Fat Embolism Syndrome in Sickle Cell β-Thalassemia Patient With Osteonecrosis: An Uncommon Presentation in a Young Adult

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Abstract
Fat embolism syndrome is a relatively infrequent presentation in sickle cell thalassemia patients. It most commonly occurs in long bone fractures in the setting of trauma. However, nonorthopedic trauma and nontraumatic cases have been reported to contribute to fat embolism. The fat embolic syndrome is an underdiagnosed, life-threatening, and debilitating complication of sickle-β-thalassemia–related hemoglobinopathies. It is primarily seen in milder versions of sickle cell disease, including HbSC and sickle cell β-thalassemia, with the mild prior clinical course without complications; hence, diagnosis can be easily missed. Pathogenesis of fat embolic syndrome is a combination of mechanical obstruction from fat globules released into systemic circulation at the time of bone marrow necrosis and direct tissue toxicity from fatty acids and inflammatory cytokines released from fat globules. Prompt diagnosis and early initiation of treatment can reduce morbidity and mortality and result in better outcomes and prognosis. Red cell exchange transfusion is the mainstay of therapy with mortality benefits. Overall mortality and neurological sequelae continue to be high despite increased red cell exchange transfusion in the last few years. In this article, we discussed a case of a 34-year-old male patient with a history of sickle cell thalassemia and avascular necrosis of the hip, who presented with fever, hypoxia, encephalopathy, and generalized body aches, found to have thrombocytopenia and punctate lesions on magnetic resonance imaging brain, which led to the diagnosis of the fat embolism syndrome. Only a few sickle cell β-thalassemia with fat embolic syndrome cases have been reported.

Keywords
sickle cell β-thalassemia, hemoglobinopathies, bone marrow necrosis, fat embolism syndrome, red cell transfusion exchange

Introduction
Fat embolic syndrome (FES) is a rare, life-threatening complication of sickle cell thalassemia disease with high morbidity and mortality. Bone marrow necrosis (BMN) and subsequent FES occurs more often in patients with the heterozygous disease, such as HbSC+ and HbSB+, and less commonly in homozygous sickle cell disease (SCD). Diagnosis of FES is challenging for clinicians as it can be easily missed because of its rarity. A high index of suspicion is required for the diagnosis. The most common presenting complaints of patients with impending BMN and FES are fever, fatigue, and persistent back and abdominal pain, which can rapidly progress to devastating multi-organ damage. Diagnosis can be made based on clinical findings including fever, pulmonary symptoms with hypoxia and tachypnea, neurological symptoms with altered mental status and petechiae, laboratory findings include anemia, thrombocytopenia, low reticulocyte count (RC), high ferritin, elevated lactate dehydrogenase, elevated nucleated red blood cells.
(RBCs), and peripheral smear with leukoerythroblastosisis and imaging studies include magnetic resonance imaging (MRI) brain showing diffuse microemboli in the white matter. Institution of red cell exchange transfusion as soon as FES is suspected can be life-saving. Exchange transfusion reduces inflammatory markers and percentage of HbS, which improves pulmonary vascular circulation by lowering the viscosity. Overall mortality and neurological sequelae continue to be high despite increased use of red cell exchange transfusion; use of therapeutic plasma exchange (TPE) has been reported in some cases after exchange transfusion, which can remove already released fat globules from circulation. In patients with persistent neurological sequelae, long-term management with chronic red cell exchange transfusion is recommended.

Case Report

A 34-year-old African American male with a past medical history of hypertension and sickle cell β-thalassemia presented with diffuse body aches. His pain progressively worsened in his lower extremities to the point that he could not get out of bed. He had no relief with Percocet and admitted to drinking a lot of malt alcohol. He denied any fever, chills, chest pain, cough, nausea, vomiting, abdominal pain, constipation, diarrhea, dysuria, or focal deficits. Of note, the patient had multiple episodes of pain crises since childhood but was not treated until his last admission 1 month ago, when he presented with right hip pain, which on further evaluation with MRI hip revealed multiple bone infarcts throughout the bony pelvis and within the right femoral head consistent with right hip avascular necrosis with the largest area of acute bone infarct within the sacrum in the midline and extending into and through most of the right sacral ala. Additional areas involved left ilium and acetabulum with chronic sickle osteopathic findings. Based on these findings, Orthopedic surgery was consulted who recommended non-operative treatment. As avascular necrosis of the hip is a rare presentation with sickle cell trait, he underwent bone marrow biopsy and hemoglobin electrophoresis at that time that revealed β-thalassemia in addition to sickle cell trait. He smoked 2 to 3 cigarettes per day for the last 15 years and drank 2 beers per day. He denied any substance abuse. The patient denied any history of drug allergies. The patient’s family history was significant for the mother with a history of sickle cell trait, the father with a history of thalassemia, and the brother with a history of hypertension, diabetes mellitus, and SCD.

