Clinical Reasoning:

An 8-year-old girl with multifocal brain lesions and cerebral edema

E.S. Seto, MD, PhD
M. Proud, MD
A.M. Adesina, MD, PhD
J. Su, MD, MS
E. Muscal, MD, MS

Correspondence & reprint
requests to Dr. Muscal:
emuscal@bcm.tmc.edu

SECTION 1

An 8-year-old right-handed girl with a history of declining school performance presented to the emergency center with acute onset altered mental status. For 3 weeks, the former straight A student had been failing classes, but her family noted no changes in her personality or ability to perform activities of daily living. On the night of presentation, the patient was found minimally responsive, lying in vomitus. She aroused briefly with stimulation but was limp.

Her past medical history was significant for a full-term birth without complications, normal acquisition

of developmental milestones, and no chronic medical conditions. She took no medications. She had no unusual food or animal exposures and had not traveled overseas. Her family had no history of seizures, strokes, blood clots, cancer, rheumatologic disorders, or recurrent miscarriages. On examination, she was afebrile with normal vital signs. Her examination was significant only for lethargy and bilateral papilledema. Initial workup revealed a normal complete blood count, electrolytes, and blood glucose.

Question for consideration:

1. What is the most appropriate next diagnostic study?

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From the Department of Pediatrics, Section of Neurology and Developmental Neuroscience (E.S.S., M.P., E.M.), Departments of Pathology (A.M.A.), Immunology (A.M.A.), and Pediatrics (A.M.A.), Department of Pediatrics, Section of Hematology and Oncology (J.S.), and Department of Pediatrics, Section of Pediatric Rheumatology (E.M.), Baylor College of Medicine, Houston, TX.

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Figure 1 Neuroimaging results

(A) Axial CT head noncontrast image shows right frontal hypodensity with accompanying cerebral edema and midline shift. (B) Axial T1 precontrast image shows right frontal hypointensity. (C) Axial T2 and (D) coronal T2 fluid-attenuated inversion recovery (FLAIR) images show prominent hyperintensity of the right and left frontal lobes, right temporal lobe, right basal ganglia, and corpus callosum. Scattered abnormalities are also present in bilateral parietal lobes and the left temporal lobe. (E) Axial diffusion-weighted imaging (DWI) shows subtle decreased diffusivity of the right frontal lobe. (F) Axial T1 postcontrast image shows subtle bilateral frontal lobe and leptomeningeal enhancement.

SECTION 2

An emergent CT of the head without contrast is indicated since emesis, altered mentation, and papilledema can be signs of elevated intracranial pressure (ICP). Prompt recognition of elevated ICP is critical as it can precipitate brain herniation that compresses vital neural and vascular structures. Early uncal herniation often compresses the oculomotor nerve which manifests as ipsilateral papillary dilatation due to unopposed sympathetic activity. Late herniation affects the brainstem by either direct compression or vascular compromise. This results in ipsilateral hemiparesis, Cushing triad (hypertension, bradycardia, altered respirations), decorticate posturing, and ultimately death.

In this patient, CT showed right frontal cerebral edema (figure 1A). The patient was started on high-dose dexamethasone to reduce any vasogenic edema and returned to baseline mental status within 24 hours. Follow-up MRI demonstrated diffuse cerebral edema with midline shift and tonsillar herniation (figure 1B). Significant T2 prolongation of the right frontal lobe extending into the right basal ganglia, temporal lobe, and corpus callosum was noted as well as smaller changes in the left frontal and bilateral parietal lobes (figure 1, C and D). There was subtle decreased diffusivity and parenchymal and leptomeningeal enhancement (figure 1, E and F).

Question for consideration:

1. What is the differential diagnosis for multifocal gray and white matter lesions with leptomeningeal enhancement?

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SECTION 3

The differential diagnosis for multifocal gray and white matter lesions is broad and includes meningoencephalitis, metastatic disease, primary CNS tumors, lymphoma, demyelinating disease, and CNS vasculitis. In the next 2 sections, each of these conditions will be discussed in regards to their applicability to this pediatric patient with elevated ICP.

