

Case Report

Sickle Cell Intra-Hepatic Cholestasis : A Rare but Fatal Disease

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ABSTRACT

Sickle cell intra-hepatic cholestasis is a rare but potentially fatal complication of sickle cell disease. It is characterized by fever, jaundice, tender hepatomegaly, coagulopathy and acute liver failure. Early identification

is essential and the only effective treatment reported is exchange transfusions. We describe one Hemoglobin SS patient and review the literature.

KEYWORDS: exchange transfusions, jaundice, sickle cell intra-hepatic cholestasis,

INTRODUCTION

In clinical studies, it was noted that there is an association between sickle cell disease and hepatic dysfunction^[1-5]. These dysfunctions occur mainly in patients with homozygous sickle cell anemia but to a lesser extent in patients with sickle cell trait, sickle C disease and hemoglobin S B-thalassemia. One of the rare but potentially fatal complications of sickle cell anemia is known as sickle cell intra-hepatic cholestasis, a clinical syndrome thought to represent a severe form of hepatic crisis^[9]. Sickle cell intra-hepatic cholestasis is characterized by the acute onset of hepatomegaly, extreme hyperbilirubinemia with a level of 273 mg/dl (around 4600 μ mol/l) documented in one patient^[6], coagulopathy and acute liver failure^[4,7].

Recent reports have described reversal of this process within 48 hours in seven patients with vigorous exchange transfusions and correction of coagulopathy with fresh frozen plasma^[6,8-12].

We describe one patient with sickle cell anemia with recurrent admissions due to fever, jaundice, leukocytosis, coagulopathy and extreme hyperbilirubinemia. We also describe the types of hepatic injuries and clinical syndromes found in sickle cell anemia patients with particular attention to sickle cell intra-hepatic cholestasis.

CASE REPORT

Mr HN is a 22-year-old Kuwaiti male studying Dentistry in Egypt and who is known to have sickle cell disease. He presented to the medical department complaining of fever and generalized body aches for two days accompanied by jaundice. He informed that jaundice was on and off for the last

two years and was associated with intermittent episodes of itching and dark urine. This was on a background history of intermittent right upper quadrant pain, anorexia and weight loss of six kilograms over the last two months. There was no history of nausea, vomiting, bleeding or change in bowel habits.

He stated that he was admitted once at the age of six years for an exchange transfusion, but he deny any previous admissions with vaso-occlusive crises.

He was on ibuprofen and mefenamic acid for pain and on phenobarbitone for itching.

On physical examination, he was febrile and deeply jaundiced with a pulse rate of 90 per minute (regular) and a blood pressure of 110/70 mmHg. He had no stigmata of chronic liver disease and no hepatic flab.

Abdominal examination revealed a tender upper abdomen with a hepatomegaly of 3 cm below the costal margin. Other systems examination was unremarkable. His initial investigations showed the following; FBC: Hb 114 g/l; MCV 104.2 fl (80-96 fl); WBC 15.7×10^9 /l; Platelets 223×10^9 /l and Reticulocyte count of 5.7 %. LFT showed total bilirubin 417 μ mol/l; direct bilirubin 236.3 μ mol/l; ALT 329 IU/l; AST 826 IU/l; LDH 1248 IU/l; ALP 625 IU/l; Amylase 324 IU/l.

Urine routine and microscopy revealed trace proteins; +urobilinogen; +bilirubin; +erythrocytes. Serum urea and electrolytes were normal. An abdominal ultrasound was normal apart from one single large stone in the gallbladder with no CBD dilatation.

