Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 6 Issue 12 December 2023

Case Report

Diagnosis of Secondary Sclerosing Cholangitis in a Young Patient with LPAC Syndrome Revealed by Gastrointestinal Bleeding

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Received: October 06, 2023

Published: November 27, 2023

Abstract

Low phospholipid-associated cholelithiasis (LPAC) is a rare genetic disorder characterized by the association of an ABCB4 mutation and low biliary phospholipid concentration with recurrent cholelithiasis, responsible for the development of intrahepatic lithiasis in adults.

The patients with the LPAC syndrome present typically with the following main features: age less than 40 years at onset of symptoms, recurrence of biliary symptoms after cholecystectomy, intrahepatic hyperechoic foci or sludge or microlithiasis along the biliary tree.

While the majority of clinical forms are simple, there also exist complicated forms, involving extended intrahepatic lithiasis and its consequences: lithiasis migration, acute cholangitis, intrahepatic abscess. Chronic evolution can lead to secondary sclerosing cholangitis or secondary biliary cirrhosis.

We report a case of a 32-year-old woman, cholecystectomized 10 years ago, who presented with hematemesis, upper gastrointestinal endoscopy revealed: Esophageal varices. Ultrasound and MRI showed the presence of intrahepatic calculi disseminated along the bile duct pathway, dysmorphic liver, and signs of secondary sclerosing cholangitis. Viral serologies and immunology tests were negative and the diagnosis of secondary sclerosing cholangitis complicating LPAC syndrome was retained and the patient was put under medical treatment with ursodeoxycholic acid (UDCA).

Keywords: LPAC Syndrome; Gastrointestinal Bleeding; Secondary Sclerosing Cholangitis; UDCA

Introduction

Low-phospholipid-associated cholelithiasis syndrome (LPAC) is a rare form of intrahepatic lithiasis linked to a defect of phospholipid canalicular secretion into bile. Young adults represent the majority of cases. LPAC belongs to the group of hepatic diseases associated with deficiencies in ABCB4/MDR3 with 30-50% of patients displaying mutations in that gene [1].

A mutation in ABCB4 gene responsible for the dysfunction in MDR3 protein causes a reduction in the concentration of biliary phosphatidylcholine, a substance responsible for the transportation and solution of cholesterol whose deficiency causes a reduction of the solubility of cholesterol, which can increase the incidence of biliary duct obstruction and calculus [2].

Chronic evolution can lead to secondary sclerosing cholangitis (SSC).

SSC is a chronic cholestatic biliary disease, characterized by inflammation, obliterative fibrosis of the bile ducts, stricture formation and progressive destruction of the biliary tree that leads to biliary cirrhosis [3].

Case Report

A 32-year-old woman, who has undergone a cholecystectomy 10 years ago, presented to emergency services with 2 episodes of hematemesis. On examination, she was not in acute distress.

The patient underwent upper gastrointestinal endoscopy which revealed esophageal varices in the mid-esophageal area but no active bleeding.

Laboratory data showed.

Serum alanine aminotransferase (ALT) 80 IU/L (N: 5-40 IU/L), aspartate aminotransferase (AST) 90 IU/L (N: 5-40 IU/L), gamma-glutamyl transpeptidase (GGT): 200 IU/L (N: 5-40 IU/L), alkaline phosphatase 300 IU/L (N: 35-140 IU/L), total bilirubin 16 µmol/L (N: 3-17 µmol/L), and a low prothrombin activity at 58%. The hemoglobin rate was 11g/dl White blood cells: 4030 elements/mm3 Platelets: 140 000 elements/mm 3.

Viral serologies were negative for hepatitis B and C virus, immunology lab tests were normal. Ultrasound and MRI showed the presence of intrahepatic calculi disseminated along the bile duct pathway and iirregularities with strictures, dilatations and pruning of intra and extrahepatic bile ducts (Figure 1). The patient was diagnosed to have Sclerosing secondary cholangitis complicating LPAC syndrome.

