Cerebral fat embolism syndrome mimicking thrombotic thrombocytopenic purpura in a patient with Hemoglobin SC disease

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Word Count (Abstract to Conclusions): 1899

Figures: 3

Tables: 0

Keywords: Fat embolism syndrome, Hemoglobin SC, Starfield pattern

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This is the author's manuscript of the article published in final edited form as:
Kammeyer, R., Devnani, R., & Mehta, R. (2016). Cerebral fat embolism syndrome mimicking thrombotic thrombocytopenic purpura in a patient with hemoglobin SC disease. American Journal of Hematology, 91(5), 539–542. https://doi.org/10.1002/ajh.24286

Running Title: Fat Embolism Syndrome Mimicking TTP

Case Presentation

A 54 year-old man with hemoglobin SC disease (HbSC) and a history of substance abuse presented to the Emergency Department from a nursing home with two days of progressive weakness, shortness of breath, and lower back pain. He developed a fever, hypoxia, and tachycardia on the day of admission. He did not have any recent changes in medications, and his family as well as the nursing home staff denied any access to illicit drugs.

The patient's clinical presentation raises concern for a vaso-occlusive crisis, specifically acute chest syndrome (ACS.) ACS should be suspected when a patient with a sickle cell disorder (SCD) experiences fever, chest pain, and dyspnea, with laboratory testing demonstrating the presence of a leukocytosis and an associated decrease in hemoglobin and platelets [1]. Supportive care with hydration, oxygen, pain control, and broad-spectrum antibiotics should be initiated while awaiting hematologic, metabolic, infectious, and radiographic workups.

On arrival to the hospital, his vital signs demonstrated a temperature of 39.4 C, a heart rate of 140 beats per minute, and a blood pressure of 159/120 mmHg. He was hypoxic and required supplemental oxygen. Physical exam was remarkable for altered mental status (AMS) and a rapidly decreasing level of consciousness, dry mucous membranes, dilated, slightly irregular and non-reactive pupils, and a torsional nystagmus. A later review of records from his ophthalmologist documented the presence of iris atrophy as a complication of his sickle cell disease. Upon evaluation, the patient was intubated for airway protection.

ACS and the systemic inflammatory response syndrome (SIRS) remain atop the differential diagnosis. Other important considerations include severe sepsis secondary to pneumonia or meningitis,

illicit drug use, metabolic disturbances, heart failure, hypertensive emergency, and embolic diseases. In general, neurologic complications are seen in 11% of patients presenting with ACS, with 31% of those patients also developing a relative thrombocytopenia [2]. While there are many etiologies that might contribute to this clinical picture, one finding that stands out is his torsional nystagmus, indicating a dysfunction in his cerebellum or brainstem. With such a finding, a metabolic or ischemic cause for his acute encephalopathy becomes more likely.

Initial complete blood count showed a decrease in hemoglobin from a baseline of 13-14 g/dL to 12.4 g/dL, a decrease in platelets from a baseline of 222 k/mm^3 to 92 k/mm^3, and serum WBCs of 11.8 k/µL. Peripheral blood smears showed moderate amount of target cells and sickle cells, a markedly elevated number of nucleated red blood cells (65 nucleated RBCs/100 WBCs), and a slight number of schistocytes. There also was evidence of neutrophil precursors with 3% neutrophil bands, 2% metamyelocytes, and 1% myelocytes. A comprehensive metabolic panel showed an elevation of serum creatinine from a baseline of 1.2 mg/dL to 1.6 mg/dL and a total bilirubin of 3.4 mg/dL. His troponin I level was 0.96 ng/mL. Further hematological work-up demonstrated an INR of 1.1, aPTT of 24.8 seconds, a lactate dehydrogenase (LDH) of 20,324 IU/L, serum ferritin of greater than 7000 ng/mL, a reticulocyte production index of 1.6%, a fibrinogen of 431 mg/dL, a negative Direct Coombs' test, and an ADAMTS13 activity of 77%. Urine toxicology screen was positive only for prescribed opiates.

His overall findings are consistent with multi-organ failure, as demonstrated by compromise of the respiratory, neurological, hematopoietic, hepatic, and renal systems. Notably present is the potential clinical pentad of thrombotic thrombocytopenic purpura (TTP): fever, neurological findings, microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute renal injury. It is tempting, therefore, to attribute his condition to a thrombotic microangiopathy (TMA). However, he has a normal level of ADATMTS13 activity, and more importantly, an inappropriately low reticulocyte response. Due

to his sickle cell disorder, it is difficult to assess for true MAHA. With his chronic hemolytic anemia, his haptoglobin will always be low, and his indirect bilirubin will be high. He does have a markedly elevated LDH, which is seen in TMAs, and he did have schistocytes seen on his peripheral blood smear. However, with the low reticulocyte count, the likelihood of his current condition being primarily from a TMA is unlikely. Alternatively, fat embolism syndrome (FES) has also been shown to lead to acute multi-organ dysfunction, particularly in patients with variants of SCD, and may mimic TTP [3].

