

Fat Embolism Syndrome Mimicking Thrombotic Thrombocytopenic Purpura in a Patient With Hemoglobin S/Beta-Thalassemia

Bobby Se^{a, c}, Austin Frisch^a, Min Woo Hwang^a, Faran Polani^b,
Najeebah Bade^b

Abstract

Thrombotic microangiopathies cause ischemic organ damage and require urgent management for a favorable prognosis. Fat embolism syndrome from bone marrow necrosis is a rare and unique pathology that carries a high mortality rate. It can mimic thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP). Herein, we present a patient with sickle cell-beta-thalassemia who initially presented with a vaso-occlusive crisis, lab evidence of hemolysis, schistocytes and thrombocytopenia who developed acute encephalopathy with respiratory distress, consistent with TTP. She was found to have multiple infarcts in the brain. She was intubated and underwent plasma and red cell exchange. Bone marrow biopsy confirmed marrow necrosis from her vaso-occlusive crisis and subsequently, fat embolism syndrome. Here, we discuss the complex presentation and the complications of fat embolism from bone marrow necrosis and how it can mimic TTP.

Keywords: Fat embolism; Hemolytic anemia; Thalassemia; Thrombocytopenia

Introduction

Thrombotic microangiopathies (TMAs) are a group of disorders defined by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and microthrombi, which lead to organ damage through ischemia. Thrombotic thrombocytopenic purpura (TTP) is a TMA pathology that requires quick identification and treatment to avoid severe complications

and death [1]. TTP is defined by the presence of the classic TMA features of hemolytic anemia, schistocytes on peripheral smear, and thrombocytopenia in addition to low ADAMTS-13, and can present with signs of organ damage such as neurological impairment, renal dysfunction, or cardiac ischemia [2]. Similarly, fat embolism syndrome (FES) is characterized by pulmonary insufficiency, neurologic symptoms, thrombocytopenia, and anemia [3]. FES is most commonly seen after traumatic injuries such as long bone fractures, but other risk factors can include non-traumatic etiologies such as pancreatitis, liver disease, and sickle cell disease [4]. There have been case reports of TTP clinically mimicking FES and thus, making the diagnosis challenging [5]. Table 1 outlines the similarities and differences in the clinical and laboratory features between TTP and FES. We review the clinical presentation, pathophysiology, and current literature on the intersection between TTP and FES in sickle cell patients while highlighting the diagnosis and treatment needed to quickly differentiate these diseases and prevent death.

Case Report

Investigations

A 40-year-old female with a history of sickle-beta-thalassemia who presented to an outside hospital with severe back and bi-

Table 1. Clinical and Laboratory Features Differentiating Between TTP and FES

Clinical/laboratory features	TTP	FES
Thrombocytopenia	Common	Common
Acute kidney injury	Common	Common
Altered mental status	Common	Common
Fever > 100.4 °F or 38 °C	Common	Common
Respiratory failure	Less likely	More likely
Bone marrow necrosis	Less likely	More likely
Schistocytes	More likely	Less likely
ADAMTS-13	< 10%	Normal

FES: fat embolism syndrome; TTP: thrombotic thrombocytopenic purpura.

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^aInova Fairfax Hospital Department of Internal Medicine, Falls Church, VA 22042, USA

^bInova Schar Cancer Institute, Fairfax, VA 22031, USA

^cCorresponding Author: Bobby Se, Inova Fairfax Hospital Department of Internal Medicine, Falls Church, VA 22042, USA.

