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CASE REPORT | LIVER

Unveiling the Genetic Culprit: A Diagnostic Dilemma of Recurrent Cholestasis With Intrahepatic Stones

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ABSTRACT

Recurrent cholestasis poses diagnostic challenges and necessitates repeated testing. The *ABCB4* (adenosine triphosphate-binding cassette, subfamily B, member 4) gene encodes a protein that removes phospholipids from the hepatic canalicular membrane through bile salts. Mutations lead to a spectrum of clinical syndromes that cause recurrent cholestasis, pruritus, and jaundice. This case follows a young female with recurrent cholestasis postcholecystectomy, intrahepatic stones on endoscopic retrograde cholangiopancreatography, and repeated intrahepatic cholestasis of pregnancy. Phenotypes of *ABCB4* mutations should be considered when facing cholestasis of unclear etiology. Early genetic testing and ursodeoxycholic acid treatment may prevent progression toward hepatic fibrosis and end-stage liver disease.

KEYWORDS: cholestasis; ABCB4 mutations; ABCB4/MDR3 transporter protein; LPAC; GBD1; PFIC3; intrahepatic stones; UDCA

INTRODUCTION

Cholestasis occurs when bile excretion is impaired, often identified by elevated liver biochemistries. Initial presentation can range from asymptomatic to jaundice, pruritus, fatigue, and abdominal pain. Etiologies vary but are typically classified as intrahepatic, extrahepatic, or both. Differential diagnosis is broad and includes obstructive processes, inflammatory disorders, drug-induced injury, infection, pregnancy, and genetic syndromes.[1]

The *ABCB4* gene encodes the ABCB4/MDR3 (multidrug-resistance protein 3) transporter protein that moves phospholipids from the inner to outer lipid bilayer of the canalicular membrane to be excreted by bile salts. Mutations can lead to cholestasis and numerous phenotypic syndromes, including low phospholipid-associated cholelithiasis (LPAC). LPAC is typically seen in young female patients with symptomatic cholelithiasis, recurrence after cholecystectomy, intrahepatic sludge of microlithiasis, and/or pregnancy exacerbation.[2]

CASE REPORT

A 17-year-old adolescent girl with a history of obesity presented with 2 days of right-sided abdominal pain. Her vitals were stable, and she had right upper quadrant tenderness. Initial laboratory results were notable for aspartate aminotransferase 272, alanine transaminase 536, alkaline phosphatase 272, total bilirubin 3.4 (2.7 direct), international normalized ratio 1.0, and lipase 46. Ultrasound revealed gallstones without cholecystitis, biliary dilation, or choledocholithiasis. With supportive treatment, her symptoms improved, and she underwent cholecystectomy within a week of discharge. Abnormal intraoperative cholangiogram prompted intraoperative endoscopic retrograde cholangiopancreatography (ERCP) for clearance of obstructive material from her common bile duct. Pathology from cholecystectomy showed eosinophilic cholecystitis.

At 1-month follow-up, she was asymptomatic but had persistent elevation of liver biochemistries. Magnetic resonance demonstrated elevated liver stiffness with 2.86 kPa, normal fat fraction of 3.29%, and mild ductal irregularities without beading, stenoses, or residual filling defects. Serologic workup included negative viral hepatitis panel, antinuclear antibody, antimitochondrial antibody, anti-

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smooth muscle antibody, liver-kidney microsomal antibody, celiac, parietal cell Ab, and soluble liver antibody IgG, IgG4, gp-210, and sp-100.

Owing to persistent liver enzyme elevation, she underwent magnetic resonance cholangiopancreatography months later, which showed segmental right hepatic parenchymal volume loss with associated biliary ductal dilation and irregularity, suspicious for cholangiopathy process. Liver biopsy was pursued, which lacked steatosis, fibrosis, or interface hepatitis. Biopsy noted portal tracts with mild-moderate mixed inflammatory cells, normal caliber bile ducts with minimal reactive change without ductopenia, and mild sinusoidal dilation. She was unfortunately lost to follow-up.

Three years after the initial presentation, she became pregnant, and liver biochemistries flared. The pregnancy ended with incomplete abortion, but she became pregnant again shortly thereafter with another cholestatic rise in liver enzymes. She was referred to an adult hepatologist during her second trimester with a working diagnosis of intrahepatic cholestasis of pregnancy (ICP). Repeat magnetic resonance cholangiopancreatography >3 years after the initial presentation showed 2 segmental areas of intrahepatic biliary ductal dilation suspicious for strictures. Repeat liver biopsy (Figure 1) was concerning for obstruction but could not rule out early primary sclerosing cholangitis (PSC). ERCP was performed with no evidence of PSC, but cholangiogram images revealed a persistent filling defect in a left intrahepatic branch, likely an intrahepatic stone (Figure 2). The filling defect was located within a tortuous duct and could not be reached for balloon extraction. After discussion at Hepatobiliary Conference, interventional radiology recommended conservative management, as stone removal would be challenging.