He was noted to be afebrile, pulse rate of 124 beats per minute on the initial examination. Blood pressure was 215/144 mm Hg, and oxygen saturation was 100% on room air. He was noted to be diaphoretic, in mild distress, and mild agitation. Lungs were clear to auscultation bilaterally. The rest of the examination was unremarkable. Admission laboratory results are summarized in Table 1.

| Laboratory          | Result (normal value) |
|---------------------|------------------------|
| White blood cell    | 10.75 H (4.10 × 10^9/µL) |
| Hemoglobin          | 11.9 (11.2-15.7 g/dL)  |
| Platelet            | 61 000 L (163-369 × 10^9/µL) |
| Sodium              | 134 L (136-144 mEq/L)  |
| Potassium           | 4.8 (3.5-5.1 mEq/L)    |
| Chloride            | 98 (98-110 mEq/L)      |
| Bicarbonate         | 17 L (20-30 mEq/L)     |
| Glucose             | 161 (98-110 mEq/L)     |
| Blood urea nitrogen | 7 (7-23 mg/dL)         |
| Creatinine          | 1.35 H (0.57-1.11 mg/dL)|
| Aspartate transaminase | 733 H (5-42 units/L)   |
| Alanine transaminase | 221 H (5-49 units/L)   |
| Alkaline phosphatase | 211 H (35-141 units/L) |
| Total bilirubin     | 2.1 H (0.1-1.2 mg/dL)  |

*Urinalysis normal and chest X-rays are unremarkable.

Hospital Course

On admission, the patient was complaining of persistent pain and was started on narcotics. He was noted to have hypertensive urgency on admission and was started on Nicardipine drip. His initial laboratory results were positive for transaminitis and thrombocytopenia. He was somewhat agitated as well. The following day, he rapidly deteriorated with more confusion. His vitals revealed a temperature of 40 °C, tachycardia, and tachypnea with a respiratory rate of 35 to 40 breaths per minute. A stat computed tomography (CT) head was ordered that revealed no acute hemorrhage or mass but showed questionable areas of cerebral edema. Electroencephalogram showed no focus of epilepsy. MRI brain with and without contrast revealed extensive punctate multifocal areas of diffusion restriction throughout the basal ganglia, thalami, and white matter of both hemispheres consistent with multifocal areas of punctate ischemic infarction in the acute to subacute stages as shown in Figure 1. A 7 mm signal abnormality in the left frontal region appeared to contain blood products consistent with a small hemorrhage focus. Neurosurgery was consulted who recommended repeat CT head, and no intervention was recommended, especially due to lack of hyperintense signal on CT suggesting not a true hemorrhage. Neurology recommended lumbar puncture—although it was not done due to low platelet count and was empirically started on antibiotics. He was evaluated further with CT chest, abdomen, and pelvis to evaluate possible infection sources that revealed the right lower lobe infiltrate. The patient developed respiratory failure requiring intubation.

Hematology was consulted for worsening thrombocytopenia. Antinuclear antibody, anti-neutrophil cytoplasmic antibody, lupus anticoagulant, HIV, and hepatitis were negative. ADAMTS13 activity 42% (normal >61%, should be <10% for acquired thrombotic thrombocytopenic purpura
Peripheral smear showed thrombocytopenia with leukocytosis. Sickled cells are present. There are rod-like molecular aggregations (polymerization) of hemoglobin S. No schistocytes were seen. Prothrombin time/partial thromboplastin time/international normalized ratio was elevated, which was likely related to liver dysfunction. Due to normal fibrinogen and the absence of schistocytes, disseminated intravascular coagulation was felt to be less likely. Although ADAMTS 13 activity was low but not significantly low enough to confirm the diagnosis of TTP. The low production of ADAMTS 13 is likely from liver dysfunction. Hemoglobin electrophoresis revealed significantly high HbS levels. Patients underwent exchange transfusions that dropped Hb S from 60% to 17%. Additional laboratory results are summarized in Tables 2 and 3.