Email: Bobby4801@gmail.com

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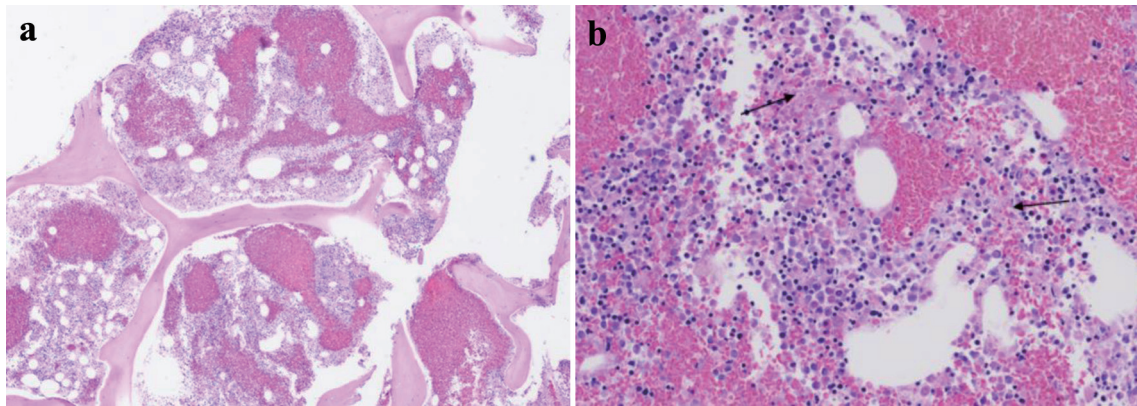


Figure 1. Bone marrow biopsy with evidence of bone marrow necrosis (a, $\times 4$ magnification; b, $\times 20$ magnification) (arrows).

lateral lower extremity pain was transferred for management of acute sickle cell crisis. Upon arrival, lab work was largely unremarkable with hemoglobin of 12.8 g/dL, white blood cell counts of $12.9 \times 10^3/\mu\text{L}$, and platelet count of $253 \times 10^3/\mu\text{L}$. The patient was initially managed with fluids and pain medication for vaso-occlusive crisis but then developed acute encephalopathy. Follow-up lab work showed worsening hemolytic anemia and new onset thrombocytopenia with platelets of $105 \times 10^3/\mu\text{L}$. Laboratory testing showed elevated lactate dehydrogenase (LDH) to 1,070 U/L, low haptoglobin of $< 8 \text{ mg/dL}$, elevated indirect bilirubin of 2.8 mg/dL and schistocytes were seen on the peripheral smear. She was intubated for airway protection given her worsening mental status and transferred to the intensive care unit (ICU). The following day, thrombocytopenia worsened to $79 \times 10^3/\mu\text{L}$. At this time, a computed tomography (CT) angiogram and CT of head were both negative. Her PLASMIC score was 6, which corresponds to a 72% risk of severe ADAMTS-13 deficiency. Therefore, the leading diagnosis at this time was TTP with other differential being fat embolism progressing to FES from non-traumatic bone marrow necrosis given the hemoglobinopathy and vaso-occlusive crisis.

Diagnosis

The patient underwent emergent plasma exchange and was started on high-dose steroids (1 g of solumedrol). Subsequently, ADAMTS-13 level was normal, and follow-up brain magnetic resonance imaging (MRI) showed multiple, scattered infarcts, highly suspicious for fat emboli. Bone marrow biopsy showed marrow necrosis (Fig. 1). Given these findings, FES became the established diagnosis.

Treatment and outcomes

The patient therefore underwent red cell exchange (RCE) immediately which reduced the hemoglobin S levels to 17%. Throughout her stay in the ICU, the patient continued to have minimal neurologic recovery and electroencephalogram continued to show cerebral dysfunction in a non-specific manner. Hospital course was further complicated by continued

fevers and tachycardia with leukocytosis prompting infectious workup and anti-microbial coverage. Her neurological status continued to show minimal recovery and eventually, tracheostomy and peg procedure were pursued prior to discharge to a long-term care facility.

Thrombocytopenia is defined as platelet levels $< 150 \times 10^3$ U/L. Acute kidney injury is defined as an increase in serum creatinine by 0.3 mg/dL within 48 h, increase in serum creatinine > 1.5 times the baseline level within 7 days, or a decrease in urine output $< 0.5 \text{ mL/kg/h}$ for $> 6 \text{ h}$. These definitions are consistent with the 2012 KDIGO clinical practice guidelines. Respiratory failure is defined as either hypoxemic or hypercapnic with $\text{PaO}_2 < 60 \text{ mm Hg}$ or $\text{PaCO}_2 > 50 \text{ mm Hg}$, respectively. Altered mental status is defined as an acute change in cognitive function, psychological function, and/or level of consciousness in the form of behavior changes, alertness or confusion.

