Clinical Reasoning: A 7-Year-Old Boy With Acute-Onset Altered Mental Status

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Section 1

A 7-year-old boy presented with acute-onset headache, vomiting, and confusion during summer. Two months previously, he developed right thigh pain, causing intermittent limping. Three days before admission, he developed headache; 1 day later, he experienced fatigue, nausea, and vomiting. On the day of presentation, symptoms included behavioral change (showered 15 times), unsteadiness, and new palmoplantar rash. He presented with confusion and lethargy and was transferred to our facility. His father had a recent gastrointestinal illness, but there were no other sick contacts. There were no recent weight changes, fever, tick/animal exposure, or travel. Past medical history included prior herpes simplex virus (HSV)–positive facial lesion (at 5 years old). The patient took no medications, had no known allergies, was developmentally normal, and was appropriately vaccinated. On general examination, he was somnolent and irritable, and had a palpable right thigh mass and palmar/solar petechiae. Neurologically, he was arousable to light touch, followed only simple midline commands, answered yes/no to orientation questions and responded to all naming questions with “I don’t know.” Cranial nerves were intact. He had normal muscle bulk/tone and at least 3/5 strength throughout, but encephalopathy limited assessment. He had normal sensation to light touch and muscle stretch reflexes, neutral plantar responses, and no dysmetria. The patient sat in bed independently but refused to stand or walk.

Questions for Consideration:
1. What is the localization?
2. What is the differential diagnosis?
Section 2

Altered consciousness broadly localizes to bihemispheric processes or the reticular activating system. Compulsive behavior may suggest orbitofrontal/anterior cingulate involvement. Possible aphasia indicates the dominant hemisphere. Given acuity and multifocality, stroke should be considered along with infectious meningoencephalitis (especially given rash), focal seizures, intracranial malignancy/metastasis (given thigh mass), toxic-metabolic encephalopathy, and autoimmune/postinfectious phenomena.

Given acutely altered mental status and need for sedation to tolerate MRI, CT was obtained, demonstrating right parietal and left medial occipital hypoattenuation with associated vasogenic edema. Subsequent brain MRI/magnetic resonance angiography confirmed acute multifocal infarcts in the bilateral posterior temporal and parietal and left occipital lobes, left posterior cerebral artery occlusion, and paucity of posterior left middle cerebral branches (figure, A–C). Continuous video EEG was without epileptiform activity. Right thigh plain films and MRI were suspicious for osteosarcoma vs Ewing sarcoma. Initial laboratory studies included mild transaminase elevations (aspartate aminotransferase 116, alanine aminotransferase 78), mild bicytopenia (hemoglobin 10.5, normocytic; platelets 145), elevated C-reactive protein (47.6) and erythrocyte sedimentation rate (19), and elevated lactate dehydrogenase (1,336). There were no indications of metabolic, endocrine, urinary, or coagulation abnormalities. CSF was unremarkable. Cardiac evaluation was negative for arrhythmia/conduction block although transesophageal echocardiogram on hospital day 2 revealed a pedunculated mass (5.5 × 5.0 mm) on the atrial surface of the posterolateral mitral leaflet with mild to moderate regurgitation.

Question for Consideration:
1. What additional testing is needed?
Section 3

Multifocal strokes, sarcoma, and cardiac vegetations necessitate testing for infection, coagulopathy, and malignancy sequelae (e.g., tumor emboli, nonbacterial thrombotic endocarditis [NBTE]). Infectious workup with serial blood cultures was consistently negative. Although fever and leukocytosis were not present, the patient received appropriate empiric antimicrobials (acyclovir, vancomycin, ceftriaxone). 

* Bartonella quintana/henselae* and *Coxiella burnetti* serologies were negative. CSF Gram stain/culture and PCR for enterovirus, par-echovirus, HSV, and varicella-zoster virus were negative. Coagulopathic workup was negative including antiphospholipid antibody screening and extremity Doppler ultrasounds. A biopsy of the right femur demonstrated an osteosarcoma (figure, E). CT-based staging revealed no metastasis or lymphadenopathy, but multifocal splenic and renal infarcts (patent vessels).

Questions for Consideration:
1. What are possible treatment options?
2. What factors limit treatment choice?
Section 4

After evaluating and treating for possible infections, thoughtful management balanced treating stroke, likely NBTE, and potential intracranial pressure (ICP) elevations. Our patient presented outside thrombolyis or thrombectomy windows. Thus, stroke management prioritized secondary prevention. On hospital day 2, a multidisciplinary group weighed the risks/benefits of cardiac surgery for vegetation removal. The risks (intracranial hemorrhage while aggressively anticoagulated or extension of stroke during prolonged cardiac bypass time) were thought to outweigh benefits, given no clear recurrent thromboembolic events or profound valvular/cardiac dysfunction. Therefore, NBTE treatment required anticoagulation when safe.

