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CASE REPORT

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Low-Phospholipid-Associated Cholelithiasis Syndrome (LPAC): when to suspect? Case report

Phospholipid-Associated Cholelithiasis Syndrome (LPAC): quando suspeitar? Relato de caso

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Abstract

Introduction*: Low-phospholipid-associated cholelithiasis syndrome (LPAC) is a rare form of intrahepatic lithiasis linked to a defect of phospholipid canalicular secretion into bile. It is part of the spectrum of liver diseases associated with ABCB4/MDR3 deficiencies and is characterized by recurrent events of biliary colic, acute cholangitis, or pancreatitis in patients after cholecystectomy.* ***Objectives****: To report a suspected case of LPAC to expand the knowledge of this pathology.* ***Case report****: Patient, female, 39 years old, sought medical attention with pain on the right hypochondrium associated with nausea and vomit that initiated two days ago. The patient reported the first episode of acute pancreatitis in 2019 and six more episodes afterward. In the last episode, on April 2020, cholecystectomy was performed during hospitalization. Three more episodes of acute pancreatitis occurred since then. Elevated lipase levels appeared on laboratory evaluation. Therefore, the diagnosis of acute pancreatitis was made based on clinical and laboratory signs and the diagnosis of LPAC was suspected based on clinical signs.* ***Conclusion****: Althought there is few articles about LPAC syndrome it must be reminded as a differential diagnosis in cases of recurrence of biliary pain, acute pancreatitis after cholecystectomy, and when these events occur in young patients with no classic risk factors for such diseases.*

Keywords: *Cholestasis, Ursodeoxycholic acid, Cholelithiasis*

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Resumo

Introdução: *A Síndrome LPAC (Low-phospholipid-associated cholelithiasis syndrome) é uma forma rara de colelitíase intra-hepática, associada ao defeito na secreção canalicular de fosfolipídios para a bile. Faz parte do espectro de doenças hepáticas associadas a deficiências do ABCB4/MDR3 e é caracterizada por eventos recorrentes de cólica biliar, colangite aguda ou pancreatite em pacientes após a colecistectomia.* ***Objetivo:*** *Relatar um caso suspeito de LPAC de forma a expandir o conhecimento da doença.* ***Relato de Caso:*** *Paciente feminino, 39 anos, procurou atendimento por quadro de dor em região de hipocôndrio direito com irradiação para dorso, associada a náuseas e vômitos há dois dias. Relatou primeiro episódio de pancreatite aguda em 2019, com seis episódios subsequentes, sendo o último em abril de 2020 quando foi submetida à colecistectomia videolaparoscópica durante a internação. Desde então, referiu outros três episódios. Alterações laboratoriais incluíam aumento significativo de lipase. Baseado nos critérios clínicos e laboratoriais, estabeleceu-se diagnóstico de pancreatite aguda e por critérios clínicos suspeita-se do diagnóstico de LPAC.* ***Conclusão:*** *A síndrome LPAC, apesar de pouco documentada na literatura, deve ser lembrada como hipótese diagnóstica em casos de cólica biliar e pancreatite de origem biliar, que recorrem mesmo após a colecistectomia ou se manifestam em pacientes jovens sem fatores de risco clássicos para tais doenças.*

Palavras chave: *Colestase, Ácido ursodesoxicólico, Colelitíase*

Introduction

Low-phospholipid-associated cholelithiasis syndrome (LPAC) is a rare form of intrahepatic lithiasis linked to a defect of phospholipid canalicular secretion into bile[1-2]. Young adults represent the majority of cases. This condition was described for the first time in 2001 by Rosmorduc et al. LPAC belongs to the group of hepatic diseases associated with deficiencies in ABCB4/MDR3 with 30-50% of patients

displaying mutations in that gene. It is characterized by recurrent biliary colic events, acute cholangitis or pancreatitis in patients who had cholecystectomy surgery[2–4]. 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. Phosphatidylcholine also takes part in the protection of the biliary epithelium by reducing the emulsifying effect of the bile salts. MDR3 deficiency results in a chronic inflammatory reaction which is responsible for the increase of GGT (gamma glutamyl transpeptidase) and the precipitation of cholesterol in the biliary ducts (intrahepatic lithiasis)[2,5].

