Clinical Reasoning: A Case of Acute Akinetic Mutism and Encephalopathy

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Section 1

A 70-year-old, right-handed African American man presented with 5 days of severe abdominal and diffuse body pain. He has a history of hemoglobin SC (Hb SC) disease, rheumatoid arthritis (RA), and a provoked pulmonary embolism (PE) 1 year before the current presentation. He was not on anticoagulation or any psychotropic medications but recently had completed a short steroid course for joint pain. Initial evaluations included a complete blood count, comprehensive metabolic panel, lipase, urine culture, blood cultures, urine toxicology, and CT scan of the abdomen and pelvis (with and without contrast). The diagnostic evaluations were unremarkable, except for a leukocytosis of 22,000/mm^3 believed to be steroid-induced. He was subsequently treated for a vaso-occlusive pain crisis with intravenous fluids and opioids. On day 3 of hospitalization, he was nonverbal and unable to follow commands and move his extremities. Examination revealed normal vital signs. He was awake with spontaneous eye opening with intermittent tracking; pupils were symmetric, round, and reactive; oculocephalic reflex was intact; and no facial asymmetry was present. Signs of meningeal irritation were absent. He had no vocalizations, did not follow commands, had sparse spontaneous antigravity movements in all extremities, and no response to noxious stimuli. He had hyperreflexia in upper and lower extremities with normal tone. No involuntary movements were observed. Neuroimaging included CT angiography of the head and neck and MRI of the brain (without contrast) inclusive of gradient echo sequences (GREs), which did not reveal an acute intracranial process. MRI of the brain without contrast with susceptibility-weighted imaging (SWI) performed a week later showed supratentorial multifocal microhemorrhages (Figure). CSF revealed 0 white blood cells (WBCs), 1 red blood cell (RBC), an elevated protein of 178 mg/dL, and xanthochromia. EEG revealed no epileptiform discharges. Given his unexplained neurologic decline, he was transferred to our hospital.

Question for Consideration:

1. What is the syndromic diagnosis and its localization based on the patient's presenting symptomatology?

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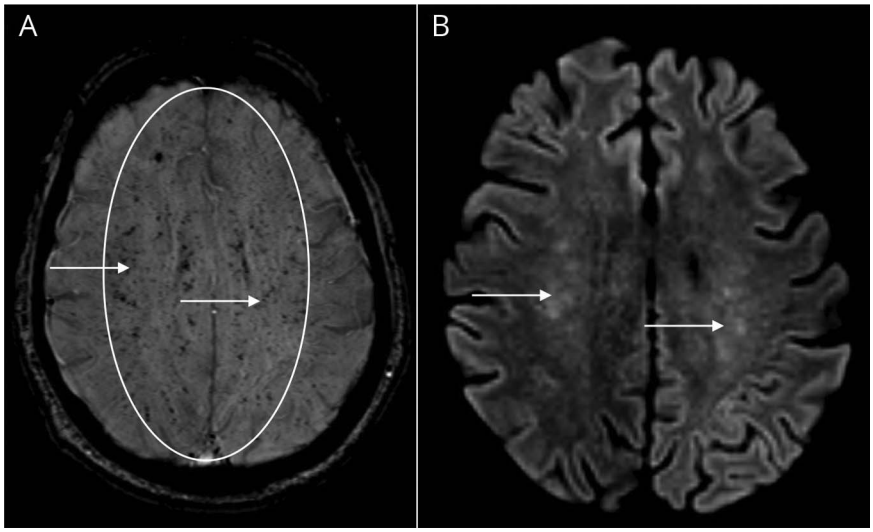
Figure MRI Brain, Axial SWI, and DWI



(A) SWI with walnut kernel pattern of multiple hypointensities in the subcortical regions. (B) DWI with starfield pattern of multiple hyperintense, patchy lesions in the bilateral deep and subcortical white matter. DWI = diffusion-weighted imaging; SWI = susceptibility-weighted imaging.

