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# UNCOMMON HEPATIC SEQUELAE FROM AN ACUTE SICKLE CELL CRISIS

Kimberly Lim, MD, James Walter, MD

## Background

Sickle cell crises are commonly treated at our institution given its large sickle cell patient population and well-established hematology department. While pain management is a crucial aspect to these patients' care, it is important to remember that a vaso-occlusive crisis can be life threatening. Many organs can be at risk, including the lungs (acute chest syndrome), brain (stroke), eyes (retinopathy) and as in our case, the liver. We hope this case report can become incorporated in future differential diagnoses pertaining to sickle cell crises.

## Case Presentation

A 48-year-old black female with a past medical history of sickle cell anemia, HIV on antiretroviral therapy, pulmonary hypertension on 4L of home oxygen, lymphocytic interstitial pneumonitis, chronic obstructive pulmonary disease, remote history of deep vein thrombosis, and pulmonary embolism, presented to the emergency department with complaints of shortness of breath, increased abdominal girth and lower extremity swelling for four days. She also complained of lower back and leg pain typical of her sickle cell crises. Her prescribed medications included tenofovir/emtricitabine, atazanavir, ritonavir, folic acid, oxycodone/acetaminophen, oral hydromorphone, and furosemide. Her social history was significant for smoking one fourth of a pack of cigarettes daily.

## Investigations

On presentation her vitals were temperature 98.1°F, blood pressure 106/48 mmHg, heart rate 87 beats per minute, and respiratory rate 19, with an oxygen saturation of 88% on 4L of oxygen by nasal cannula. Her physical exam revealed scleral icterus, diffuse abdominal pain most pronounced in the right upper quadrant to palpation, hepatomegaly and abdominal distention. She did not have any lower extremity edema. Her initial labs showed a total bilirubin of 49.4 (mg/dl), direct bilirubin 42 (mg/dl), AST 165 (IU/L), ALT 110 (IU/L), alkaline phosphatase 434 (IU/L), ammonia level 150 (mcmol/L). Her coagulation studies were partial thromboplastin time (PTT) 32, and an international normalized ratio (INR) of 1.9. She was also found to have a hemoglobin of 6.6 g/dL (down from 9 g/dL three days prior to presentation), white blood cell count of 13.6 (B/L) and platelet count of 276 (B/L). Additionally, the Hemoglobin S (HbS) percentage was 90%. Her creatinine was 2.8 (mg/dL), urea nitrogen 74 (mg/dL), potassium 6.2 (mmol/L), bicarbonate 6 (mmol/L), anion gap of 25. Her

other serum electrolytes were within normal limits. Her lactate dehydrogenase was 1405 (IU/L) and haptoglobin <10 (mg/dL). Her ABG showed a pH of 7.2, pCO<sub>2</sub> 24 (mm Hg), pO<sub>2</sub> 91 (mm Hg). Lactate was 8.4 (mmol/L). Her CD4 count was 432. A limited abdominal ultrasound showed cholelithiasis with gall bladder sludge, but normal wall thickness and no pericholecystic fluid. The liver measured 22.1 cm in sagittal length consistent with hepatomegaly, but showed normal echogenicity and texture. There was no intra or extrahepatic bile duct dilatation. Renal ultrasound showed no hydronephrosis. An echocardiogram showed a pulmonary artery systolic pressure of 90 mm Hg, normal left ventricle systolic function, right ventricle enlargement and decreased function, but no significant changes from a prior echocardiogram.

## Differential Diagnosis

Table 1 highlights our initial broad, problem-based, differential diagnosis. In terms of the workup of her liver failure, the differential was narrowed by the aforementioned lab findings and imaging. The abdominal ultrasound did not show signs of biliary obstruction or thrombus. Hepatitis panels and initial screening for medication induced liver failure were negative. Given her initial liver function elevations and lactic acidosis, it was thought that a vaso-occlusive hepatic crisis was most likely the etiology of her liver failure. Tenofovir, known to cause a severe lactic acidosis, was initially held. The patient was empirically started on broad-spectrum antibiotics, but with negative bacterial cultures and lactic acid resolution following appropriate intervention, the vaso-occlusion from sickled red blood cells (RBC) leading to end organ ischemia was believed to be the most likely etiology. Likewise, this would also explain the pathogenesis behind her renal failure.

The patient was admitted to the medical intensive care unit. A femoral pheresis catheter was urgently placed and she received six units of red blood cell exchange transfusion. Her Hemoglobin S percentage decreased to 42% from 90% after the transfusion and her hemoglobin increased to 9.4 (g/dL), while total bilirubin decreased to 36.3 (mg/dl) and direct bilirubin 29.4 (mg/dl).

