unremarkable.

He had been given a clinical diagnosis of multiple sclerosis by a neurologist in California based on his symptoms and imaging that raised concerns for demyelination. The patient was started on natalizumab and subsequently transitioned to interferon beta-1a owing to lack of response. His symptoms continued to progress, and his family brought him to the emergency department of an academic medical center at the recommendation of his local physician.

This previously healthy young man has a history of additive, progressive visual and neurological symptoms that were attributed to multiple sclerosis, but did not improve with therapy for this condition. The most likely localization for diseases that cause acute, isolated, painless monocular blindness is either the posterior pole of the eye or the optic nerve. The second phase of illness suggested new involvement of upper motor neurons, sensory pathways, and autonomic tracts controlling sphincter function. Possibilities for neuroanatomic localization include the

cervicothoracic spinal cord, the brainstem, the frontal and parietal lobes, and their associated deep white matter tracts. The additional geographical history (both his residence in Pakistan and Central California) raises concern for endemic infectious disease risks (e.g., coccidioidomycosis, tuberculosis, or reactivation of measles infection leading to subacute sclerosing panencephalitis).

On exam, his temperature was 36.9°C, blood pressure 102/55 mm Hg, pulse 75 beats per minute, and oxygen saturation 98% breathing ambient air. He appeared chronically ill. Cardiovascular, pulmonary, and abdominal examinations were normal. On neurologic exam, he was awake and oriented to being in a hospital but not to the city or date. He followed simple commands and had a paucity of speech. Pupils were equal but nonreactive to light bilaterally. Visual acuity was severely impaired bilaterally on confrontational testing, with perception of light and finger movements only. His extremities had decreased muscle bulk with increased tone and paratonia. Reflexes were 3+ throughout and Babinski sign was present bilaterally. Sensation was intact to light touch. Cerebellar testing was normal. He was unable to ambulate without assistance.

The visual examination shows profound visual loss, and the nonreactive pupils indicate a localization anterior to the optic chiasm. The neurological exam is most striking for the combination of cognitive deficits, a spastic quadriparesis, and visual deficits, suggestive of a multifocal disease process. Since the initial history also raised the possibility of spinal cord disease, it is important to check for a sensory level.

This would be an unusually protracted course for many central nervous system infections. Similarly, aggressive malignancies that occur in this age group likely would have resulted in additional non-neurological morbidity or even mortality if they had gone untreated for this length of time.

Complete blood count and chemistries were normal with the exception of a sodium of 148 millimole per liter (mmol/L). A lumbar puncture demonstrated clear fluid with 11 white blood cells per cubic millimeter (reference, < 6) with 94% lymphocytes and 6% monocytes, 5 red blood cells per cubic millimeter, glucose 44 mg/dL, and protein 110 mg/dL (reference, 15-50) in the 3rd tube. Oligoclonal bands were present.

Magnetic resonance imaging of the brain revealed areas of nodular ependymal and leptomeningeal enhancement on a background of extensive periventricular, white matter signal abnormality (Figure 1). Additionally, there was symmetric abnormal signal along the bilateral optic tracts. MRI of the spinal cord with and without contrast was normal.

The cerebrospinal fluid provides evidence of central nervous system (CNS) inflammation, which essentially limits consideration to 3 categories of CNS disease: neoplastic, infectious, and non-infectious inflammatory processes. While oligoclonal bands are most commonly associated with MS, they are nonspecific and can occur in other disease processes. Similarly, hypoglycorrhachia commonly occurs in the setting of acute or chronic infectious meningitis, but it too may be a feature of all categories of CNS disease mentioned above.

Neuroimaging findings indicate intracranial involvement (optic tracts, meninges, and white matter) without apparent spinal cord pathology, although this is not definitively ruled out. Periventricular white matter hyperintensities are abnormal but non-specific findings. Subependymal enhancement is a rare, striking imaging finding that substantially narrows the range of diagnostic considerations. When it is described as nodular, neoplastic causes including glioma, primary CNS lymphoma, ependymoma, germ cell tumor, and (leptomeningeal) metastases are the most likely explanation, although granulomatous processes such as sarcoidosis and granulomatous angiitis of the CNS are also possible. Most infectious etiologies of chronic subependymal enhancement and ventriculitis such as tuberculosis, syphilis, and cryptococcosis demonstrate a thinner, more linear pattern of enhancement.

The presence of contiguous intracranial meningeal enhancement along with the abnormal CSF findings raises the question of whether this illness might represent a chronic form of meningitis and ventriculitis, such as CNS coccidioidomycosis or tuberculosis. This is unlikely, however, given the substantial neurologic deficits in the absence of evident cerebral infarction or hydrocephalus, the protracted duration of disease, and lack of headache.

