HHS Public Access

Author manuscript

Am J Med Case Rep. Author manuscript; available in PMC 2019 September 18.

Published in final edited form as:

Am J Med Case Rep. 2019 ; 7(4): 67–70. doi:10.12691/ajmcr-7-4-4.

Intrahepatic Cholestasis in a Sickle Cell Patient Unresponsive to Exchange Blood Transfusion

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Abstract

With the advent of hydroxyurea, the sickle cell population has been enjoying a prolonged life span as compared to the pre-hydroxyurea era. Traditionally, acute complications of sickle cell disease includes acute chest syndrome, MI and stroke. In this report we present a case of an elderly man with sickle cell disease who presented with intrahepatic cholestasis (SCIC); a rather rare and fatal complication of sickle cell hemoglobinopathy. The patient presented with jaundice and elevated bilirubin up to 53, his hospital course was complicated by coagulopathy and encephalopathy, and expired on day 43 of presentation after failing multiple therapeutic interventions including exchange transfusion. In this report, we will provide literature review and discuss the underlying pathophysiologic mechanisms of intrahepatic cholestasis in the sickle cell population highlighting the need for immediate recognition and institution of therapy for this fatal complication of sickle cell disease, particularly in elderly populations with low metabolic reserve.

Keywords

liver transplantation; exchange transfusion; sickle cell; cholestasis; intrahepatic

1. Introduction

SCD is characterized by ischemic infarcts of multiple organ systems, as a result of a sickling deformity of red blood cells. Hepatomegaly, mild to moderate indirect hyperbilirubinemia as well as pigmented biliary stones are relatively common liver related complications in sickle cell disease. [1] Cell hypoxia is believed to be the underlying mechanism for intrahepatic cholestasis. [3] With progressive damage to hepatocyte and sludging of red blood cells (RBCs) into the hepatic sinusoids, end organ damage begins to take place in the liver. Microscopy could reveal ballooned and necrotic hepatocytes, microinfarcts, and canaliculi plugged with bile.

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Exchange transfusion (ET) is the only effective treatment for SCIC; early intervention with exchange transfusion helps to minimize sickling thus lowering the fraction Hemoglobin S (ideally below 30%). [2] ET is the only intervention which decreases patient mortality as compared to solely supportive measures. [2] Cholelithiasis and viral hepatitis must be ruled out before a diagnosis of SCIC can be made (often a diagnosis of exclusion). [4] The disease can present in its most severe form when the patient is already coagulopathic with renal failure and ultimately fulminant hepatic failure. [4] We discuss a case of an elderly male who initially presented with hyperbilirubinemia likely secondary to SCIC; his bilirubin continued to trend upward and he ultimately went into liver failure. The patient received exchange transfusion and had a decrease in Hgb S to less than 30%; however his clinical status did not improve and the patient succumbed to his disease.

2. Case Report

A 64 year old man with medical history of Hemoglobin S/β thalassemia, hypertension, Atrial fibrillation, CAD, and ESRD on hemodialysis presented with anuria, fever, vomiting, and icterus to the emergency room. The patient was alert and oriented, and his exam was negative for abdominal tenderness. Patient was not taking any hepatotoxic medications or supplements; he had been dialyzed at his center the day prior to presentation. The vital signs revealed a blood pressure of 148/74, heart rate of 93 beats per minute, respiratory rate of 18 breaths per minute, temperature of 98.9°F, and oxygen saturation of 97% on admission.

Initial labs were significant for cholestasis with total bilirubin of 20 mg/dL, and a direct bilirubin > 10 mg/dL, anemia with hemoglobin of 6.8 g/dL (patients baseline is 8.0 g/dL), and elevated liver enzymes with aspartate aminotransferase (AST) of 109 U/L, alanine aminotransferase (ALT) of 18 U/L and alkaline phosphatase (ALP) of 202 U/L. A viral hepatitis panel was unremarkable (for labs, see Table 1). Patients Hemoglobin S was 78.7%, his lactate dehydrogenase (LDH) was 1083 U/L and haptoglobin was <30 mg/dL.

On right upper quadrant sonogram (Figure 1) the liver was noted to be 18.4 cm with normal echogenicity, no surface nodularity, and patent veins with normal flow. The intrahepatic ducts were normal, and the common bile duct diameter was 3mm at the porta hepatis; the gallbladder was not visualized. The CT Abdomen and Pelvis with IV contrast (Figure 2) was consistent with a surgical history of cholecystectomy and no evidence of biliary ductal dilation. The liver was of a normal contour, with patent portal veins.