Although the rate of prevalence for this syndrome was considered low, it is unknown[6]. In a recent study with the largest cohort and case control in LPAC patients, Dong et al[2] has provided the first estimate of the prevalence of this condition in patients with symptomatic cholelithiasis: approximately 1% of patients hospitalized in France with biliary calculus symptoms. Unlike regular biliary calculus[4,7], this syndrome affects women and young adults predominantly. It is defined by at least two criteria displayed below (Chart 1).

Chart 1

Clinical criteria for presumptive diagnosis[2]

Diagnostic criteria
Biliary symptoms beginning before the age of 40.
Intrahepatic echogenic focuses or microlithíasis
Symptom recurrence after cholecystectomy

Adapted from: Dong C, Condat B, Picon-Coste M, Chrétien Y, Potier P, Noblinski B, et al. Low-phospholipid-associated cholelithiasis syndrome: Prevalence, clinical features, and comorbidities. JHEP Rep. 2020; 3(2):100201[2].

These criteria were proposed by taking into consideration a limited number of case control studies in order to predict mutations of ABCB4 gene[2]. These mutations were absent in approximately half of the patients with the syndrome. Thus, the diagnostic criteria currently established may not contemplate all the clinical spectrum manifested by LPAC[2]. Other diagnostic criteria that can be taken into consideration include biliary lithiasis history in first degree relatives, previous history of gestational cholestasis and response to ursodeoxycholic acid treatment[8-9].

In addition to diagnostic criteria, there are radiological aspects, analysis of bile composition collected during catheterization and mutation research of ABCB4 gene which help in the diagnosis of the syndrome.

The early diagnosis of LPAC is important because the management of the syndrome differs from the regular calculous biliary tract disease. Since it is a syndrome with intrahepatic cholelithiasis, the symptoms and complications are drastically reduced with the administration of ursodeoxycholic acid[2]. Besides that, patients demand specific monitoring because there is potential risk in the development of gestational intrahepatic cholestasis in women, chronic cholestatic disease and related complications, including cirrhosis and hepatobiliary cancer, not to mention cardiovascular complications[2].

Case report

The report was submitted to the Research Ethics Committee and has been approved under the legal opinion 4.734.178 – CAAE: 46559721.8.0000.5065 – Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória.

F.O.A., female, 39 years old, was admitted in the gastroenterology service of Hospital Santa Casa de Misericórdia in Vitória in November, 2020, reporting pain in the right hipocondrium with irradiation to the dorsum region associated with nausea and vomit for 02 days. No fever or jaundice was reported.

Relevant previous medical history included the first acute pancreatitis episode in 2019, followed by 6 episodes, with the last one taking place in April, 2020, when a magnetic resonance cholangiography evidenced signs of acute pancreatitis and biliar microlithiasis making it necessary to submit the patient to a videolaparoscopic cholecystectomy during her stay in the hospital. Since then, the patient reported 3 episodes. The patient's comorbidity include overweight and a diagnosis of hypertension and dyslipidemia which are being treated with ciprofibrate 100mg/day, losartan 100mg/day and simvastatin 40mg/day. Patient denied alcoholism, smoking or drug use.

Upon physical examination she presented atypical and tympanic abdomen, painfully sensitive to deep palpation of the epigastric region, absence of masses or palpable visceromegalies with no signs of peritoneal irritation or defense. Other systems presented no alterations.

Laboratory tests performed when the patient was admitted can be seen in Table 1. Based on the clinical and laboratorial criteria an acute pancreatitis diagnosis was established.

