

Case Report

Neonatal Cholestasis Due to Biliary Sludge- Review and Report of a Case Associated with Use of Diflucan

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- Diflucan Fluconazole

Abstract

Causes of neonatal cholestasis are varied and complex with biliary sludge representing a rare etiology. Biliary sludge has been reported in association with metabolic disorders, biliary malformation, hormonal effect, and medication effect amongst others. Herein we report a case of cholestasis secondary to biliary sludge associated with recent use of diflucan (fluconazole). An infant presented on the 85th day of life with jaundice, weight loss, hepatosplenomegaly and recent acholic stools. His clinical history was significant for diflucan therapy one month prior. On presentation, patient's total bilirubin, alkaline phosphatase, and gamma-Glutamyl transpeptidase were elevated. Cholangiography showed biliary ductal dilatation with obstructing debris. There was no evidence of cystic malformation. Trans-catheter irrigation of the biliary tree, cholecystectomy, and biopsy of liver were performed. The gallbladder and cystic duct were unremarkable, save for mural bile deposition on histology. Liver biopsy had canalicular cholestasis, mild ductular proliferation, and was otherwise unremarkable; there was no ultra-structural anomaly. Clinic-pathologic work ups for screening infectious, metabolic and heritable disease were unremarkable. Few days post-op, bilirubin levels and liver function tests normalized; repeat ultrasounds showed a normal-caliber biliary tree. The patient's follow up 7 months after presentation remains unremarkable.

ABBREVIATIONS

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TORCH: Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes Simplex; VDRL: Venereal Disease Research Laboratory; TSH: Thyroid stimulating hormone; T4: Thyroxine; BA: Biliary atresia

INTRODUCTION

Neonatal cholestasis can be defined as a prolonged conjugated hyperbilirubinemia and occurs in approximately 1 in 2500 to 5000 live births [1,2]. Its causes in the neonatal period can be quite varied, because susceptibility to infection is increased, and the possibility of previously unrecognized congenital malformations and metabolic disorders is the highest. Distinguishing between potential etiologies of neonatal cholestasis is challenging, yet critical, as there is a limited window for optimal medical therapy

of infectious or metabolic disorders or surgical treatment of obstructive conditions [1].

Neonatal cholestasis should be suspected in any newborn jaundiced after 14 days of life, at which point transient physiologic jaundice of the newborn should have been abated. Additional signs include acholic stools, dark urine, and bleeding. Depending on the underlying cause, the infant may be otherwise asymptomatic or may be acutely ill when due to sepsis or a metabolic etiology. The patient may have poor hepatic synthetic function at birth as evidenced by hypoglycemia and coagulopathy not correctable by standard vitamin K replacement therapy [1].

Cholestasis is not a final diagnosis, but a signal for further evaluation. The differential diagnosis in children is broad and include infections (TORCH infections, hepatitis B, hepatitis C, bacteremia, and sepsis), anatomic abnormalities (biliary atresia, choledochal cyst, inspissated bile syndrome, choledocholithiasis,

neonatal sclerosing cholangitis, spontaneous perforation of common bile duct), metabolic and genetic disorders (alpha-1 antitrypsin deficiency, galactosemia, cystic fibrosis, tyrosinemia, Alagille syndrome, progressive familial intrahepatic cholestasis [PFIC, 3 types with impairment of bile salt or phospholipid secretion], bile acid synthesis defects, trisomy 18 or 21), endocrine disorders (panhypopituitarism, hypothyroidism), toxic causes (parenteral nutrition-associated liver disease, drugs), and systemic diseases (shock, congestive heart failure, neonatal lupus erythematosus [1-8].

Laboratory values in neonatal cholestasis demonstrate elevated conjugated bilirubin, elevated delta bilirubin, and elevated total alkaline phosphatase. Gamma-glutamyl transpeptidase (GGT) is generally high, but paradoxically low or normal levels can be found in patients with sepsis, some infections, subsets of progressive familial intrahepatic cholestasis (PFIC) and inborn errors of bile acid synthesis. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) can be normal or elevated [1-4]. Physical examination may show jaundice, syndromic features, and/or hepatosplenomegaly.