His chest radiograph and chest CT scan demonstrated a right lower lobe infiltrate. A head CT scan showed no abnormalities. However, his brain MRI demonstrated multiple areas of acute infarction, documented as a "starfield" pattern, as shown in figure 1. No abnormalities were noted on transesophageal echocardiogram. The patient was initially diagnosed with a thrombotic microangiopathy (TMA) and transferred to another facility to start plasma exchange (PLEX) due to his multi-organ failure. He underwent four sessions of PLEX and ten packed RBC (pRBC) transfusions, as shown in figure 2, but with minimal clinical response. A repeat MRI four days after presentation demonstrated acute and sub-acute infarctions in multiple anterior and posterior vascular distributions and the development of microhemorrhages, as shown in figure 3. At the cessation of treatment, the patient was able to withdraw from pain, but did not respond to commands. He developed triple flexor and Babinski reflexes in his bilateral lower extremities, with roving eye movements. His progress was discussed daily with his family, and they elected for a terminal extubation ten days after initial presentation due to his poor neurological prognosis. The family declined an autopsy.

His laboratory findings of decreasing hemoglobin, thrombocytopenia, and a markedly elevated LDH led initially led to a diagnosis of TMA. However, in retrospect, the "starfield" pattern seen on the MRI solidifies the diagnosis of FES, rather than a TMA. In cases of cerebral FES, a "starfield" pattern on diffusion-weighted MRI is seen, consisting of numerous punctuate foci in the white and grey matter,

suggesting the presence of acute micro-infarcts caused by the emboli [4-7]. Given the "starfield" pattern with microhemorrhages seen on our patient's MRI, and a cardiac emboli source ruled out by echocardiogram, it is likely that his neurologic abnormalities were due to cerebral FES rather than due to cerebral vaso-occlusion from a TMA.

Discussion

This case highlights the complexities of the evaluation and treatment of a patient with AMS and a sickle cell disorder (SCD). It also demonstrates the potential role of radiologic imaging in aiding the diagnosis and differentiation of TMA and FES. FES, while a recognized complication of SCD, may be underdiagnosed, if it is not considered early on in the differential diagnosis of an acutely ill patient with SCD. In a proposed pathologic model, bone marrow necrosis secondary to a vaso-occlusive crisis releases fat emboli into the circulation, causing pulmonary and systemic organ infarcts and dysfunction. A continuum of vaso-occlusive pain crises, fat embolism syndrome (FES), and ACS has been proposed [3], as the occlusion of pulmonary vessels by fat emboli has been identified as a cause of ACS [2]. One-fourth of FES patients are comatose on admission [8] and 43% of patients with an underlying SCD and FES have HbSC disease [3]. Laboratory investigation of patients with FES will typically show thrombocytopenia, worsening anemia, and leukocytosis secondary to bone marrow necrosis noted upon biopsy [8]. A review of the peripheral blood smear will often demonstrate a leukoerythroblastic picture, while the patient will also have high levels of serum LDH [9].

MRI is an underutilized, non-invasive modality that can aid in distinguishing between a TMA and FES. The presence of numerous hypointensities predominantly in the white matter on susceptibility-weighted or gradient echo (GRE) sequences is considered to be pathognomic for microhemorrhages, and can also be seen in 60-88% of the acute to late stages of cerebral FES [5, 10-12]. These correlate with the petechial cerebral hemorrhages observed on autopsy [13]. While occasional punctate foci of

diffusion restriction may also be seen in TMAs, they are not as numerous as those seen in the starfield pattern of FES [14]. Medium and large vascular distributions are more likely to be infarcted during TMA [15-17], including that of the cerebral grey matter, brainstem, cerebellum [18] or the deep white matter [19]. Microhemorrhages are rare [18], but may be seen in the presence of a larger infarct [20].

Although our patient did not have a bone marrow biopsy or an autopsy performed to confirm the presence of bone marrow necrosis or fat globules, a recent review of FES suggests that a clinical diagnosis could be made if the patient had the appropriate clinical course with specific laboratory findings. Namely, the authors noted a typical clinical course of FES consisting of a vaso-occlusive crisis that leads to a rapid clinical decline with respiratory failure and encephalopathy, in association with the presence of thrombocytopenia, worsening anemia, a leukoerythroblastic picture, and a grossly elevated LDH [3]. Importantly, the addition of the "starfield pattern" on MRI should also be included as a non-invasive way to confirm FES. Our patient clearly fulfilled the clinical and laboratory criteria for FES, and in addition had the radiographic findings as well. Therefore, while it was initially thought that he had a TMA, his true etiology for his rapid decline and death was FES.