Patient responded well to the management of the pancreatitis. Requested computed tomography of the abdomen showed absence of dilation of both intra and extrahepatic biliary ducts, but showed the pancreas was displaying collections in the peripancreatic spaces and left anterior pararenal region (Figure 1). Taking

Table 1

Laboratory tests	
Hemoglobin (g/dL)	**9,9**
Hematocrit (%)	29,3
Leukocytes / Band cells (%)	7.250 / 3
Platelets (μL)	232.000
Aspartate aminotransferase – AST (U/L)	35
Alanine aminotransferase – ALT (U/L)	16
Gamma glutamyl transpeptidase – GGT (U/L)	18
Alkaline phosphatase (U/L)	60
Total Bilirrubin (mg/dL)	0,4
Direct Bilirrubin (mg/dL)	0,3
Amylase (UI/L)	92
Lipase (UI/L)	1.238
C-reactive Protein (mg/dL)	99,3
Triglycerides (mg/dL)	536

Source: Reserch data.

into consideration the clinical criteria, LPAC diagnosis was proposed. Upon patient's discharge from the hepatology ambulatory of the Hospital Santa Casa de Misericórdia de Vitória, treatment with ursodeoxycholic acid was recommended.

Discussion

LPAC was first described in France. Although LPAC is considered a rare disease, it is estimated that 1 to 5% of patients with symptomatic cholelithiasis have the syndrome[2,10]. New studies carried out point to a prevalence of LPAC in female patients[2]. It is made necessary to question if it is less prevalent because it is little known, underdiagnosed and has a broad clinical spectrum.

The diagnosis of the syndrome is done following clinical criteria. When it comes to the case reported in this article, LPAC diagnosis was suspected and established by the presence of two of the three criteria that characterize the syndrome[2]: beginning of symptoms before the age of 40 and recurrence of biliary symptoms after surgical approach, with a total of three episodes of acute pancreatitis after the surgery. The third criterion was not present: Intrahepatic echogenic focuses or microlithíasis after cholecystectomy.

The most common pancreatitis etiology is biliary (38%), followed by alcoholic (36%)[11]. For the patient depicted in this article, the biliary hypothesis was suspected and treated after the first episodes of pancreatitis. Posterior to the cholecystectomy, with new episodes of the disease, other causes for the pancreatitis must be investigated, such as trauma and/or surgical interventions in the superior abdomen, hypertriglyceridemia, autoimmune causes, medication and genetics. To determine pancreatitis etiology, it is paramount to perform detailed anamnesis. Concerning the reported case other etiologies such as alcoholic, traumas or autoimmune causes were discarded during anamnesis. Hypertriglyceridemia and the use of medication with the potential to cause pancreatitis were the confusional etiologies of the case.

Acute pancreatitis induced by pharmaceuticals is a rare etiology and the mechanisms proposed for the pancreatic lesion are diverse[12]. Drugs are classified in 4 different categories and from the medication reported in the case, simvastatin has been previously associated with the recurrence of pancreatitis once it is reintroduced, excluded other known causes (Ia),