Biliary atresia is a major cause of neonatal cholestasis [1,4,5]. Early recognition is imperative as the initial management (surgical intervention with Kasai hepatopertoenterostomy) improves outcome when performed by 60 day of life. Certain clinical features can favor this diagnosis, including female gender, normal birth weight, early onset of jaundice, acholic stools, and an enlarged firm liver [1]. A fasting ultrasound may be normal or may demonstrate an absent or contracted gallbladder [3]. Diagnosis is made by liver cholangiogram and biopsy. Classic obstructive pattern is encountered in majority and biopsy can aid in diagnosis in 65 to 90% of cases [5].

Neonatal obstructive hyperbilirubinemia associated with biliary ductal dilation can occur in the context of inspissated bile syndrome, an uncommon condition characterized by biliary sludge [9]. Certain medications including antibiotics and medical conditions such as cystic fibrosis or bile duct malformations are found associated with developing biliary sludge. Herein, we report and review neonatal cholestasis due to biliary sludge, in our case associated with diflucan use.

CASE PRESENTATION

Report of a Case

A previously healthy 85 day old male infant presented with jaundice, weight loss, and 10 days of acholic stools. The patient was born at term (41+0 weeks). He was small for gestational age, weighing 3050 grams (6 pounds 11.6 oz) at birth. He experienced a transient mild hypoglycemia of 37 mg/dl (ref 40-100 mg/dl) five hours after birth, corrected with formula supplementation. His prenatal tests and newborn screens had been unremarkable. At 27 days of life, secondary to episodes of vomiting, the patient underwent abdominal ultrasound to rule out pyloric stenosis. The ultrasound showed no evidence of pyloric stenosis and no other abnormality. At 2 months of age for treatment of oral candidiasis, he was prescribed diflucan, otherwise his history was unremarkable with normal well-child checks. He began to develop acholic stools at 75 days of life, and parents reported

to pediatrician at 85 days of life. There was no family history of hepatobiliary disease; infant's three older siblings were healthy.

At presentation, patient's weight was 4.8 kg (8%ile for age), height was 58.4 cm (22%ile for age) and weight/length ratio was 6%ile for age. His skin and sclera were jaundiced and hepatosplenomegaly was noted. Laboratory work up was significant for a total bilirubin of 4.5 mg/dl (ref 0.1-1.4 mg/dl), with 2.0 mg/dl conjugated (ref 0.0-0.3 mg/dl) and 1.0 mg/dl unconjugated (ref 0.1-1.2 mg/dl). Delta bilirubin was 1.5 mg/dl (ref 0.0 mg/dl), total alkaline phosphatase was 492 U/L (ref 145-320 U/L) and GGT was 222 U/L (ref 4-18 U/L). ALT and AST were mildly elevated (60 U/L and 75 U/L, respectively), albumin was 4.2 g/dl (ref 2.6-4.2 g/dl), and prothrombin time was normal (10.8 seconds). Complete blood count with differential was unremarkable except for an elevated platelet count of 453 k/cmm (ref 156-312 k/cmm). He had evidence of fat soluble vitamin deficiency (25-OH vitamin D <4.0 ng/ml [ref range: deficient = <10 mg/ml]).

On abdominal ultrasound, there was intra- and extra-hepatic biliary ductal dilatation with a sludge-filled common bile duct (Figure 1). Liver span measured 7.2 cm. The gallbladder was normal in length and wall thickness. Both the cystic duct and the gallbladder contained sludge. There was no evidence of liver calcification or echogenic bowel. Because of the appearance of the bile ducts, the patient was brought to the operating room for a cholangiogram and liver biopsy. Intraoperative cholangiography confirmed dilation of the intra- and extra-hepatic bile ducts, including the cystic duct, common hepatic duct, and common bile duct, with debris obstructing the distal common bile duct (Figure 2). There was no evidence of choledochal cyst or biliary atresia. Subsequently, trans-catheter irrigation of the biliary tree was performed to clear the common duct along with a cholecystectomy. Final cholangiogram demonstrated removal of the filling defect from the distal common bile duct and free flow of contrast into the duodenum, thereby excluding biliary atresia (Figure 3). The enlarged liver was without evidence of cirrhosis.

