Mystery Case:

A case of fulminant encephalopathy in a 69-year-old woman

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SECTION 1

A 69-year-old right-handed woman was admitted to the medical intensive care unit for acute encephalopathy. Her medical history included sickle cell disease (hemoglobin sickle cell [HbSC]) with bone involvement (bilateral femoral head osteonecrosis) and rare sickle cell crises with joint pain and hemolytic anemia requiring red blood cell transfusions, sarcoidosis, diabetes, hypertension, and hypothyroidism. She never smoked cigarettes and never used recreational drugs or alcohol, and there was no history of recent travel. The patient's daughter reported that the patient was found unresponsive lying on the floor in the morning. She was last seen normal the day prior, but had complained of diffuse muscle pain and body aches for 1 day.

At presentation, the patient was comatose with a Glasgow Coma Scale score of 7 (eyes spontaneously opened, decerebrate posturing with extensor response with arm adduction, internal rotation of shoulder, pronation of forearm and extension at elbow, flexion of wrist and fingers, and no verbal response). Upon testing of higher cortical functions, the patient was nonverbal, comprehension was altered to the point that she was unable to follow

commands, and there was no selective attention and no eye tracking. Corneal reflexes, caloric reflexes, and horizontal oculocephalic reflexes were present bilaterally. The pupils were equal, round, and reactive to light (3–2 mm), and the pharyngeal reflex was diminished but present. The face was symmetrical, and eye examination revealed a skew deviation with a vertical misalignment with adduction and hypotropic position of the left eye. There were no spontaneous or abnormal movements of the face or limbs, and muscle tone was not increased. The sensory examination was limited by the patient's comatose state, and she displayed decerebrate posturing to painful stimuli. Plantar reflexes were equivocal bilaterally, and no clonus was found on examination. The neck was supple with negative Brudzinski and Kernig signs. There was no ocular bobbing, nystagmus, or cerebellar abnormalities on examination. The rest of the physical examination did not reveal any abnormalities.

Questions for consideration:

1. In which area(s) could you localize a possible lesion?
2. Which initial tests would you order?

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SECTION 2

History and physical examination were consistent with an acute process leading to coma. Diffuse brain dysfunction without specific structural lesions (i.e., metabolic endocrine encephalopathy, poisoning, and generalized tonic-clonic seizures), bilateral supratentorial structural lesions (bilateral hemispheric or bilateral thalamic lesions), and infratentorial structural lesions (brainstem lesion or compression of the brainstem secondary to a unilateral hemispheric lesion or a cerebellar lesion) can present with coma.¹ Skew deviation can be peripheral or central, and central causes of skew deviation classically occur anywhere within the posterior fossa (brainstem and cerebellum). However, thalamic lesions can also cause skew deviation and a variety of oculomotor abnormalities.¹

Given the possible multifocal hemispheric dysfunction, pertinent studies include neuroimaging with brain MRI or head CT with vascular imaging to look for an acute vascular process, such as an intraparenchymal hemorrhage or an ischemic stroke (i.e., basilar occlusion), EEG to rule out nonconvulsive status epilepticus, a lumbar puncture to look for ongoing infectious, inflammatory or autoimmune processes, as well as laboratory investigations to look for treatable metabolic conditions. Head CT with angiography was performed on admission and did not reveal any vascular thrombosis or intracranial abnormalities. Basic hematology on admission showed anemia with a hemoglobin level of 9 g/dL, mean corpuscular volume of 99.3 fL, thrombocytopenia with a platelet count of 120,000/mm³, and

no leukocytosis. The triglyceride level was high (411 mg/dL) and the fibrinogen level was normal. Basic biochemistry did not show any abnormalities, and metabolic profiles were normal. The hemoglobin electrophoresis test was consistent with the diagnosis of sickle cell (HbSC), the reticulocyte percentage was high (8.4%), the ferritin level was high (2,080 ng/mL), the lactate dehydrogenase (LDH) level was high (545 units/L), and the haptoglobin level was normal. A peripheral blood smear performed 48 hours after admission did not show any sickle cell or schistocyte. A lumbar puncture showed 5 lymphocytes, no red blood cells, a protein level of 79 mg/dL, and a normal CSF glucose level, and cultures were negative. The workup for infectious and autoimmune causes of encephalitis was negative in the serum and the CSF. EEG showed generalized continuous suppressed and slow activity without epileptiform patterns. Brain MRI with gadolinium showed extensive foci of restricted diffusion in the cerebral white matter, including the corpus callosum, internal capsule, pons, and left middle cerebellar peduncle with sparing of the cerebral cortices (figure). Innumerable petechial foci were seen throughout the white matter, including the corpus callosum, as well as the deep gray matter structures, brainstem, and cerebellum (figure). Brain magnetic resonance angiography (MRA) did not show any abnormalities of the blood vessels.