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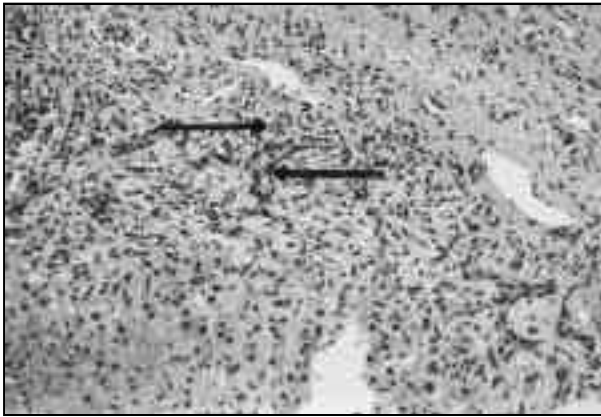


Fig 1: Liver biopsy showing early fine fibrosis (top arrow) and bile duct proliferation (bottom arrow) [H&E x 300]

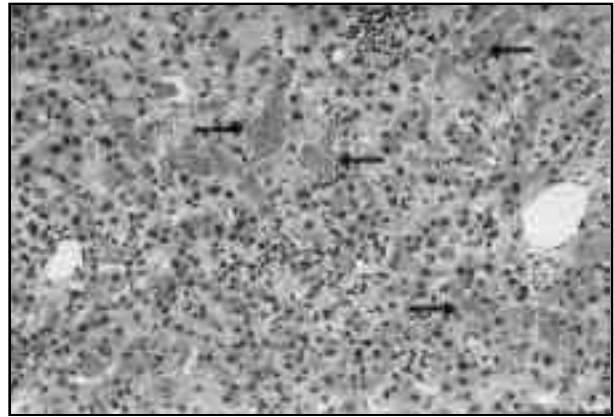


Fig 2: Liver biopsy showing sickled cells in sinusoids (arrows) [H&E x 300]

HN was admitted to the medical ward where i.v. fluids, cefotaxime and metronidazole were initiated. The next morning, an urgent ERCP was done which was found to be normal apart from the single large gallbladder stone. Later, the hematologist and hepatologist were consulted. Our hematologist advised for exchange transfusion and the hepatologist asked for the following investigations:

Ceruloplasmin: normal. Ferritin 1185.9 $\mu\text{g/l}$ (20-260 $\mu\text{g/l}$); IgA 6.22 g/l (0.8-4 g/l); IgG 17.2 g/l (7-18 g/l); IgM 0.82 g/l (0.4-2.5 g/l). ANA, AMA, LKM, ASM and reticulin were negative.

Virology screening: Hep B_sAg (negative); Anti HCV (negative); HIV test (negative)

Hemoglobin electrophoresis post first exchange transfusion showed: HbF 3%, HbS 35%, HbA₂ 2.2%.

Four days later, the condition of the patient improved and all cultures were found to be negative. On the seventh day, the patient was discharged home and his liver function tests on discharge were as follows:

Total bilirubin 415 $\mu\text{mol/l}$; direct bilirubin 271.4 $\mu\text{mol/l}$; ALT 55 IU/l; AST 187 IU/l; ALP 103 IU/l.

Ten days post discharge, the patient was re-admitted with fever, deep jaundice and right upper quadrant pain. Serum biochemical findings included AST/ALT 157/56 IU/l; total bilirubin 593 $\mu\text{mol/l}$; direct bilirubin 374 $\mu\text{mol/l}$; ALP 99 IU/l; Reticulocyte count was 7.22%; LDH was not done.

Next day, a liver biopsy was done and showed: bile plugs in some bile ducts; moderately expanded portal tracts with edema; bile duct proliferation (Fig.1); early fine fibrosis (Fig.1); sickled cells in sinusoids (Fig. 2); areas of peliosis hepatic; mild siderosis in kupffer cells. These histologic findings are consistent with a major bile duct obstruction; therefore, a second ultrasound abdomen was done which showed mild common bile duct dilatation of six mm with mild intra-hepatic dilatation. It was followed by a second ERCP which was the same as the first one and papillotomy was done. Post-

procedure, the patient had worsening of his liver function biochemistry and was discharged against medical advice.

