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Case Report

Low Phospholipid Associated Cholelithiasis Syndrome: A Rare Cause of Biliary Colic and Cholangitis

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Abstract

Low phospholipid associated cholelithiasis (LPAC) syndrome is a recently described condition that causes the formation of bile duct stones. It is linked to a mutation in the ATP-binding cassette subfamily B member 4 (ABCB4), which lead to impaired solubilization of biliary cholesterol, and its precipitation as cholesterol crystals in the intrahepatic bile ducts. The diagnosis is considered if at least two of the following three criteria are met: onset of biliary symptoms before age 40, echogenic intrahepatic images or microlithiasis, and recurrence of biliary symptoms after cholecystectomy. Radiologic examinations, such as ultrasound and MRI, are essential for confirming the diagnosis of LPAC syndrome, alongside genetic screening. Simple cases can be managed with medical treatment only using ursodeoxycholic acid (UDCA), However, endoscopic or surgical interventions are required if complications arise.

The clinical case that we report is for a 58-year-old female, with a prior cholecystectomy 19 years previously, who presented with biliary colics and jaundice. The biological examinations revealed a hepatic cytolysis and biological cholestasis, ultrasound and MRI showed the presence of multiple gallstones in the intra-hepatic bile ducts, associated with a dilated common bile duct, which is filled with lithiasis upstream of a large stone. The diagnosis of LPAC syndrome complicated with cholangitis was retained. The patient was transferred to the gastrology department, where a treatment based on UDCA was initiated, and an Endoscopic retrograde cholangiopancreatogram (ERCP) was programed.

Keywords: *LPAC Syndrome; Intra-Hepatic Lithiasis; Cholangitis; Imaging*

Introduction

LPAC (Low Phospholipid-Associated Cholelithiasis) syndrome is a very specific form of biliary lithiasis, first described in 2001. It is caused by a mutation in ABCB4 (ATP-binding cassette subfamily B member 4), which codes for MDR3 (multidrug resistance protein 3), a biliary transporter responsible for transporting phospholipids into the bile. This syndrome is generally manifested by biliary symptoms such as pain in the right hypochondrium, jaundice, and even complications such as cholangitis or acute pancreatitis, which may occur after cholecystectomy. A better understanding of this newly described condition and wider awareness of its diagnostic criteria should improve screening and treatment of patients.

We report the case of a 58-year-old woman, with a history of cholecystectomy, who diagnosed with LPAC syndrome complicated by cholangitis.

Case Report

A 58-year-old patient, who had undergone cholecystectomy 19 years previously, presented with persistent pain in the right hypochondrium, resistant to analgesic treatment. Clinical examination revealed a febrile patient (38,5°C), with the presence of an icterus. The laboratory work-up revealed hepatic cytolysis with Aspartate aminotransferase (ASAT)=85 IU/L, Alanine aminotransferase (ALAT)=90 IU/L, as well as biological cholestasis with Alkaline phosphatase (ALP)=399 IU/L, Gamma glutamyl-transferase (GGT)=458 IU/L, and a total Bilirubin =10.8 mg/l with a predominance of direct Bilirubin=6.5 mg/l. The work-up was completed by serological tests, in particular for hepatitis B and C viruses, and HIV, all of which came back negative. Tests for overload diseases such as haemochromatosis were negative. An ultrasound scan showed dilatation of the intra-hepatic biliary duct (IHBD), with hyperechoic images generating a posterior shadow cone scattered along the IHBD, suggestive of lithiasis. A complementary MRCP (Magnetic resonance cholangiopancreatography) was carried out, showing dilatation of the intra-hepatic biliary tree which contain multiple lithiasis, as well as impacted stones of the common bile duct (CBD), upstream of a large lithiasis of 22 mm. The CBD was enlarged with a diameter of 23 mm. In the light of all these data, the diagnosis of low phospholipid associated cholelithiasis (LPAC) complicated with cholangitis was retained, and the patient was referred to the gastrology department, where treatment with ursodeoxycholic acid (UDCA) was initiated, and an Endoscopic retrograde cholangiopancreatogram (ERCP) was scheduled.

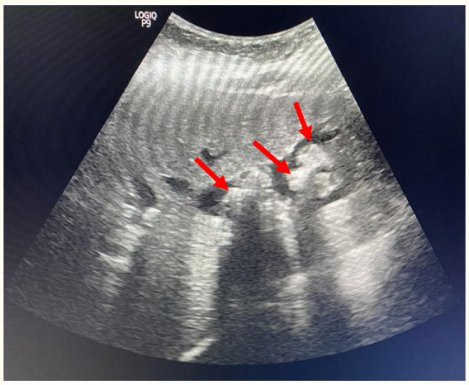

Figure 1: *Hepatic ultrasound image in B mode showing a dilated bile ducts with the presence of hyperechoic formations generating a posterior acoustic shadowing indicative of bile ducts lithiasis (Red arrows).*