Of these conditions, meningitis and encephalitis have the highest incidence within the pediatric population. Patients with meningoencephalitis often present acutely with altered mentation and meningeal signs such as headache, nuchal rigidity, and nausea. In severe cases, a combination of interstitial, cytotoxic, and vasogenic edema can result in life-threatening elevated ICP. The indolent onset of this patient's symptoms is atypical for most infectious etiologies except for fungi and mycobacterium. In this patient, serum studies were sent to evaluate for infection since lumbar puncture during ICP elevation can precipitate herniation. The patient was empirically treated with acyclovir for herpes simplex virus and azithromycin for a positive mycoplasma immunoglobulin M (IgM), which may be present acutely or persistently following infection. After 8 days of steroids, she underwent a lumbar puncture under neurosurgical supervision. CSF revealed 1 leukocyte, 0 erythrocytes, glucose 68, protein 21, normal immunoglobulin G (IgG) index, indeterminate oligoclonal banding, and cytology without atypia. Infectious studies from the CSF showed no evidence of bacterial, viral, fungal, or mycobacterial infection, arguing against meningoencephalitis.

Neoplasms such as metastases, lymphoma, and primary brain tumors can also cause multifocal brain lesions. Within tumors, abnormal vascular permeability often produces vasogenic edema and elevated ICP. Metastases are the most common

cause of CNS tumors in adults but are infrequent in children. Similarly, CNS lymphoma is rare in children, producing multifocal disease more commonly in immunocompromised adults. Lymphoma also exhibits a characteristic T2 hypointensity with homogeneous enhancement not seen in this case. Furthermore, this patient showed no evidence of systemic malignancy such as fever, malaise, weight loss, bleeding diathesis, lymphadenopathy, hepatosplenomegaly, or peripheral smear abnormality. Notably, however, primary brain tumors may lack these systemic features. Primary malignant CNS tumors represent the most common solid malignancy during childhood. The majority arise from glial cells (astrocytes, oligodendrocytes, ependymal cells). Since the patient's initial MRI was consistent with a glioma, repeat neuroimaging was performed on hospital day 13 and a brain biopsy was considered. MRI of the brain showed stable signal abnormalities and enhancement. Magnetic resonance spectroscopy demonstrated moderately decreased *N*-acetylaspartate and increased choline, consistent with neuronal breakdown and increased cell membrane turnover. MRI of the spine showed no abnormalities.

Demyelinating conditions such as multiple sclerosis and acute disseminated encephalomyelitis are common causes of multifocal T2 hyperintense lesions, usually exhibiting enhancement in the acute setting. However, only fulminant demyelination produces elevated ICP. In this case, the lack of significant enhancement and minimal radiologic improvement despite treatment with high-dose steroids argue against a demyelinating process.

Question for consideration:

1. The differential diagnosis for this patient includes CNS vasculitis. What are its radiographic features? What is the diagnostic workup?

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SECTION 4

MRI has 90%–100% sensitivity for CNS vasculitis,¹ showing the effects of vascular inflammation and lumen narrowing. Adults with primary angiitis of the CNS (PACNS) most commonly exhibit infarcts and white matter T2 hyperintensities, often occurring bilaterally.^{2,3} Fifteen percent of cases present with mass lesions resembling tumors.¹ Children with PACNS most frequently have multifocal T2 abnormalities with unilateral involvement of the deep gray and deep white matter.⁴ Depending on the areas affected, symptoms range from behavioral changes to focal neurologic deficits. Due to vasogenic and cytotoxic edema, symptoms of elevated ICP may be present.

Diagnosis of PACNS is based on the presence of a newly acquired neurologic deficit, angiographic or histologic evidence of CNS angiitis, and absence of a systemic condition that may explain these findings.⁵ Since vascular imaging by magnetic resonance angiography has a 14%–40% false-negative rate in adults, 4-vessel conventional angiography is recommended.⁴ Given that this patient's presentation and MRI were consistent with vasculitis, a cerebral angiogram was performed, revealing irregularity in the distal branches of the right anterior and middle cerebral arteries, concerning for vasculopathy. While the majority of MRI abnormalities in adult CNS vasculitis have good angiographic correlates,² this patient's dense right frontal lobe MRI abnormality and scattered left hemisphere changes were not concordant with the limited angiographic findings. Notably, however, small vessel vasculitis can be difficult to detect angiographically and usually requires brain biopsy for definitive diagnosis and exclusion of infectious or malignant processes.⁶

Having established angiographic evidence for vasculopathy, systemic causes of CNS vasculitis were considered. As previously described, tests for infection including HIV, syphilis, tuberculosis, and fungal disease were negative. Additionally, markers of

systemic inflammation (erythrocyte sedimentation rate, C-reactive protein), systemic lupus erythematosus (antinuclear antibodies, anti-double-stranded DNA antibodies, antiphospholipid antibodies, C3, C4, urinalysis), granulomatous polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis (antineutrophil cytoplasmic antibodies), and sarcoid (angiotensin converting enzyme, lysozyme) showed no abnormalities. Thus, secondary CNS vasculitis due to infection or systemic rheumatologic disease was unlikely.