Since there is transaminitis, a liver ultrasound was ordered, which was unremarkable. Liver function tests (LFTs) were significantly elevated with aspartate transaminase to alanine transaminase ratio >2:1, suggesting it was due to alcohol-induced hepatitis. The alcohol level was elevated at 67 mg/dL. Blood pressures were normal to high negating ischemic hepatitis. Hemolysis was to be less likely with normal hemoglobin and haptoglobin level as in Table 1. Also, hemolysis usually does not cause such high transaminitis. Although abnormal LFTs are uncommon in FES, It has been reported that fat can embolize to the lungs, brain, skin, retina, kidneys, liver, and even the heart. If it embolizes to the liver, it can result in abnormal LFTs. Ammonia level was normal.

Following exchange transfusions and empiric antibiotic therapy, the patient was eventually extubated, was awake but nonverbal, and did not answer any questions. He was able to follow some commands. CT angiogram head and neck was

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**Figure 1.** Magnetic resonance imaging showing extensive punctate multifocal areas of diffusion restriction throughout the basal ganglia, thalami (a), and white matter of both hemispheres (b).

**Table 2.** Additional Relevant Laboratory Results.

| Test                        | Value          | Normal Range            |
|-----------------------------|----------------|-------------------------|
| ANA                         | SS-A IgG 4.3 AU/mL | normal = 0.2 to 0.9    |
| ESR                         | 5 (0 to 5 mm)   |                         |
| CRP                         | 12.7 mg/dL H (0.02 to 0.5) |                     |
| Acute hepatitis panel       | Negative       |                         |
| HIV                         | Negative       |                         |
| Lupus anticoagulant         | Negative       |                         |
| Parvovirus                  | Ig G positive, Ig M negative |             |
| Proteinase 3                | Negative       |                         |
| Myeloperoxidase             | <0.2 negative  |                         |
| Vitamin B₁₂                 | 355 pg/mL (213 to 1041) |                   |
| Reticulocyte count          | 4.7 H (0.9% to 2.5%) |                  |
| Haptoglobin                 | 68 (30 to 258 mg/dL) |             |
| Blood alcohol level         | 67 H (0 to 10 mg/dL) |                  |
| Prothrombin time            | 17.6 H (12.3 to 14.4 seconds) |            |
| International normalized ratio | 1.47 H (0.92 to 1.13) |              |
| Partial thromboplastin time | 55.2 H (25.3 to 35 seconds) |          |
| Fibrinogen                  | 410 (267 to 484 mg/dL) |                     |

Abbreviations: ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Ig, immunoglobulin.

**Table 3.** Laboratories Before and After Exchange Transfusion.

| Test                        | Before exchange transfusion | After exchange transfusion |
|-----------------------------|-----------------------------|----------------------------|
| Hb a (96-98)                | 20.7                        | 72.5                       |
| Hb a2 (2.1-3.5)             | 6.1                         | 3.7                        |
| Hb f (0-1.5)                | 2.2                         | 0.0                        |
| Hb s (<0)                   | 71                          | 23.8                       |
| Platelet count              | 37                          | 510                        |

Abbreviation: Hb, hemoglobin.
done to rule out moyamoya disease, and it showed no signifi-
cant stenosis. Based on the presentation, with ongoing sickle
cell thalassemia crisis, osteonecrosis, thrombocytopenia, tachyphoea, and MRI pattern of infarctions, it was believed
that his presentation was likely due to FES. There is no spe-
cific treatment. Hematology recommended lifelong exchange
transfusions every 4 to 6 weeks to keep hemoglobin S level
to a goal of <30%. Quinton catheter was placed and eventually
discharged to a rehabilitation center.