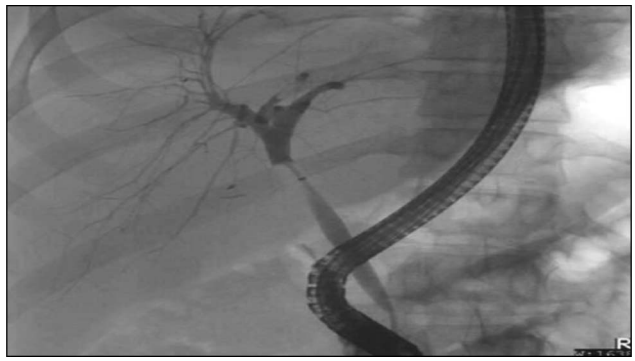

Figure 2. Endoscopic retrograde cholangiopancreatography images revealed a persistent filling defect in a left intrahepatic branch, compatible with suspected intrahepatic stone. The remainder of the left intrahepatic branches, right intrahepatic branches, left and right hepatic ducts, and the entire common duct appeared normal. There was no evidence of primary sclerosing cholangitis as concerned for based on liver biopsy. Of note, the left intrahepatic filling defect was located within a tortuous duct such that it could not be reached to attempt balloon extraction.

Thus far, underlying small duct PSC was highest on the differential. However, given unclear etiology of cholestasis and intrahepatic cholelithiasis, a genetic panel was performed and revealed *ABCB4* heterozygosity. Her clinical picture aligned best with GBD1 (gallbladder disease 1), also known as LPAC (low phospholipid cholelithiasis) (Table 1). Ultimately, she was placed on ursodeoxycholic acid (UDCA) with improvement in her pruritus, jaundice, and enzymes, with counseling against future pregnancy.

DISCUSSION

ABCB4 mutations are a rare genetic cause of cholestasis in adulthood. The hepatocanalicular ABCB4/MDR3 transporter

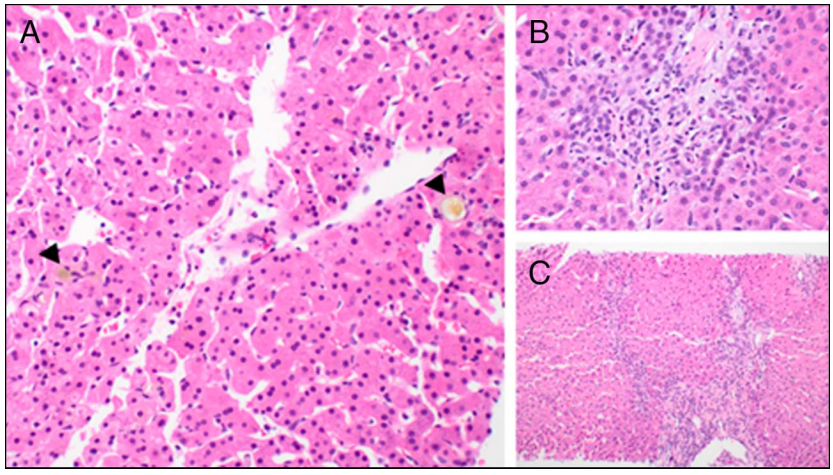

Figure 1. Pathology slides from repeat liver biopsy more than 3 years from the initial presentation **A** (200×): multifocal, centrilobular cholestasis (arrowheads). **B** (400×): portal tracts with bile ductular reaction and mild, nonspecific periductal fibrosis without evidence of duct loss. **C** (100×): overall architecture of liver biopsy at lower magnification with above findings including patchy mild periportal fibrosis (stage 2). Per pathology, overall findings typically suggestive of extrahepatic bile duct obstruction could not rule out primary sclerosing cholangitis. However, this was not the case based on endoscopic retrograde cholangiopancreatography. Overall, these results show progression of disease compared with liver biopsy approximately 3 years ago.

