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Decompensated Liver Cirrhosis Secondary to Iron Overload in Non-Blood Transfusion Dependent Patients with Sickle Cell Disease (SCD): Report of Two Cases

Mohammed Al-Dugdugi[1] and Erwa Elmakki[2*]

[1]Department of Internal Medicine, Division of Gastroenterology, King Fahd Hospital-Jazan, Saudi Arabia.
[2]Department of Internal Medicine, Faculty of Medicine, Jazan University, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration between the two authors. Author MAD designed and wrote the first draft of the manuscript. Author EE managed, revised and evaluated the literature search. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The prevalence of sickle cell disease (SCD) is high in the southwest region of Saudi Arabia. Liver involvement in patients with SCD represents a challenging medical problem in clinical practice and carrying a high morbidity and mortality rates. We reported two cases of young patients (19 year male and 22 year female), both of them were known to be non-blood transfusion SCD patients. They have had almost the same clinical presentation with advanced decompensated liver cirrhosis and severe progressive jaundice. Early screening of SCD patients for iron overload, beside commencement of iron chelating agents can prevent the long-term sequel of iron overload.

**Corresponding author: Email: erwamakki@gmail.com;*

Keywords: Non-blood transfusion dependent SCD; iron overload; liver cirrhosis.

1. CASE PRESENTATION

1.1 First Case

She was a 22- year -old female known case of SCD (Hb SS), had received blood transfusion only 3 times in her life, was admitted to our hospital with progressive abdominal distension. Physical examination revealed pallor, jaundice, finger clubbing, hepatomegaly and ascites, which was complicated by spontaneous bacterial peritonitis (SBP). Otherwise she had no other abnormal physical signs. Serology for viral hepatitis was negative (for HBV and HCV), as well as for autoimmune markers including ANA ASMA AMA ALKMA-1. Serum ceruloplasmin was within normal limits. The other laboratory data of the patient are shown in Table 1. Color Doppler ultrasonography reported patent hepatic vein with no portal vein thrombosis (PVT) or biliary dilatation. However, sonographic picture was consistent with liver cirrhosis (Fig. 1). During the hospital course she developed variceal bleeding, which was controlled with endoscopic band ligation (Fig. 2), but unfortunately she passes out due to overwhelming sepsis and multi-organ failure.

1.2 Second Case

He was a 19-year- old male, known case of SCD (HbSS), had received blood transfusion infrequently (5times, two of them during childhood period). He was admitted with picture of advanced liver disease (Child class C) with grade II hepatic encephalopathy. Physical examination disclosed deep Jaundice, ascites and hepatomegaly, but no other abnormal physical signs. Liver function tests showed a marked elevation in bilirubin and alkaline phosphatase. Doppler ultrasonography revealed dilated portal vein and cirrhotic changes (Fig. 3); whereas (MRCP) reveled no biliary obstruction (Fig. 4). Serology was negative for HBV, HCV and autoimmune markers. Serum ceruloplasmin was within normal limits. The other laboratory data of the patient are shown in Table 1. The management of hepatic encephalopathy was offered in addition to IV antibiotics for SBP which was documented during an ascetic tapping; also he received one unit of packed RBCs for hemolytic crises. Upper GI endoscopy showed grade 3 esophageal avarices with moderate gastropathy. Unfortunately the patient was rejected from the liver transplant program due to limited experience and possible unfavorable outcome. He was expired due to massive spontaneous intra-cerebellar hemorrhage secondary to intractable coagulopathy.

2. INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive condition characterized by the presence of abnormal hemoglobin S. The prevalence of SCD in Saudi Arabia is highest in the Eastern and southwestern provinces respectively. Clinical and hematological differences are existing in patients with SCD in Saudi Arabia with two main phenotypes (mild and severe) [1].

In sickle cell disease, transfusion of blood, improves blood flow by decreasing the rate of red cells that forms sickle hemoglobin polymer. The major and unpreventable complication of transfusions in patients with sickle cell disease is iron overload [2]. Long-term blood transfusion therapy of, for example, 20-units Red blood cells (RBCs) /year are associated with a significant iron overload [3].

In the absence of multiple blood transfusions, as in the healthy subjects, storage iron rarely exceeds 2000 mg in patients with SCD, being present mainly in macrophages of the liver, spleen, and bone marrow [4].

However, some patients with SCD like a similar group of patients with thalassemia can develop iron overload despite being non-transfusion-dependent as a result of low hepcidin which stimulates more intestinal absorption of iron [5,6].

The role of hepcidin in the pathophysiology of iron overload in patients with SCD remains controversial. Patients with SCD suffer from recurrent infections and continuing endothelial damage from reperfusion injury which results in a chronic-inflammatory-like state [7].

