

Acute fulminant cholestatic jaundice in sickle cell disease

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Liver patients with sickle cell disease (SCD) are subjected to many insults. Hepatic injury, which might be caused by the sickling process, blood transfusion complications (viral hepatitis or iron overload) or drug toxicity. Sickle cell hepatopathy is quite complex and distinguishing between different types of syndromes is difficult. In this paper we report on three SCD patients who presented with sickle cell intrahepatic cholestasis (SCIC) (fever, leukocytosis, coagulopathy, and extreme hyperbilirubinemia). The literature on sickle cell-associated liver diseases is reviewed.

Case 1

A 32-year-old Saudi male with SCD and a history of recurrent admissions due to painful crisis was admitted with abdominal pain, deepening jaundice, vomiting, poor appetite, low grade fever, and dark urine. He had no hematemesis or melena. He had cholecystectomy 5 years previously. On admission, he looked ill and deeply jaundiced with mild pallor. He was restless, dehydrated, and febrile to 37.8°C. The abdomen was distended by an old scar from a cholecystectomy. He had tender hepatomegaly (liver span, 18 cm) and there was no splenomegaly or ascites. Hematology studies included hemoglobin 9.5 g/dL, WBC 55 000/mm³, and platelets of 482 000/mm³. Serum chemistry test results were ALT 125 U/L, AST 171 U/L, total bilirubin 1105 µmol/L, direct bilirubin 638 µmol/L, BUN 33 mmol/L, and creatinine 534 µmol/L. Coagulation screening studies included a PT of 26 seconds, PTT 82 seconds, and INR of 1.8. Hepatitis screening, including HBsAg and HCV were negative. The patient was admitted to ICU, placed on broad-spectrum antibiotics, and his coagulopathy was treated with vitamin K and fresh frozen plasma. Manual blood exchange was performed using packed red blood cells in addition to hydration. After 6 days of management all his hematological and coagulation parameters improved. However, over the next several days his renal function rose, with serum creatinine reaching 729 µmol/L. He had three sessions of hemodialysis. After 15 days of intensive management his total bilirubin decreased to 189 µmol/L, and his creatinine had fallen to 117 µmol/L. The patient was discharged from the hospital after 3 weeks. At the time of writing, the patient was well.

Case 2

A 16-year-old Saudi female with SCD presented to the emergency room with complaints of abdominal pain, fever and worsening jaundice of two days. On admission, the temperature was 38°C, and the patient was pale and deeply jaundiced. She was restless and right conjunctival hemorrhage was noticed. The chest and cardiac examination were normal. The abdomen was distended, with tender hepatomegaly (liver span, 16 cm) and moderate splenomegaly, with no ascites. Her hemoglobin was 8.1 g/dL, WBC 10 000 mm³, and platelets were 27

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000/mm³. Blood chemistry values were total bilirubin 962 µmol/L, direct bilirubin 593 µmol/L, AST 455 U/L, and ALT 600 U/L. BUN was 24.5 mmol/L and creatinine 306 µmol/L. Her coagulation studies showed a PT of 26 seconds, PTT 82 seconds, and INR of 1.8. HBsAg and HCV were negative. A sonogram of the abdomen found hepatosplenomegaly, no gallbladder stones, and no common bile duct dilatation. She was admitted to ICU, and placed on broad-spectrum antibiotics, with partial blood exchange using packed red blood cells and fresh frozen plasma in addition to vitamin K, and she was rehydrated. With 4 days of intensive management in the ICU, her renal, hepatic function, and coagulation status improved. On day 8, she had another spike of fever (39°C) with a diffuse maculopapular rash, which was diagnosed by the dermatologist as toxic shock syndrome. On the basis of this diagnosis, she was treated with vancomycin and clindamycin and within 5 days the skin rash disappeared but the fever persisted. She complained of left hypochondrial pain and a CT of the abdomen revealed the presence of splenic infarction, which responded to conservative management. During her admission all her cultures were negative, and after 23 days of admission she was discharged home.

Case 3

A 15-year-old Saudi female with SCD was admitted to the general ward with 6 days of abdominal pain and a 2-day history of fever and worsening jaundice. At the time of admission she was deeply jaundiced, pale and dehydrated. She was febrile with a temperature of 39.2°C. The chest and cardiovascular system were normal. The liver, which extended several centimeters below the costal margin (liver span, 20 cm), was tender. Hematological results were hemoglobin 8 g/dL, WBC 32 000/mm³, and platelets 82 000/mm³. Serum chemistries included ALT 107 U/L, AST 411 U/L, total bilirubin 860 µmol/L, BUN 11 mmol/L, and serum creatinine 110 µmol/L. Coagulation screening studies included a PT of 27 seconds, a PTT >100 seconds, and an INR of 1.7. Hepatitis screening for HBsAg and HCV were negative.