Discussion

Fat embolism syndrome is a rare occurrence usually described
in the setting of traumatic long bone fractures.\textsuperscript{1} However,
there are infrequent non-trauma–related causes such as hema-
tologic malignancy, sickle cell hemoglobinopathies, BMN,
osteonecrosis, pancreatitis, osteomyelitis, cardiopulmonary
bypass, liposuction, parenteral infusion of lipids, antiphos-
pholipid syndrome, and sepsis.\textsuperscript{2} The cause of FES in SCD
is attributed to BMN. Ninety percent of patients with BMN are
secondary to underlying hematological malignancy and rarely
caused by autoimmune disease, infection, and SCD.\textsuperscript{3}

Diagnosis of FES is mainly based on clinical findings con-
sisting of a triad of pulmonary symptoms with hypoxemia,
axillary and subconjunctival petechiae, and neurological
symptoms with altered mental status. Fat embolism can pres-
cent with symptoms as early as 12 hours after the insult to the
bone, but predominantly in 24 to 72 hours. Pulmonary symp-
toms are the first manifestations of the syndrome that can
develop within 24 hours after the inciting event and present in
almost all patients. Several clinic criteria for diagnosing FES,
but the most relevant in our case are Gurd and Wilson’s criteria
established in 1974 (Table 4).\textsuperscript{4,5} An additional sign which is
very specific for FES is a brain MRI showing multiple micro-
emboli in the white matter.\textsuperscript{6} Our patient had acute hypoxic
respiratory failure requiring intubation, acute encephalopathy,
fever 40 °C, sudden thrombocytopenia, tachycardia, and MRI
of the brain revealed extensive punctate ischemic infarcts in
the white matter of both hemispheres.

Sickle cell β-thalassemia (HbSB) is an inherited disorder
that can present in 2 forms. The first form is one in which
there is a small amount of normal hemoglobin present called
sickle cell β-thalassemia + (HbSB +). The second form is the
absence of normal hemoglobin called sickle cell β-
thalassemia zero (HbSB0), and these patients present similarly
to those with SCD. Our patient likely had HbSB + based on his hemoglobin electrophoresis. Sickle cell crisis is used
to describe acute conditions, including the vaso-occlusive
crisis, hepatic crisis, splenic sequestration, and acute
chest syndrome.\textsuperscript{7} The complications of sickle cell crisis can be a stroke, avascular necrosis, and deep vein thrombosis.\textsuperscript{7}
However unlikely, but patients with HbSB + can develop
sickle cell crisis.

The pathophysiology of fat embolism is not well under-
stood. There are 2 mechanisms that are associated with it,
including mechanical and biochemical theories. The mecha-
nical theory suggested that fat globules dislodges from bone
marrow during the process of vaso-occlusive crisis, enter
into the pulmonary vascular bed, and form emboli in the lung
leading to an acute chest syndrome, but when the BMN is
extensive, a large amount fat globules release into circulation
leads to the FES.\textsuperscript{8,9}. Please check if the renumbering is cor-
rect.] From there, it transports into the systemic circulation to
form emboli in the skin, retina, and brain. The biochemical
theory proposed that embolized fat globules trapped in the
lungs degrade by phospholipase A2 into toxic intermedi-
aries, including free fatty acids and inflammatory cytokines.
Elevated C-reactive protein during acute crises or trauma
causes chylomicrons and very low-density lipoproteins to
aggregate to form fat globules, and elevated catecholamines
promote the release of free fatty acids, which can directly
affect pneumocytes and gas exchange.\textsuperscript{10,11} It is a combination
of mechanical obstruction and tissue toxicity from inflam-
matory cytokines. An association of human parvovirus B19
with BMN and fat embolism has been identified with a rate
of 24% and plays a major role in pathogenesis.\textsuperscript{12} For reasons
not entirely known at this time, BMN and subsequent FES
occurs more often in patients with heterozygous, such as
HbSC +, rather than homozygous SCD.\textsuperscript{12,13}

The most common presenting complaints of patients with
impending BMN and FES are fever, fatigue, and persistent
back and abdominal pain, which can rapidly progress to dev-
astating multi-organ damage, including neurological symp-
toms with confusion and diffuse infarction and respiratory
failure with hypoxia and tachyphoea. Patients undergoing
BMN and are at the early stages of FES are often misdiag-
nosed as TTP, as both subsets of patients will suffer from
thrombocytopenia, encephalopathy, acute anemia, fever, and
acute kidney injury.\textsuperscript{14} The severity of thrombocytopenia and
peripheral smear are the differentiating findings between

