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CASE REPORT | PEDIATRICS

Conjugated Hyperbilirubinemia in a Child with *Streptococcus pneumoniae*-associated Hemolytic Uremic Syndrome

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Abstract

Conjugated hyperbilirubinemia is a rare complication of hemolytic uremic syndrome (HUS). We report a case of a 2-year-old female with *Streptococcus pneumonia*-associated HUS (SP+ HUS) who developed severe cholestasis. It is important for pediatric gastroenterologists to be aware of manifestations of HUS, and that although rare, cholestasis can be one of the early findings in patients with SP+ HUS.

Introduction

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Cholestasis in the setting of HUS is rare. However, it is important that clinicians evaluating patients with HUS be aware of this complication. We report a case of a 2-year-old female with Streptococcus pneumonia-associated HUS (SP+ HUS) who developed severe cholestasis.

Case Report

A 2-year-old female with no past medical history was transferred to our institution for further management of her respiratory distress. One week prior to admission she developed an upper respiratory infection with rhinorrhea, cough, and tactile fever. She worsened over 24 hours, developed a fever to 39.4°C, had decreased oral intake and urine output, and had 2 episodes of non-bloody, non-bilious emesis. She was initially brought to an outside hospital, where initial labs revealed a Hb 9.8 g/dL, hematocrit 29.5%, and platelets 31,000/μL. One hour later, her labs decreased to a Hb 8.4 g/dL, hematocrit 25.2%, and platelets 14,000/μL. Chest X-ray showed consolidation of the right upper lobe. She was given intravenous doses of ceftriaxone and vancomycin, and transferred to our institution for further management.

Her family reported travel to Jamaica 3 weeks prior to presentation, but she had no illness during her visit there. The patient was not on any medications. She was born full term by normal spontaneous vaginal delivery in Jamaica. Her immunizations were up to date, except her fourth pneumococcal dose was not administered, which should have been given between 12 and 15 months of age. The family history was noncontributory.

On presentation to our institution, vital signs showed a temperature of 36.8°C, heart rate 158 bpm, respiratory rate 44 bpm, blood pressure 105/62 mmHg, and O_2 saturation 100% on 2 liters nasal canula. Patient had scleral icterus bilaterally and moist mucus membranes. She had suprasternal and subcostal retractions, and diminished breath sounds of the right lung and left lower lung. Her liver was palpable 2 cm below the costal margin, but no splenomegaly was noted. She was jaundiced down to her abdomen. There was no bruising, petechiae, rash, or pitting edema of her extremities. Capillary refill time was less than 2 seconds.

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Her labs over 48 hours showed a drop in her Hb to 3.9 g/dL, hematocrit to 12%, and platelets to 5,000/μL. Her WBC count was 6.6 with 49% bands, 4% metamyelocytes, 35% neutrophils, 8% lymphocytes, and evidence of schistocytes. Chemistry panel showed sodium 130 mmol/L, BUN 55 g/dL, creatinine 1.3 g/dL, bicarbonate 17.3 mmol/L, and calcium 7.9 mg/dL. Liver panel showed albumin 2.5 g/dL, aspartate aminotransferase (AST) 290 U/L, alanine aminotransferase (ALT) 25 U/L, and total and direct bilirubin 18.48 mg/dL and 17 mg/dL, respectively. Lactate dehydrogenase was 6,890 U/L. Urinalysis showed 3+ protein, large bilirubin and positive ichotest (used to test for the presence of bilirubin in the urine). Coagulation studies showed elevated prothrombin time of 12.1, partial thromboplastin time 79.9, INR 1.18, fibrinogen >740 mg/dL, and d-dimer 5.32 mg/L. Flow cytometry showed no loss of CD46. Right upper quadrant ultrasound showed evidence of diffuse gallbladder sludge with wall thickening and edema, but no intrahepatic or extrahepatic biliary duct dilatation or gallstones; pancreas and liver were normal; right kidney parenchyma was noted to be echogenic. With evidence of liver dysfunction, her antibiotics were changed to cefotaxime and vancomycin. Within 24 hours, the patient's blood culture was positive for pan-sensitive *Streptococcus pneumonia*. Patient's antibiotic coverage at that time was narrowed to IV penicillin.

