American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2015; 16: 840-843
DOI: 10.12659/AJCR.895218

Received: 2015.07.03
Accepted: 2015.08.30
Published: 2015.11.28

Rare but Lethal Hepatopathy-Sickle Cell Intrahepatic Cholestasis and Management Strategies

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 31
Final Diagnosis: Sickle cell intrahepatic cholestasis
Symptoms: Abdominal pain • fever • jaundice
Medication: —
Clinical Procedure: Exchange transfusion
Specialty: Hematology

Objective: Rare disease

Background: Sickle cell disease can affect the liver by way of the disease process, including sickling in hepatic sinusoids, as well as its treatment, including repeated blood transfusions leading to hemosiderosis and hepatitis. Sickle cell intrahepatic cholestasis (SCIC) is an extreme variant of sickle cell hepatopathy, and is associated with high fatality.

Case Report: We present the case of a 31-year-old man with past medical history of sickle cell disease and cholecystectomy who was admitted with uncomplicated vaso occlusive crisis and during the hospital stay developed fever, upper abdominal pain, and jaundice. There was an accelerated rise in total bilirubin to 50 mg/dL, direct bilirubin 38 mg/dL, and Cr 3.0 mg/dL. Hb was 6.4 g/dL, reticulocyte count 16%, ALT 40 IU/L, AST 155 IU/L, ALP 320 IU/L, and LDH 475 IU/L. Hepatitis panel was negative and MRCP showed normal caliber of the common bile duct, with no obstruction. Exchange transfusion of 9 units of packed red blood cells led to great improvement in his condition.

Conclusions: SCIC, unlike the other sickle cell hepatopathies, requires urgent and vigorous exchange transfusion. Renal impairment in SCIC has not been well studied but usually is reversible with the hepatic impairment, as in this case. Unresolved renal impairment requires dialysis and is associated with poor outcome. There is limited data on use of hydroxyurea to prevent SCIC, and liver transplant is associated with high mortality. A timely diagnosis of SCIC and appropriate management is life-saving.

MeSH Keywords: Anemia, Sickle Cell • Cholestasis, Intrahepatic • Exchange Transfusion, Whole Blood • Hydroxyurea • Liver Transplantation

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/895218

Background

Sickle cell disease can have varying hepatic manifestations ranging from mild to lethal. A sickle cell patient's liver is affected by iron overload and is prone to hepatitis through multiple blood transfusions. The sickling of erythrocytes in the hepatic sinusoids causes additional damage. It can manifest as a spectrum of complications varying from benign hyperbilirubinemia at one end, to the most severe one at the other, called sickle cell intrahepatic cholestasis (SCIC) [1]. If diagnosed in a timely manner, urgent exchange transfusion of RBCs in SCIC can prevent death.

Case Report

We report the case of a 31-year-old African American man with homozygous sickle cell disease (HbSS) who presented with a 3-day history of increasingly severe pain throughout the body. He denied any chest pain, dyspnea, or cough. The past medical history included vaso-occlusive crisis, acute chest syndrome, contrast-induced acute kidney injury (AKI), peripherally inserted central line (PICC) line-induced venous thrombosis of the upper extremity, hemosiderosis due to blood transfusions, and cholecystectomy. His home medications included chelating agent and opioid analgesics. The patient had 4-pack/year smoking history and occasional alcohol and marijuana use. He denied any use of recreational intravenous drugs. Family history was significant for sickle cell disease.

On examination the patient was in moderate distress. Vital signs included blood pressure of 107/60 mm Hg, heart rate of 96 beats per minute, respiratory rate of 16 breaths per minute, temperature 98.7°F, and oxygen saturation of 96% on room air. A port was visualized on the left side of chest; the site was non-tender. There was scleral icterus and conjunctival pallor. Breath sounds were clear to auscultation bilaterally. Heart examination demonstrated regular rate and rhythm, with no audible murmur. The abdomen was scaphoid with a surgical scar; it was soft with positive bowel sounds. There was tenderness in the lumbar spine and lower extremities. Initial laboratory findings included hemoglobin of 6.2 g/dL, white cell count of 16,600 with differential of 75% neutrophils, 1% bands, reticulocyte count 16.1%, total bilirubin 4.0 mg/dL, direct bilirubin 1.8 mg/dL, alanine aminotransferase (ALT) 78 IU/L, aspartate aminotransferase (AST) 132 IU/L, and alkaline phosphatase (ALP) 274 IU/L.

