Clinical Reasoning: A 71-year-old man with rapidly progressive dementia

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SECTION 1

A 71-year-old right-handed man presented to the emergency room of our institution with the chief complaint of cognitive impairment of recent onset. His medical history was notable for treated hypertension, hyperlipidemia, and depression. He noted a 3-week history of short-term memory impairment (forgetting where he parked his car, misplacing items, forgetting conversations), behavioral changes (short-tempered, apathetic, easily disoriented in unfamiliar settings), generalized fatigue, weight loss, and visual impairment (possible right homonymous hemianopsia), the last of which resolved prior to presentation. He was otherwise able to carry out his basic activities of daily living and continued to drive a car, albeit with some difficulty. Physical examination was notable for

12/30 points on the Montreal Cognitive Assessment, losing points mainly for impaired visuospatial-executive function, attention, and delayed recall. He was only mildly disoriented and could not name the hospital or the day of the week. His affect was flat and he appeared apathetic but was otherwise polite and had good insight into his current cognitive problems. Cranial nerve, motor, sensory, and cerebellar examination results were normal. Initial cell blood count, basic metabolic panel, liver function panel, thyroid studies, markers of inflammation, vitamin B₁₂, folate, and urine analysis were all normal.

Question for consideration:

1. What is the differential diagnosis of rapidly progressive dementia?

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SECTION 2

Rapidly progressive dementia is cognitive decline occurring over a period of weeks to months compared to the relatively slow cognitive decline over several years seen in neurodegenerative diseases such as Alzheimer disease. The differential is broad, but briefly encompasses vascular, infectious, toxic-metabolic, autoimmune, metastatic (neoplastic), iatrogenic, neurodegenerative, and systemic diseases,¹ easily remembered using the mnemonic VITAMINS.

A hypodense lesion was noted in the splenium of the corpus callosum on noncontrast CT of the head

(figure 1A). The lesion displayed T2 hyperintensity and T1 postcontrast enhancement with a patchy distribution and lack of diffusion restriction on MRI of the brain (figure 1, B–D and F–H). Whole-body PET-CT was negative for highly metabolic lesions other than in the splenium of the corpus callosum (figure 1E).

Questions for consideration:

1. What is the differential diagnosis for abnormal MRI signal in the splenium of the corpus callosum?
2. What further tests are indicated to elucidate the etiology of the imaging findings?

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Figure 1 Neuroimaging demonstrates a lesion of the splenium of the corpus callosum

Montage of axial cuts through the splenium of the corpus callosum depict a hypodense lesion on CT (A), which is uniformly hyperintense on T2 (B) and T2 fluid-attenuated inversion recovery (F), but hypointense on T1 (C) with patchy contrast enhancement on T1 postcontrast (G). Diffusion-weighted imaging (H) and apparent diffusion coefficient map (D) showed T2 shine-through and not true diffusion restriction. The lesion displays high metabolic activity on PET-CT (E).

SECTION 3

The boomerang sign is a descriptive term for a hyperintense lesion of the splenium of the corpus callosum on MRI. The differential diagnosis includes CNS lymphoma, glioma, metastasis, demyelinating disease, trauma, stroke, toxic-metabolic (e.g., Marchiafava-Bignami), and posterior reversible vasoconstriction syndrome, and can be seen as a transient phenomenon.² Neurosurgery was consulted to evaluate for brain biopsy while lumbar puncture was undertaken. The opening pressure was 13.5 cm H₂O. CSF analysis revealed 13 leukocytes/ μ L (100% lymphocytes), 0 erythrocytes, protein 79, glucose 59, and 0 oligoclonal bands. CSF studies for bacterial, fungal, acid-fast, or viral organisms (including Epstein-Barr virus [EBV] PCR) yielded negative results. Cytology revealed a benign reactive T-lymphocytic cell population. Blood tests similarly yielded negative results for bloodborne infection (including HIV) and rheumatologic disease. The patient underwent right parietal burr hole for stereotactic biopsy of the callosal lesion. The biopsy showed a diffuse intense lymphohistiocytic infiltrate composed predominantly of a mixture of small lymphocytes (T and B cells) and many histiocytes (figure e-1, A and B,

on the *Neurology*[®] Web site at Neurology.org), leading to the initial consideration of a demyelinating process such as atypical form of multiple sclerosis or progressive multifocal encephalopathy; however, myelin stains showed preserved myelin, negating those possibilities (figure e-2A). Bacterial, fungal, and mycobacterial cultures, special stains for acid-fast and fungal organisms on the biopsy, and EBV PCR were negative. In situ hybridization for JC virus was negative. High-dose IV methylprednisolone 1 g/d for 5 days was initiated followed by an oral dexamethasone taper as an outpatient. Steroids resulted in a modest and short-lasting subjective improvement in memory and mental clarity. Periodic acid-Schiff (PAS) stain showed intracellular PAS-positive particles in histiocytes, raising the consideration of Whipple disease (figure e-2B). Treatment with IV ceftriaxone was empirically started while awaiting results of PCR for *Tropheryma whipplei* on the brain as well as a duodenal biopsy. The case was also reviewed at a major cancer center and the diagnosis of mixed inflammatory cell lesion was rendered.