The diagnosis of *Streptococcus pneumonia*-associated hemolytic uremic syndrome (SP+ HUS) was made based on the patient's laboratory data of hemolytic anemia, thrombocytopenia, and acute renal failure. The patient became oliguric, developed renal failure and underwent peritoneal dialysis catheter placement on hospital day 2, and peritoneal dialysis was started on hospital day 2. The patient's creatinine peaked on hospital day 14 to 5.4 g/dL. Peritoneal dialysis was discontinued on hospital day 26. The patient received IV penicillin for a total of 14 days and received 6 packed red blood cell transfusions and 5 platelet transfusions. She did not have worsening hemolytic anemia after the transfusions, though the recommendation to prevent hemolytic transfusion reactions is to use washed blood products or fresh frozen plasma.[1] She was placed on a nicardipine drip on hospital day 2 and was weaned off on hospital day 9, at which point her blood pressures remained stable.

Ursodiol was started on hospital day 2, when total and direct bilirubin peaked at 36.74 mg/dL and 34.5 mg/dL, respectively. At that time, AST and ALT were 603 U/L and 96 U/L, respectively. Ursodiol was discontinued on hospital day 9. Liver enzymes at that time had normalized, with the exception of the direct bilirubin being slightly elevated at 0.62 mg/dL. Direct bilirubin normalized on hospital day 15. The patient was kept nothing by mouth on admission and started on total parenteral nutrition (TPN) on hospital day 3. TPN was continued for 12 days until she was taking adequate calories by mouth.

The patient was discharged on hospital day 31 with normal liver function and mild renal impairment. At the time of discharge her BUN and creatinine were 32 g/dL and 1.5 g/dL, respectively. Three months after discharge, the patients BUN had normalized to 17 g/dL, and she had only mild elevation in her creatinine of 1.0 g/dL. At 1-year follow-up, her BUN remains normal and her creatinine has normalized.

Table 1. Data of Patients with Conjugated Hyperbilirubinemia and *Streptococcus pneumonia*-associated Hemolytic Uremic Syndrome

	1[2]	**2**[2]	**3**[2]	**4**[3]	**5***
Age (mo)	21	10	17	10	24
Sex	F	M	M	F	F
Hgb (g/dL)	8	6.1	3	5.4	3.9
Platelets (1,000/μL)	11	19	12	7	5
Creatinine (mg/dL)	1.5	2.5	2.1	2.8	5.4
Albumin (g/dL)	2.3	2.7	2.4	2.5	1.5
Total bilirubin	11.8	20	11.6	27	36.7
Direct bilirubin (mg/dL)	9.9	18.4	10.3	18.5	34.5
AST/ALT (U/L)	390/124	506/59	1,633/278	431/117	938/250
Fibrinogen (mg/dL)	568	545	298	428	>740
Normalization of bilirubin (hospital d)	9	5	10	8	15
Duration of dialysis (d)	12	10	28	26	25
Renal function (RF)	Normal at 6 mo	Normal at 10 d	Unknown	Mild impairment at 1 y	Normal at 1 y

[2]Pan CG, Leichter HE, Werlin SL. Hepatocellular injury in *Streptococcus pneumoniae*-associated hemolytic uremic syndrome in children. *Pediatr Nephrol.* (1995);9:690–693.
[3]Chen J, Chen S, Sheu J. Unusual manifestation of severe conjugated hyperbilirubinemia in an infant with *Streptococcus pneumonia*-associated hemolytic uremic syndrome. *J Formos Med Assoc.* 2007;106(2): 517–522.
*Case presented in this article.