Bacterial cultures of the blood and CSF were negative, as were stains and cultures for mycobacteria and fungi. Polymerase chain reaction for *Mycobacterium tuberculosis* was negative. CSF and serum cryptococcal antigen were negative. Testing for herpes simplex, varicella zoster, West Nile Virus, dengue, chikungunya, JC virus, and human herpes virus-

6 were negative. The patient underwent upper and lower endoscopy which was unrevealing; biopsies to evaluate for *Tropheryma whipplei* were negative.

Testing for antinuclear, anti-dsDNA, SSA/SSB, tissue transglutaminase (TTG), and antineutrophil cytoplasmic antibodies were negative. Cytology and flow cytometry from the CSF were unrevealing. Testing for antibodies against aquaporin-4 was negative.

Biopsy of the dura, brain cortex, and periventricular white matter demonstrated increased cellularity composed predominantly of macrophages and scattered lymphocytes.

While most CSF PCR viral studies have reasonably high sensitivity for the respective CNS infections, *Mycobacterium tuberculosis* PCR testing of CSF has variable sensitivity. Reactivation of latent tuberculosis has been associated with natalizumab therapy, but the protracted clinical course makes this unlikely. Whipple's disease can in rare cases cause chronic CNS infection, but the negative endoscopic studies make this diagnosis unlikely, as most patients have concomitant gastrointestinal involvement. The absence of antibodies against aquaporin-4 argues against a diagnosis of neuromyelitis optica, but this test was probably not necessary in light of the normal spinal MR findings.

Findings on brain biopsy are nonspecific. The absence of diagnostic findings may be explained by sampling error. If representative tissue was obtained, the biopsy results would exclude many

types of malignancy and granulomatous disease, assuming there is no underlying immunocompromise that prevents him from forming granulomas.

On hospital day 10, the patient's sodium abruptly increased to 165 mmol/L. His daily urine output was approximately 3 to 4 liters, and his urine osmolality was 132 mmol/kg (reference, 300-900). He was started on free water replacement via his feeding tube. A prolactin level was 48 µg/L (reference, 3.6-18), adrenocorticotropic hormone 7 ng/L (reference, 6-50), follicle stimulating hormone 0.2 international units per liter (reference, 1-12), and luteinizing hormone 0.1 international units per liter (reference, 0.6-12.1). A cortisol level was 3 µg/dL and increased to 12 µg/dL after the administration of synthetic adrenocorticotropic hormone. A thyroid stimulating hormone level was 0.24 mIU/L (reference, 0.45-4.12) and a free T4 was 8 pmol/L (reference, 10-18). The patient was started on hydrocortisone followed by levothyroxine.

The constellation of hyperosmolality, polyuria, and inappropriately dilute urine is characteristic of diabetes insipidus (DI). This is likely to be central in origin given the close proximity of CNS disease to the pituitary and the additional evidence of panhypopituitarism. The patient's mild hypernatremia earlier in the course probably indicated early, partially compensated DI.

Dedicated pituitary imaging should be performed since lesions in and around the sella turcica may be missed by routine brain MRI. The differential diagnosis of panhypopituitarism not caused by hypophysectomy includes malignancy (primary pituitary tumors, NK T-cell lymphoma, metastases), autoimmune disease (lymphocytic hypophysitis), granulomatous

processes (sarcoid, lymphomatoid granulomatosis), infiltrative disease (histiocytosis, amyloid), and, rarely, infection (tuberculosis, pituitary abscess, syphilis).

MRI of the pituitary gland, performed with and without the administration of contrast material, revealed the absence of normal high signal intensity in the posterior lobe, a finding consistent with diabetes insipidus, as well as diffuse infundibular thickening (Figure 2). The patient was scheduled to undergo transsphenoidal biopsy of the pituitary lesion.

Craniopharyngioma is a suprasellar tumor that occurs in young people and may have cystic components. However, this tumor would not explain the progressive, systemic findings in this case. The pituitary and infundibular findings point to a limited set of potential diagnoses.

Both neurosarcoidosis and various histiocytoses may cause indolent, progressive CNS disease either in isolation or as part of a broader systemic illness. These illnesses share an inflammatory CSF profile and may present with lesions of the meninges, sella turcica, and ventricular system. In this young man, early blindness with presumptive involvement of the optic nerves and the extensive white matter disease point to sarcoidosis as the more likely diagnosis. Whether he is the rare person with disease limited to the CNS or neurosarcoidosis with subclinical disease in other organs awaits assessment of other extra-neurological sites.

