Inspissated Bile Syndrome in a Neonate Treated With Cefotaxime

Sonographic Aid to Diagnosis, Management, and Follow-up

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Case Report

This 5-lb 15-oz full-term female neonate had an uncomplicated perinatal history, a normal vaginal delivery, and normal newborn screening results. She was brought to a local hospital at 2 weeks of age with fever, abdominal distension, vomiting, jaundice, and acholic stools. Pertinent laboratory results included normal electrolyte levels, an aspartate aminotransferase (AST) level of 131 IU/L, an alanine aminotransferase (ALT) level of 41 IU/L, and an alkaline phosphatase level of 106 IU/L (all normal for age). Abnormal laboratory values included a γ-glutamyltransferase (GGT) level of 613 IU/L (normal value for age, <300 IU/L), total/direct bilirubin levels of 4.5/2.9 mg/dL (normal, <1.2/0.8 mg/dL), and a blood culture positive for Aeromonas hydrophila and Klebsiella pneumoniae. Initial sonography showed ascites with an unremarkable-appearing liver and no evidence of intrahepatic or extrahepatic biliary ductal ectasia or biliary sludge.
The neonate was treated with intravenous ampicillin and cefotaxime for 10 days. Enteral feedings were resumed by the third hospital day. On discharge, the jaundice had resolved (bilirubin, 1.0.5 mg/dL), and the liver enzymes declined to an AST level of 38 IU/L, an ALT level of 18 IU/L, and a GGT level of 535 IU/L.

One week after discharge, jaundice and acholic stools recurred without any associated symptoms, and she was referred to our institution. Physical examination was unremarkable aside from mild hepatomegaly. Laboratory blood tests revealed an AST level of 101 IU/L, an ALT level of 33 IU/L, an alkaline phosphatase level of 250 IU/L, a GGT level of 1197 IU/L, and total bilirubin levels of 4.4/4.3 mg/dL. Sonography showed a cholestatic pattern in the liver, dilatation of the intrahepatic and extrahepatic biliary ducts, common bile duct (CBD) size of 5 mm, a fluid-debris level in the extrahepatic biliary ducts consistent with dependent sludge, and a large sludge ball in the gallbladder, which contained nonshadowing brightly echoic foci suspicious for cholelithiasis (Figure 1). She was given ursodeoxycholic acid (UDCA) at a dose of 15 mg/kg twice a day, fat-soluble vitamins, a medium-chain triglyceride-rich formula, and intravenous hydration. Her stools became pigmented after 2 days, and subsequent abdominal sonography on the sixth hospital day showed decreased sludge and

Figure 1. A, Sonogram of the dilated common hepatic duct (large arrow) and dilated CBD (small arrows) with a fluid-debris level noted within the distal CBD due to biliary sludge. The diameter of the CBD measured 0.5 cm. B, Color Doppler sonogram clearly differentiating between the dilated extrahepatic ducts and the surrounding vascular structures. Once again, sludge is noted within the distal CBD (arrow). C, Transverse sonogram in the region of the head of the pancreas showing brightly echoic sludge (arrow) filling the distal CBD at the level of the head of the pancreas. GB indicates gallbladder. D, Longitudinal sonogram of the gallbladder showing the presence of a large sludge ball (arrow) within the lumen, which contains several small focal nonshadowing more brightly echoic foci suspicious for precipitated material. The gallbladder is otherwise sonographically normal.
reduction in the size of the CBD to 3 mm. She was discharged and continued to receive UDCA. At 6 months of age, she was thriving; bilirubin levels were 0.2/0.1 mg/dL; transaminase levels were less than 50 IU/ml; and her GGT level was 23 IU/L (normal). Delayed sonography showed complete resolution of the biliary ductal dilatation and gallbladder sludge (Figure 2).

