Acute B Virus Hepatitis with Fulminant Hepatic Failure Precipitating Crisis in Sickle Cell Disease

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INTRODUCTION

Sickle cell disease (SCD) is a hemoglobinopathy which involves multiple organs in the body. Hepatobiliary manifestations in SCD are many. Acute and chronic HBV infection may be transmitted through multiple blood transfusions in SCD. We report the case of a 36-year-old male with sickle cell disease who presented to us in acute liver failure and sickle cell crisis due to acute hepatitis B virus infection. Sickle cell disorder is a broad category under which all the patients who have a point mutation (haemoglobin S-HbS) on at least one Beta chain due to substitution of valine in place of glutamic acid at position 6 are included. Due to this substitution, HbS molecules have a sticky site allowing the molecules to aggregate. This aggregation worsens in deoxygenated state leading to the development of long polymers, sickling of erythrocytes and haemolysis. The most commonly affected site in SCD is the hepatobiliary system. The presentation due to this involvement varies from benign hyperbilirubinemia to a spectrum of manifestations termed "sickle cell hepatopathy".¹

Fulminant hepatitis is a rare consequence of massive necrosis of liver parenchyma due to exposure to certain hepatic viruses, toxic agents or drugs.² In patients with sickle cell crisis hepatic involvement is not uncommon.³⁻⁵ The presenting features in these patients is similar to patients without sickle cell disease characterised by encephalopathy, coagulopathy, abdominal pain, tender hepatomegaly, extremely high serum bilirubin and PT.⁶

PRESENTATION OF CASE

A 36-year-old male, a diagnosed case of SCD by Hb-electrophoresis 15 years back, presented to us with history of high-grade fever, nausea, vomiting, myalgia, bone pains and yellowish discoloration of sclera and skin since 8 days, and drowsiness since last 2 days. There was no history of cough, expectoration, burning micturition, haemoptysis, hematuria, diplopia, seizures.

On examination in the hospital, patient was febrile (101⁰ F), pulse-116 bpm regular, blood pressure was 110/70 mmHg, pallor and icterus were present. CVS, RS examinations were normal. Abdominal examination revealed tender hepatomegaly, without splenomegaly and free fluid. Central nervous system examination: patient was drowsy (GCS: E-3, V-3, M-4), deep tendon reflexes were exaggerated, flapping tremors were present. There were no cranial nerve or focal deficit. Plantars were bilateral flexor. Investigations revealed Hb: 6.9 g MCV: 90 fl, platelets: 85000/mm³ TLC: 13,600/mm³, Total Bilirubin: 10.2 mg%, Conjugated bilirubin: 6.2 mg%, unconjugated bilirubin: 4.0 mg%, Serum LDH- 146 u/L, SGOT-1042 IU, SGPT- 1282 IU, Prothrombin time was 32 seconds, INR-2.6, serum ammonia was 102 mg/dl. Random blood sugar was 68 mg%. KFT was normal. Serum amylase and Lipase were normal.

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Serologic tests for Dengue, Leptospira and scrub typhus were negative. Paracheck for Malaria was negative. Serum Ig M anti HAV, Ig M ANTI HEV, anti HCV were negative. Serology for CMV and EBV were negative. HBsAg was positive, Hb e Ag was positive suggestive of acute viral hepatitis. A quantitative HBV -DNA test showed 53, 3700 UI/ ml. UGG abdomen revealed enlarged liver 16.4 cms at midclavicular line, accentuated brightness of portal vein radical walls with overall decreased hepatic echotexture suggestive of acute hepatitis. There were no splenomegaly and free fluid in abdomen. A diagnosis of acute HBV infection induced fulminant hepatitis with sickle cell crisis was made.

Patient was treated with supplemental oxygen, IV fluids, blood transfusion, IV glutathione, iv glucose, lactulose 30 ml tid through nasogastric tube, fresh frozen plasma infusions, zinc supplement, tab. Sodium bicarbonate TID, tab hydroxyurea 500 bid, and "off level" tab entecavir 1 mg od through nasogastric tube. The patient responded to treatment gradually over the subsequent 3 weeks, by the 4th month follow up HBsAg and HBV-DNA were undetectable in serum. (Table-1) Entecavir was then stopped.