During the course of hospitalization, the patient developed fever of 103.4°F, hypotension of 86/48 mm Hg, and tachycardia of 122 beats per min. There was no chest pain, cough, dyspnea, or desaturation, but he complained of increasingly severe upper-abdominal pain. The patient did not have any nausea, vomiting, diarrhea, or constipation. On examination he was found to have no signs of bleeding, but did have severe scleral icterus, yellow discoloration of the skin, and tenderness in the right upper-quadrant with guarding. Bowel sounds were normal. Imaging of the abdomen included ultrasound and flat plate, which did not reveal common bile duct dilatation or pneumoperitoneum, respectively. He received aggressive intravenous (IV) fluids. Specimens were collected for pan culture, and he was started on broad-spectrum antibiotics (meropenem and vancomycin) for a possible abdominal source of sepsis or chest port infection.

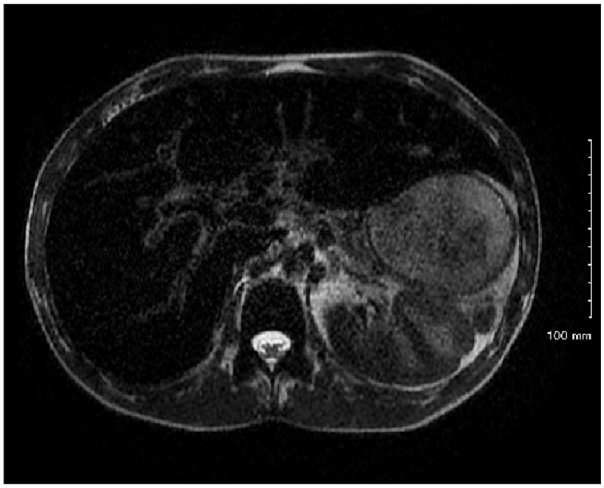

Figure 1. MRCP showing decreased signal intensity in liver, consistent with hemosiderosis.

The patient became increasingly confused, with his white cell count, transaminases, and bilirubin continuing to rise. His hepatitis panel was negative. He had a magnetic resonance cholangiopancreatography (MRCP) the following day for better visualization of the hepatobiliary system. It did not show any obstruction or dilatation of the common bile duct, but did show mild periportal edema, ascites, and diffuse decreased signal intensity throughout the liver, consistent with hemosiderosis (Figure 1). Blood cultures remained negative, although the patient continued to be febrile and tachycardic. The patient's liver function test results worsened; ALT 40 IU/L, AST 155 IU/L, ALP 320 IU/L, total bilirubin 50 mg/dL, and direct bilirubin 38 mg/dL on the fifth hospital stay (Figure 2). Also concerning was his progressively worsening kidney function, with an elevated creatinine at 3.5 mg/dL (Figure 3). At this time his Hb was 6.4 g/dL, reticulocyte count 16%, lactate dehydrogenase (LDH) 475 IU/L, and INR 1.4. Given the end-organ damage caused by sickle cell crisis, it was decided to initiate exchange transfusion in the patient. The patient was given a total of 9 units of RBC in exchange transfusion, which resulted in a remarkable improvement in his condition. His fever and abdominal pain subsided and there was steady decline in his bilirubin and creatinine over the next few days.

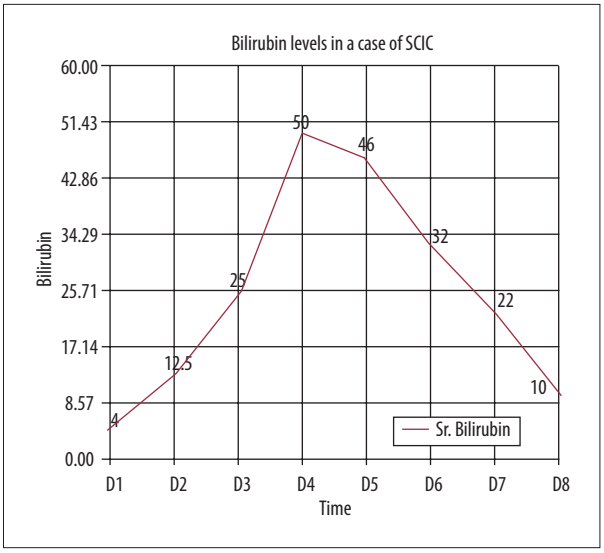

Figure 2. Trend of bilirubin (mg/dL) levels during the course of hospitalization.

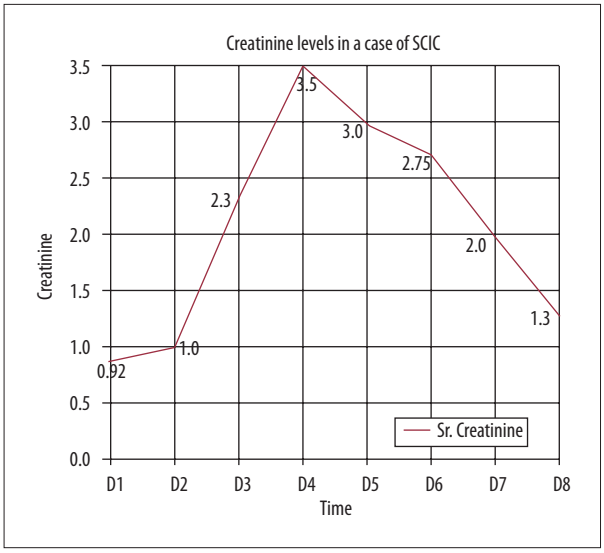

Figure 3. Trend of creatinine (mg/dL) levels during the course of hospitalization.