Question for consideration:

1. What would you consider in the differential diagnosis, given the imaging findings?

Brain MRI axial flair (A and B) revealing hyperintensities of the corpus callosum and middle cerebellar peduncle, axial susceptibility-weighted imaging (D and E) revealing innumerable petechial foci throughout the white matter as well as the deep gray matter structures, and axial diffusion (F) revealing foci of restricted diffusion in the corpus callosum and white matter. Spine MRI sagittal T2 (C) revealing patchy hyperintensities of multiple vertebral bodies within the cervical and thoracic spine.

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SECTION 3

The clinical presentation with acute encephalopathy, the laboratory findings with anemia, thrombocytopenia and some degree of hemolysis as well as a mild CSF hyperproteinorachia, and markedly abnormal brain MRI were concerning for a number of etiologies.

Vascular. The acuity of symptoms raised concern for a vascular etiology; therefore, head CT with angiography was performed on admission and did not reveal any abnormalities. The diffuse microhemorrhages and areas of restricted diffusion on brain MRI raised concern for multiple cerebral emboli; however, this etiology was unlikely given that no arrhythmia was detected on telemetry, and there was no history of atrial fibrillation. A transthoracic echocardiogram revealed normal cardiac function without right-to-left shunt.

Infection. Infection, such as a hemorrhagic form of viral encephalitis, was considered given the MRI findings and the acute clinical presentation. However, infection with herpes simplex, the most common cause of viral encephalitis, classically presents with bilateral asymmetric involvement of the limbic system and medial temporal lobes, and the arboviruses often involve the basal ganglia, and neither is the case here.² There were no risk factors or infectious prodrome aside from diffuse myalgia, and the CSF workup was negative for infection (no hypoglycorrhachia, negative CSF cultures and negative workup for herpes viruses, enteroviruses, paramyxoviruses, adenovirus, parvovirus, arboviruses, and Lyme in the CSF).

Noninfectious inflammatory conditions. The innumerable petechial foci on brain MRI raised the suspicion of an acute hemorrhagic leukoencephalitis, a severe fulminant variant of acute demyelinating encephalomyelitis. However, most reported cases are seen in children, the lumbar puncture is usually markedly

abnormal with pleocytosis, and brain MRI typically shows bilateral asymmetric patchy areas of T2 hyperintensity in white and gray matter with lesions classically larger than 1 cm with poorly defined margins.³ Diseases such as MS, autoimmune limbic encephalitis, inflammatory CNS conditions such as sarcoidosis, systemic lupus erythematosus, or Sjögren syndrome were excluded based on the fulminant clinical presentation, imaging, and the lumbar puncture results. Although the clinical presentation was atypical for a CNS vasculitis, this group of disorders can also present with extensive foci of restricted diffusion in the cerebral white matter. However, brain MRA and cerebral angiogram were normal, arguing against this diagnosis.

Toxic and metabolic disorders. Toxic and metabolic disorders should always be considered in patients with rapidly progressive encephalopathy. However, there was no known or reported exposure to toxins or new drugs. There was no history of brain trauma and no history consistent with an anoxic brain injury. The metabolic workup did not reveal any electrolyte abnormalities, there was no hypoglycemia, hepatic and kidney function were normal, and levels of thiamine, folate, and B12 were normal.

Fat embolic encephalopathy in sickle cell disease. Ultimately, the clinical presentation, the laboratory findings with markers indicative of some degree of hemolysis (elevated LDH and elevated reticulocyte count), and the brain MRI findings with extensive foci of restricted diffusion and innumerable petechial foci in the white matter were consistent with the diagnosis of fat embolic encephalopathy secondary to bone marrow necrosis in a patient with sickle cell disease.

Questions for consideration:

1. Would you order further studies?
2. What treatment might you initiate?

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SECTION 4

Given the high suspicion of encephalopathy secondary to fat embolism syndrome in a patient with sickle cell disease (HbSC), we ordered cervical, thoracic, and lumbar spine MRI with gadolinium to look for signs of bone marrow infarction. MRI is much more sensitive than plain radiography to show bone infarction and may show changes caused by altered hemodynamics early in the course of disease.⁴ Spine MRI showed scattered areas of patchy enhancement along the midportion of multiple vertebral bodies within the cervical, thoracic, and lumbar spine consistent with bone marrow infarction (figure).

The patient was first treated with 1 g of IV methylprednisolone for 3 days without significant improvement, and exchange transfusion was performed. Outcome was poor with no significant clinical improvement despite treatment.

