

Clinical Reasoning: A 50-year-old man with headache and cognitive decline

Ayush Batra, MD
Aaron Berkowitz, MD,
PhD

Correspondence to
Dr. Batra:
abatra@partners.org

SECTION 1

A 50-year-old man presented with headache and cognitive decline 10 weeks after undergoing matched-donor peripheral blood stem cell transplantation for treatment of mixed-phenotype acute leukemia. His pretransplant treatment included systemic chemotherapy (cyclophosphamide, daunorubicin, vincristine, prednisone, L-asparaginase, dasatinib, and cytarabine), intrathecal chemotherapy (methotrexate), and total body irradiation. His posttransplant course had been complicated by cutaneous graft-vs-host disease. Over 1 month, he developed holoccephalic, throbbing, temporal headache worse when standing and reported feeling confused. His family members reported progressively withdrawn affect, depressed mood, and decreased spontaneous activity. Before his illness, he worked in a cognitively demanding profession with no history of cognitive deficit.

On examination, he was arousable to voice but had difficulty sustaining alertness for more than a few seconds and was unable to state the days of the week backward. He was oriented to self, place, and month, but not year. He was able to follow simple 1- and 2-step commands but with profound psychomotor slowing and abulia. His cranial nerve examination was notable for mild anisocoria (right pupil being 1 mm larger than left and slightly sluggish in its response) but otherwise unremarkable including funduscopy. There was no weakness or incoordination, but all movements were performed slowly. Sensory and reflex examinations were normal. The patient was able to ambulate slowly with assistance.

Question for consideration:

1. What is the localization and differential diagnosis for his presentation?

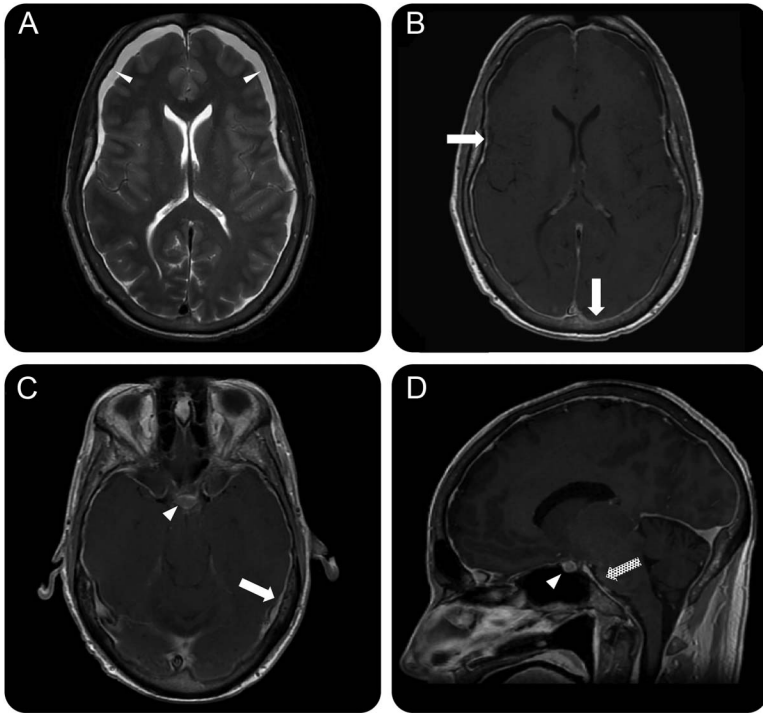
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From the Department of Neurology, Brigham and Women's Hospital (A. Batra, A. Berkowitz), and Department of Neurology, Massachusetts General Hospital (A. Batra), Harvard Medical School, Boston, MA.

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Figure Brain MRI



(A) Axial T2-weighted and (B) postcontrast T1-weighted images demonstrate bilateral subdural collections (thin white arrowheads) and diffuse pachymeningeal enhancement (white arrows). (C) Axial and (D) sagittal postcontrast T1-weighted contrast highlight pituitary hyperemia (white arrowhead), pachymeningeal enhancement (white arrow), and brainstem sag (checkered arrow).

SECTION 2

Progressive headache and cognitive decline with no focal signs beyond isolated anisocoria suggest alteration in intracranial pressure. The predominant cognitive symptoms and signs could suggest the following: a frontal or diffuse infiltrating lesion with mass effect; a posterior fossa or intraventricular lesion causing obstructive hydrocephalus; a diffuse infectious or inflammatory parenchymal process; venous sinus thrombosis with cerebral edema; idiopathic intracranial hypertension; or an extra-axial process such as leptomeningeal metastasis, infectious or inflammatory meningitis, or subdural hematoma. Given his recent stem cell transplant and immunosuppressed state, potential opportunistic CNS infections to consider include herpes simplex virus, varicella zoster virus, human herpes virus 6, Epstein-Barr virus, aspergillosis, and toxoplasmosis. CNS graft-vs-host disease is also a consideration, as it has rarely been reported to cause cerebral vasculitis, demyelination, and immune-mediated encephalitis.¹

MRI of the brain was obtained by the patient's oncologists, and the results prompted neurology consultation (figure).

Question for consideration:

1. How should the MRI findings be interpreted?

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SECTION 3

MRI of the brain demonstrates diffuse pachymeningeal enhancement, bilateral frontal subdural fluid collections, slit-like ventricles (figure, A and B), pituitary hyperemia (figure, C), and sag of the brainstem with effacement of the prepontine cistern and decreased distance between the pons and mammillary bodies (figure, C and D).