Discussion

SCIC is a rare condition with high mortality, and evidence of AKI worsens the prognosis [2]. Signs and symptoms suggestive of end-organ damage, including, but not limited to, the liver and kidneys, should raise a high suspicion for SCIC.

Our patient presented with sudden development of right upper-quadrant abdominal pain on the second day of admission, with scleral icterus and rapidly rising bilirubin levels. The patient had undergone cholecystectomy in the past, thus cholecystitis and cholelithiasis were not in the differential diagnosis. MRCP ruled-out choledocholithiasis and showed mild periportal edema, ascites, and hemosiderosis. The patient's altered mental status, right upper-quadrant pain, rising bilirubin levels peaking to 50 mg/dL, moderately elevated liver enzymes, and AKI led to the diagnosis of a rare sickle hepatopathy, SCIC.

The pathogenesis is uncertain but it is thought that there is progressive damage to the hepatocytes, beginning with sludging of RBCs in the sinusoids, followed by hypoxia and cell death, leading to liver dysfunction. Manifestations of end-organ damage included jaundice, AKI, altered mental status, and coagulation defects. Microscopy may reveal swollen hepatocytes, plugging of canaliculi with bile, necrosed cells, and occasional microinfarcts. As discussed earlier, SCIC can cause further hepatic damage in a sickle cell patient's liver if affected by iron overload and/or hepatitis. In our patient, hepatitis was ruled-out with negative serologies but the MRCP revealed changes in hemosiderosis.

Ahn et al. reported cases of sickle cell hepatopathy and classified the patients into 2 major groups [1]. The patients in the first group had milder disease with no manifestation of severe hepatic damage and a mean bilirubin of 27.6 mg/dL. The patients in the second group had more severe hepatic dysfunction, with a mean bilirubin of 76.8 mg/dL, accompanied by altered mental status and/or prolonged coagulation times. Mortality in the first group was 4% and in the second group 64%. RBC exchange transfusion was successful in saving 7 out of 9 lives. Twelve out of 13 patients died who did not submit to exchange transfusion. These results clearly highlight the importance of RBC exchange transfusion in SCIC [3–5]. Our patient had exchange transfusion with 9 units of packed RBC, with rapid improvement in the clinical condition along with kidney and liver functions.

In cases of SCIC, the reason for AKI is uncertain and may be caused by acute tubular necrosis or renal infarcts. Management of liver failure may simultaneously improve AKI. There have been 2 reported cases of SCIC with renal failure, which underwent dialysis but did not survive [6,7]. There are no randomized control trials to date assessing the optimum treatment for this condition [8]. Three cases have been reported in which SCIC was managed without exchange transfusion [9]. Hydroxyurea increases levels of HbF and is often used to prevent complications in sickle cell patients, including painful crisis, acute chest syndrome, priapism, and stroke, and decrease the need for blood transfusion. It has been shown to result in improvement of splenic function, with revisualization on 99m Tc-sulfur colloid liver-spleen scans [10], but its role in preventing SCIC is still uncertain and it has not been shown to influence frequency of hepatic sequestration crisis [11,12].

Liver transplantation used as management strategy for SCIC has not been widely studied. So far, the reported cases of liver

transplantation have not shown promising outcomes and re-transplantations have not been successful, mainly due to vascular complications in the allograft [13–15]. A literature review identified 10 adults and 5 children with sickle cell disease (SCD) who underwent orthotopic liver transplantation (OLT). Out of the 10 adults, 4 died in the immediate post-operative period and 5 out of the remaining 6 eventually died due to sickle cell-related allograft complications; in the pediatric group 3 out of 5 patients survived post-operatively [16]. Aggressive exchange transfusion of RBC during the pre- and post-operative periods may prolong survival, but mortality after OLT remains high [16].

Conclusions

It is anticipated that sickle hepatopathy, including SCIC, will become an increasing problem in the aging SCD population. A clinical trial is ongoing to investigate the role of reduced-intensity hematopoietic stem cell transplantation in regression of liver disease [17]. For now, the therapeutic options for SCIC remain limited. Given the uncertain role of hydroxyurea and the high mortality associated with OLT, it is imperative to make a timely diagnosis and initiate exchange transfusion of RBC.

Conflict of interest

None.

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