Acute Hepatic Crisis in Sickle Cell Anemia: Favorable Outcome After Exchange Transfusion

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Abstract

Pediatric acute liver sickle crisis, also known as sickle cell intrahepatic cholestasis (SCIC), is an uncommon but fatal complication of sickle cell disease observed mainly in patients with homozygous sickle cell anemia. Herein we describe a case of pediatric SCIC treated successfully with manual exchange transfusion (ET). The patient was admitted for jaundice, enlarged liver and signs of hepatic failure, such as hyperbilirubinemia and coagulopathy. There was no evidence of viral hepatitis or biliary obstruction. We performed a session of ET in order to reduce the percentage of Hb S to level inferior to 30% which was successfully accomplished. The patient had complete recovery of hepatic function. This case has shown that ET is an effective treatment of pediatric SCIC and should be introduced early on the onset of this severe complication.

Keywords: Acute hepatic crisis; Exchange transfusion

Introduction

Sickle cell disease (SCD), a qualitative hemoglobinopathy, can cause widespread sickling and vaso-occlusive events in all organ systems. Although not commonly seen, liver involvement can be life threatening. Sickle cell hepatopathy has been a term used to generally describe varying etiologies of liver dysfunction in sickle cell patients [1].

A number of liver abnormalities have been described in association with SCD including hepatic infarction, pyogenic liver abscess, Budd-Chiari syndrome, autoimmune hepatitis, focal nodular hyperplasia, malignant histiocytosis, primary

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sclerosing cholangitis, and mesenteric thrombosis. The etiologic role of SCD in some of these settings is uncertain [2].

Multiple blood transfusions subject patients to increased risk of infectious processes, such as hepatitis B and C, and iron overload. Chronic hemolysis also causes sickle cell patients to be more prone to development of gallstones, which can lead to acute cholecystitis and/or biliary duct obstruction. Hepatic sequestrations can cause hepatic enlargement and rapidly falling hemoglobin. These complications can present similarly to acute sickle crisis and need to be excluded to make a diagnosis [1-3]. Herein, we report a case of pediatric sickle cell intrahepatic cholestasis (SCIC) with a favorable outcome after exchange transfusion (ET) of packed red blood cell (PRBC).

Case Report

A 4-year-old girl, known to have SCD diagnosed at the age of 8 months old, was admitted for generalized jaundice of few hours duration. She denied any respiratory, gastrointestinal or articular symptoms at the beginning. Her urine was darker than usual. She was afebrile. Physical exam showed generalized jaundice with icteric sclera with hepatosplenomegaly. No rash was detected. Her laboratory profile showed white blood cells 16,800 mm^3 (neutrophils = 42.5%; lymphocytes = 44.3%), hemoglobin 9.4 g/dL with a hematocrit of 28.7%, and platelets 572,000 mm^3. C-reactive protein was slightly positive 8.1 mg/L, aspartate aminotransferase was 1,664.5 U/L, alanine aminotransferase was 1,268.6 U /L, total bilirubin level was 13.15 mg/dL, direct bilirubin level was 8.51 mg/dL, gamma-glutamyl transferase level was 432 U/L, alkaline phosphatase was 391 U/L, international normalized ratio was 1.5, prothrombin time was 17.3 s (control 13 s), and partial thromboplastin time was 39.5 s (control 33 s). Albumin level was 36.2 g/L. Fibrinogen was 257 mg/dL. Ammonia level was 29 μmol/L. Reticulocyte percentage was 16.8% and decreased to 3.5% on day 19 of admission. Direct Coombs test was positive while indirect Coombs test was negative. Lactate dehydrogenase was 835 U/L. Uric acid was 3.1 mg/dL. Parvovirus IgM was 5.84 IU/mL and IgG was 5.5 IU/mL. Serologies for hepatitis A, B, and C viruses, cytomegalovirus and Ebstein-Barr virus viruses and herpes simplex type 1 and 2 were negative. Salmonella and Brucella titers were negative. Purified protein derivative test was negative. Anti-nuclear antibodies (ANAs)

