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Clinical Reasoning: A young adult presents with focal weakness and hemorrhagic brain lesions

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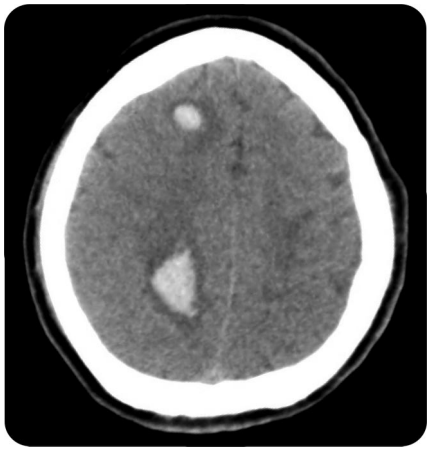
SECTION 1

A 25-year-old man who emigrated from Mexico 5 years ago presented with headache, altered mental status, and left hemiparesis. Initial history obtained from collateral sources indicated the patient had complained of a headache of increasing severity for the past 2 months. Two weeks prior to presentation, he experienced malaise, decreased appetite, nausea and vomiting, visual changes, and gait difficulties resulting in 2 falls. The day of presentation, he developed acute onset left upper and lower extremity weakness prompting emergency evaluation. On arrival he was lethargic, disoriented, and did not follow commands. Following intubation in the emergency department, he was transferred to the neurologic intensive care unit (ICU).

He was febrile and tachycardic on arrival to the ICU. Upon cessation of sedation, the patient was ill-appearing but awake and able to cooperate with the neurologic examination. He was oriented to hospital name and year and was able to follow one-step commands. His pupils were equal, round, and reactive to light and accommodation. Bedside funduscopic examination showed normal discs and vessels. His extraocular movements were full except for the inability to adduct his right eye. He blinked to threat bilaterally but had left-sided visual neglect with a right gaze preference. He had left lower facial weakness. On motor examination, he had left flaccid paralysis as well as mild decreased strength in his right upper and lower extremities (4+/5) that might have been attributable to incomplete cooperation. Sensation was intact to light touch on the right but only to noxious painful nail bed stimulation on the left. Reflexes were brisk on the right and diminished on the left. He had a left Babinski sign.

Figure 1 CT findings



Two foci of hemorrhage are seen in the right frontal and parietal lobes with surrounding vasogenic edema.

Head CT revealed 2 foci of hemorrhage in the right frontal and parietal lobes with associated vasogenic edema (figure 1).

Questions for consideration:

1. What is the differential diagnosis?
2. What would be the next step in your management of this patient?

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SECTION 2

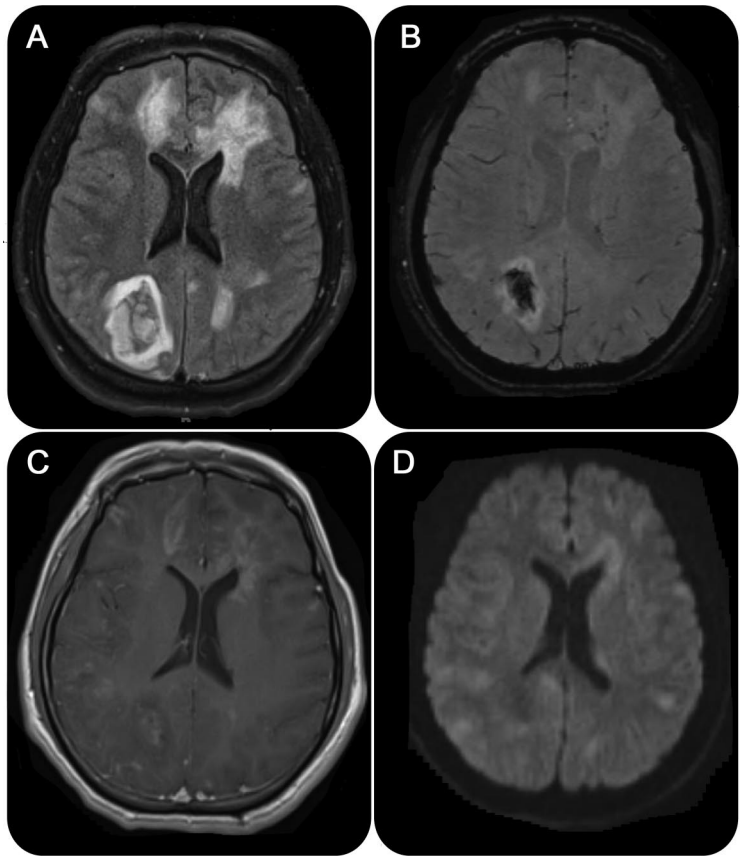
The differential diagnosis for this presentation with multiple neurologic symptoms rapidly cumulative over time should initially be kept broad to avoid missing a treatable disease. Both the neurologic examination and initial imaging implicate a multifocal localization. Given the prolonged headache, malaise, and fever at presentation, one must first consider infectious processes such as viral and bacterial meningitis or encephalitis including tuberculous meningitis, cysticercosis, and aspergillosis. Infective endocarditis leading to multiple septic emboli could also account for the clinical picture and the potential involvement of both anterior and posterior circulation territories. Other causes of multifocal stroke with hemorrhagic conversion include CNS vasculitis and moyamoya disease. Central demyelinating conditions such as acute hemorrhagic leukoencephalitis are possible given the patient's age and presentation. Finally, neoplasms (primary CNS tumors, metastatic disease, or primary CNS lymphoma) could potentially cause multiple hemorrhagic lesions that become symptomatic with dissemination in time.

