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CASE REPORT

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Low-phospholipid associated cholelithiasis (LPAC) syndrome: an unusual form in an elderly and overweight woman

Chantelli Iamblaudiot Razafindrazoto[1*], Behoavy Mahafaly Ralaizanaka[2], Jolivet Auguste Rakotomalala[3], Christiane Stern[4], Soloniaina Hélio Razafimahefa[2], Rado Manitrala Ramanampamonjy[1] and Pascal Lebray[4]

Abstract

Background Low-phospholipid associated cholelithiasis (LPAC) remains an under-diagnosed condition. It can be revealed by complications such as acute cholecystitis, acute angiocholitis and acute pancreatitis. We report a case of acute pancreatitis secondary to LPAC syndrome.

Case presentation A 58-year-old woman was hospitalized for recurrent biliary-type abdominal pain after cholecystectomies. The diagnosis of acute biliary pancreatitis revealing a low-phospholipid associated cholelithiasis syndrome was retained after explorations. An abdominal ultrasound performed by an expert radiologist allowed us to confirm the diagnosis of LPAC syndrome, showing a comet tail image along the intrahepatic bile ducts. Ursodeoxycholic acid was started without waiting for the result of the ABCB4 mutation. The outcome was spectacular with complete disappearance of the symptoms after the first week.

Conclusion Expert ultrasound remains the key examination for the confirmation of the diagnosis of a low-phospholipid associated cholelithiasis syndrome. It should be requested at the slightest warning signs such as a young age less than 40 years and recurrence of biliary symptoms after cholecystectomy.

Keywords Low-phospholipid associated cholelithiasis syndrome, Biliary lithiasis, Ursodeoxycholic acid, Case report

Background

Low-phospholipid associated cholelithiasis (LPAC) is a genetic disease responsible for the development of intrahepatic lithiasis [1, 2]. It is associated with a mutation of the ABCB4 gene which codes for protein MDR3, a biliary carrier [3, 4]. A mutation of the ABCB4 (ATP-binding cassette, subfamily B, member 4) gene, responsible for a dysfunction of the MDR3 (multidrug resistance 3) protein, is at the origin of a decrease in the biliary concentration of phosphatidylcholine, which will lead to a modification of the mixed micelles into simple micelles, which solubilize less cholesterol, which then precipitates into cholesterol calculus in the biliary tract [1–4]. Up to 10% of the European and American population carry gallstones, approximately 25% of cases have symptoms and less than 2% present with severe complications (cholangitis or pancreatitis). Based on previous epidemiological data, we consider that LPAC syndrome is infrequent and corresponds to a peculiar subgroup of patients with symptomatic gallstone disease. The exact prevalence of LPAC remains unknown [5, 6]. This entity is among the under-diagnosed pathologies due to the

*Correspondence:
Chantelli Iamblaudiot Razafindrazoto
iamblaudiotchantelli@yahoo.com
[1] Unity of Gastroenterology, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar
[2] Unity of Hepato-Gastroenterology, University Hospital Andrainjato, Fianarantsoa, Madagascar
[3] Unity of Hepato-Gastroenterology, University Hospital Mahavoky Atsimo, Mahajanga, Madagascar
[4] Unity of Hepatology, University Hospital Pitié Salpêtrière, Paris, APHP, France

lack of knowledge of physicians of the frequency and the suggestive signs of the disease [1–3]. The disease is more common in young adults, the usual age at the onset of the symptoms is typically lower than 40 years [6]. 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. While the majority of clinical forms are simple, there also exist complicated forms, involving extended intrahepatic lithiasis and its consequences: lithiasis migration, angiocholitis, intrahepatic abscess. Chronic evolution can lead to secondary sclerosing cholangitis or secondary biliary cirrhosis. In unusual cases, degeneration into cholangiocarcinoma may occur [1–6]. Treatment is based on long-term medical therapy with ursodeoxycholic acid (UDCA) [1–3]. We report a case of LPAC syndrome revealed by acute pancreatitis in a 58-year-old woman and discuss it based on the literature.