The hematology service was consulted for further management of the patient; they initially believed that the hyperbilirubinemia was secondary to sickle cell hemolysis and underlying liver disease in the setting of elevated LDH, decreased haptoglobin and imaging negative for obvious obstructive disease. They also suggested exchange transfusion if the patient did not clinically improve. The nephrology service was also consulted to facilitate hemodialysis, which was maintained three times a week as scheduled during the patients' hospital course. The patients' bilirubin continued to rise and peaked at 52.8mg/dL on day 13 of his admission (Figure 3). The international normalized ratio (INR) also continued to uptrend to a peak of 3.2 (from a baseline of 1.2) on day 12 of his admission. Towards the end of his 12th day of the hospital stay, the patient became altered and developed tender hepatomegaly.

He was promptly transferred to the intensive care unit for exchange transfusion (ET). ET was carried out with 7 units of PRBCs via his A-V fistula; the HbS concentration on HPLC was noted to be <30% after the ET. The patients' total bilirubin decreased to 40 mg/dL following ET, however he remained altered and coagulopathic. Since the patients HbS concentration decreased below 30% further ET was not warranted.

Patient continued to have altered mental status, however a CT Head was negative for acute intracranial pathology. Hyperbilirubinemia causing bilirubin neurotoxicity was proposed as the plausible explanation of the mental status alteration, particularly in the setting of normal ammonia levels. The patient was started on vitamin K for coagulopathy and ursodiol for hyperbilirubinemia. The patient continued to decompensate further and palliative care evaluation recommended supportive therapy. On day 43 patient expired.

3. Discussion

SCIC is a rare, but severe complication in patients who have either hemoglobin (Hb) SS or Hb S/β thalassemia disease states. Patients with SCIC commonly present with right upper quadrant pain, hepatomegaly, elevated conjugated bilirubin, and elevated transaminases, as was seen in our patient. While the incidence of SCIC is higher in children than in adults, adults tend to experience a more aggressive disease course with mortality rate as high as 50%. [5] Diagnosis of SCIC calls for primary biliary disease to be ruled out, which is most commonly done using ultrasound which has a positive predictive value of 95% in diagnosing acute cholecystitis. [7] Since our patient had a history of cholecystectomy, cholecystitis was not in the differential diagnosis, and there was no evidence of biliary obstruction on either abdominal ultrasound or CT scan. Infectious workup for viral hepatitis was unrevealing and there was no clinical suspicion for drug-induced liver injury.

According to Ahn et al., SCIC can be classified as either mild or severe disease; mild disease presents with a mean direct bilirubin level of 27.6 mg/dL without manifestations of significant hepatic damage. Severe disease presents with a mean direct bilirubin of 76.8 mg/dL, presence of a coagulation disorder or altered mental status. [8] Based on the above, our patient initially presented with mild disease, however progressed to severe disease. With this progression to severe disease, there is an increased mortality rate as high as 64%, compared to only 4% in mild disease. [11] Once the diagnosis of SCIC has been made, prompt efforts to treat must be undertaken as disease progression is rapid and fatal. According to Ahn et al., ET is an important treatment modality that resulted in success in 7 out of 9 patients reported in the study. On the other hand, in those who did not have ET, twelve out of thirteen patients expired. Their findings collectively support the empiric use of ET pending randomized control trials. In our patient with severe disease, despite receiving ET with 7 units of packed RBCs resulting in a decrease of Hb S to 30%, our patient did not survive, underscoring the high mortality rate among this vulnerable population. Other treatment options such as albumin dialysis have shown some benefit in limited case reports, however its efficacy has not been clearly documented or studied. [11]

Liver transplantation has also been used to manage SCIC, however this treatment strategy has not been widely evaluated as these patients are generally poor candidates for transplant

due to multiorgan failure, as was the case with our patient. Furthermore, in reported cases of liver transplantation for SCIC, outcomes are poor and transplantation is not successful due to sequela of ongoing SCD including vascular complications.

4. Conclusions

As the sickle cell population continues to age with better symptom control and availability of effective therapeutics options including hydroxyurea, rare complications such as SCIC come to the forefront of SCD management. As demonstrated in our report, SCIC, while a rare occurrence, is a highly fatal complication of SCD that calls for early diagnosis and initiation of ET therapy, if possible within 48 hours of diagnosis. To our knowledge, our report represents the oldest patient with documented SCIC that presented with a rather gradual onset, making the diagnosis hard to ascertain given the broad differential of hyperbilirubinemia. This atypical presentation has resulted in delayed initiation of ET; the only known viable therapeutic option available to date. In addition to late presentation, advanced age and end-stage renal disease in our patient likely contributed to his deteriorating status.