Additional history revealed no prior illness. He had not visited Mexico since arrival to the United States. A brother presented with sudden onset of weakness at age 17 with a fluctuating course that resulted in death. His father died of renal failure.

Initial studies showed normal serum chemistries except for low sodium (127 mmol/L). White blood cell (WBC) count was elevated at 18,000/mm^3 with 90% neutrophils. Additional testing included negative antinuclear antibodies, antineutrophil cytoplasmic antibodies, and extractable nuclear antigen screens with a mildly elevated erythrocyte sedimentation rate at 16 mm/hour (0–12). HIV testing was negative. Lumbar puncture was remarkable for mildly elevated protein (53 mg/dL), normal glucose, 1 WBC/mm^3, 2 red blood cells (RBC)/mm^3, negative bacterial culture, and negative varicella zoster virus, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and enterovirus PCRs.

Brain MRI (figure 2) revealed multiple foci of hyperintensity in bilateral cerebral hemispheres, brainstem, and cerebellum on fluid-attenuated inversion recovery (FLAIR) images with associated enhancement on T1 postgadolinium sequences in a majority of lesions. Susceptibility-weighted images suggested hemorrhage in more locations than appreciated on head CT. There was no evidence of diffusion restriction.

Figure 2 MRI findings



Multiple scattered T2 hyperintensities are appreciated on fluid-attenuated inversion recovery images (A) with evidence of hemorrhage on susceptibility-weighted images (B), contrast enhancement on T1 postgadolinium images (C), and without diffusion restriction on diffusion-weighted imaging (D).

Questions for consideration:

1. How does the presence of multiple foci of hemorrhage and enhancement on MRI narrow the differential diagnosis?
2. What additional testing would you request?

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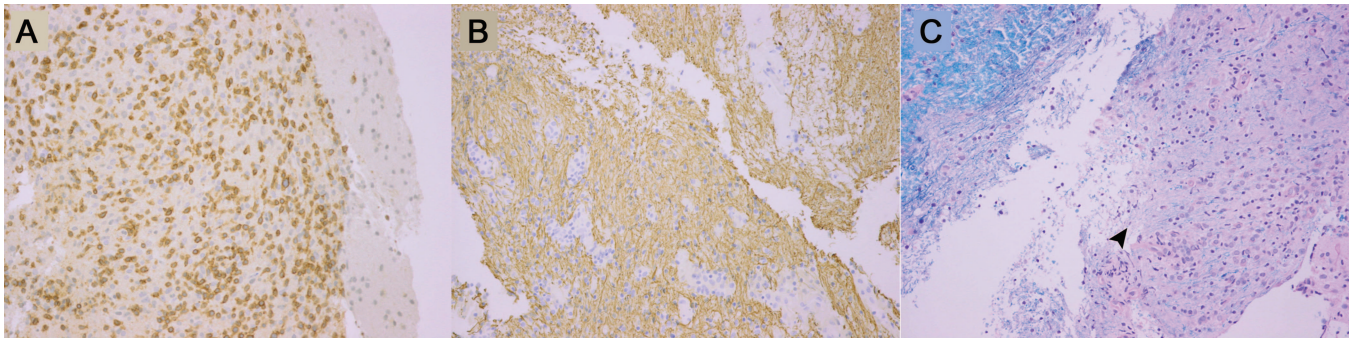
Figure 3 Pathology findings



Histology demonstrates inflammatory infiltrate on CD3 staining (A), relative preservation of axons on neurofilament staining (B), and a significant paucity of myelin on Luxol fast blue/periodic acid–Schiff staining in the region demarcated by the arrowhead (C).