Three weeks later, the patient was admitted again with abdominal pain, nausea and vomiting. His liver function test showed; total bilirubin 433 $\mu\text{mol/l}$; direct bilirubin 213 $\mu\text{mol/l}$; ALT 33 IU/l; AST 127 IU/l; ALP 158 IU/l. The patient agreed for a second exchange transfusion (40 days after the first one) and liver function biochemistry showed ; total bilirubin 342 $\mu\text{mol/l}$; direct bilirubin 164 $\mu\text{mol/l}$; ALT 22 IU/l; AST 99 IU/l; ALP 102 IU/l. Ten days later, a third exchange transfusion was done with a liver biochemistry post transfusion showing; total bilirubin 192 $\mu\text{mol/l}$; direct bilirubin 95 $\mu\text{mol/l}$; ALT 34 IU/l; AST 137 IU/l; ALP 127 IU/l. Later, the patient decided to travel to the UK for continuation of his treatment. On discharge, his HbS was 18%. Patient expired two months later.

DISCUSSION

Hepatic injuries in sickle cell disease most commonly occur due to multiple transfusions secondary to iron overload, or acute/chronic hepatitis C. It can also occur as a complication of chronic hemolysis, like the development of pigment stones with consequent cholecystitis or choledocholithiasis.

Furthermore but less common, hepatic injury can be directly related to the sickling process and hence the term most often used to describe these syndromes is sickle cell hepatopathy e.g., acute hepatic crisis and hepatic sequestration crisis.

Sickle cell intra-hepatic cholestasis is a rare form of sickle cell hepatopathy. It is potentially fatal with a poor prognosis^[3,13-16]. Therefore, early identification is essential. It is thought to represent a severe form of hepatic crisis^[3].

The presentation is similar to acute sickle hepatic crisis with fever, right upper quadrant pain, nausea, vomiting, tender hepatomegaly and a

striking jaundice. Sheehy^[3] described this syndrome as a very severe form of hepatic crisis marked by sudden onset of severe right upper quadrant pain, progressive hepatomegaly, coagulopathy with hemorrhage and extreme hyperbilirubinemia.

In one case report, bilirubin level reached 273 mg/dl^[6] (around 4600 μ mol/l). This is caused by a combination of ongoing hemolysis, intra-hepatic cholestasis and renal impairment.

Despite its fatality, we were able to find reports describing seven patients who did survive with vigorous exchange transfusions and correction of coagulopathy with fresh frozen plasma^[6,8-12].

Shao and Orringer^[9] have described two cases of sickle cell intra-hepatic cholestasis with similar presentations, but in which very different therapeutic approaches led to very different clinical outcomes.

The first patient presented with jaundice, right upper quadrant pain, nausea, fever and leukocytosis. Ultrasound abdomen showed multiple gallbladder stones with no ductal dilatation. The decision was made to perform a cholecystectomy for him. The procedure went well with no complications but eleven days later the patient expired.

The second patient had similar clinical features and even worse blood chemistry. His surgery was cancelled and the decision was made to perform exchange transfusions using packed red blood cells and fresh frozen plasma. Post exchange transfusion, all his hematological parameters improved and he underwent an uneventful cholecystectomy six weeks later.

They concluded that early identification of this clinical syndrome is essential, as exchange transfusions with both packed red blood cells and fresh frozen plasma can often correct the coagulopathy. They also suggested that any type of surgical intervention is best deferred until the patient has had sufficient time to recover from the acute illness.

In our patient, sickle cell intra-hepatic cholestasis was not the first in our list of differential diagnosis, first due to its rarity, and secondly due to the fact that this patient had a fairly uncomplicated sickle cell anemia over twenty two years of his life, with no history of vaso-occlusive crisis or regular exchange transfusions.

Once the diagnosis had been made and exchange transfusions started, the patient's condition along with his liver function biochemistry improved dramatically.

In summary, we have reported a case of sickle cell intra-hepatic cholestasis. Whereas the presenting manifestations include fever, right upper quadrant pain, tender hepatomegaly and leukocytosis, the most striking clinical feature is extreme hyperbilirubinemia.

Awareness and early recognition of this potentially fatal condition is important, as exchange transfusions can often reverse the process of intra-hepatic cholestasis and can be life saving.

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