Acknowledgements

This work is supported, in part, by the efforts of Dr. Moro O. Salifu M.D., M.P.H., M.B.A., M.A.C.P., Professor and Chairman of Medicine through NIH Grant number S21MD012474.

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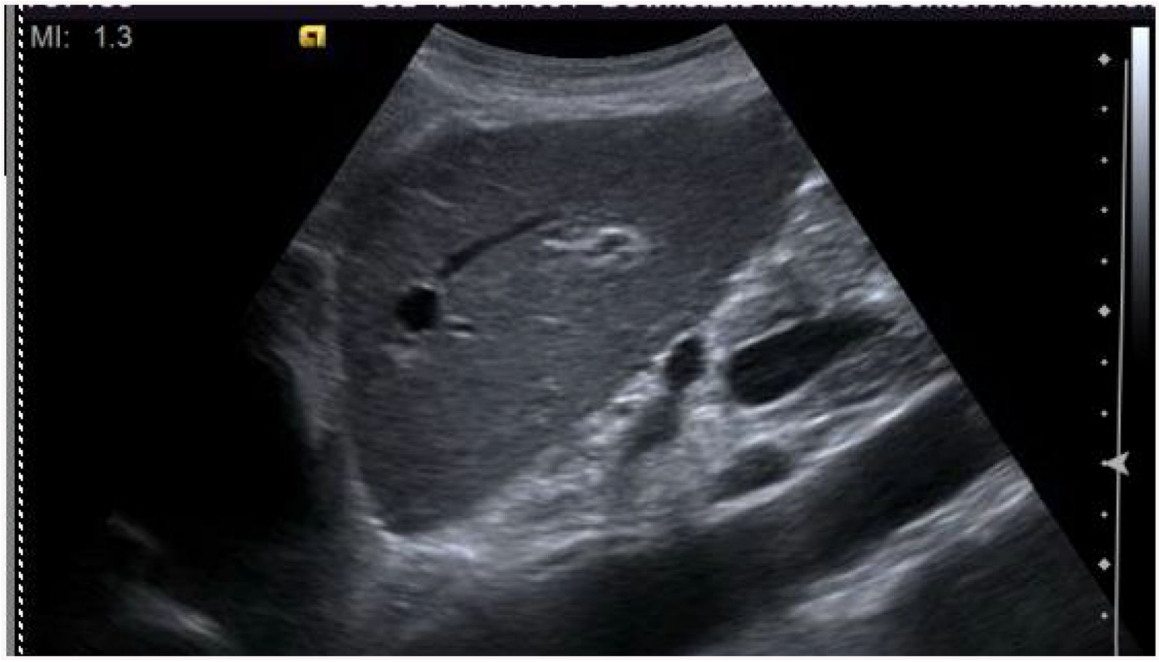

Figure 1.
Right Upper Quadrant Ultrasound demonstrates no biliary obstruction with evidence of cholecystectomy

