Familial Low-Phospholipid-Associated Cholelithiasis Syndrome Presenting with Recurrent Intrahepatic Stones After Cholecystectomy with a Heterozygous ABCB4 Variant

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To the Editor,

Low-phospholipid-associated cholelithiasis (LPAC) syndrome is a rare form of intrahepatic lithiasis that often occurs in young adults and is characterized by recurrent biliary symptoms that typically occur after cholecystectomy. The pathogenesis of LPAC is primarily driven by impaired biliary phospholipid secretion due to mutations in the adenosine triphosphate–binding cassette, subfamily B, member 4 (*ABCB4*) gene, which encodes the bile canalicular protein multidrug resistance 3 (MDR3), a phosphatidylcholine translocator across the canalicular membrane of hepatocytes. The underlying pathology involves the intrahepatic bile ducts rather than the gallbladder; therefore, cholecystectomy does not prevent recurrence. Consequently, LPAC syndrome is frequently underdiagnosed and may be misdiagnosed as recurrent choledocholithiasis.[1-3] We present a case of LPAC syndrome in a young adult with recurrent intrahepatic stones after cholecystectomy, which was associated with a heterozygous *ABCB4* variant that was also identified in his father. Ethical committee approval was received from the Ethics Committee of Koç University School of Medicine (Approval no: 2024.433.IRB2.191, Date: 12.12.2024) and written consent was obtained.

A 25-year-old man was referred to our outpatient clinic for evaluation of recurrent right upper quadrant pain and persistent abnormalities in liver tests. Nine years earlier, routine laboratory evaluation revealed a mixed hepatocellular and cholestatic liver injury pattern, with alkaline phosphatase (ALP) 188 U/L (upper limit normal (ULN), <120); gamma-glutamyl transferase (GGT) 126 U/L (ULN, <55); alanine aminotransferase (ALT) 172 U/L (ULN, <41); aspartate aminotransferase (AST) 185 U/L (ULN, <40); total bilirubin 1.90 mg/dL; and direct bilirubin 1.30 mg/dL. No further investigations were performed at that time. Five years later, the patient presented with right upper quadrant abdominal pain. Laboratory tests showed a cholestatic pattern of liver test abnormalities, with ALP 323 U/L, GGT 536 U/L, ALT 158 U/L, AST 56 U/L, total bilirubin 1.63 mg/dL, and direct bilirubin 1.11 mg/dL. Abdominal ultrasonography revealed multiple gallstones, the largest measuring 2.5 cm in diameter. The patient subsequently underwent laparoscopic cholecystectomy. The patient's medical history was unremarkable. He denied tobacco use, alcohol consumption, and regular medication use. Family history revealed that the patient's father had undergone cholecystectomy at the age of 47 years and was later hospitalized for cholangitis associated with intrahepatic and common bile duct stones. Although the patient was asymptomatic after cholecystectomy, persistent abnormalities in liver tests were observed during follow-up. Four years later, he developed recurrent right upper quadrant pain and was diagnosed as cholangitis; he was referred to our hospital for further evaluation. Laboratory tests revealed the following results: ALP 325 U/L, GGT 506 U/L, ALT 260 U/L, AST 97 U/L, and total bilirubin 1.32 mg/dL. Magnetic resonance cholangiopancreatography (MRCP) demonstrated marked dilatation of the intrahepatic bile ducts with multiple intraluminal filling defects consistent with intrahepatic calculi, predominantly involving the right posterior segment, both at the time of cholecystectomy and at the current admission.

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Further etiological evaluations for liver disease were unremarkable, including negative autoimmune markers (antimitochondrial antibody, antinuclear antibody, anti-smooth muscle antibody, liver kidney microsomal type 1 antibody, perinuclear antineutrophil cytoplasmic antibody) and viral serology and normal ceruloplasmin, ferritin, IgG, and IgG4 levels. The patient underwent percutaneous transhepatic cholangiography (Figures 1 and 2) followed by endoscopic retrograde cholangiopancreatography (ERCP), during which multiple intrahepatic and biliary stones were successfully extracted (Figure 3). The extracted biliary stones were white cholesterol stones, which are typically observed in LPAC (Figure 4). The cholesterol composition of the intrahepatic bile duct stones, in conjunction with a positive family history, raised suspicion of LPAC syndrome, and genetic testing was subsequently performed. Sequencing of the *ABCB4* gene in the patient identified a heterozygous c.1646G>A (p.Arg549His) variant, which was classified as a variant of uncertain significance according to the American College of Medical Genetics and Genomics criteria. He received ursodeoxycholic acid (UDCA) therapy for 6 months, during which no episodes of cholangitis or pancreatitis were observed.