Investigations	On Admission	1 st week	2 nd Week	3 rd Week	4 th Week	4 Months
Total bilirubin (mg/dl)	10.2	8.6	7.4	2.3	1.1	0.82
SGOT (IU)	1042	568	252	146	41	38
SGPT (IU)	1282	728	321	138	32	24
INR	2.6	2.0	1.6	1.2	1.3	1.2
Sr. Ammonia (mg/dl)	102	60	46	21	10	6
Hb(mg/dl)	6.9	7.8	8.6	10.2	12.4	12.7
LDH(mg/dl)	146	124	86	62	56	62
HBsAg	positive	-	-	-	-	undetectable
HBV-DNA	positive	-	-	-	-	undetectable

Table 1. Course of Investigations

DISCUSSION

HBsAg in sickle cell anaemia patient is a common occurrence due to history of repeated transfusions. Fulminant hepatic failure is defined as onset of encephalopathy within 8 weeks of onset jaundice in a previously normal liver.⁷ Diagnosis and treatment of hepatobiliary manifestations of SCD is challenging. The clinical spectrum may be myriad from relatively asymptomatic gallbladder sludge to as lethal fulminant hepatitis. The term "sickle cell hepatopathy" refers to acute and chronic hepatobiliary manifestations of SCD.

Acute SCD Hepatopathies	Chronic SCD Hepatopathies
1. Acute Sickle cell hepatic crisis	1. Cholelithiasis
2. Acute hepatic sequestration	2. Choledocholithiasis
3. Acute intrahepatic cholestasis	3. Iron overload
4. Acute viral hepatitis	4. Viral hepatitis
	5. SCD cholangiopathy

Table 2. Various Acute and Chronic SCD Hepatopathies

Patients with SCD can present with acute or chronic viral hepatitis. Repeated blood transfusions is likely to be a significant risk factor for hepatitis in SCD. Apart from this endemics of viral hepatitis, transfusion needs, lack of adequate vaccination can predispose to the development of hepatitis. Literature has shown that in chronic hepatitis patients asymptomatic persistent elevation of ALT/AST is seen despite the absence of sickle cell crisis.

The presenting features of viral hepatitis in SCD patients mimic that of general population. They include malaise, jaundice and abdominal pain with tender hepatomegaly. Just like the similarities in clinical features with general population patients with acute viral hepatitis in SCD have raised transaminase values (usually 500-1000 IU/mL). However, the total serum bilirubin was at a much higher range in SCD patients ranging from 8-64 mg/dL with an average of 45 mg/dL.⁸ Upon liver biopsy, balloon cells with cellular derangement and leucocyte infiltration suggestive of viral hepatitis can be seen in these patients. Treatment recommendations for viral hepatitis remain similar to AASLD guidelines in general population.

In our case, HBsAg disappeared from the serum by 4th month after starting entecavir after which it was stopped as recommended by AASLD guidelines.^{9,10} Contrary to the EASL guidelines which recommend therapy to be continued for at least 3 months after anti-HBs appearance,¹¹ AASLD guidelines suggest to stop anti-viral therapy after clearance of HBsAg.¹⁰ Hence the ideal duration of treatment remains a matter of debate. Choice of entecavir should be entertained in patients with acute hepatitis B especially when the illness is severe. Further research is warranted to establish the appropriateness of use and duration of entecavir treatment in patients with acute severe hepatitis B.

CONCLUSIONS

Sickle cell hepatopathies are a group of multiple liver and gall bladder related manifestations which occur in patients of SCD. The predominant risk factor for acquiring viral hepatitis is blood transfusions. Any patient of SCD, presenting with features of crisis with acutely enlarged liver, and abnormally elevated bilirubin and transaminases should be promptly investigated for viral markers. Treatment in less severe cases are as per general protocols, but in severe cases anti-viral therapy is indicated.

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