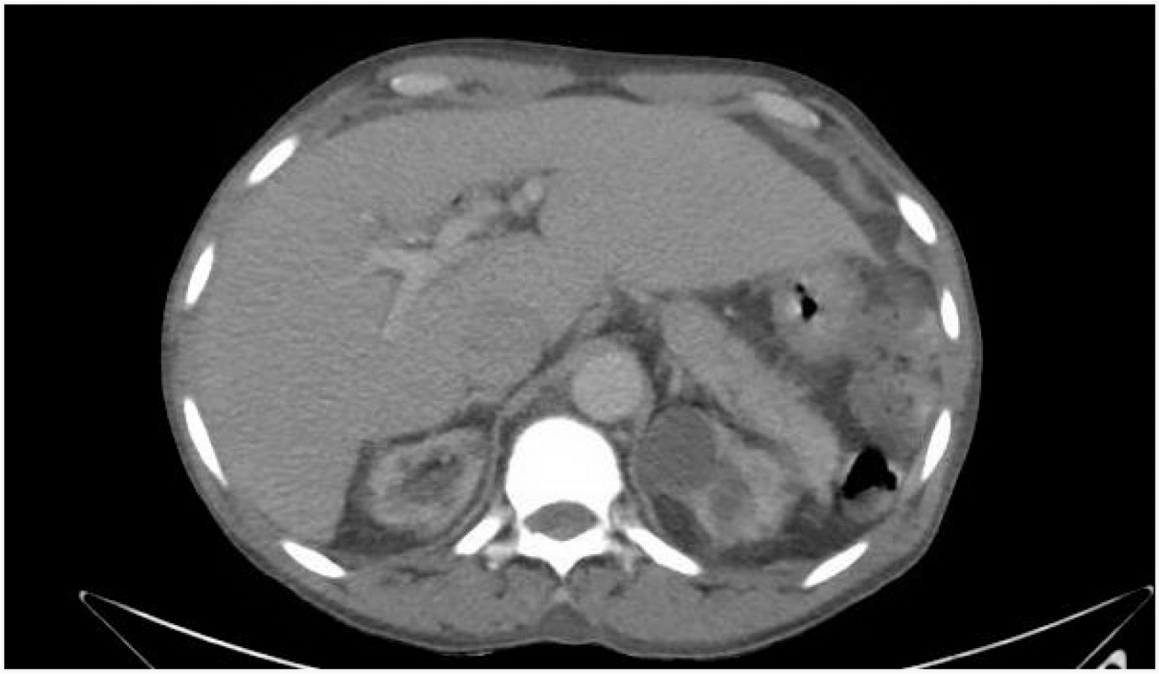

Figure 2.
CT Abdomen and Pelvis with IV Contrast with evidence of cholecystectomy and no evidence of biliary ductal dilation. The liver was of a normal contour, with patent portal veins

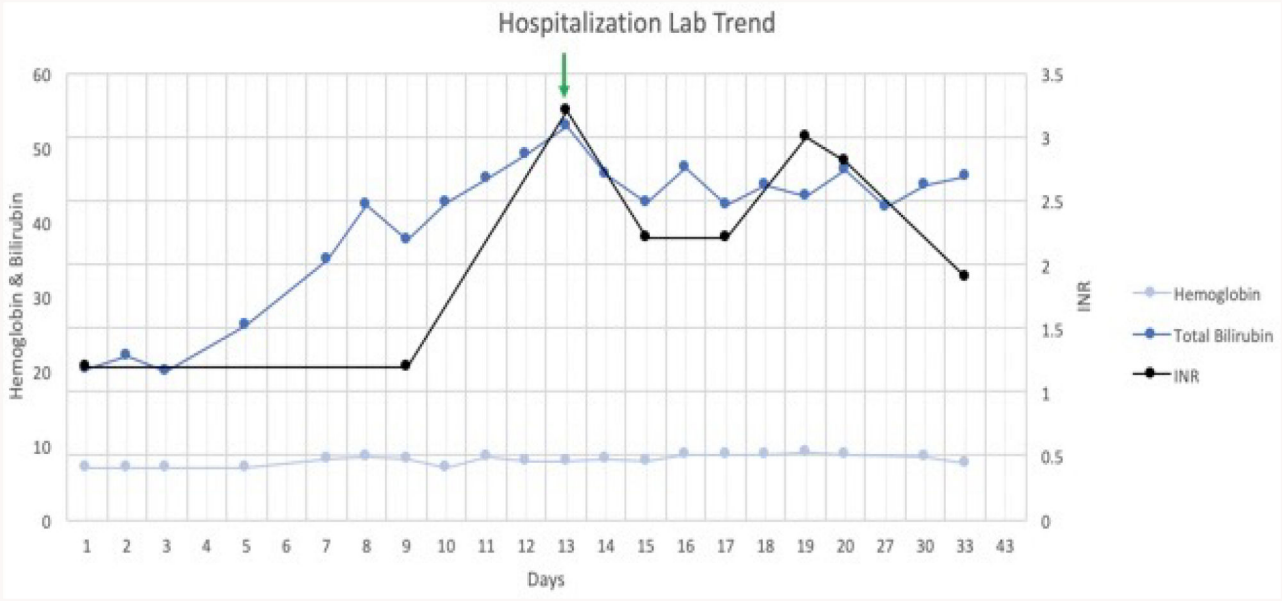

Figure 3.

Demonstrates trends in hemoglobin, total bilirubin and international normalized ration (INR) with peak values on day 13 of hospitalization

Table 1.

Laboratory values including hemoglobin, hemoglobin S, total bilirubin and International normalized ration (INR)

Hospital Day	Hemoglobin	Hemoglobin S Concentration	Total Bilirubin	INR
1	6.9		20.1	1.2
2	6.9	78.7	21.8	
3	7		19.8	
4				
5	6.9		26.10	
6				
7	8.2		34.90	
8	8.4		42.10	
9	8		37.5	1.2
10	6.9		42.5	
11	8.3		45.8	
12	7.7		49.1	
13 (Exchange Transfusion)	7.8		52.8	3.2
14	8.1	25.4	46.3	
15	7.7		42.6	2.2
16	8.6		47.2	
17	8.8		42.2	2.2
18	8.7		44.9	
19	9.1		43.5	3.0
20	8.7	33.5	47	2.8
27	Not checked		41.9	
30	8.3		44.9	
33 (last day labs checked)	7.6		46.2	1.9
43 (Patient passed away)				