SECTION 3

The MRI findings help narrow the differential diagnosis by excluding acute ischemic stroke. Infectious, demyelinating, inflammatory, and neoplastic processes should continue to be considered. The low serum sodium was likely secondary to the syndrome of inappropriate anti-diuretic hormone secretion from the multiple CNS lesions.

Subsequent CSF testing demonstrated normal immunoglobulin G index and synthesis rate and no oligoclonal bands. Extensive infectious evaluation including CSF acid fast bacteria (AFB) stain and culture, CSF toxoplasma PCR, blood and urine histoplasma antigen, CSF and blood *Cryptococcus* antigen, *Aspergillus galactomannan* antigen, CSF and nasal *Mycoplasma pneumoniae* PCR, CSF ova and parasites screen, and CSF *Acanthamoeba* culture were all negative. The patient was still without a definitive diagnosis.

Ultimately, biopsy of an enhancing left frontal cortical lesion revealed an inflammatory process, consisting of CD3-positive T cells, numerous CD68-positive histiocytes/macrophages, and only rare CD20-positive B cells (figure 3). There was no evidence of vasculitis. No atypical cells indicative of a neoplasm were identified. Tissue cultures from the biopsy were also negative for AFB, fungal, and bacterial elements. Neurofilament staining showed relative preservation of axons. Severe loss of myelin was demonstrated on Luxol fast blue/periodic acid-Schiff staining. Scattered macrophages with blue-staining material consistent with myelin in their cytoplasm were identified.

Question for consideration:

1. Given the findings on brain biopsy, how would you diagnose this patient?

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SECTION 4

This patient initially had a headache followed by rapid progression of neurologic symptoms resulting in decreased level of consciousness and left hemiparesis. MRI showed multiple T2 hyperintensities, some with hemorrhagic involvement. Brain biopsy showed patchy demyelination with axon preservation. Presence of CD3-positive T cells and CD68 histiocytes/macrophages with rare B cells indicated a reactive process, less likely to be neoplastic. These findings are consistent with a diagnosis of acute hemorrhagic leukoencephalitis (AHLE).

Interestingly, the cause of death of the patient's brother is unknown, but he presented in a similar fashion. One could speculate that it is possible the 2 siblings had the same disorder.

AHLE is a rare disorder on the spectrum of acute postinfectious leukoencephalopathies including acute disseminated encephalomyelitis and Bickerstaff brainstem encephalitis.[1] AHLE typically presents with an abrupt onset of neurologic symptoms including encephalopathy, focal neurologic deficits, seizures, and coma up to 20 days after a nonspecific viral illness, similar to this case report.[2] CSF typically shows a lymphocytic pleocytosis, elevated RBC count, and elevated protein. MRI may demonstrate white matter T2 hyperintensities with associated edema and often hemorrhage.[3,4] Contrast enhancement is not typically present but was appreciated in this patient. Pathology shows fibrinoid vascular necrosis, widespread perivascular polymorphonuclear infiltrates, "ring and ball" hemorrhages, and loss of myelin with preservation of axons.[5] The etiology of AHLE remains unclear, with a prevailing theory that infectious agents trigger the formation of T-cell clones, resulting in an inflammatory cascade targeting myelin basic protein. The perivascular infiltrate has been suggested to represent an acute vasculitis with occlusion of vessels eventually leading to vessel wall necrosis and subsequent hemorrhage.[3,6,7] Treatment currently includes surgical decompression for increased intracranial pressure with craniectomy or ventriculostomy if necessary. Immunosuppressive agents such as IV steroids, IV immunoglobulins, and cyclophosphamide have also been employed with varying success, although morbidity and mortality remain high.[8,9]

This patient was treated with IV methylprednisolone (5 g) over 5 days. His symptoms improved with in-patient physical, occupational, and speech therapy over his 3-week hospitalization. At the time of discharge to a specialized rehabilitation hospital, he still had a significant left hemiparesis. After a 1-month stay in the rehabilitation hospital, he continued to recover, improving to only a mild left hemiparesis. Although prognosis is variable in AHLE, further improvement in strength could be expected in this case.

This case emphasizes that demyelinating conditions should be included in the differential diagnosis of a young adult presenting with multifocal complaints with a decreased level of consciousness and evidence of hemorrhage on neuroimaging.

DISCLOSURE

Dr. Virmani and Dr. Agarwal report no disclosures. Dr. Klawiter has served on a scientific advisory board and as a consultant for Teva Pharmaceutical Industries Ltd.; has served on speakers' bureaus for and received speaker honoraria from Teva Pharmaceutical Industries Ltd. and Bayer Schering Pharma; and has received research support from the NIH and an American Academy of Neurology Foundation Clinical Research Training Fellowship.

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