She was treated in the intermediate care unit with broad spectrum antibiotics, blood exchange, infusion of fresh frozen plasma, and vitamin K. Her blood culture grew *Klebsiella* that was sensitive to the antibiotics she was being given. After 4 days of treatment her liver function and coagulation profile had improved but she was still running a low grade fever;

repeated cultures were negative. A CT scan of the abdomen showed a huge liver and enlarged spleen with splenic infarction. We continued with the same management and supported her with a simple blood transfusion. Later antibiotics were stopped as her general condition improved; all her septic work up was negative. She was discharged home after 15 days of hospitalization.

Discussion

The hepatobiliary system is frequently abnormal in SCD. Abnormalities are manifested acutely or chronically as hepatomegaly in 40% to 80% of cases,^{1,2} high bilirubin, elevated transaminases, and gall bladder stones. A variety of conditions in SCD result in acute and marked elevations of bilirubin, transaminases, and acute hepatic enlargement, including viral hepatitis, which clinically presents with nausea, malaise, jaundice, low grade fever, a tender enlarged liver and high bilirubin. An elevated transaminase and positive viral serology are needed for definite diagnosis.³ Hepatic sequestration is characterized by acute liver enlargement, a drop in hemoglobin, and disorders in hepatic function (mild-moderate elevation in transaminase). Most episodes resolve spontaneously or following transfusion but death may occur.^{2,4,5,6} In acute sickle hepatic crises, patients commonly present with acute right upper quadrant pain, nausea, low grade fever, tender hepatomegaly, and jaundice. Plasma AST and ALT levels seldom exceed 300 IU/L, although levels of 1000 IU/L or greater have occasionally been reported, presumably because of more severe hepatic hypoxic injury. Serum bilirubin levels are usually less than 15 mg/dL.⁴

SCIC is a rare, but potentially fatal complication of SCD, characterized by extreme hyperbilirubinemia, abdominal pain, progressive hepatomegaly, coagulopathy, and a modest elevation of transaminase.^{2,4,7,8} The term cholestasis was originally derived from Greek and literally means "a standing still of bile." This disruption of bile flow can occur on a cellular level in the hepatocyte, at the level of the intrahepatic biliary ductules or from an extrahepatic mechanical obstruction of the bile ducts.⁹ The pathophysiology of SCIC results from sickled red blood cells plugging the hepatic sinusoids, causing vascular stasis and local hypoxia. Kupffer cell hypertrophy develops and the canaliculi become plugged with bile.^{10,11,12,13}

The prognosis in cases of SCIC is thought to be poor initially, and the causes of death were hemorrhage and/or overt liver failure.^{7,14} Once acute liver

failure develops, transplantation is the only option, but the outcome of the transplantation with SCIC is inconstant.^{15,16,17} Dramatic improvement with greater survival has been reported in patients treated with exchange transfusion with both PRBC and FFP.^{4,7,8,13,14,18} We report on three SCD patients who fulfill the criteria of SCIC. They were serology negative for viral hepatitis with no evidence of gallbladder stones by sonogram. The three patients managed with partial blood exchange (both packed red blood cells and fresh frozen plasma) survived with no long-term sequelae. An invasive procedure was avoided during this crucial period, as serious complications (bleeding and mortality) can be expected.^{7,11,19} Two of our patients developed renal impairment, in one of whom

hemodialysis was needed for full recovery. Their renal impairment was thought to be multifactorial (hyperbilirubinemia, perhaps combined with volume depletion and antibiotics). Acute renal failure has been a recognized complication of obstructive jaundice from any cause.¹² Splenic infarction had developed in two of our patients, which reflects the character of the SCD pattern in the eastern province of Saudi Arabia (high Hb-F and preservation of a clinically enlarged spleen until adult age).²⁰ In conclusion, the process of SCIC can be reversed, and a successful outcome can be achieved by early recognition of this syndrome, partial blood exchange (both packed red blood cells and fresh frozen plasma), and avoidance of invasive procedures in the emergency setting.

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