Case presentation

A 58-year-old woman was admitted to the emergency department in December 2019 for recurrent acute abdominal pain. Her history included autosomal dominant polycystic hepatorenal disease, heterozygous factor V Leiden mutation, metabolic syndrome (hypertension, dyslipidemia, overweight with body mass index 26), gastroesophageal regurgitation, and hiatus hernia. The patient had recurrent epigastric pain over a 3-year period (December 2016 to December 2019). The abdominal pain started in December 2016 associated with abnormal liver function tests such as cytolysis and cholestasis. Morphological explorations (ultrasound and echo-endoscopy) showed vesicular lithiasis, a thickened vesicular wall and dilatation of the main bile duct. Magnetic resonance Cholangiopancreatography reported no bile duct abnormalities. The patient had undergone cholecystectomy. Histological examination of the surgical specimen showed chronic lithiasis cholecystitis with cholesterolosis. The evolution was marked by a recurrence of abdominal pain associated with episodes of acute angiocholitis post-cholecystectomy. In December 2019, a recurrence of severe abdominal pain, associated with vomiting motivated the patient to visit the emergency department. Laboratory tests on admission reported a serum lipase level at 206 U/L. Serum calcium and triglyceride levels were normal. Hepatitis A, B and C serologies were negative. Polymerase chain reaction for cytomegalovirus, herpes simplex virus and Epstein-Barr virus were negative. Serum immunoglobulin G4 (IgG4) was normal. The other laboratory tests are reported in Table 1. First abdominal ultrasound performed in the emergency department reported normal liver parenchyma, non-dilated bile ducts, absence of intra- and extra-hepatic biliary lithiasis and normal pancreatic morphology. Abdominal computed tomography at 72 h showed a known polycystic hepatorenal disease and hiatal hernia, with no abnormalities of the pancreatic parenchyma (Fig. 1). Uncomplicated idiopathic acute pancreatitis was initially suggested. The patient failed to refeed on several occasions with recurrence of epigastric pain. LPAC syndrome was suspected in view of this recurrent post-cholecystectomy pain. Second abdominal ultrasound performed by an expert and knowledgeable radiologist showed comet tail artifacts along the intrahepatic bile ducts, consistent with LPAC syndrome (Fig. 2). Upper gastrointestinal endoscopy showed a hiatal hernia and ulcerated D2 lesions. Upper echo-endoscopy showed a comet tail image of the left liver suggesting LPAC syndrome. A therapeutic trial with ursodeoxycholic acid (UDCA) (Cholurso®) at a dose of 10 mg/kg/day was started, without waiting for the result of an ABCB4 genotyping and pantoprazole® 80 mg/day. The in-hospital outcome was favorable with disappearance of the epigastric pain from the first week with a good resumption of the feeding. The clinical evolution remained favorable at 3 months under UDCA with no recurrence of pain. The abdominal ultrasound at 6 months was normal. The patient was referred to the expert center for further follow-up. We ultimately the diagnosis of acute pancreatitis secondary to LPAC syndrome.

Discussion

We reported a rare case of LPAC syndrome in a 58-year-old woman. In its classic form, LPAC syndrome is a disease of young, low weight women [2–4]. In our patient, LPAC syndrome was diagnosed late in relation to the onset of symptoms. This could be explained by the age of our patient over 50 years and the presence of metabolic syndrome in our patient. Therefore, she presented from an epidemiological point of view an exceptional form of the disease. According to the literature, it is quite exceptional to see this syndrome after 50 years of age and only 3% of patients have a BMI greater than 25 [4]. Biliary complications such as acute cholecystitis, recurrent acute angiocholitis and acute pancreatitis can be indicative of LPAC syndrome [5]. In our case, the LPAC syndrome was discovered following a biliary complication such as acute pancreatitis.

The diagnosis of LPAC syndrome is currently based on the presence of at least 2 criteria: (1) onset of biliary symptoms before the age of 40, (2) recurrence of symptoms after cholecystectomy, (3) presence of intrahepatic hyperechoic foci ("comet tails" or micro-lithiasis). There are also minor diagnostic criteria such as family history