Transsphenoidal biopsy of the pituitary lesion revealed histologic findings consistent with a suprasellar CNS germinoma (Figure 3). The CSF human chorionic gonadotropin (HCG) was elevated at 4.5 IU/L (reference, < 1.1). The patient was ultimately diagnosed with a

pituitary-based CNS germinoma presumed to be complicated by neoplastic meningitis and parenchymal infiltrative disease leading to profound neurologic disability, although definite tissue or cytologic evidence of disease in these compartments was lacking. The patient was started on chemotherapy with etoposide and carboplatin, followed by radiation therapy. Ten months following diagnosis, he had clinical and radiographic response to treatment, but continued to experience hypopituitarism (for which he was maintained on hydrocortisone and levothyroxine) and substantial neurologic disability requiring assistance with all of his activities of daily living.

DISCUSSION

At first consideration, this patient's course of early ocular manifestations (felt clinically to represent optic neuritis) later followed by additive upper motor neuron neurologic deficits appropriately raised consideration of multiple sclerosis. While this condition is the most common CNS cause of permanent disability in young adults, establishing the diagnosis can be challenging. Diagnostic criteria require the demonstration of a compatible demyelinating syndrome (e.g., optic neuritis, brainstem/cerebellar syndromes, transverse myelitis) with objective neurologic findings disseminated both in space and time.[1] Misdiagnoses are common, with 30-67% of patients referred to MS centers ultimately receiving a different diagnosis.[1] The most common alternative diagnoses in one series included migraine, functional disorders, and neuromyelitis optica spectrum disorder; other inflammatory conditions also can mimic this disease.[2]

The finding of nodular ependymal and meningeal enhancement and CSF pleocytosis expanded the differential diagnosis to a range of infectious, infiltrative, and neuroinflammatory disorders. Many conditions can involve the meninges, including bacterial, mycobacterial, fungal, viral, autoimmune, and malignant processes. Chronic meningitis, defined as symptoms lasting longer than 4 weeks with a CSF pleocytosis, is most commonly caused by atypical bacteria, fungi, and noninfectious processes.[3] Imaging studies can help delineate the pattern of meningeal enhancement (e.g., leptomeningeal, pachymeningeal, basal meningeal) and thereby focus the differential diagnosis. For example, bacterial and viral meningitis tends to produce a thin and linear enhancement of the leptomeninges, whereas fungal or neoplastic meningitis often is associated with thicker, nodular enhancement.[4]

Neoplastic meningitis is an uncommon cause of CSF pleocytosis and can be caused by hematologic malignancies, metastatic solid tumors, and, rarely, primary brain cancers. Metastases to the CSF occur due to either hematogenous spread or contiguous extension by brain parenchymal tumors or bony disease.[5] The gold standard for diagnosing neoplastic meningitis is finding abnormal cells on CSF cytology or a monoclonal population on flow cytometry. The sensitivity for a single CSF cytology specimen is low (70% in one series), but increases to approximately 90% when specimens are assessed from 3 serial lumbar punctures.[5] MRI often shows ependymal, leptomeningeal, or dural enhancement consistent with neoplastic meningitis.[4]

The development of diabetes insipidus provided an important diagnostic breakthrough in this difficult case, leading the discussant to consider pathologies in the pituitary and hypothalamus. Causes of disease in these regions include benign tumors (e.g., pituitary adenomas),

malignancies (both primary CNS cancers and metastases), inflammatory disorders (e.g., neurosarcoidosis, Langerhans cell histiocytosis, granulomatosis with polyangiitis), infections, and congenital abnormalities.[6] Symptoms of sellar lesions are variable and depend on whether the lesion is hormone-secreting, the size of the lesion, and whether its growth interferes with hypothalamic or pituitary function. In non-secretory lesions, the most common presentations include visual impairment, hypopituitarism, hyperprolactinemia due to pituitary stalk compression, and headache. Diabetes insipidus or cranial neuropathies are rare complications.[7]

CNS germ cell tumors are rare primary brain tumors that occur more commonly in children and young adult men. They have a propensity to occur in midline structures, including the neurohypophysis and pineal gland, where they can lead to headache, hydrocephalus, ocular symptoms, and pituitary gland dysfunction.[8] CNS germ cell tumors may also spread throughout the CNS, including the brain parenchyma (which can radiographically mimic demyelinating disease), optic tracts, and the CSF, as was seen in this case.[9-11] As such, whole neuroaxis imaging and CSF testing should be performed when these tumors are identified.