Discussion

The pathophysiology behind marrow necrosis causing FES is not yet fully understood. Classically, FES presents after long bone or pelvic trauma and only 10% of these cases have clinical manifestations such as anemia, thrombocytopenia, neurologic symptoms, and pulmonary insufficiency [6]. In patients with acute chest syndrome, circulating phospholipids from bone marrow necrosis have been found to activate the inflammatory cascade leading to fat emboli formation [7]. This observation agrees with the biochemical theory that explains non-traumatic causes of FES [8]. Therefore, patients with hemoglobinopathies are at increased risk for bone marrow necrosis leading to fat embolism and subsequently, FES [9]. Furthermore, there seems to be an increase in prevalence with sickle cell patients that have heterozygous genotypes compared to their homozygous counterparts. This correlation is poorly understood but patients with hemoglobin $\text{S}\beta^+$ compared to SC and SS have a higher rate of developing FES [5, 9, 10]. The mortality rate for FES in the reported literature for sickle patients is 46%. Twenty percent of these patients that died also tested positive for parvovirus B19 [11, 12]. Therefore, hemoglobin $\text{S}\beta^+$, SC and SS along with parvovirus are risk factors for the development of FES in patients with sickle cell disease.

While this disease is severe and life-threatening, diagnosing FES can be a challenge given clinically similar presentation as TTP. Distinguishing between the two diagnoses can be more complex in the setting of hemoglobinopathy due to chronic hemolysis. FES can rarely cause a triad of neurological impairment, thrombocytopenia, and organ failure making presentation nearly identical to TTP [13, 14]. Respiratory distress appears to be a distinguishing feature between the two as it is more common in FES; however, as demonstrated with our patient, relying on clinical presentation can be deceiving in these cases.

FES treatment is generally supportive care with a level of definitive management in sickle cell patients. This is because FES can cause acute chest syndrome in sickle cell patients, thus lending to RCE as an option. This exchange prevents the removed sickled cells from propagating more vaso-occlusive events and thus minimizing bone marrow necrosis [15]. Other treatment options include trialing high-dose steroids in patients with life-threatening FES which theoretically prevents more formation [16]. However, high-dose steroids can have adverse effects like infection like in our case thus making it a controversial treatment decision [17].

Given the high mortality rate of TTP and clinical findings in this case, it is reasonable to treat as TTP with plasma exchange while waiting on ADAMTS-13 levels on initial presentation. In the rare cases where FES was misdiagnosed as TTP, initial plasma exchange did not seem to negatively affect these patients [11, 18, 19]. However, it is important to re-evaluate the diagnosis based on clinical progression and new lab results. Here, our patient had a normal ADAMTS-13 level with MRI findings of multiple infarcts suggestive of fat embolization. Bone marrow biopsy to corroborate bone marrow necrosis confirmed our diagnosis of FES. While RCE is definitive in FES caused by sickle cell disease, the primary treatment modalities are supportive which further emphasizes the importance of prevention.

Learning points

FES resulting from bone marrow necrosis is an uncommon and distinctive pathology characterized by a significant mortality risk. Patients with sickle cell variant Hb S β^+ who test positive for parvovirus B19 are at an increased risk of developing FES from bone marrow necrosis.

FES can imitate TMAs like TTP. Thus, plasma exchange is a reasonable initial therapy while waiting for ADAMTS-13 level to result before starting RCE.

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Conflict of Interest

The authors have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

Bobby Se: original draft preparation with literature review (lead); Austin Frisch: original draft preparation with literature review (support); Min Woo Hwang: review and editing; Faran Polani: review and editing; Najeebah Bade: review, editing, visualization of concept.

Data Availability

The authors declare that the data supporting the findings of this study are available withing the article.

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