Discussion

Early diagnosis of the underlying etiology of cholestasis in neonates is essential so that appropriate therapy can be promptly instituted. A direct bilirubin level of greater than 1 mg/dL (if the total bilirubin level is <5 mg/dL) or greater than 20% of the total bilirubin level (if the total bilirubin is level is >5 mg/dL) is diagnostic of conjugated hyperbilirubinemia. Jaundice, persistent acholic stools, and an elevated GGT level are suggestive of obstructive jaundice. In the neonatal period, the differential diagnosis of obstructive cholestasis includes biliary atresia, a choledochal cyst, gallstones or biliary sludge, inspissated bile syndrome, cystic fibrosis, neonatal sclerosing cholangitis, and congenital hepatic fibrosis/Caroli disease. Meticulous sonographic evaluation of the liver, spleen, pancreas, biliary ducts, and biliary vessels along with clinical and laboratory correlation allows for accurate diagnosis of anatomic abnormalities that may cause biliary obstruction and in most cases obviates the need for higher-tech imaging studies and prevents unnecessary interventional procedures or surgery.

The incidence of inspissated bile syndrome is 1 per 175,000 live births in England and accounts for about 8% of all surgical jaundice during infancy. Biliary sludge appears sonographically as low-level echoes. On microscopy a mixture of particulate matter appears when various biliary solutes precipitate cholesterol, calcium bilirubinate or other calcium salts, mucus, undefined residues, and protein-lipid complexes. The diagnosis of sludge is almost always based on imaging. The pathogenesis of sludge is similar to that of gallstones, which are formed from precipitating sludge. There are many predisposing factors to the development of inspissated bile, sludge, or choledolithiasis in neonates. Ceftriaxone pseudolithiasis, composed of precipitated ceftriaxone, is reported to occur in 29.5% to 45.7% of children treated with ceftriaxone.3 The pseudolithiasis occurs after 4 to 22 days (mean, 9 days) of ceftriaxone therapy and resolves after 2 to 63 days (mean, 15 days) from the end of treatment.2 Cefotaxime, a third-generation cephalosporin, was previously reported to be associated with pseudolithiasis in 2 of 34 infants (6%) who had cholelithiasis. This relationship was not found in 38 older children receiving cefotaxime for 4 to 7 days. Therefore, this association may be unique in the neonatal population.

In most patients, removal of the precipitating factor can lead to spontaneous resolution of biliary sludge. The refractory cases of inspissated bile syndrome and those associated with biliary-type pain, cholecystitis, cholangitis, or pancreatitis are treated with open or laparoscopic cholecystectomy. Some may require endoscopic retrograde cholangiopancreatographic sphincterotomy, percutaneous transhepatic cholangiographic saline flushing, or infusion of N-acetylcysteine into the extrahepatic biliary ducts to prevent further episodes of cholangitis and pancreatitis. In asymptomatic patients, the sludge can be managed expectantly. Our patient’s cholestasis resolved with hydration and high-dose (30-mg/kg/d) UDCA. Ursodeoxycholic acid is a hydrophilic bile acid that enriches the bile

Figure 2. After treatment with UDCA, fat-soluble vitamins, and intravenous hydration, the neonate’s stools became pigmented after 2 days, and subsequent abdominal sonography showed no evidence of intrahepatic or extrahepatic biliary ductal ectasia, stones, sludge, or pericholecystic fluid.
acid pool, decreases the biliary saturation of cholesterol, and may prevent sludge formation. It was found to resolve symptoms in pediatric patients with gallstones; however, the stones transiently disappeared in only 2 of 15 patients in one study and in 8 of 180 in another.

The neonate we report was born full term, had normal newborn screening results, and was not dehydrated when she had inspissated bile syndrome. The initial outside liver sonography during the septic period did not reveal sludge despite biochemical cholestasis. Obstructive jaundice recurred 1 week after recovery from sepsis. Because the neonate did not have any other risk factors for development of inspissated bile, the potential association was treatment with cefotaxime, which may be unique in the neonatal period.

In conclusion, obstructive jaundice in neonates, as a consequence of inspissated bile or sludge, may follow treatment with cefotaxime and is likely to respond to hydration and medical management with UDCA. We emphasize the use of sonography in the diagnosis, treatment, and follow-up of neonates with inspissated bile syndrome, which in most cases obviates the need for higher-tech imaging studies and prevents unnecessary interventional procedures or surgery. The cholestasis and extrahepatic obstruction resolved with hydration and high-dose UDCA.

References