Table 1 Laboratory results

Laboratory tests	Value	Normal range
Leukocytes (cells/L)	7.97×10^9	4–10 10^9 cells/L
Hemoglobin (g/dL)	14.6	12–18 g/dL
Platelet count (cells/L)	255	150–450 10^9 cells/L
C-reactive protein (mg/L)	80	0–6 mg/L
Aspartate aminotransferase (U/L)	32	5–34 U/L
Alanine aminotransferase (U/L)	35	0–55 U/L
Total bilirubin (µmol/L)	8	0–20 µmol/L
Gamma-glutamyl transpeptidase (U/L)	34	9–36 U/L
Alkaline phosphatase (U/L)	73	42–98 U/L
Serum lipase level (U/L)	206	13–60 U/L
Blood sodium level (mmol/L)	138	136–145 mmol/L
Blood potassium level (mmol/L)	4	3.5–5.1 mmol/L
Serum calcium level (mmol/L)	2.2	2.1–2.55 mmol/L
Serum triglyceride level (g/L)	2.1	0–1.99 g/L
Serum creatinine level (µmol/L)	70	49–90 µmol/L
Fasting blood glucose (mmol/L)	6.2	4.1–5.6 mmol/L
Serum Immunoglobin G4 level	0.68	0.011–1040 g/L
Cytomegalovirus polymerase chain reaction	Negative	–
Herpes simplex virus polymerase chain reaction	Negative	
Epstein-Barr virus polymerase chain reaction	Negative	
Hepatitis B surface antigen	Negative	–
Hepatitis C antibody	Negative	–
Hepatitis A antibody type IgM	Negative	–
Human immunodeficiency virus serology	Negative	–

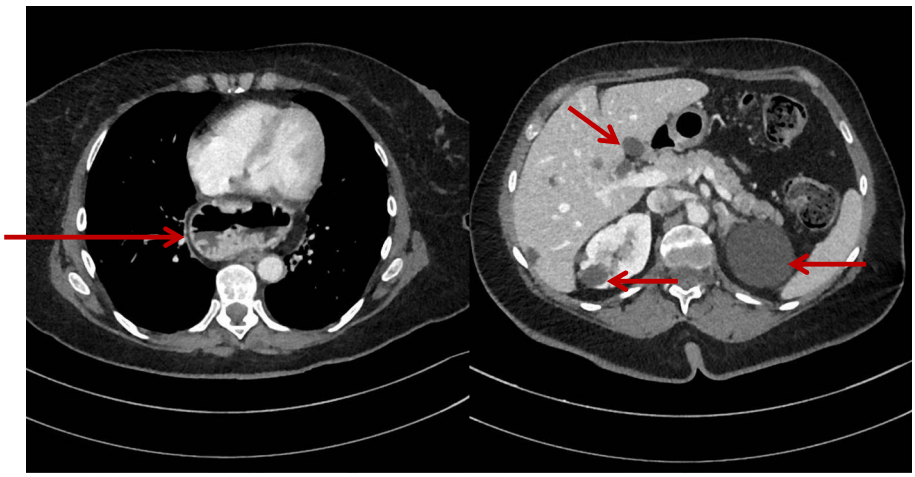

Fig. 1 Abdominal CT scan showing a polycystic hepatorenal disease and hiatal hernia, with no abnormalities of the pancreatic parenchyma

of first-degree biliary lithiasis, history of gravid cholestasis, and sensitivity to treatment with ursodeoxycholic acid [1–5]. Our patient had two of the three diagnostic criteria listed above, associated with improvement on UDCA, which allowed us to make the diagnosis of LPAC syndrome. The recurrence of typical epigastric pain after cholecystectomy and the history of biliary complications such as episodes of acute angiocholitis and acute pancreatitis, allowed us to orientate towards an LPAC syndrome. In front of suggestive symptoms, LPAC syndrome can be confirmed in 3 different ways such as ABCB4 genotyping, bile analysis and abdominal ultrasound [2–5]. In