Discussion

HUS is defined by a triad of hemolytic anemia, thrombocytopenia, and acute renal failure.[4] The 2 subgroups include diarrhea-associated HUS (D+ HUS) and HUS without diarrhea (D– HUS). With D+ HUS, E. coli 0157.H7 is the most common pathogen. D+ HUS usually develops abruptly with the onset of diarrhea, and patients are typically younger than 5 years and have a better prognosis.[5] D– HUS occurs at any age, has a relapsing course, and a worse prognosis. Multiple genes have been attributed to atypical HUS; one of them is CD46, a complement regulatory protein. This was found to be negative in our patient. HUS can present with many gastrointestinal manifestations. Most commonly, these include abdominal pain, diarrhea, emesis, rectal prolapse, colonic strictures, colonic perforation, intussusception, elevated hepatic enzymes, pancreatitis, and indirect hyperbilirubinemia.[1] The liver manifestations have been thought to be secondary to hemolysis, and rarely do patients develop cholestasis.[6] There are only 4 other cases in the literature that presented with cholestasis in the setting of SP+ HUS.[2,3]

Our patient presented with hemolytic anemia, thrombocytopenia, worsening renal function, and a significant conjugated hyperbilirubinemia. On hospital day 2, her total bilirubin peaked to 31 times the upper limit of normal (highest level of 36.74 mg/dL) and direct bilirubin to 173 times the upper limit of normal (highest level of 34.5 mg/dL). At that time, her AST and ALT also peaked, to an AST of 59 times the upper limit of normal (peak of 938 U/L), and ALT of 7 times the upper limit of normal (peak 250 U/L). The patient's prothrombin time, partial thromboplastin time, and international normalized ratio remained normal, but she did have hypoalbuminemia. This, however, was likely secondary to nutritional causes rather than hepatic synthetic dysfunction. In addition, antibiotics were used in our patient and are recommended in all cases of invasive pneumococcal infection. Coverage with vancomycin and an extended spectrum cephalosporin is recommended before culture and antibiotics sensitivities are back.[7] This is in contrast to treatment for *E. coli* 0157.H7, where antibiotics may cause more verotoxin production, therefore increasing the risk of HUS.

Other patients in the literature had elevated AST, ALT, and bilirubin, though not as significantly elevated as our patient.[2,3] Table 1 compares the peak lab findings in all 5 patients (including ours) reported in the literature. Our patient's labs normalized within 9 days after hospitalization. As compared with all the other cases, our patient required dialysis for 25 days, while the other cases ranged from 10 to 28 days. In all 5 patients, the cholestasis improved prior to the discontinuation of dialysis. Therefore, the liver dysfunction is likely due to multiple phenomena.

Different infectious processes can cause jaundice. Elevated bilirubin levels are also often seen in invasive pneumococcal infections. However, in these cases the bilirubin is usually minimally elevated, so there is most likely another component causing elevated levels in these patients. In addition, the transaminitis that occurs with bacterial infections is usually minimal.[1,2,4] In HUS there is a significant hemolytic component, and RBC hemolysis is likely the cause for the greater rise in AST compared to ALT. Significant hemolysis leads to hepatic congestion and cholestasis, and this can also lead to further increases in transaminases and hepatic dysfunction.[2]

Cholestasis can also occur with lack of enteral nutrition during the initial period of illness. It is thought that the lack of oral intake thwarts hormone stimulation of the hepatobiliary system, thus leading to cholestasis.[6] However, in our patient liver function normalized prior to her taking full enteral feeds, so this cannot fully explain her liver dysfunction.

SP+ HUS is an extremely rare entity compared to D+ HUS, and very little is known about the true pathogenesis of liver dysfunction. In our patient, multiple factors most likely played a role in the development of cholestasis. Our case highlights the importance of close vigilance in these patients to monitor for cholestasis and elevated liver enzymes so appropriate treatment can be initiated. It is not clear whether the urosdiol or dialysis had a greater impact in improving the cholestasis in this patient, as both treatments were started at the same time.

It is important to note that none of the reported cases had synthetic liver dysfunction and all of the patients' liver complications resolved. Nonetheless, it is important for pediatricians to be aware of manifestations of HUS, and understand that although rare, cholestasis can be one of the early manifestations in patients with SP+ HUS.

Disclosures

Author contributions: M.G. Patel drafted the initial article, reviewed and revised the article, approved the final article, and is the article guarantor. A.F. Porto reviewed and revised the article, and approved the final article.

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