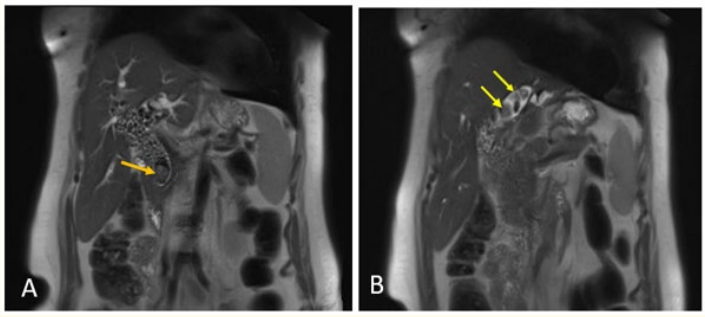

Figure 2: *Coronal sections of a Bili-MRI in T2 HASTE sequence, (A): impaction of lithiasis in the common bile duct (CBD) above a large stone (orange arrow), with significant enlargement of the CBD. (B): showing dilated bile ducts with multiple intraductal gallstones (yellow arrows).*

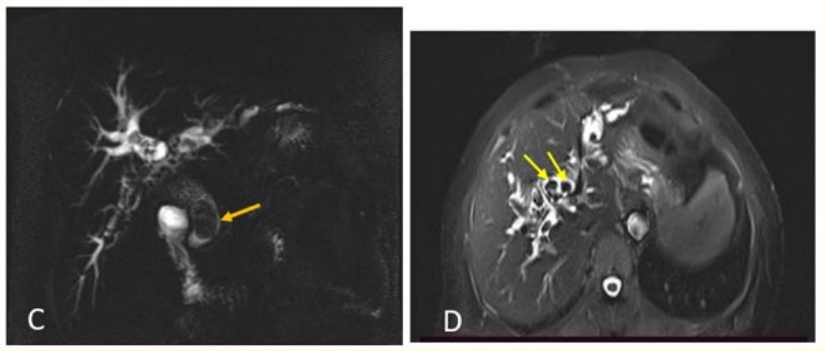

Figure 3: *Axial section of a 3D MRCP (C), and a Bili-MRI in T2 HASTE STIR sequence (D), showing multiples gallstones in the dilated intra-hepatic bile ducts (yellow arrows), and an enlarged CBD above a large lithiasis (orange arrow).*

Discussion

Low-phospholipid associated cholelithiasis (LPAC) is a genetic condition that leads to the formation of intrahepatic stones. It was initially described by Rosmorduc and colleagues of the hospital Saint Antoine in 2001 [1]. It is a condition associated with a mutation of the ABCB4 gene (ATP binding cassette subfamily B member 4) which codes for the protein MDR3 (multidrug resistance protein 3), a biliary carrier, needed for phospholipid secretion, specifically phosphatidylcholine. This mutation leads to low phospholipids concentration and therefore the formation of intra-hepatic bile ducts gallstones [2].

The exact prevalence of LPAC in the population remains unknown, but some studies conducted in France estimate that it represents approximately 1% of the cases of adults with symptomatic cholelithiasis [3]. It is a condition more frequent in women than men with a sex ration of 3/1, and occurs in the young age, more often in patients with normal body mass index (IMC), contrary to classical biliary gallstones which occurs in overweight patients [1,4].

The LPAC syndrome is caused by a mutation in the ABCB4 gene on chromosome 7, which encodes the MDR3 protein, that transport phosphatidylcholine, a type of phospholipid, into the bile. Various mutations of this gene were identified, including nonsense, missense, and partial gene deletions, and they have been found in 50 to 65% of patients with LPAC syndrome [5,6].

These phospholipids, when associated with bile acids, help to solubilize and transport cholesterol into the bile. They form micelles that preserve the biliary epithelium from the toxic effects of hydrophobic bile acids. Therefore, a dysfunction in the MDR3 protein will result in a reduced concentration of phospholipids, leading to the precipitation of cholesterol crystals in the canaliculi and intrahepatic bile ducts, which causes the formation of intrahepatic gallstones and chronic damage to the biliary epithelium [5-7].

LPAC syndrome should be considered in the presence of two out of the following three criteria: onset of symptoms before the age of 40, recurrence of symptoms following cholecystectomy, and detection of hyperechogenic intrahepatic foci, sludge, or intrahepatic microlithiasis on ultrasound. Additional minor diagnostic criteria include: a family history of biliary lithiasis among first-degree relatives, a past history of gestational cholestasis, and responsiveness to Ursodeoxycholic acid treatment [5,6].