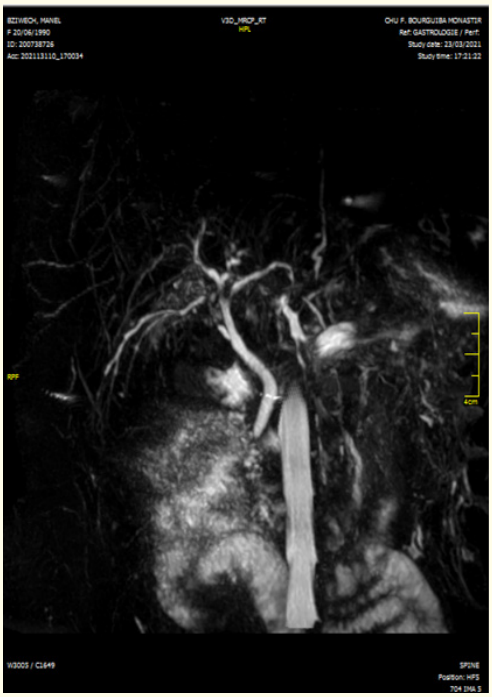

Figure 1: 3D - Magnetic resonance Cholangiopancreatography Showing presence of intrahepatic calculi disseminated along the bile duct pathway and irregularities with strictures, dilatations and pruning of intra and extrahepatic bile ducts.

The patient was put under medical treatment with ursodeoxycholic acid, No clinical or biological improvement (hepatic colic and sustained cholestasis without bleeding recurrence) was noted. Then she was referred for liver transplantation.

Discussion

Low phospholipid-associated cholelithiasis (LPAC) is characterized by the association of ABCB4 mutations and low biliary phospholipid concentration with symptomatic and recurring cholelithiasis. It is a genetic disease responsible of the formation of intrahepatic stones [4].

The MDR3 (Multidrug Resistance 3) protein, encoded by the ABCB4 gene, transports phosphatidylcholine which is the main phospholipid in human bile. These phospholipids, in association with bile acids, ensure the solubilization, the transport of cholesterol in bile and protect the biliary epithelium from the detergent effects of the hydrophobic physiological bile acids. A mutation of the ABCB4 gene, responsible for the dysfunction of the MDR3 protein, leads to a decrease in the concentration of biliary phosphatidylcholine. This deficiency is responsible of a decrease in cholesterol solubilization, a chronic damage in the biliary epithelium, an inflammatory reaction increasing GGT levels (Gamma Glutamyl transferase) and a precipitation of cholesterol in the various bile ducts (intrahepatic lithiasis) [2].

As a nosological entity, it is defined by presence of two of the three following criteria: age less than 40 years at onset of biliary symptoms, recurrence of biliary symptoms after cholecystectomy, and intrahepatic hyperechogenic foci detected by ultrasound [5].

Typically, the clinical course is progressive, with multiple recurrence until UDCA treatment is started. The majority of patients with LPAC syndrome described in the literature do not develop recurrence or end-stage liver disease under medical treatment.

Even though cases are rare, LPAC syndrome can complicate with secondary bile cirrhosis or secondary sclerosing cholangitis because of the chronic aggression of the biliary epithelium or intrahepatic cholangiocarcinoma due to the dysplasia caused by the constant inflammation.

LPAC syndrome is an indication for treatment with UDCA at a dosage of 10 mg/kg/d.

This treatment increases the pool and the percentage of hydrophilic bile acids in the bile that protect the cholangiocyte membrane leading to a better solubilization of cholesterol and to the dissolution of cholesterol crystals and stones [6].

In the majority of cases, the symptoms disappear within the first few weeks of treatment. Ultrasound abnormalities disappear within months or even years.

Indications of hepatic surgery remains limited to complicated forms (abscess, massive intrahepatic lithiasis, recurrent angiocholitis, neoplasic complications).

In the event of terminal liver failure with secondary biliary cirrhosis or massive intrahepatic lithiasis complicated by repeated bouts of sepsis, a liver transplant indication maybe justified [7].

For our patient the diagnosis was made in an advanced stage liver disease. No response to UDCA was noted. She was referred for liver transplantation.

Conclusion

Low-phospholipid-associated cholelithiasis syndrome (LPAC) is a rare form of intrahepatic lithiasis which might lead to adulthood biliary cirrhosis and subsequent complications.

Early diagnosis and timely initiation of medical treatment would improve disease management.

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