Table 1. Evolution of Liver Function Tests During Hospitalization

	SGOT (U/L)	SGPT (U/L)	GGT (U/L)	Alkaline phosphatase (U/L)	Bilirubin total (mg/dL)	Bilirubin direct (mg/dL)	INR	PTT (s)
Day 1	1,664.50	1,268.60	432	-	13.15	8.51	-	-
Day 2	-	-	-	-	-	-	1.5	39.5
Day 3	1,334	1,269	419	391	20.09	11.6	1.3	37
Day 4	1,059	1,127	389	427	18	10	1.3	39.8
Day 5	611	838	378	400	14.5	7.8	1.3	40.5
Day 6	524.4	656.2	368	386	18.7	11	1.2	38
Day 7	492.5	556	340	365	16.9	9.85	1.3	40.2
Day 8	507.4	462.7	329	374	17.38	8.85	1.4	-
Day 9	-	406.7	-	350	15.48	9.4	-	-
Day 10	696.4	474	325	385	18.27	8.93	1.2	34.4
Day 11	592.5	419.3	263	340	13.12	9.11	1.2	33
Day 12	566.6	420.3	282	359	12.42	8.2	1.2	-
Day 13	543.1	421.1	315	331	10.34	7.06	1.1	-
Day 14	-	402.5	-	-	13.04	9.18	1.2	-
Day 15	622.2	453.2	314	320	12.34	6	-	-
Day 16	688	496.7	314	308	9.96	4.66	-	-
Day 17	-	605.3	353	-	9.4	6.56	1.1	30.7
Day 18	-	653.6	338	-	11.98	8.48	-	-
Day 19	811.5	661.6	312	322	20	12.3	1.1	-
Day 20	1057	696.4	254	277	19.24	10.04	-	-
Day 21	641.5	622.3	255	280	16.92	11.11	1.1	-
Day 22	-	479.5	253	-	10.12	6.59	-	-
Day 23	185.8	348.8	257	224	9.24	3.63	1.1	27.1
Day 24	120.4	251.3	243	178	6.73	3.82		-

SGOT: aspartate aminotransferase; SGPT: alanine aminotransferase (U/L); GGT: gamma-glutamyl transferase; INR: international normalized ratio; PTT: partial thromboplastin time.

and anti-neutrophil cytoplasmic antibody profiles were both negative. Soluble liver antigen antibodies (anti-SLA) were not done. Ferritin level was 3,651 ng/mL. Polymerase chain reaction for parvovirus was negative.

The follow-up of her liver function tests during her hospitalization is shown in Table 1.

Ultrasound of the abdomen and pelvis showed a liver measuring 10 cm and a thick gallbladder wall (4 mm) without any stones. Magnetic resonance cholangiopancreatography (MRCP) showed hepatosplenomegaly, thickening of the gallbladder wall and diffuse peri-portal thickening without any dilatation of the intra- and extrahepatic biliary ducts and absence of gallstones. Minimal ascites was noted and an abnormal hypersignal in T8, T9 and L2 was noted. Liver biopsy was not done.

During her hospitalization, she had fever with positive extended spectrum beta-lactamase producing *Escherichia coli* in urine culture for which a 10-day course of ertapenem was given. She also had 2 days of back pain and abdominal pain with right knee pain. She was given intravenous vitamin K 5 mg twice daily. Deferasirox was stopped and N-acetylcysteine

was given at a loading dose of 140 mg/kg/dose then 70 mg/kg/dose q4h for 3 days *per os*.

She was given PRBC transfusion at a dose of 15 mL/kg on day 11 of admission (hemoglobin was 7.7 g/dL) with a post-transfusion Hb S 32% on hemoglobin electrophoresis. ET at 1.5 times her blood volume was done with almost no immediate decrease in the liver function tests (day 19 of admission) with an unknown post-exchange Hb S percentage. Intravenous immunoglobulins were given at a dose of 1 g/kg/day for 3 days with methylprednisolone at a dose of 4 mg/kg/day for 3 days at the hospital after which the levels of the liver function tests decreased progressively (days 20 - 23 of admission). A progressive prednisone tapering over the next 2 weeks was done with total bilirubin of 3.2 mg/dL and indirect bilirubin of 1.5 mg/dL at the end of the first week.

Discussion

Acute hepatic crisis has been observed in approximately 10%

of adult patients with SCD [2]. This proportion may be overestimated because of imprecise definition. In children, hepatic crisis has been very rarely described, mostly as isolated case reports [4-8]. Ahn and colleagues reported seven cases of pediatric and adult cases combined in their institution and another 37 cases from the literature published between 1953 and 2002 [5].

Its etiology remains unknown, but it is believed that the deformed erythrocytes adhere to the hepatic vascular endothelium resulting in sludging and congestion of vascular beds, followed by tissue infarction, and liver dysfunction in the more severe cases [6].