Early recognition of FES is imperative to limit the morbidity and mortality from this disorder. Unfortunately, mortality is high in this condition, most likely due to the degree of damage done by the emboli by the time it can be diagnosed and the subsequent initiation of appropriate therapy. Due to its relationship with ACS, the suggested management of FES is similar to those used for ACS. Repetitive simple transfusions [21] or red cell exchange transfusions [12, 22-23] have been shown to be effective, while steroids remain controversial [24]. These patients do not typically respond to PLEX therapy [23, 25]. In the case discussed here, both repetitive PLEX sessions and simple transfusions were performed, with little hematologic or neurologic response.

In conclusion, fat embolism syndrome has classically been diagnosed with a bone marrow biopsy showing necrosis or an autopsy revealing the fat globules. However, laboratory and radiographic markers may help to identify FES, and prevent confusing it with other disorders such as TMA. In this case, an earlier recognition of FES could have been made by recognizing the "starfield" emboli pattern on diffusion weighted MRI. Furthermore, the low reticulocyte count should have led to away from the diagnosis of a TMA, while the leukoerythroblastic picture should have helped point to the diagnosis of FES. While repetitive simple transfusions were utilized, a red cell exchange transfusion may have provided a better outcome. For sickle cell patients presenting with AMS and multi-organ dysfunction, it is imperative to maintain a high index of suspicion for FES, as earlier recognition may impact the patient's condition before it leads to irreversible injury.

Consent: Written informed consent was obtained from the patient's healthcare power of attorney for publication of this case report and for its accompanying images.

Conflict of Interest: The authors declare that they have no competing interests or financial disclosures regarding the publication of this paper.

Author Contributions:

RK collected clinical data for the report, performed the literature review, and participated in the initial and final drafting of the manuscript. RD conceived of the report, participated in analysis of the clinical data, and participated in the initial and final drafting of the manuscript. RM provided guidance for the design of the report and the literature review, participated in analysis of the clinical data, and participated in the initial and final drafting of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: None

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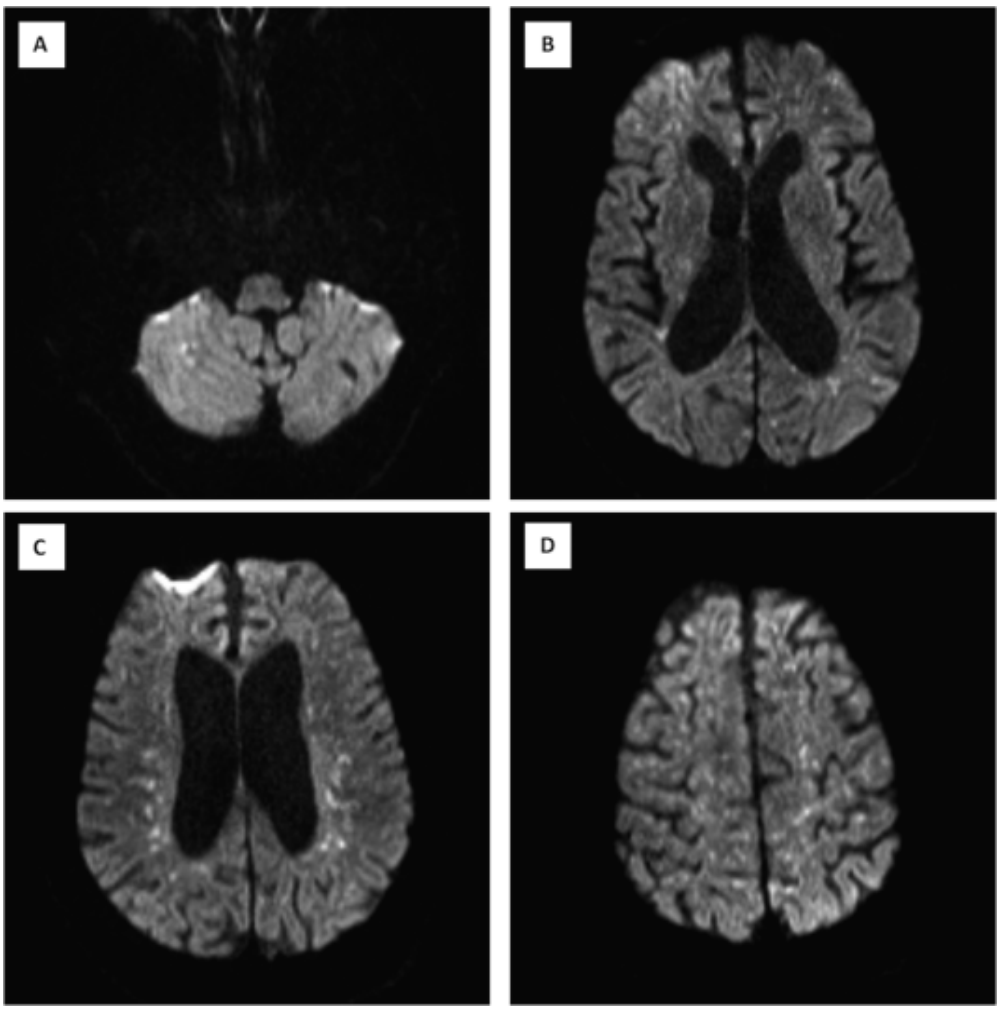