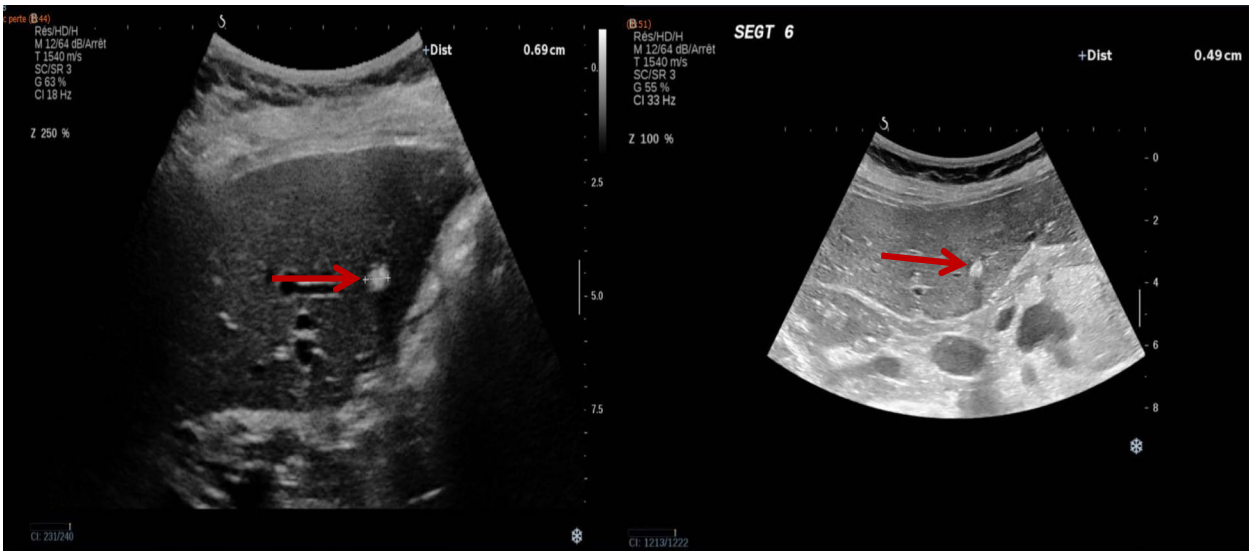

Fig. 2 Abdominal ultrasound showing the presence of comet tail artifacts along the intrahepatic bile ducts, consistent with LPAC syndrome

routine practice, abdominal ultrasound performed by an operator trained to look for suggestive signs is the most relevant way to confirm the diagnosis. This expert ultrasound reveals typical anomalies in 80 to 85% of cases [3–6]. In our patient, the diagnosis was made with a second ultrasound performed by an expert radiologist, finding a typical comet tail image. Our patient had several previous ultrasounds performed by a non-expert radiologist who was not aware of the suspected diagnosis of LPAC syndrome and did not detect any particular abnormality in this sense. This finding confirms the data in the literature where non-expert ultrasound will describe signs of the disease in only 5% of LPAC cases [3, 7].

The treatment of LPAC syndrome is based on long-term medical treatment with UDCA at a dosage of 10 mg/kg/day. In the majority of cases, UDCA allows the disappearance of symptoms within the first few weeks of treatment [5–8]. In our case, the outcome was spectacular with disappearance of pain from the first week of treatment. However, the ultrasound anomalies take longer to disappear, in a few months or even years [4, 5]. Clinical improvement may be partial with UDCA 10 mg/kg/day, with a decrease in pain without disappearance. In the absence of poor compliance with UDCA treatment or pain of another origin, it may then be proposed to increase the dosage of UDCA to 15 to 20 mg/kg/day. If optimization of UDCA therapy fails, adjuvant treatment with ezetimibe may be proposed on pathophysiological grounds, without proof of clinical efficacy. In case of hypercholesterolemia, statins are preferable to fibrates, which increase cholesterol secretion into the bile [1–8]. The effects of UDCA on symptoms can be observed after only a few weeks or months of treatment, when stones have not yet been substantially modified by the treatment. This suggests that cholesterol crystals, which disappear rapidly from bile during treatment, and/or the associated inflammatory lesions play an important role in the appearance of symptoms. Precisely when stones do eventually disappear is not known at the present time [1–8]. In eight patients with large bile duct dilatations treated by UDCA, a decrease in the number of stones was documented after 3 years or more of treatment, and stones were no longer detected by ultrasound and magnetic resonance imaging in one patient [1].

Consequently, the dissemination of knowledge about the suggestive signs of LPAC syndrome to our colleagues in visceral surgery or even in hepato-gastroenterology, and about the radiological signs of this syndrome to our colleagues in radiology, should allow the detection of many cases of LPAC syndrome and avoid many cholecystectomies thanks to the early use of UDCA.

Conclusion

LPAC syndrome must be evoked in front of all symptomatic lithiasis before the age of 40 years or recurrent pain after cholecystectomy. Ultrasound performed by a radiologist expert in the typical signs of this condition allows its confirmation in most cases. UDCA should be introduced without waiting for the results of the ABCB4 mutation search.

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Authors' contributions
CIR, BMR, and JAR were major contributors in drafting the manuscript and revised the content. CS and PL were the gastroenterologists responsible for treating the patient and revised the manuscript for important content. SHR and RMR revised the manuscript for important content. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A signed consent form authorizing the publication is available and included in the patient's chart.

Competing interests
The authors declare that they have no competing interests.

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