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Case Reports

BENIGN EXTREME HYPERBILIRUBINEMIA IN A 9 YEAR-OLD GIRL WITH SICKLE-THALASSEMIA AND THE PROBABLE ROLE OF HBF IN PREDICTING THE OUTCOME

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ABSTRACT

Hepatic dysfunction is a frequent manifestation in patients with sickle cell anemia. It is usually a multifactorial process. A rare benign form of extreme hyperbilirubinemia, presumably due to intrahepatic sickling, may be the cause. We report a 9 year old girl with sickle-thalassemia hemoglobinopathy, presenting with profound jaundice. Sickle cell disease is often mild in the Iranian population due to relatively higher levels of HbF, suggesting that the βs gene is associated with a gene capable of producing high levels of HbF. Moreover, sickle thalassemia disease is generally milder than sickle cell disease. In this patient, the previous electrophoresis had shown a relatively high HbF level (34.3%). This may account for the benign course of hyperbilirubinemia and no need for blood transfusion in this case, despite the majority of previous reports.

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INTRODUCTION

Hepatic dysfunction is a frequent manifestation in patients with sickle cell anemia[8,18,21] leading eventually to liver cirrhosis in some patients. It is usually a multifactorial process.[14] Post-transfusion viral hepatitis,[1,22] cholelithiasis and choledocholithiasis,[2,4,6,14] and massive intrahepatic sickling with subsequent cholestasis[5,10,12,17] are common etiologies, whereas hepatic biloma,[13] hepatic abscess,[11] and choledochal fungal ball[9] are rare reported causes.

A rare benign form of extreme hyperbilirubinemia presumably due to intrahepatic sickling may be seen with sickle cell anemia.[3] We report a 9 year old girl with sickle-thalassemia hemoglobinopathy who presented with profound jaundice presumably due to this latter cause.

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Table I. Laboratory data in the first episode.

Day*	Total/Conjugated Serum bilirubin (mg/dL)	SGOT (U/L)†	SGPT (U/L)‡	Alkaline Phosphatase (U/L)§	Hb (g/dL)	PT**(s)	PTT (s) Patient/Control
1	50 / 19	183	136	599	9.2	12.5	49 / 35
3	32.5 / 14.1	201	127	537	9.6	12	38.5 / 32
19	14.4 / 10.5	201	156	703	8.9	12	48 / 35

* Days after hospital admission.
† Normal value: 0-49.
‡Normal value: 1-46.
§ Normal value: 100-290.
** Control = 12 Seconds.

Table II. Laboratory data in the second episode.

Day*	Total/Conjugated Serum bilirubin (mg/dL)	SGOT (U/L)†	SGPT (U/L)‡	Alkaline Phosphatase (U/L)§	Hb (g/dL)
1	9.6 / 1.6	118	48	653	8.6
7	6.9 / 4.9	93	69	536	8.3

* Days after presentation.
† Normal value: 0-49.
‡Normal value: 1-46.
§ Normal value: 100-290.

Case report

A 9 year-old girl, a known case of sickle-thalassemia hemoglobinopathy, referred to our ward after three days of jaundice, tea-colored urine, mild epigastric pain, and intermittent low back pain. She had two episodes of jaundice in the past four years, which resolved spontaneously after 2-3 days. On physical examination there was no abnormal finding except for profound jaundice and a palpable spleen 6-7 cm below the costal margin. On the first day of admission, laboratory studies were as follows: total serum bilirubin 50 mg/dL, conjugated bilirubin 19 mg/dL, SGOT 183 U/L, SGPT 130 U/L, alkaline phosphatase 599 U/L, Hb 9.2 g/dL, Hct 28%, retic. count 8%, WBC count 7000/mm^3, platelet count 119000/mm^3, a normal PT and a mildly elevated PTT. Blood films showed hypochromic target cells and sickle cells. Liver sonography to rule out cholelithiasis was repeated three times by independent observers and was normal. HBsAg and HCV Ab were negative. G6PD was not studied, but the study done at her very first admission about 5 years ago was normal.

Two days later, laboratory studies were: total serum bilirubin 32.5 mg/dL, conjugated bilirubin 14.1 mg/dL, SGOT 201 U/L, SGPT 127 U/L, alkaline phosphatase 537 U/L, Hb 9.6 g/dL, Hct 30.8%, WBC count 4900/mm^3, platelet count 107000/mm^3, a normal PT and a mildly elevated PTT. One week later the spleen size was reduced, though still palpable 3 cm below the costal margin. 19 days after admission laboratory studies were: total serum bilirubin 14.4 mg/dL, conjugated bilirubin 10.5 mg/dL, SGOT 201 U/L, SGPT 156 U/L, alkaline phosphatase 703 U/L, Hb 8.9 g/dL, retic. count 15%, WBC count 7400/mm^3, platelet count 80000/mm^3, a normal PT and a mildly elevated PTT.