The differential diagnosis for meningeal enhancement depends on whether the enhancement is pachymeningeal (dural) or leptomeningeal (pial/subarachnoid). Pachymeningeal processes can result from inflammatory diseases such as Wegener granulomatosis, neurosarcoidosis, IgG-4-related hypertrophic pachymeningitis; neoplastic processes such as dural metastases (most common with breast and prostate cancer) or CNS lymphoma; and intracranial hypotension. Leptomeningeal processes that cause diffuse leptomeningeal enhancement include neoplastic processes such as lymphoma and carcinomatous meningitis, and infectious processes such as bacterial,

viral, fungal (particularly *Cryptococcus*) or tubercular meningitis. Focal cranial nerve deficits are more likely to be seen with leptomeningeal processes but can be present with either. This patient's MRI showed no leptomeningeal abnormalities.

This patient's MRI demonstrates all of the MRI findings of intracranial hypotension, which can be remembered by the mnemonic SEEPS: subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperemia, and sagging of the brain.² Cognitive decline and focal cranial nerve deficits can develop when decreased CSF pressure leads to sagging of the brain and brainstem.³

Questions for consideration:

1. What is the differential diagnosis for intracranial hypotension?
2. What additional testing can confirm the diagnosis and distinguish among etiologies of intracranial hypotension?

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SECTION 4

Intracranial hypotension is most often due to CSF leaks but can also be caused by over-shunting in patients with ventricular catheters. CSF leaks can occur due to brain or spine trauma, surgery, or lumbar puncture causing disruption of the dura; meningeal diverticulum; or may be classified as spontaneous if there is no clear precipitant. Although the exact cause of the leak is often not found in patients with spontaneous intracranial hypotension, a precipitating mechanical event can be identified in up to one-third of patients.⁴ Certain connective tissue disorders are also associated with an increased risk of spontaneous CSF leaks and increased incidence of spontaneous intracranial hypotension, such as Marfan syndrome, Ehlers-Danlos syndrome type II, and autosomal dominant polycystic kidney disease.²

Intracranial hypotension can be confirmed by demonstrating low opening pressure (<60 mm H₂O) on

lumbar puncture. This was not pursued in our patient because of the degree of brain sag and concern for herniation. CT myelography has historically been the diagnostic technique of choice in localizing CSF leaks in cases of spontaneous intracranial hypotension. However, magnetic resonance myelography does not require intrathecal contrast or radiation exposure and is now more commonly used.⁵ Contrast-enhanced MRI of the spine was performed in our patient and showed no evidence of CSF leak, meningeal diverticula, or extrathecal CSF collection. In our patient, intracranial hypotension was attributed to his history of multiple dural punctures for intrathecal chemotherapy, although no radiologic evidence of a precise site of leak was found.

Question for consideration:

1. How is intracranial hypotension due to CSF leak treated?

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SECTION 5

Treatment of intracranial hypotension requires normalizing CSF pressure and addressing the suspected etiology of the CSF leak, if found. In cases in which dural defects are found, definitive treatment is by surgical repair, although not all defects are amenable to repair.² Fortunately, most cases of intracranial hypotension with absence of identified CSF leak resolve spontaneously. For those patients requiring treatment, a range of options exist, although none have been studied through randomized controlled trials. Conservative approaches to treating orthostatic headache due to spontaneous intracranial hypotension include bed rest, aggressive oral hydration, and increase in caffeine intake. IV caffeine, theophylline, and steroids are utilized by some practitioners, but data on their efficacy are limited.²

The primary treatment for headache with intracranial hypotension refractory to conservative measures is epidural blood patching. In this procedure, 10 to 20 mL of a patient's blood is injected into the epidural space, and symptomatic relief of headache is often immediate. Targeting epidural blood patching to the site of leak (if found) is more likely to be successful in resolving CSF leaks.⁶ Given our patient's severely altered cognition in addition to his headache, he was treated immediately with empiric lumbar epidural blood patching. Over the following 48 hours, he reported a dramatic decrease in headache and had increased spontaneous speech production and was more engaged with his surroundings. On follow-up examination at 3 months, he had returned to his prior cognitive baseline such that he was able to resume his previous professional activities. Repeat brain MRI revealed interval resolution of bilateral frontal subdural fluid collections, although mild residual pachymeningeal enhancement remained.

DISCUSSION Although orthostatic headache is the most common presentation of intracranial hypotension, low CSF pressure has been reported to lead to profound alterations in cognition and consciousness.^{7,8} The mechanism of the headache in intracranial hypotension is postulated to be caused by downward displacement of the brain due to lack of buoyancy normally provided by CSF, stretching pain-sensitive intracranial structures such as the dura.² Because the brain sags and becomes compressed against the skull base, patients may present with cognitive changes similar to those seen in the behavioral variant of frontotemporal dementia, a condition described as the frontotemporal brain sagging syndrome.⁹ Given the rarity of this condition, treatment is based on case reports/series, and dramatic responses have been reported with epidural blood patching and intrathecal infusions of saline.^{10,e1}

Incomplete resolution of pachymeningeal enhancement despite clinical improvement in severe cases of

intracranial hypotension (as was the case with our patient) may be attributed to microstructural changes within the pachymeninges due to fibrocollagenous proliferation caused by an inflammatory response induced by intracranial hypotension.^{e2}

This patient's case highlights the importance of recognizing the variety and severity of symptoms that can be caused by intracranial hypotension and the associated neuroimaging findings. Although the true incidence of cognitive decline in the setting of intracranial hypotension remains unknown, early recognition and prompt treatment can result in complete normalization of neurologic deficits.

AUTHOR CONTRIBUTIONS

Dr. Batra drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient. Dr. Berkowitz revised the manuscript and was involved in the clinical care of the patient.

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