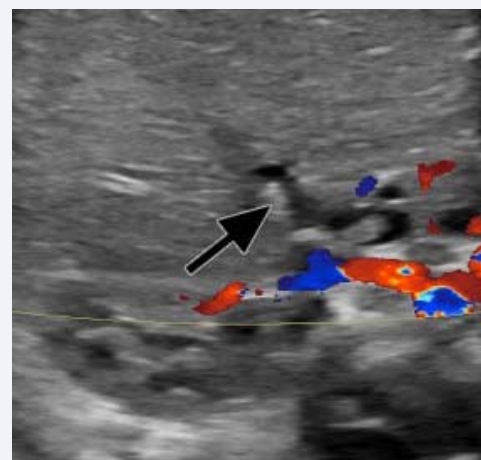


Figure 1 Right upper quadrant ultrasound with color Doppler demonstrates echogenic material representing inspissated bile (black arrow) in the dilated common bile duct. This echogenic bile was mobile on real-time imaging.



Figure 2 Intraoperative cholangiogram demonstrates a filling defect representing inspissated bile (black arrow) in the dilated common bile duct (white arrow). The intrahepatic biliary tree is also dilated.

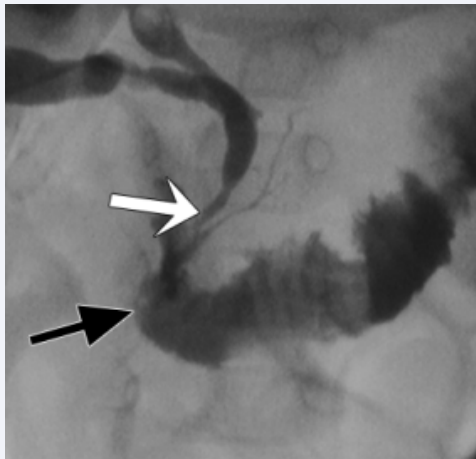


Figure 3 Following intraoperative irrigation of the bile ducts, repeat cholangiogram demonstrates successful removal of the filling defect with a decreased common bile duct diameter (white arrow). Free flowing contrast into the duodenum (black arrow) excludes biliary atresia.

The gallbladder and cystic duct were unremarkable with no stones. Microscopically, the gallbladder contained mural bile but otherwise no alteration. The cystic duct had mural edema and bile deposition. Liver biopsy contained canalicular cholestasis associated with foci of hepatocytic rosetting, rare lobulitis, portal expansion with mild bile ductular proliferation and edema. There was no significant fibrosis. Electron microscopy of the liver was positive for evidence of cholestasis, otherwise unremarkable. Hepatocytes had mitochondria in normal numbers, distribution and morphology. Lysosomes were present. There was abundant canalicular bile without the features of bile sometime seen in PFIC, type 1.

To further exclude the possibility of PFIC, blood samples were submitted to the reference laboratory, the result of which was negative (no mutations of ATP8B1, ABCB11, or ABCB4). The remainder of the workup was unremarkable, including negative

sweat test, normal alpha-1 antitrypsin level (218 mg/dl) with MS genotype, normal thyroid studies and normal cortisol level.

Post-operatively, the patient was prescribed ursodiol (ursodeoxycholic acid), 15 mg/kg twice daily in addition to ADEK vitamin supplementation. By post-operative day 2, the patient's stool became yellow. By post-operative day 3, total bilirubin had dropped to 2.4 mg/dl. Two weeks after the procedure, total bilirubin had normalized, dropping to 0.9 mg/dl with no conjugated bilirubin present.

Follow-up abdominal ultrasounds, at two and four months post-operatively, showed no biliary ductal dilatation or liver alteration. Given the unremarkable appearance of the biliary tree on follow up imaging, biliary dilatation at presentation was attributable to sludge. The patient is currently developing well at 10 months of age and is without jaundice or acholic stools.

DISCUSSION

Neonatal cholestasis classically manifests as a jaundiced infant with acholic stools and conjugated hyperbilirubinemia. Conjugated hyperbilirubinemia is defined as a direct bilirubin greater than 1 mg/dl or more than 20% of the total bilirubin level. Jaundice with persistent acholic stools and elevated GGT level are suggestive of an obstructive etiology [10].

Obstructive jaundice is non-specific with etiologies including biliary atresia, choledochal cyst, gallstones, cystic fibrosis, congenital hepatic fibrosis/Caroli disease or inspissated bile syndrome.

Accurate and prompt diagnosis is essential in order to avoid potential end-stage complications [1,11].