Figure 1. Select diffusion-weighted (B1000) MR images from initial presentation. Demonstration of innumerable punctuate foci of acute infarction (bright), including the regions of A) the right inferior cerebellum and B,C,D) the periventricular and subcortical white matter.

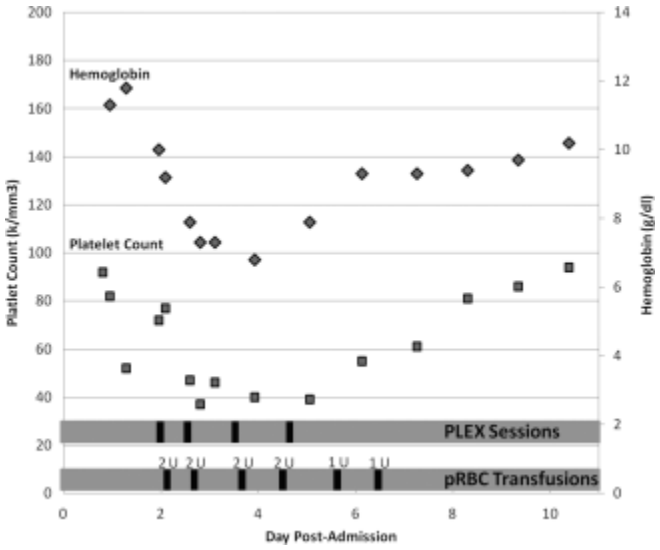

Figure 2. Platelet and hemoglobin counts during hospitalization. A total of four PLEX sessions and ten pRBC transfusions were performed.

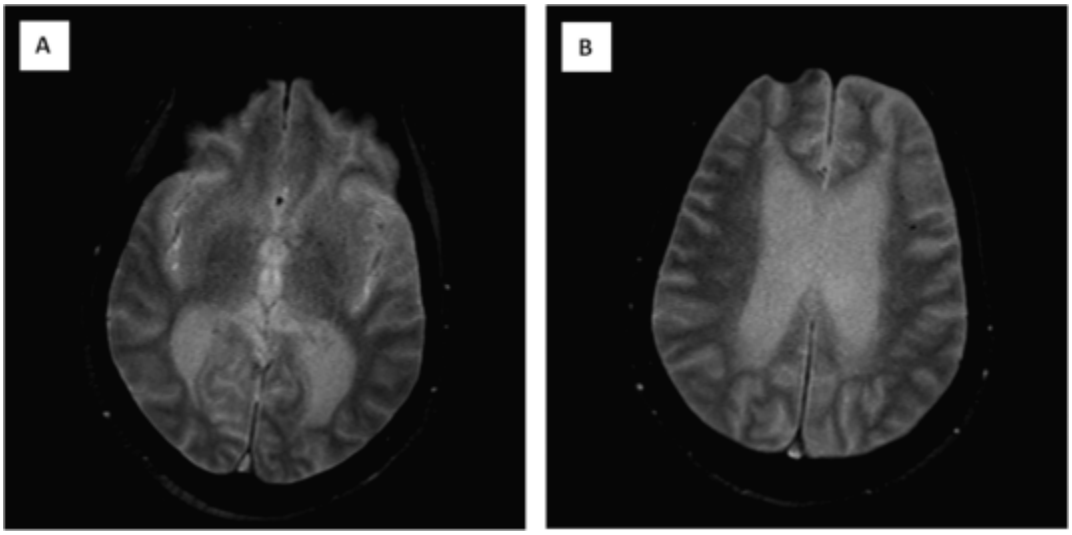

Figure 3. Select gradient echo (GRE) brain MR images obtained four days after presentation. Demonstration of new bilateral ovoid microhemorrhages (dark) in A) deep grey and B) subcortical white matter.