DISCUSSION Cerebral fat embolism syndrome is a rare and potentially devastating complication seen in patients with sickle cell disease.⁵ Vaso-occlusive crises can lead to bone marrow necrosis and release of fat particles into venous circulation. Paradoxical emboli can occur through a patent foramen ovale (no cardiac shunt was found in our patient), and microemboli can pass from venous to arterial circulation through the lungs.⁵ In addition, toxic intermediaries of plasma-derived fat promote an inflammatory and prothrombotic state.⁵

Diagnosing cerebral fat embolism syndrome can be challenging. The classic clinical triad of fat embolism syndrome includes respiratory symptoms, petechial rash, and neurologic dysfunction.⁵ Cerebral changes, reported in up to 86% of cases, are not uncommon in patients with fat embolism syndrome, and presentation varies from confusion to coma, and even death.⁶ It is important that these findings are not consistently present, and brain imaging is essential for diagnosis. Brain MRI is the method of choice to detect a cerebral fat embolism, and classic findings include diffuse microinfarcts with foci of restricted diffusion and T2 hyperintensity affecting the cerebral white matter, basal ganglia, thalamus, brainstem, corpus callosum, and cerebellum, as well as diffuse microhemorrhages in susceptibility-weighted imaging throughout the supratentorial and infratentorial regions of the brain.^{6,7} These microhemorrhages, secondary to fat emboli causing increased vascular pressure, are evident on pathologic examination as well.^{6–8} MRI can also confirm bone marrow infarcts in the acute phase of the disease and help with the diagnosis.⁸ Parvovirus B19 infection has been reported to precipitate fat embolism syndrome secondary to bone marrow necrosis in patients with sickle cell disease

(PCR, IgM, and IgG for parvovirus B19 were negative in our patient).⁹ Common laboratory findings include arterial hypoxemia in cases of lung involvement, anemia, thrombocytopenia, leukocytosis, elevated ferritin, elevated LDH, and laboratory markers of renal dysfunction. Of interest, consistent with this case, the literature shows that patients most at risk of fat embolism syndrome appear to be those with milder forms of sickle cell disease.⁹ A recent review reports that 81% of patients diagnosed with fat embolism syndrome in the setting of sickle cell disease had a genotype other than homozygous sickle cell disease (hemoglobin SS), and the majority of patients had no history of significant sickle cell disease complications.⁹ Treatment for fat embolism syndrome is based on supportive measures and red cell exchange transfusion, which if implemented early has been associated with improved prognosis.⁵

In conclusion, cerebral complications of fat embolism syndrome in sickle cell patients are underrecognized and require prompt diagnosis, as red cell exchange transfusions have been shown to improve survival.

AUTHOR CONTRIBUTIONS

Guillaume Lamotte: conceptualization, writing and preparation of the manuscript, and review and critique of the manuscript. Cassie Williams: writing and review of the manuscript.

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DISCLOSURE

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

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*[®] Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group email sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media.

One hundred ninety-two people provided answers to this mystery case that discussed a 69-year-old woman with a history of sickle cell disease presenting to the hospital acutely encephalopathic. The most striking imaging finding was the one most reported with 87.5% of respondents correctly observing multiple petechial foci in the white matter and deep gray matter on susceptibility-weighted imaging. A majority, 56%, also found corpus callosum and middle cerebral peduncle FLAIR hyperintensities, while less, 37.5%, picked up on diffusion restriction in the corpus callosum and white matter. Only 18.5% of respondents, however, indicated that there were diffuse cervical and thoracic vertebral body hyperintensities. These latter findings, though subtle, suggest that bone marrow necrosis and infarction and were an important clue to the ultimate diagnosis. Given the patient's acute presentation, medical history, examination, laboratory test results, nonictal EEG, and vessel imaging, the leading differential diagnoses included sickle cell crisis, acute

hemorrhagic leukoencephalitis, primary CNS vasculitis, and fat embolism syndrome with 45.3%, 36.5%, 29.2%, and 15.6%, respectively. In addition to exchange transfusions, the patient was treated with IV methylprednisolone but did not improve, arguing against acute hemorrhagic leukoencephalitis. The case also mentioned that CT and MR angiography were overall normal, making CNS vasculitis less likely.

In the context of the clinical presentation and objective data, fat embolism syndrome is the final diagnosis, chosen by 11% of responders. To say this patient was in a sickle cell crisis is not specific enough. Cerebral fat embolism syndrome is a rare complication of sickle cell disease and is caused by vaso-occlusive crises leading to bone marrow necrosis and the release of fat particles into the venous circulation. Fat microemboli can be shunted through the heart on their way to the brain where they cause inflammation, occlusion, and vascular injury. The classic clinical triad of fat embolism syndrome—respiratory symptoms, petechial rash, and neurologic deficits—is not present in all patients. MRI is the modality of choice to detect injury to brain parenchyma as well as bone marrow infarcts. Treatment with prompt red cell exchange transfusions can improve survival in some cases.¹

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