She was asymptomatic soon after, but two months later she developed another episode of jaundice associated with abdominal pain, nausea and vomiting. On physical examination there was jaundice, a liver 2-3 cm below the costal margin, and a palpable spleen 4-5 cm below the costal margin. Laboratory data were: total serum bilirubin 9.6 mg/dL, conjugated bilirubin 1.6 mg/dL, SGOT 118 U/L, SGPT 48 U/L, alkaline phosphatase 655 U/L, Hb 8.6 g/dL, Hct 27.9%, WBC count 8100/mm^3, and platelet count 110000/mm^3. She received phenobarbital, 50 mg daily, and one week later laboratory studies were: total serum bilirubin 6.9 mg/dL, conjugated bilirubin 4.9 mg/dL, SGOT 93 U/L,

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SGPT 62 U/L, alkaline phosphatase 536 U/L, Hb 8.3 g/dL, Hct 28.5%, and WBC count 7200/mm^3. There was no remaining symptom after a few days.

One month later, she had been admitted in another hospital with RUQ pain and jaundice, the liver being 2-3 cm and the spleen 7 cm palpable below the costal margin. Total serum bilirubin was 6.33mg/dL, conjugated bilirubin 2.96 mg/dL, SGOT 101 U/L, SGPT 74 U/L, alkaline phosphatase 542 U/L, Hb 6.5 g/dL and platelet count 159000/mm^3. PT was 13.5 with a control of 13.5. Liver sonography was insignificant and HBsAg and HCV Ab were negative. Serum ceruloplasmin level was 752 mg/L with a normal value of 233-402 mg/L. Percutaneous needle liver biopsy showed preserved lobular architecture, focal extracellular accumulation of bile as bile lakes, and cholestasis. The individual hepatocytes showed hydropic changes. Blood transfusion was done (150 cc of packed cells) and she became asymptomatic with a Hb level of 10 g/dL.

The result of a previously performed Hb electrophoresis was: Hb S 58.9%, Hb F 34.3%, HbA 4.7%, and Hb A_2 2.1%.

Table I and II summarize the laboratory data.

DISCUSSION

A normal liver sonography ruled out cholelithiasis, choledocholithiasis, or other causes of choledochal obstruction. Absence of a Hb drop and a high level of conjugated bilirubin were strongly against an acute hemolytic crisis. HBsAg and HCVAb were negative. Hepatitis A is endemic in Iran, but recurrence of the same symptoms, the fact that most of our population are serologically positive until early childhood, and absence of any other clue in favor of hepatitis A, make it a diagnostic impossibility. Absence of inflammation and necrosis in the liver pathology also rules out all viral causes. The patient is not G6PD deficient. In conclusion, "benign extreme hyperbilirubinemia" is the diagnosis in this patient. Preserved hepatic lobular architecture and focal extracellular accumulation of bile as bile lakes and cholestasis are consistent with this diagnosis.[14]

In contrast to acute liver failure,[19] as far as we know, a benign form of intrahepatic sickling has not been reported with sickle-thalassemia disease previously.

There was no leukemoid reaction[17] in this case. Hepatomegaly was not present or was very mild. Huge splenomegaly was invariably present in all episodes. The ceruloplasmin level was about two times normal values. The PT was not elevated but there was a mild elevation of PTT in the first episode.

In Buchanan's series of benign extreme hyperbilirubinemia in sickle cell anemia,[3] no recurrence was reported. In other reports of intrahepatic sickling, recurrence is frequent, requiring exchange transfusion.[16] In this patient there were two previous and two later episodes of jaundice with a benign course, suggesting that the benign form of intrahepatic sickling in sickle cell anemia may be recurrent. In other words, this may be an intermediate form of this entity.

The βs gene is frequently found in the Iranian population.[15] Sickle cell disease is often mild in this population due to relatively higher levels of Hb F, suggesting that the βs gene is associated with a gene capable of producing high levels of HbF.[7] Moreover, sickle thalassemia disease is generally milder than sickle cell disease. In this patient, the previous electrophoresis had shown a relatively high Hb F level (34.3%). This may account for the benign course of hyperbilirubinemia and no need for blood transfusion in this case, despite the majority of previous reports.[16,19,21,23] Unfortunately these reports and the Buchanan report[3] have not mentioned the Hb electrophoresis of their patients, except for the report given by Stephan[23] reporting Hb S 98% (and therefore Hb F equal to or less than 2%). Future studies are needed to define the role of Hb F in predicting the outcome of hyperbilirubinemia associated with intrahepatic sickling.

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