Edema from large infarctions can cause elevated ICP. On hospital day 3, brief anisocoria prompted medical intervention to lower ICP. Repeat CT demonstrated new right frontal infarct. To better manage ICP, a transdustral bolt monitor was placed because it offered lower bleeding risk and shorter delay in the initiation of anticoagulation compared to external ventricular drain (EVD) or craniotomy. On hospital day 4, intermittent ICP elevations were medically managed, but later required burst suppression. Twenty-four hours after bolt placement, bleeding risk was deemed low and unfractionated heparin was started.

ICP management proved difficult. On hospital day 6, new left superior cerebellar infarct was noted and ICP elevation necessitated pentobarbital-induced coma. To prevent herniation, anticoagulation was stopped and an EVD placed. Subsequently, 2 near-herniations were aborted with medical management and EVD repositioning. On hospital day 7, the family expressed desire for comfort care. ICP continued rising, resulting in herniation (figure, D) and eventual death. Autopsy findings included tan, fibrinous, friable mitral vegetations (1.0 × 0.4 × 0.3 cm), an 8-cm right distal femoral mass, diffuse brain edema, the abovementioned territorial infarcts, and several watershed microinfarcts. Brain histology demonstrated bland infarction without evidence of tumor emboli (figure, F). Notably, kidney sections demonstrated a fibrin thromboembolus with identical histology to the cardiac vegetations (figure, G).

Discussion

Pediatric stroke has an estimated incidence of 1.0–2.0 per 100,000 annually in developed countries.1 It may present with focal deficits, but nonfocal symptoms like headache, altered mental status, and seizure compound with a low index of suspicion to make timely diagnosis a challenge. Etiologies are predominated by arteriopathies and cardioembolism, followed by hematologic (e.g., thrombophilia, sickle cell), inflammatory/infectious, and genetic/metabolic causes.12 Stroke management is primarily based on adult evidence, but guidelines suggest that children with adult criteria should be considered for thrombolysis and endovascular intervention for large vessel occlusions.1 Guidelines also affirm decompression, if timely performed, can be lifesaving after weighing patient-, disease-, and procedural-specific factors.

NBTE is an extremely rare cause of childhood stroke. NBTE has been identified in 0.3%–9.3% (mean 1.3%) of autopsies, and among those autopsy series, only 3%–4% of NBTE cases were identified in children 0–19 years of age.3,4 In 1 meta-analysis, thromboembolism occurred in 42% of all cases, commonly to cerebral, coronary, renal, and mesenteric vasculature.4 The highest risk factor of NBTE is malignancy, especially adenocarcinoma, as well as acute conditions like sepsis or burns. Due to its uncommon nature and necessary extensive diagnostic evaluation, NBTE is a difficult diagnosis. Many patients are initially asymptomatic, and most cases do not have a murmur or obvious immunologic sequelae. NBTE may first be suspected when vegetations are found on echocardiography in the absence of obvious infection. Negative cultures and absence of valvular destruction should raise concern about NBTE; however, other culture-negative endocarditis causes (e.g., HACEK organisms) should be investigated.5

NBTE is uncommon and management derives from infective endocarditis and other systemic thromboembolism treatment. The cornerstone of NBTE therapy is anticoagulation with unfractionated or low-molecular-weight heparin.6 Warfarin is often a poor choice for malignancy-related coagulopathies, and there is little experience with non–vitamin K oral anticoagulants in this setting. As with all recent stroke, potential intracranial hemorrhage risk must be considered. Whereas no strict criteria guide this decision, thromboembolic risk should be balanced with that of symptomatic hemorrhagic transformation (HT). Adult data suggest anticoagulation may be started days after small/medium infarcts upon confirming HT absence; for larger strokes, anticoagulation is often held for weeks.7 Pediatric HT predictors, rate, and effects may differ.8 If anticoagulation fails, surgery may prevent further embolism.9 Early cardiac surgery is indicated for recurrent emboli, persistent/enlarging vegetations despite appropriate therapy, severe regurgitation, and large (>10 mm), mobile vegetations.10 Surgery requires aggressive anticoagulation, thus large infarction is often prohibitive.

This case presents many important teaching points for adult and child neurologists. First, pediatric stroke is an important cause of acute neurologic changes in pediatric patients, and clinicians should be aware that a child presenting with stroke may have nonspecific changes like altered mental status. Second, the etiologies of pediatric stroke are varied, but cardioembolic processes should always be considered. NBTE is an uncommon entity, therefore diagnosis requires a high index of suspicion.4 Third, association of NBTE with sarcoma is uncommon and rarer yet with osteosarcoma.4,11,12 Fourth, patients with NBTE may have multiple thromboembolic complications including large cerebral infarcts that prohibit...
anticoagulation and surgical therapies. This case highlights a rare but important cause of pediatric stroke. Neurologists should be familiar with this challenging diagnosis and recognize that its management requires a multidisciplinary effort.

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### Appendix

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### References