Question for consideration:

1. What other diagnoses should be considered?

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SECTION 4

PCR for *T. whipplei* was negative. Continued review of the biopsy showed occasional scattered larger cells and additional lymphoid markers performed to evaluate them raised the possibility of lymphoma (figure e-3, A–D). The biopsy was sent to an expert in lymphoproliferative disorders at the NIH for a third opinion. Additional stains performed at the NIH identified the scattered lymphoid cells as immature B cells, supporting the diagnosis of diffuse large B-cell lymphoma. EBV PCR on biopsy tissue was negative and gene rearrangement studies could not be performed as insufficient DNA could be extracted. The absence of extracranial disease, including negative PET-CT, further supported the diagnosis of primary CNS lymphoma (PCNSL). The patient was admitted for specific treatment consisting of high-dose methotrexate-based chemotherapy.

DISCUSSION PCNSL is a rare and aggressive form of extranodal non-Hodgkin lymphoma, comprising 2.1% of all CNS tumors,³ the vast majority of which are diffuse large B-cell lymphoma,⁴ as in our patient. The majority of patients with cerebral involvement (as opposed to neurolymphomatosis, spinal cord, or leptomeningeal disease) present with focal neurologic deficits, behavioral changes, or signs of raised intracranial pressure, while seizures and ocular symptoms are less commonly seen.⁵ Workup should include contrast-enhanced MRI of the brain, CSF analysis using cytology and flow cytometry, slit-lamp examination of the eyes to evaluate for ocular disease, and exclusion of extranodal disease, e.g., with PET-CT, bone marrow biopsy, and testicular ultrasound in men. Steroids are lymphocytotoxic and should be avoided prior to diagnostic studies, although radiographic response to steroids may be suggestive of PCNSL, but could also be seen in demyelinating, infectious, or autoimmune conditions (e.g., sarcoidosis). Disease is typically unifocal in 66% of cases, the majority of which (86%) are supratentorial. The most commonly affected supratentorial locations include frontal, parietal, or temporal lobe (53%), basal ganglia (13%), and corpus callosum (11%), while cerebellum, brainstem, and other regions account for the rest.⁵ High-dose methotrexate-based chemotherapy is the first-line treatment for PCNSL, and combinations with different chemotherapeutic agents as adjuncts, with or without radiation therapy or autologous stem cell transplantation, have been attempted with variable responses and side effects.⁶

There was a high risk of anchoring bias in our case, such as when the preliminary pathologic diagnosis suggested demyelination and later hinted towards CNS Whipple disease. Anchoring bias is a common human tendency to rely heavily on the first piece of evidence presented (the anchor) and use the initial

set of information to base subsequent decisions. This underscores the importance of continued good communication among all disciplines involved in the care of such a case and persistence in arriving at a diagnosis that unifies clinical, imaging, and pathologic findings. The paucity and scattered nature of the larger lymphoma cells in a background of an intense mature mixed chronic inflammatory infiltrate is unusual in PCNSL, particularly if previously untreated, and contributed to the difficulty in making the correct diagnosis. The possibility that the biopsy was taken from the edge of the lesion should also be considered. This underscores the importance of including PCNSL in the differential diagnosis of lesions that may appear inflammatory/infectious, particularly if previously treated with steroids.^{4,7} We elected to treat with steroids and then antibiotics due to the low risk/benefit ratio while continuing to pursue alternative diagnoses and were later able to make a diagnosis of PCNSL.

PCNSL should be considered in the differential diagnosis of lesions of the corpus callosum and in steroid-responsive encephalopathy.

AUTHOR CONTRIBUTIONS

Dr. Niemann: caring for the patient, drafting/revising the manuscript, interpretation of data, assembling montages of pictures. Dr. Jalali: caring for the patient, critically reviewing the manuscript, interpretation of data, collecting pictures. Dr. Rouah: revising the manuscript, analysis and interpretation of data, prepared pathologic slides.

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REFERENCES

1. Geschwind MD. Rapidly progressive dementia: prion diseases and other rapid dementias. *Continuum* 2010;16:31–56.
2. Fitsiori A, Nguyen D, Karentzos A, Delavelle J, Vargas MI. The corpus callosum: white matter or terra incognita. *Br J Radiol* 2011;84:5–18.
3. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. *Neuro Oncol* 2014;16(suppl 4):iv1–iv63.
4. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma: The Massachusetts General Hospital experience 1958–1989. *Cancer* 1994;74:1383–1397.
5. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *J Neurosurg* 2000;92:261–266.
6. Nayak L, Pentsova E, Batchelor TT. Primary CNS lymphoma and neurologic complications of hematologic malignancies. *Continuum* 2015;21:355–372.
7. Hochberg FH, Miller DC. Primary central nervous system lymphoma. *J Neurosurg* 1988;68:835–853.

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