Our patient's work up for congenital infections, metabolic disorders including alpha-1-antitrypsin deficiency, galactosemia, cystic fibrosis and thyroid and adrenal endocrine dysfunction was negative. There was no suggestion of PFIC by clinic-pathology, and genetic studies further confirmed exclusion of PFIC. Lack of structural anomalies and presence of interlobular bile ducts helped in ruling out Alagille syndrome.

In this case, ultrasound features and intraoperative cholangiography were consistent with inspissated bile syndrome. Temporal association with medication use, in view of negative work up otherwise, suggested medication-induced sludge leading to cholestasis. There was a dramatic improvement with gradual resolution subsequent to irrigation of the biliary tree and cholecystectomy.

In 1935 Lad published the first report of inspissated bile syndrome/biliary sludge. It is a rare cause of neonatal cholestasis, with obstruction of the extra-hepatic biliary system by a luminal bile plug, sludge, or gallstone in the distal common bile duct. This condition is also known as microlithiasis, microcrystalline disease, pseudolithiasis, biliary sediment, thick bile, and biliary sands. The diagnosis is based on history and typical radiologic findings of biliary ductal dilatation when other known causes of neonatal cholestasis have been excluded. Jaundice, weight stagnation, acholic stools and hepatomegaly are often the only signs of this disease. A meticulous sonographic evaluation of the liver, biliary ducts/vessels, and pancreas along with operative

cholangiography can support this diagnosis. Discontinuation of the inciting agent with simple irrigation of the biliary tree can be curative in a subset. [10-12].

Biliary sludge can develop transiently during the neonatal period, the majority of which clear by 6 weeks postpartum. It can be seen in relation to metabolic disorders such as cystic fibrosis, bile duct malformations including strictures and choledochal cysts, total parenteral nutrition, hormonal fluctuation, or medication use [9,13-15].

A variety of drugs are also reported to induce biliary stasis by different pathogenic mechanisms. A correlation with antibiotic use has been reported. Correlation of ceftriaxone therapy and formation of biliary sludge is established, reported in 29.5% to 45.7% of children treated with ceftriaxone, with pseudolithiasis observed 4 to 22 days after the antibiotic therapy [10,16,17].

In the presented case, the temporal association with fluconazole therapy and otherwise negative work-up is suggestive of medication-induced sludge. Fluconazole's mechanism of action is through inhibition of the fungal cytochrome P-450 dependent enzyme, causing loss of normal sterols and accumulation of 14-alpha-methyl sterols. Fluconazole also leads to inhibition of aromatase and subsequent interference with the biosynthesis of estrogens from cholesterol [18-20].

There is sufficient evidence that fluconazole is excreted in bile. Brammer *et al.*'s study of 400 healthy individuals found that 11% of the fluconazole dose is metabolized in the liver [20]. In the pediatric population hepatotoxicity and gastrointestinal toxicity are reported as the most common adverse effect of this drug, which can manifest as hepatic enzyme elevation, clinical hepatitis, cholestasis, and fulminant hepatic failure [20-23]. It is therefore conceivable that diflucan may contributed to the formation of sludge in this otherwise healthy infant.

If inspissated bile syndrome persists untreated, severe cholestasis can lead to liver damage and eventually to biliary cirrhosis. When treated early, however, the prognosis is excellent. In a subset, biliary sludge will resolve upon removal of the inciting agent. In asymptomatic patients, sludge can be managed with hydration. In patients with symptoms or with refractory disease, high dose ursodeoxycholic acid, cholecystectomy, sphincteroplasty, or saline flushing may be required with excellent follow up outcome. Surgical intervention is most often needed when the extra-hepatic bile ducts are dilated more than 3 mm [9,10,12,14,24,25].

Our patient's repeat radiologic surveillance remains stable with no evidence of biliary tract or liver disease. He is currently healthy at 10 months of age, 7 months after the surgery with normal development.

CONCLUSION

Causes of cholestasis in the neonatal period are both varied and complex and require an accurate and timely diagnosis for effective management. Our case of inspissated bile syndrome highlights an uncommon cause of neonatal cholestasis. The time course for the development of jaundice in this patient, and negative work up otherwise, suggests that inspissated bile

syndrome may potentially be associated with diflucan use in this neonate.

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