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Section 2

The absence of spontaneous movement and speech with impaired comprehension is characteristic of akinetic mutism. This is a relatively rare neurologic syndrome characterized by an intact level of consciousness and sensorimotor capacity but with a simultaneous decrease in goal-directed behavior and decrease in emotions. Patients exist in a wakeful state of profound apathy, seemingly indifferent to pain, thirst, or hunger. Akinetic mutism must be differentiated from coma (by metabolic abnormalities or herniation syndromes), brainstem lesions such as encephalitis or osmotic demyelination, drug overdose (opioids, benzodiazepines, etc), basilar artery occlusion (locked-in syndrome), and catatonia.

Akinetic mutism can be challenging to localize. It can result from disruption to many areas of the brain including the dorsolateral or prefrontal cortices, fronto-subcortical circuits, anterior cingulate cortex, caudate, putamen, mesencephalon, or thalamus (bilaterally).[1]

Differential diagnosis of akinetic mutism includes ischemic or hemorrhagic infarcts, septic cerebral emboli, primary or secondary vasculitis, bacterial or viral encephalitis, demyelinating disorders such as multiple sclerosis or acute disseminated encephalomyelitis, autoimmune encephalitis, sarcoidosis, other inflammatory encephalitis, primary CNS malignancy (i.e., lymphoma), and leptomeningeal carcinomatosis.

Several fronto-subcortical structures including the anterior cingulate cortex, basal ganglia, medial thalamus, ventral tegmental area, and substantia nigra pars compacta are involved in the neurocircuitry of motivation and action initiation. In our patient, the diffuse microhemorrhages likely disrupted the integration of information between the fronto-subcortical structures resulting in akinetic mutism.

Question for Consideration:

1. What is the differential diagnosis of hemorrhagic strokes involving multiple vascular territories? What investigations would you perform at this point?

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Section 3

The differential diagnosis of hemorrhagic strokes involving multiple vascular territories includes trauma, cerebral amyloid angiopathy, reversible cerebral vasoconstriction syndrome, metastatic tumors, and abscesses from CNS or systemic infections such as endocarditis, vasculitis, and coagulopathies. A MRI brain with and without contrast revealed abnormal T2 fluid-attenuated inversion recovery hyperintensity with linear and nodular enhancement and extensive SWI hypointensities involving the corona radiata, corpus callosum, periventricular white matter, basal ganglia, brainstem, and cerebellum demonstrating microhemorrhages consistent with "walnut kernel" pattern and diffusion restriction in bilateral deep and subcortical white matter consistent with a "starfield" pattern (Figure). This pattern suggested cerebral fat embolism (CFE).

Repeat CSF studies revealed 2 WBC/μL, 5 RBC/μL, elevated protein (129 mg/dL), and xanthochromia (860 RBC/μL). Xanthochromia is likely from extensive microvascular injury, high CSF proteins, and disruption of the blood brain barrier. CSF venereal disease research laboratory and meningitis panel, flow cytometry, and cytology were unremarkable. Repeat laboratory tests showed a decrease in hemoglobin from 10 to 8 g/dL, platelets 50,000/mm^3, reticulocyte count of 11%, lactate dehydrogenase 688 U/L, ferritin 780 ng/mL, and haptoglobin <30 mg/dL. Alkaline phosphatase was 170 IU/L. ADAMTS13 activity was normal at 111%. A peripheral blood smear demonstrated abnormal RBC morphology with tear drop cells, sickle cells, large platelets, and large number of nucleated RBC, suggestive of bone marrow necrosis.

An antinuclear antibody panel and rheumatoid factor were positive with titer of 1:160, consistent with his RA diagnosis. A C-reactive protein and an erythrocyte sedimentation rate were normal, making an RA exacerbation or another autoimmune disease unlikely. Parvovirus B19 IgM, a Lyme disease antibody, and a hepatitis panel were unremarkable.

Blood, urine, and CSF cultures were unremarkable. A CT of the chest, abdomen, and pelvis with and without contrast was unremarkable for infectious or neoplastic etiologies. Partial visualization of the humeral heads on the body CT scan demonstrated osteonecrosis. Transthoracic echocardiogram did not reveal any vegetations or valvular pathology, and the bubble study was normal ruling out septic or venous emboli. Digital subtraction angiography of the brain did not reveal any overt large or medium vessel vasculitis. A right frontal brain biopsy was performed to evaluate for vasculitis in the setting of RA, elevated CSF protein and WBC, and the clinical presentation. Pathology revealed parenchymal foci of hemorrhage and organizing necrosis with vacuolation without evidence of inflammation or vasculitis.