Patients usually present with acute right upper quadrant pain, nausea, low grade fever, tender hepatomegaly, and jaundice. The serum alanine and aspartate aminotransferase are seldom > 300 IU/L like in our patient. Levels > 1,000 IU/L have been described. The serum aspartate aminotransferase level is also raised by hemolysis. So serum alanine aminotrasferase may more accurately reflect hepatocyte injury. Elevation of serum alkaline phosphatase is common particularly during bony pain crises [2]. The level of bilirubin is not a good predictor of outcome [4]. Coagulopathy is common and worsens as hepatocyte necrosis spreads [1].

Liver histology may reveal sickle cell thrombin in the sinusoidal space with engorgement by red blood cells. Other features that have been described include Kupffer cell hypertrophy, mild centrilobular necrosis, and occasional bile stasis. However, percutaneous liver biopsy has been associated with serious complications like bleeding and liver rupture when performed in sickle cell patients with acute hepatic disease and thus should be avoided [2, 9, 10].

The cornerstone treatment is rapid Hb S fraction reduction through ET. Additional supportive treatment includes intravenous hydration, analgesia, coagulopathy correction and electrolyte monitoring [1]. In a study, five surviving children's symptoms resolved in few days to 2 weeks. Liver function test results returned to their previous level in less than 3 months, faster than viral hepatitis [4]. Liver transplantation has been proposed as a therapeutic option in patients with fulminant failure from an acute crisis. However, transplantation experience is very limited: only 22 transplant cases have been reported in the literature [7]. Recurrence of sickle hepatopathy in graft was reported [9].

Our patient had a typical clinical and laboratory presentation. It is important to exclude other causes of liver dysfunction in SCD (including alcohol, medication, viral disease, autoimmune disease, iron overload, etc.) [9]. Direct Coombs was positive but ANA which is 90-100% present in autoimmune hepatitis was negative. This is probably due to a prior immunization to a PRBC transfusion.

Her articular and back pain compelled us to ask for salmonella, Brucella and parvovirus serologies. Parvovirus hepatitis is normally associated with aplasia in sickle cell patients. It is reported to be associated with antimitochondrial antibodies [11], and is treated with immunoglobulins, dehydrocortisone and immunosuppressive therapy if it is part of hemophagocytic lymphohistiocytosis [12]. Parvovirus IgM proved to be a false positive result since polymerase chain reaction (PCR) was negative and the patient did not go into aplasia [11]. Hence,

intravenous immunoglobulins and corticosteroids were given only as preliminary parvovirus treatment whilst PCR results were out, then corticosteroids duration was shortened.

Biliary disease was easily excluded with ultrasonography, which must be performed as an urgency [4]. Ultrasound is the most sensitive imaging technique for assessment of acute calculous cholecystitis with a positive predictive value of 95% when the gallbladder wall is more than 3.5 mm thickness. Abdominal CT, which was not done, is useful in diagnosing complications of biliary disease, perforation, cholangitis and liver abscess. MRCP is the imaging technique of choice for diagnosis of cholangiopathy with an accuracy of 98% for detecting calculi [9].

Studies to date do not account for usage of acetylcysteine in acute liver failure non- acetaminophen-related in children [10]. However, it has been attempted in our patients to reduce possible deferasirox injury to the liver.

Simple PRBC transfusion helped in decreasing bilirubin levels temporarily (day 5) to 14 mg/dL with an Hb S level of 32% associated with a rise of hemoglobin from 7.7 to 12 mg/dL. Additional simple PRBC transfusion was not feasible due to increased risk of hyperviscosity.

Following ET (day 19), there was mild decrease in bilirubin level on the following day (day 20) after which it declined significantly to her baseline levels (total bilirubin 3 mg/dL) only after 2 weeks from ET. The recovery after ET is explained by dilution of sickling erythrocytes, the correction of anemia, and the reversion of tissue hypoxemia by increasing the oxygen-carrying capacity [4]. Suggested thresholds of Hb S% have been reported as < 20% and 30% [13].

Our patient did not have the severe syndrome of acute liver failure where bilirubin could reach extreme levels of 145 mg/dL which is associated with a very high mortality [4]. Coagulopathy was mild and required solely intravenous vitamin K.

Although hepatic sickle crises are uncommon in children, this potentially severe complication of SCD should be recognized by pediatric hematologists. After exclusion of biliary, viral and immune disease, the evaluation of the crisis is an emergency. Liver and kidney functions should be monitored. When the crisis does not resolve rapidly with hyperhydration or if symptoms of organ failure are present, aggressive transfusion therapy should be performed early. In children with recurrent crises chronic liver disease may develop [4].

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