\begin{table}[h]
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\begin{tabular}{|l|l|}
\hline
\textbf{Major criteria} & \textbf{Minor criteria} \\
\hline
Respiratory symptoms, signs, radiographic changes & Fever (38.5 °C) \\
Cerebral involvement & Tachycardia (110 beats/min) \\
Petechial rash & Jaundice \\
 & Retinal changes \\
 & Renal changes (anuria or oliguria) \\
 & Drop of 20% in hemoglobin after admission \\
 & Sudden thrombocytopenia with a drop of 50% in platelets after admission \\
 & Erythrocyte sedimentation rate 71 mm/h \\
 & Fat macroglobulinemia \\
\hline
\end{tabular}
\caption{Gurd and Wilson Criteria; Requires at Least 2 Major Signs or Symptoms or 1 Major and 4 Minor Signs and Symptoms.}
\end{table}
FES and TTP as thrombocytopenia is more severe in TTP. Common peripheral smear finding reported in FES is leukoerythroblastosis and less commonly schistocytes than TTP. However, in patients with TTP, the RC is elevated; while in FES, due to BMN, there is a low RC. Thus prompt recognition of FES can be done via clinical signs or symptoms, especially if the patient has a documented history of sickle cell disorders, regardless of homozygous or heterozygous. The most common cause of death in acute chest syndrome in sickle cell patients is FES, as it has been misdiagnosed as bacterial pneumonia and treated with antibiotics later identified in the post mortem examination. The diagnosis of FES is largely clinical. As an aid in the diagnosis, physicians should limit their evaluation to simple blood work such as complete blood count with differential, basic metabolic panels, and arterial blood gas analyses, as they are fairly quick to obtain. Acute drop in hemoglobin and platelets, significantly increased lactate dehydrogenase and ferritin are the most frequently reported abnormal laboratory findings. Although bone marrow biopsy can help the diagnosis of FES, delay of care until it is done without instituting appropriate management can worsen outcomes. Bone marrow biopsy cannot exclude BMN as it depends on the timing of the biopsy because of its rapid recovery from the acute injury. Findings of cerebral fat embolism (CFE) include embolic microinfarcts from occlusion of capillaries from fat globules, vaso- genic edema, and petechial hemorrhages in the brain. CFE can happen either by fat globules entering the left atrium directly from the right heart through a patent foramen ovale (PFO) or by fat microglobules can filter directly through the lung capillaries to enter the arterial circulation. The latter mechanism is explained by the absence of PFO in many patients with CFE. In our patient, the transthoracic echocardiogram did not show PFO. Diagnosis of CFE can be easily missed, and it was underdiagnosed until autopsy reports. All these findings can be seen only in susceptibility-weighted MRI, which is preferred over conventional T2-weighted MRI as it is more sensitive.

Patients with FES who are treated with multiple RBC transfusions or exchange transfusions within hours of the presentation may help with rapid neurologic recovery, and the superior therapy seems to be exchange transfusion. Red cell exchange transfusion reduces inflammatory markers and the percentage of hemoglobin S, which improves pulmonary vascular circulation by lowering the viscosity. As in our case, delays in recognizing FES are common and have been associated with fatal results and permanent neurological damage. Unfortunately, in patients with hemoglobinopathies and other non-traumatic causes of FES, the diagnosis is often missed, especially if they do not have a prior diagnosis of the non-traumatic causes. FES is primarily associated with long bone fractures, and treatment, in that case, is a prompt orthopedic intervention. The uses of exchange transfusion or multiple RBC transfusions are only beneficial treatments in FES due to hemoglobinopathies and should be used within hours of patient presentation after a clinical diagnosis of FES and can be a life-saving treatment. A study conducted by Tsitsikas et al elucidated that mortality continues to be high at 33%, and neurological impairment is 20% even after red cell exchange transfusion. Given that overall mortality and neurological sequelae continue to be high despite increased use of red cell exchange transfusion, TPE is recommended after exchange transfusion as per Tsitsikas et al, which can remove already released fat globules from circulation and harmful circulating cytokines, which were released from BMN. TPE was used in 2 cases in their case series. However, it was used safely in patients with SCD to treat microangiopathic hemolytic anemia/TTP as in patients with multi-organ failure. TPE as a treatment has not been reported in other case reports or case series, and hence we need more published literature before it can be used as a standard practice. For patients with persistent neurological damage or other sequelae, Tsittikas et al are recommending long-term management with chronic red cell exchange transfusion or hydroxyurea. As our patient has neurological sequelae, our hematologist recommended lifelong treatment.
Informed Consent
Verbal consent was obtained from the patient.

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