The diagnosis was made of akinetic mutism secondary to CFE. The fat embolization likely resulted from bone marrow necrosis due to underlying Hb SC disease.

Diagnostic workup when suspecting CFE should include MRI brain with diffusion-weighted imaging (DWI) and SWI sequences. Most reports of CFE in the literature are in the setting of long bone fractures; however, in the absence of trauma, workup should include evaluating for causes of bone marrow necrosis. Diagnostic tests should evaluate for hemoglobinopathies, coagulopathies/thrombotic disorders (i.e., disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, antiphospholipid syndrome), autoimmune disease, infections, HIV infection/AIDS, and malignancy.

Question for Consideration:

1. How would you manage the patient at this time?

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Section 4

Given the diffuse microhemorrhages secondary to CFE in the setting of active hemolysis, we recommended emergent exchange transfusion with 12 units of packed RBCs. He developed 2 days of fever after the transfusion. An infectious evaluation was unremarkable. A chest CT angiogram and duplex ultrasound of all extremities revealed an acute PE and right midbrachial deep venous thrombosis, and thus, anticoagulation was started. Ophthalmologic evaluation showed scattered "cotton wool spots," which supported vascular occlusion.

Although no significant improvements were noted in the patient's examination at the end of a 4-week hospital stay, a repeat electrophoresis showed 88% Hb A, 5% Hb S, and 5% Hb C. Monthly exchange transfusions were recommended. A future trial of dopamine agonist or amantadine therapy for akinesia was considered, however not trialed during this hospitalization. He remained in a medical facility where he passed due to unknown causes after 3 months from the initial presentation.

Discussion

Fat embolism syndrome (FES) requires the presence of fat globules in the systemic circulation with an identifiable clinical pattern such as respiratory symptoms, petechial rash, neurologic signs, fever, hematologic abnormalities, and death.[2-4] This syndrome frequently results from orthopedic trauma but also from a nontraumatic event such as bone marrow necrosis.[3] Fat emboli that enter the cerebral circulation are called cerebral fat emboli.[4] Neurologic symptoms from CFE include encephalopathy, ischemic strokes, hemorrhagic strokes, or seizures.[5]

Sickle cell disease (SCD) can be associated with FES.[6] In 81% of cases, FES manifested in non-Hb SS SCD, suggesting bone marrow necrosis, and FES may more likely occur in mild phenotypes of SCD such as Hb SC.[6,7]

RBC sickling may lead to avascular necrosis in the bone marrow. FES pathophysiology has not been fully elucidated; however, it is believed that fat microglobules enter the venous circulation after trauma. Another theory is that biochemical and inflammatory processes underpin the fat embolization.[4] A systemic embolization mechanism could involve fat emboli traveling through a patent foramen ovale; however, this is not applicable to our patient.[4] FES has been associated with an exaggerated inflammatory response and high morbidity and mortality.[4] To date, there are no studies reporting long-term outcomes in CFE in individuals with SCD.

Our patient with Hb SC disease experienced an acute neurocognitive decline after a vaso-occlusive crisis. Our patient's presentation is important for 2 reasons. First, this may be the only reported diagnosis of akinetic mutism resulting from CFE in the setting of severe neuronal injury, as seen on MRI.[1] Important imaging findings in CFE include the starfield pattern on DWI and walnut kernel pattern on SWI.[8,9] Second, the delayed diagnosis resulted in a delayed exchange transfusion.[6,7] The falsely reassuring GRE sequence on initial MRI brain likely contributed to this delay.[10] The SWI sequence could have been helpful in making an earlier diagnosis because it may be superior to the GRE sequence in detecting microhemorrhages, which commonly occur in CFE.[11]

CFE should be considered in patients with sickle cell with acute neurologic symptoms. SWI rather than GRE MRI sequence may be more sensitive and may expedite the diagnosis. Delays in exchange transfusion may affect outcomes.

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Continued

Appendix *(continued)*

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Bhavana Patel, DO	Department of Neurology, University of Florida, Gainesville	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

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