To differentiate between neoplasm with secondary vasculopathy and PACNS, the patient underwent a brain biopsy of the affected right frontal lobe and overlying leptomeninges. Histology revealed a diffusely infiltrating neoplasm with elongated cells, nuclear atypia, and p53 positivity consistent with a diagnosis of at least grade III gliomatosis cerebri (GC) (figure 2). The infiltrating pattern and degree of nuclear atypia exceed the characteristics of lower grade gliomas, and the lack of neovascularization and necrosis differentiate GC from grade IV glioblastoma. While angiography was suggestive of vasculopathy, there was no histologic evidence of vessel wall inflammation. These findings may reflect vasculopathy without vasculitis or a sampling bias.

DISCUSSION The World Health Organization defines GC as a malignant neuroepithelial neoplasm of uncertain origin composed of elongated cells resembling astrocytes that diffusely involves at least 2 cerebral lobes.⁷ Patients with this rare condition typically present in early adulthood with cognitive/behavioral changes, headaches, or seizures.⁸ Later features include focal neurologic deficits and elevated ICP. Radiologically, GC exhibits poorly defined areas of T2 hyperintensity with T1 isointensity or hypointensity. Areas most commonly affected on autopsy include the cerebral white matter, midbrain, pons, and corpus callosum. GC imaging resembles that of demyelinating disease, encephalitis, ischemia, CNS vasculitis, multifocal glioma, and infiltrating astrocytoma. Interestingly, GC can cause vessel irregularity and stenosis due to vascular tumor invasion or reactive inflammation.⁹ Since neoplasm and CNS vasculitis can be difficult to differentiate based on clinical presentation and neuroimaging, biopsy is often required for definitive diagnosis. Unfortunately, the prognosis for GC is poor, with a median adult survival of 11.4–38.4 months and median pediatric survival of 27 months.¹⁰ Given the rarity of pediatric GC, optimal treatment protocols are not well-established. This patient participated in an institutional clinical trial including both radiation and chemotherapy. Her tumor responded to therapy for

Figure 2 Histology

Biopsy of right frontal lobe, images taken at 200× magnification. (A) Cortex stained with hematoxylin & eosin shows nuclear pleomorphism and atypia (arrows) indicative of a high-grade tumor. (B) Cortex shows increased p53 positivity characteristic of higher grade tumors.

10 months but then progressed, and she died 18 months after diagnosis.

AUTHOR CONTRIBUTIONS

Drs. Seto, Proud, Adesina, Su, and Muscal all worked on the drafting of this manuscript as well as analysis of data.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Calabrese LH, Duna GF, Lie JT. Vasculitis in the central nervous system. *Arthritis Rheum* 1997;40:1189–1201.
2. Pomper MG, Miller TJ, Stone JH, Tidmore WC, Hellmann DB. CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. *AJNR Am J Neuroradiol* 1999;20:75–85.
3. Salvarani C, Brown RD, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007;62:442–451.
4. Aviv RI, Benseler SM, Silverman ED, et al. MR imaging and angiography of primary CNS vasculitis in children. *AJNR Am J Neuroradiol* 2006;27:192–199.
5. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angitis of the CNS. *Lancet Neurol* 2011;10:561–571.
6. Hutchinson C, Elbers J, Halliday W, et al. Treatment of small vessel primary CNS vasculitis in children: an open-label cohort study. *Lancet Neurol* 2010;9:1078–1084.
7. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. *WHO Classification of Tumours of the Central Nervous System*. Lyon: IARC; 2007.
8. Yip M, Fisch C, Lamarche J. Gliomatosis cerebri affecting the entire neuraxis. *Radiographics* 2003;23:247–253.
9. Maramattom BV, Giannini C, Manno EM, Wijdicks EF, Campeau NG. Gliomatosis cerebri angiographically mimicking central nervous system angitis: case report. *Neurosurgery* 2006;58:E1209.
10. Armstrong GT, Phillips PC, Rorke-Adams LB, Judkins AR, Localio AR, Fisher MJ. Gliomatosis cerebri: 20 years of experience at the Children's Hospital of Philadelphia. *Cancer* 2006;107:1597–1606.

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