In a one study hepcidin levels in non-transfused steady-state SCD are not increased when compared with normal control, even though in SCD patients with infections and end organ damage [8]. Another study, comparing hepcidin in 16 subjects with SCD (HbSS, HbS thalassemia, HbSC) versus controls heterozygous for HbS or HbC, also found no difference among the different groups. In 5

patients with SCD in that study, hepcidin levels were less the lower limit of normal, which was explained by increased erythropoietic activity [9]. Coexistent iron deficiency can also affect hepcidin estimation. Iron deficiency anemia has been described in the pediatric population with SCD, both due to nutritional status and intravascular hemolysis with urinary iron losses. [10]. Also, a large study, including> 8000 individuals in India found that iron deficiency was more common in adult females with SCD (67%) than in subjects with sickle trait (26%) or healthy controls (22%) [4]. Therefore, only when repeated blood transfusions are given does iron overload occur in patients with SCD.

Table 1. Showing some laboratory data for the two cases

Laboratory tests	Case (1) results	Case (2) results	Normal values
Hb	8.9 gm/dl	8 gm/dl	12.0-16.0 gm/dL
WBC	8700/cmm	13,000/cmm	4,000-11,000/cmm
Platlets	11000/cmm	75,000/cmm	15,0000-400,000/cmm
T.bilirubin	237 µmol/L	310 µmol/L	2-17µmol/L
ALT	28 U/L	60 U/L	8-20 U/L
AST	57 U/L	70 U/L	8-20 U/L
LDH	200 U/L	250 U/L	45-90 U/L
Alkaline phosphatase	225 U/L	300 U/L	25–100 U/L
Albumin	24 g/L	20 g/L	35-55 g/L
INR	2	2.5	0.9-1.3
Blood urea	2.1 mmol/L	10 mmol/L	1.2-3.0 mmol/L
Serum creatinine	41 µmol/L	150 µmol/L	53-106 µmol/L
K	4 mmol/L	3 mmol/L	3.5-5.0 mmol/L
Na	139 mmol/L	128 mmol/l	136-145 mmol/L
Hb genotype	Hbss	Hbss	
HbS	78%	80%	
HbF	19%	17%	
HbA2	3%	3%	
Serum iron	130 µ mol	131 µ mol	9-30 µ mol/L
Serum ferritin	1550 ng/ml	>2000 ng/ml	12-150 ng/ml
TIBC	200 µg/dl	172 µg/dl	240–450 µg/dl
Transferrin saturation	65%	76%	12–45%)

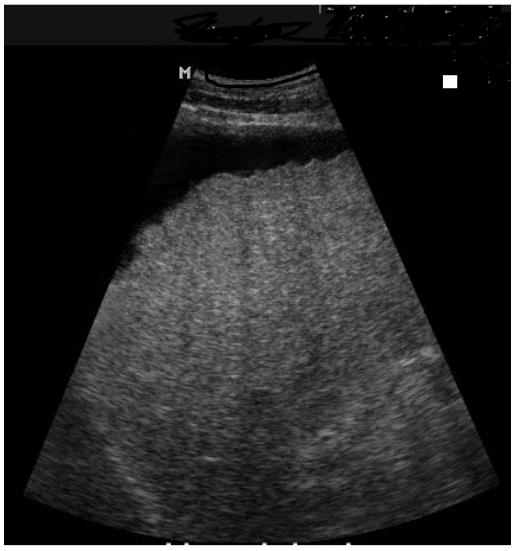

Fig. 1. Liver ultrasonography showing liver cirrhosis

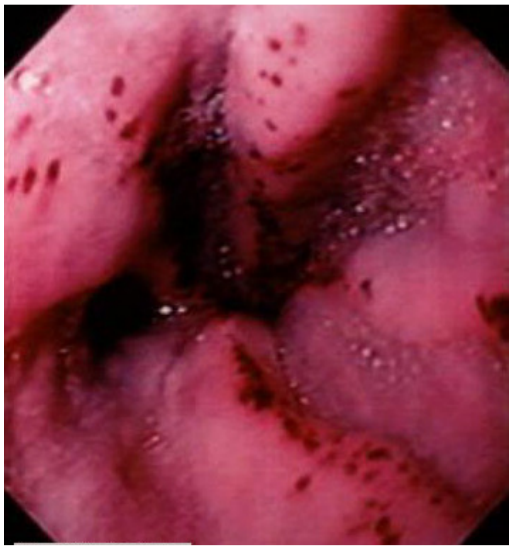

Fig. 2. Endoscopic view showing Bleeding esophageal varices

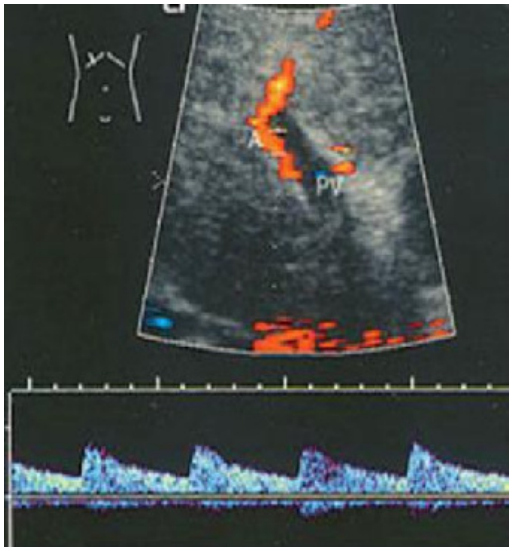

Fig. 3. Doppler ultrasonography: Showing dilated portal vein and cirrhotic changes