Given their rarity and nonspecific presentation, the diagnosis of CNS germ cell tumors can be challenging and is often delayed. There are many reports of such patients initially being given such disparate diagnoses as multiple sclerosis (with oligoclonal bands having been noted in some case reports), infectious chronic meningitis, and lymphocytic hypophysitis.[9-12] While definitive diagnosis requires histologic confirmation, several findings can suggest the presence of an underlying CNS germ cell tumor. Characteristic findings on magnetic resonance imaging, as seen in this case, include predominantly midline localization, infundibular thickening, isointense

or hypointense signal on T1 imaging, occasional cystic components, and variable T2 intensity.[13] Elevated beta-HCG levels, and less commonly alpha fetoprotein, may be present in the serum and CSF; in a retrospective case series of patients with histologically confirmed CNS germ cell tumors, 41% had elevated beta-HCG levels in CSF while 31% had elevated serum levels.[14] Treatment of CNS germinomas relies on conventional chemotherapy and radiation therapy and is primarily guided by evidence from retrospective series and prospective observational studies.[15] Response rates are favorable but permanent neurologic disability is common and these tumors can recur later in life.[15]

This case represented a diagnostic challenge, owing in large part to the nonspecific findings on initial presentation and the rarity of the final diagnosis. Although neither the discussant nor treating team suspected the presence of an intracranial germinoma, the development of DI led them to the pituitary stalk, where they were able to finally track down the diagnosis.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Solomon AJ, Naismith RT, Cross AH. Misdiagnosis of multiple sclerosis: Impact of the 2017 McDonald criteria on clinical practice. Neurology. 2019;92(1):26-33.

2. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008;14(9):1157-1174.

3. Helbok R, Broessner G, Pfausler B, Schmutzhard E. Chronic meningitis. J Neurol. 2009;256(2):168-175.

4. Smirniotopoulos JG, Murphy FM, Rushing EJ, Rees JH, Schroeder JW. Patterns of contrast enhancement in the brain and meninges. Radiographics. 2007;27(2):525-551.

5. Rigakos G, Liakou CI, Felipe N, Orkoulas-Razis D, Razis E. Clinical Presentation, Diagnosis, and Radiological Findings of Neoplastic Meningitis. Cancer Control. 2017;24(1):9-21.

6. Turcu AF, Erickson BJ, Lin E, et al. Pituitary stalk lesions: the Mayo Clinic experience. J Clin Endocrinol Metab. 2013;98(5):1812-1818.

7. Freda PU, Post KD. Differential diagnosis of sellar masses. Endocrinol Metab Clin North Am. 1999;28(1):81-117, vi.

8. Gao Y, Jiang J, Liu Q. Extragonadal malignant germ cell tumors: a clinicopathological and immunohistochemical analysis of 48 cases at a single Chinese institution. Int J Clin Exp Pathol. 2015;8(5):5650-5657.

9. Birnbaum T, Pellkofer H, Buettner U. Intracranial germinoma clinically mimicking chronic progressive multiple sclerosis. J Neurol. 2008;255(5):775-776.

10. Krolak-Salmon P, Androdias G, Honnorat J, et al. Beware of optic neuritis! Lancet Neurol. 2002;1(8):516-517.

11. Suresh TN, Mahadevan A, Santosh V, Shankar SK. Subarachnoid spread of germinoma mimicking tuberculous meningitis. Neurol India. 2004;52(2):251-253.

12. Guzzo MF, Bueno CB, Amancio TT, et al. An intrasellar germinoma with normal tumor marker concentrations mimicking primary lymphocytic hypophysitis. Arq Bras Endocrinol Metabol. 2013;57(7):566-570.

13. Liang L, Korogi Y, Sugahara T, et al. MRI of intracranial germ-cell tumours. Neuroradiology. 2002;44(5):382-388.

14. Takami H, Fukuoka K, Fukushima S, et al. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. Neuro Oncol. 2019;21(12):1565-1577.

15. Osorio DS, Allen JC. Management of CNS germinoma. CNS Oncol. 2015;4(4):273-279.

Figure Legends

Figure 1: **MRI of the brain.** Panels A and B demonstrate nodular ependymal lesions (arrows) and leptomeningeal enhancement. Panel C shows periventricular white matter changes.

Figure 2: **MRI of the pituitary.**

A T1-weighted, fat-suppressed image, obtained after the administration of contrast material, shows abnormal diffuse infundibular thickening (arrow) and the absence of normal high signal intensity in the posterior lobe.

Figure 3: **Histopathological findings.**

Routine hematoxylin and eosin stained sections demonstrate a background of dense inflammation and scattered large, epithelioid tumor cells with round to oval, centrally placed nuclei, prominent nucleoli and moderate pale to clear cytoplasm (A). The tumor cells are positive for the germ cell markers SALL4 (B) and OCT4 (C). The findings are diagnostic of germinoma.