When the patient's father's medical history was reviewed in detail, he had no prior medical history until the age of 47 years, when he presented with right upper quadrant pain and jaundice. Abdominal ultrasonography revealed multiple gallstones, and he was diagnosed with acute cholecystitis. He subsequently underwent cholecystectomy. Four years later, he was admitted with acute cholangitis. MRCP revealed dilation of the common bile duct, dilation of the right posterior intrahepatic bile duct with intraductal stones, and dilation of the left intrahepatic bile duct. ERCP was performed for biliary drainage and stone extraction. Three years later, he experienced a recurrent episode of acute cholangitis requiring repeat ERCP. Following this recurrence, treatment with UDCA was initiated, after which the patient remained asymptomatic. Given the similar clinical history of his son, genetic testing was performed, which identified the same heterozygous



Figure 1. Percutaneous transhepatic cholangiography via the right posterior bile duct revealed dilation of the right posterior intrahepatic bile ducts with multiple filling defects consistent with stones, similar to the findings observed in the left intrahepatic bile ducts.



Figure 2. Approximately 2 months after placement of internal–external drainage catheters in both the right and left intrahepatic bile ducts.

ABCB4 missense variant, c.1646G>A (p.Arg549His) (ClinVar ID: 502568; rs761238221).

The present case demonstrates the key diagnostic features of LPAC syndrome, including early-onset biliary disease before the age of 40 years, recurrence of biliary symptoms after cholecystectomy, and intrahepatic lithiasis on imaging. The extracted biliary stones were white cholesterol stones, which are characteristic of LPAC. In LPAC syndrome, pathogenic variants in the *ABCB4* gene impair biliary phosphatidylcholine secretion via the MDR3 transporter, leading to cholesterol-saturated bile and the formation of soft, white cholesterol-rich intrahepatic stones, which further supports the diagnosis in our patient. Additionally, the patient's father had a similar history of gallstone disease requiring cholecystectomy, followed by cholangitis associated with intrahepatic stones. Genetic analysis revealed that both patients carried the same heterozygous *ABCB4* c.1646G>A (p.Arg549His) variant. This variant has been reported in genetic databases but has not been previously described in a clinical case report of LPAC syndrome. Although it is currently classified as a variant of uncertain significance, its presence in 2 affected first-degree relatives with a classical LPAC phenotype suggests a potential role in the disease pathogenesis.

LPAC syndrome is often misdiagnosed because its symptoms are similar to those of gallstone disease. Many patients undergo cholecystectomy before diagnosis. Imaging plays an important role in the diagnosis of this disease. Ultrasonography may reveal characteristic hyperechoic intrahepatic foci or comet-tail-like artifacts. MRCP and cholangiography are useful imaging modalities for detecting intrahepatic bile duct dilation and the presence of calculi. The treatment differs from that of conventional gallstone disease. UDCA is the cornerstone of long-term therapy and may reduce biliary symptoms and the rate of stone recurrence in patients with LPAC. Endoscopic or percutaneous interventions are required in cases of biliary obstruction or cholangitis. Early recognition of LPAC syndrome is essential to avoid repeated



Figure 3. Stones retrieved during the combined endoscopic–percutaneous procedure.

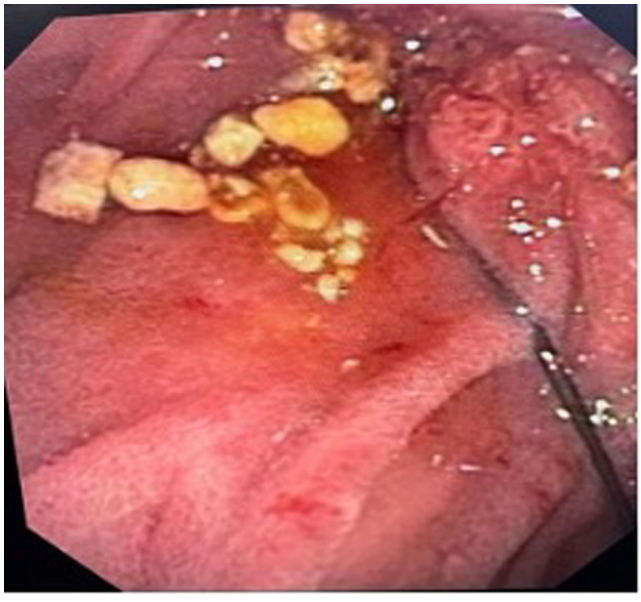


Figure 4. Cholesterol stones retrieved during the combined endoscopic–percutaneous procedure.

surgical procedures and to initiate appropriate medical therapy.[4]

In conclusion, LPAC syndrome should be suspected in young patients with recurrent biliary symptoms and intrahepatic stones after cholecystectomy. The identification of the same *ABCB4* variant in both the patient and his father highlights the importance of family genetic screening. Recognition of this rare disorder is essential for appropriate management and long-term follow-up.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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