## Outcome and Follow-up

Once stabilized, the patient was transferred to the general medicine floor for routine care. Her hospital course included episodic shortness of breath and hypoxia, which improved with diuresis. Five days after presentation, her total bilirubin reached a nadir of 9.4 (mg/dl), with a direct bilirubin of 6 (mg/dl) and

AST / ALT levels of 76 (IU/L) and 140 (IU/L) respectively. Her creatinine stabilized at 1.6 (mg/dL) from a peak of 3.2 (mg/dL) at time of discharge.

## Discussion

Sickle cell disease (SCD), as a hemoglobinopathy, can cause widespread sickling and vaso-occlusive events in all organ systems. Although not as commonly seen, liver involvement can be life threatening. Sickle cell hepatopathy has been a term used to generally describe varying etiologies of liver dysfunction in sickle cell patients. Multiple blood transfusions subject patients to increased risk of infectious processes, such as hepatitis B and C, and iron overload. Chronic hemolysis also causes sickle cell patients to be more prone to development of pigmented gallstones, which can lead to acute cholecystitis and/or biliary duct obstruction. Hepatic sequestrations can cause hepatic enlargement and rapidly falling hemoglobin. These complications can present similarly to acute sickle hepatic crisis and need to be excluded to make a diagnosis.<sup>1-4</sup>

Acute sickle hepatic crisis has been seen in about 10% of patients with SCD. Common presenting symptoms include right upper quadrant pain, low-grade fever, tender hepatomegaly, jaundice and elevated liver function tests. The pathogenesis stems from sickle cell thrombi in the sinusoidal space leading to ischemia. In a more extreme form, this can lead to intrahepatic cholestasis, which is rooted in widespread ischemia secondary to a massive sickled RBC load leading to hepatocyte edema and obstructive biliary outflow.<sup>2</sup> AST/ALT levels can run in the thousands, with total bilirubin levels reported as high as 300.<sup>5</sup> Coagulopathy is common and worsens as hepatocyte necrosis spreads. Histological hallmarks include sickle cell thrombi within sinusoids that can lead to bile plugs formation in canaliculi, inflammatory cell infiltration and hepatocyte edema/necrosis from prolonged ischemia. Such hepatic damage makes the prognosis of sickle cell intrahepatic cholestasis poor. Of the limited published cases report, mortality from intrahepatic cholestasis is greater than 50%.<sup>5</sup>

The cornerstone treatment for intrahepatic cholestasis is rapid HgS fraction reduction. While there are no specific studies looking at target fractions in acute hepatic sickle cell crises, previous studies focusing on stroke risk in sickle cell patients show risk reduction with HgS fractions less than 30%.<sup>6</sup> Reduction can be achieved through exchange transfusion using pheresis, which allows for better fluid management and avoids rapid changes in volume that can impact intravascular viscosity. Additional supportive treatment includes hydration, pain management, coagulopathy correction, and electrolyte monitoring.

Liver transplantation has been proposed as a therapeutic option in patients with fulminate failure from an acute crisis.<sup>7</sup> However,

transplantation experience is very limited. Only 18 transplant cases have been reported in the literature.<sup>7</sup> Hepatic vascular re-thrombosis and associated phenomenon (i.e. neurovascular injury) from post-operative sickle cell crises add to the inherent morbidity/mortality risk.<sup>7</sup> Consequently, the overall mortality rate in SCD patients with acute hepatic failure undergoing transplant is 60%.<sup>6</sup> Optimization of post-operative management will improve as transplantation is considered early in patients where fatal hepatic failure is anticipated.

Given the clinical presentation of our patient, she showed signs of ischemia with an elevated lactate, liver and kidney failure. Her hepatitis panels were negative, and ultrasound showed no signs of obstructive disease. Given her significant direct hyperbilirubinemia, it was thought that she was suffering from acute intrahepatic cholestasis causing liver and renal failure. This was confirmed by her immediate improvement after red blood cell exchange transfusion. This case reiterates the need for early detection of liver involvement in sickle cell disease. Early management with exchange transfusion usually prevents potentially fatal liver failure.<sup>1</sup>

## Key Points

- Acute sickle cell hepatic crisis is an uncommon, but potentially fatal sequela of sickle cell disease if not diagnosed early in the disease course.
- Common findings include profound jaundice, hepatomegaly, high AST / ALT, total bilirubin and renal failure.
- Primary therapy is aimed at rapid reduction of the HgS fraction through exchange transfusion via pheresis.
- Liver transplantation is a possible option in patients with fulminant hepatic failure.

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