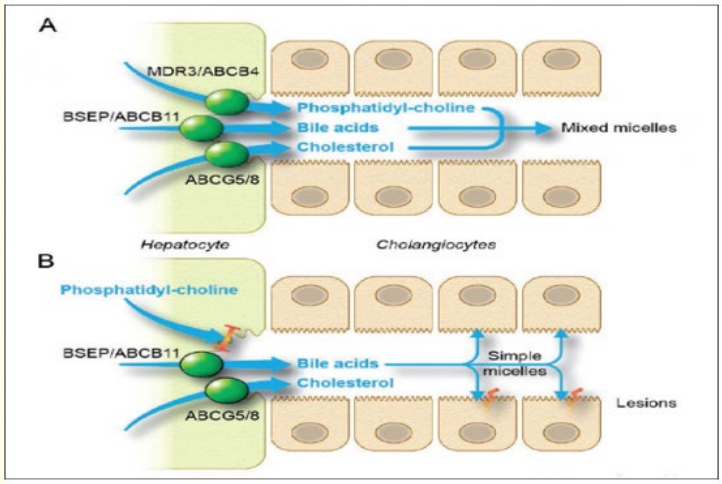

Figure 4: *(A) All transporters of phosphatidyl-choline, bile acids and cholesterol are functional, which allows the formation of mixed micelles and the solubilization of cholesterol. (B) A defective transporter of phosphatidyl-choline, due to a mutation in ABCB4 gene which encodes for MDR3, and resulting in the formation of simple micelles incapable of solubilizing cholesterol. The bile acids have toxic effects on the biliary epithelium [8,9].*

The diagnosis of LPAC syndrome relies on the criteria previously mentioned, along with radiological findings, bile composition analysis (obtained via duodenoscopy and aspiration with a catheter inserted into the distal common bile duct), and screening for mutations in the ABCB4 gene. Although routine clinical examination does not typically include bile analysis. The biological analysis finds an elevation in gamma glutamyl transferases (GGT), which is associated with a cholangiocytes aggression [5,7,8].

Radiological examinations are crucial for diagnosing LPAC syndrome, and the proficiency of the radiologist plays a significant role in detection rates. The range of detection varies widely-from 5% with a debutant and non-informed radiologist to up to 90% with an expert, according to a French study [4,10].

Ultrasonography is considered as the main imaging technique for identifying key signs of LPAC syndrome in a majority of patients. These signs include Intrahepatic hyperechoic foci which are often accompanied by posterior acoustic shadowing or "comet tail" artifacts, indicative of microlithiasis. Other findings are intrahepatic sludge, and micro-lithiasis which may be visible as small, echogenic particles within the bile ducts. When there are numerous intrahepatic stones, their presence often leads to the dilatation of both proximal and peripheral intrahepatic bile ducts [1,6].

Doppler ultrasound can be useful by detecting color comet-tail artifacts, also known as "twinkling artifacts", indicating the presence of microlithiasis. Unlike pneumobilia (air in the bile ducts), these artifacts are not mobile [5].

The radiological examinations can be completed by a CT-scan or ideally by an MRCP which is important for showing intra-hepatic lithiasis, and dilatation of the bile ducts. It also helps to eliminate other differential diagnosis like Caroli disease or primary sclerosing cholangitis [1,11].

The most common presentation of LPAC syndrome is suggestive of lithiasis migration (biliary pain associated with a transient rise in transaminases), but without a proper diagnosis and treatment, some serious complications may occur, like cholangitis and acute

pancreatitis or gestational cholestasis during pregnancy. In exceptional situations, cases of biliary cirrhosis were reported in the literature, and the risk for the development of cholangiocarcinoma was present even if it's rare. However, the long-term prognosis is yet to be determined [1,2,8].

The treatment of LPAC syndrome is based mainly on Ursodeoxycholic acid (UDCA), which enhances the function of MDR3, protects the biliary epithelium from the harmful effects of hydrophobic bile acids, solubilizes cholesterol to prevent gallstone formation, and controls inflammation by decreasing pro-inflammatory cytokine levels [6,10]. This treatment has a rapid positive impact on symptoms and biological tests, although its effects on imaging findings may take longer to manifest [1]. In the case of extended intrahepatic lithiasis causing abscesses and repeated cholangitis, interventional treatments (endoscopic or radiological) should be considered. These interventions aim to drain biliary ducts and remove intrahepatic lithiasis. If these methods are not effective, surgical options are recommended. The surgical approach is based on resecting the affected part of the liver and clearing the bile ducts [8,10]. Finally, family screening by an ultrasound expert should be offered to adult first-degree relatives of individuals with LPAC syndrome, for an early diagnosis [8,10].

Conclusion

LPAC syndrome is a relatively new described entity that leads to the formation of bile ducts gallstones. This case study aims to elucidate the clinical and radiological features indicative of LPAC syndrome, thereby facilitating early diagnosis and improving management and outcome. The treatment is based on oral medication by UDCA as it achieves good results on the long term with no recurrence of symptoms, and avoids the need for surgery, which remains reserved for complications. Finally, Genetic screening for the ABCB4 mutation in family members helps to make an early diagnosis and have an appropriate treatment, helping to prevent complications.

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