Table 1. Common phenotypes of *ABCB4* mutations

Phenotype—*ABCB4* mutations	Zygosity	Symptom onset	Clinical features
PFIC3	Homozygous or compound heterozygous	Infancy—childhood	Pruritus/jaundice, fibrosis/cirrhosis, evidence of portal hypertension, steatorrhea, sometimes cognitive impairment
LPAC I GBD1	Heterozygous	Childhood—early adulthood (<40 yr)	Biliary colic symptoms, jaundice, intrahepatic sludge +/− stones, cholesterol microlithiasis, cholelithiasis, cholangitis, biliary pancreatitis, recurrent symptoms postcholecystectomy, pregnancy exacerbations
ICP	Heterozygous	Late 2nd–3rd trimester	Gestational pruritus, fetal complications, improvement in symptoms/enzyme elevations with delivery
Chronic cholangiopathy	Usually heterozygous	Late adolescence—adulthood	Intrahepatic sludge, hepatolithiasis, fibrous obliteration of biliary ducts with ductopenia, fibrosis/cirrhosis
Adult biliary fibrosis	Usually heterozygous	Adulthood	Unexplained chronic liver disease/fibrosis, portal hypertension

GBD1, gallbladder disease 1; ICP, intrahepatic cholestasis of pregnancy; LPAC, low phospholipid-associated cholelithiasis; PFIC, progressive familial intrahepatic cholestasis.

protein is responsible for translocating phospholipids to be extracted as bile salts. Defect leads to intrahepatic production of bile with detergent-like properties, causing damage to hepatocytes and cholangiocytes.[2] Usually, homozygosity for *ABCB4* gene mutations causes progressive familial intrahepatic cholestasis type 3 (PFIC3). However, there have been upward of 300 disease-causing variants of *ABCB4*, resulting in a spectrum of phenotypes briefly summarized in Table 1.[2] Per some data, heterozygous *ABCB4* mutations were detected in 34% of adults with unexplained cholestasis and could result in significant liver fibrosis with a broad spectrum of disease processes.[2–6]

Our patient offers a challenging diagnostic case of recurrent cholestatic pattern of liver injury. This case is unique given the presence of intrahepatic stones on ERCP and was especially difficult to diagnose in the setting of pregnancy. It illustrates that genetic testing should be considered in young individuals with elevated alkaline phosphatase with unrevealing serologies and/or imaging in the appropriate clinical context.

Three independent factors have been found to be predictive of an *ABCB4* mutation: age less than 40 years, recurrence after cholecystectomy, and intrahepatic hyperechoic foci, sludge, and/or microlithiasis. Rosmorduc et al developed a score using these factors and found that a score of 2 or more was highly sensitive for an *ABCB4* point mutation.[7] Our case included all 3 of these features. It took years to conclude that our patient most likely has LPAC, one of many phenotypes of the heterozygous *ABCB4* mutations. This diagnosis is often missed and a high degree of suspicion especially in the context of the intrahepatic stones and ICP should prompt genetic workup.

Schatz et al analyzed the *ABCB4* gene in pediatric and adult patients with phenotypes consistent with PFIC3, ICP, and LPAC syndromes.[8] This cohort demonstrated that when a mutation was identified during adulthood, the clinical presentation was typically less severe but still varied broadly. Earlier onset of symptoms in younger patients caused a more severe PFIC3 phenotype. Ultimately, 9 pediatric patients were previously misdiagnosed with other cholestatic diseases, 7 of which necessitated transplant. This study provides context between the timing of clinical presentation and severity of disease, reminding clinicians to consider early genetic testing when the diagnosis is unclear.

Patients may benefit from long-term UDCA, which is recognized as the first-line therapy in patients with ABCB4-related disorders.[5,9,10] By inducing the expression of ABCB4/MDR3 and other canalicular proteins, UDCA stimulates the secretion of bile salts and protective phospholipids. This results in protection of hepatocytes and cholangiocytes through reduced bile acid cytotoxicity, improved bile flow, and decreased cellular apoptosis.[9,10] More than half of patients with PFIC3 or high-gamma-glutamyl transferase PFIC demonstrate symptom reduction and laboratory improvement with UDCA.[10] However, mutational analysis is needed as response may vary based on type mutation and resulting residual protein function. Those with a premature stop codon do not respond to UDCA, while the majority of patients harboring a missense mutation do respond clinically.[5,10] ERCP, biliary drainage, and surgical treatment may be indicated with symptomatic lithiasis. Transient elastography can be obtained noninvasively to monitor the progression of fibrosis. Recurrent cholestasis and inflammation can be carcinogenic; therefore, early identification of disease is

crucial. With early consideration of genetic testing and management with UDCA, the development of hepatic fibrosis in patients with *ABCB4* mutations may be slowed or halted.

DISCLOSURES

Author contributions: All authors had substantial contributions based on ICMJE authorship guidelines. JA Ciricillo was responsible for theorizing of the manuscript including development of background and introduction, case portrayal, discussion, and reference tracking. F. Rahim assisted with the above, while playing a large role in writing and editing. Y. Sharma assisted with theorizing of the manuscript, case development, and editing. JA Ciricillo is the article guarantor.

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