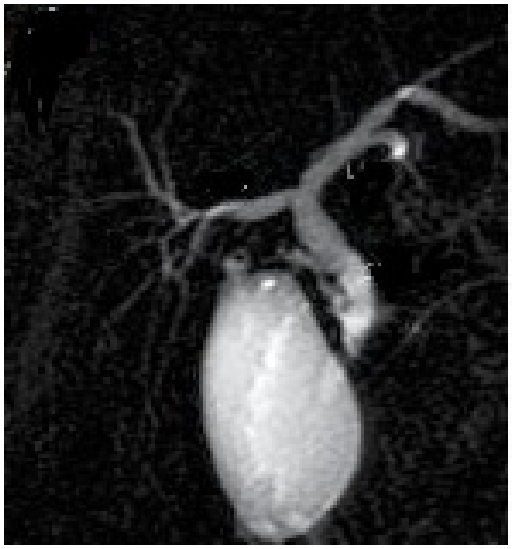

Fig. 4. MRCP showing normal biliary tree

3. DISCUSSION

Unusual complications of SCD are sometimes seen in the southwestern region of Saudi Arabia as the prevalence of SCD is highest in this part of the country. In the field of gastroenterology we observed aggressive involvement of the liver in some SCD patients. In the two reported cases there was a high level of serum ferritin ranging from 1500-3000ng/ml. Also, both patients were never screened for iron-overload or end organ damage. It has been reported that, patients with SCD are far less likely to be screened for iron overload than patients with thalassemia, despite a similar transfusion history [11]. The late presentation of the two cases with clinical evidence of portal hypertension and other features of chronic liver failure make a further assessment of hepatic iron concentration of no value, moreover, there was a great hazard of bleeding from liver biopsy as they had severe coagulopathy. Therefore, knowledge of iron toxicity in SCD is of great importance for physicians caring for SCD patients**.** Both cases had severe intra-hepatic cholestasis, with marked elevation of alkaline phosphatase more than four to five folds. The much elevation of alkaline phosphatase in these cases relates to bile duct damages.

Our patients (The two reported cases) being non-transfusion-dependent the possible mechanism of iron overload in them was excessive intestinal iron absorption. It has been reported that patients with hemoglobinopathy can have an excessive intestinal iron absorption secondary to low hepcidin. [5,6,9] However, chronic hemolysis could account for iron release and accumulation in patients with SCD. Some cases of hereditary hemochromatosis (H.H) in association with SCD have been reported with mutations in the hemochromatosis gene (HFE gene) [12,13]. Moreover, few studies have shown that the prevalence of HFE gene mutations is common in Caucasians, which may result in non-blood transfusion-related iron overload in them. However, HFE mutations are not determined in another ethnic group like African-Americans with SCD [14]. On the other hand, single gene mutations have not shown to increase the risk of iron overload in patients with SCD and Thalassemia who are blood transfusion-dependent [14,15]. In our reported cases, the possibility of H.H was unlikely, taking into consideration the ages of the patients (being young) and one of them was a female, who had regular menstrual periods, and both of them had no other features of H.H or organ damages other than the liver.

In SCD patients, early recognition of iron overload, and prompt therapy using iron

chelaters, may prevent the cirrhosis of the liver, and development of hepatocellular carcinoma, in addition to joint and gonadal damage [16,17].

Unfortunately, the two reported cases presented with advanced liver cirrhosis, so treatment was directed towards complications of cirrhosis and they didn't receive iron chelating agents. While caring for patients with SCD who have iron overload, some dilemma questions still remain, as follows: 1-Does serum ferritin is a good predictor of high hepatic iron concentration (HIC) in non-transfusion dependent patients or not? 2-What is the effectiveness of iron chelating agents in patients who already developed cirrhosis?. And 3-Is there any role for phlebotomy in these patients?. In the top of that, the overall experience of liver transplant in SCD patients is limited. This report should stimulate further researches on non-transfusion related causes of iron overload in SCD patients.

4. CONCLUSION

Secondary hemochromatosis can occur in non-blood transfusion dependent SCD patients. Early Screening of SCD patients, even though non-blood transfusion dependent for iron overload, beside early commencement of iron-chelating agents are of paramount importance in order to prevent liver cirrhosis and its complications.

CONSENT AND ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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