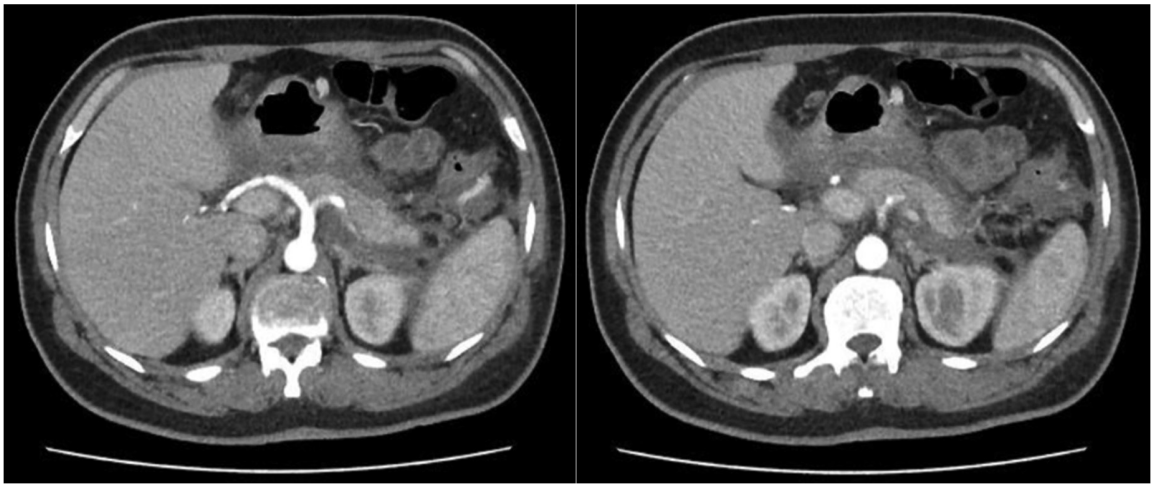

Figure 1 – Abdomen computed tomography contrasted in arterial fase showing cholecystectomy with metallic clips, chronic liver disease and poorly individualized pancreas, displaying collections in peripancreatic spaces and left anterior pararenal region. Source: Research data.

and losartan has also been reported to have a similar effect although other possible causes hadn't been excluded (Ib)[12]. To consider drug induced pancreatitis, re-exposure to the medication leading to a recurrence of pancreatitis is needed by definition and should only be done if the benefits of the medication in question surpass the risk of a new pancreatitis episode[13]. That makes it hard to establish a clear connection between pancreatitis and its induction by medication[13].

Hypertriglyceridemia represents around 2 to 4% of acute pancreatitis etiology and is a pathology generally associated with the condition when the triglyceride level (TG) is superior to 1.000 mg/dL[14]. However, the limit value in which acute pancreatitis can happen is not yet well defined and it can vary from patient to patient[14]. It's important to point out that TG levels should be dosed as soon as acute pancreatitis is suspected or confirmed since its values tend to reduce with fasting[14]. In that way, the diagnostic hypothesis of this etiology ends up being overlooked if TG levels are inferior to 1.000 when collected in timely fashion.

Literature points to the fact that LPAC generally affects young woman with normal BMI and no metabolic syndrome. However, in the 2021 French study which analysed 308 cases of the syndrome, 30% of cases were overweight at the time of diagnosis and 13% were obese[2]. Besides the presence of two of the three diagnostic criteria, the patient reported in this article has prevalent characteristics present in patients with the syndrome: female (77%), overweight (30%), dyslipidemia (8%) and hypertension (7%)[2]. The presence of acquired risk factors for biliary calculus like overweight, diabetes and dyslipidemia can be explained by the age in which LPAC usually develops: adults around 27 years of age[2]. These factors can also aggravate cholelithiasis[2].

Due to the ample clinical spectrum of LPAC, some common findings did not occur in the case in question. There is no history of cholestasis during gestation, which usually occurs in 56% of women with LPAC[9], explained by the action of estrogen which inhibits the excretion of phospholipids in the bile[15]. Also, there isn't any similar medical history in relatives (Mother, sisters and others), which doesn't exclude the necessity for the genetic test to find the mutation of ABCB4 gene and screening of first degree family members[4].

ABCB4 gene mutation research has not been done since it should be used in cases where the confirmation of the diagnosis becomes necessary when other elements are absent. Once the identification of a case has its gene mutation confirmed, family screening is recommended with the object of providing early diagnosis and genetic counseling focused on the family so that treatment can be established and further complications can be prevented[6]. However, it's important to point out that since the mutation of ABCB4 gene is not present in 100% of cases, its absence does not invalidate the diagnosis of the LPAC syndrome. Especially because current techniques can't detect all mutations since some are not yet known or associated with bile acid or cholesterol transportation.

Patient's treatment was instituted based on the relevant diagnostic hypothesis backed by the presumptive diagnosis by fulfilling the clinical criteria. The patient was provided with guidelines when it comes to changes in dietary behavior (reduction of food rich in fat and physical activity implementation) and comorbidity control (prescription of statin, fibrate and antihypertensive). The prescription of ursodeoxycholic acid was implemented specifically for LPAC (300mg twice a day). Even though restriction diets are not recommended for LPAC due to their ineffectiveness[6], they were indicated in this case to help control comorbidities and improve the quality of life of the patient.

Ursodeoxycholic acid, a hydrophilic bile acid, is the basis of the treatment for LPAC. It solubilizes cholesterol, reduces pro-inflammatory cytokines, protects biliary epithelium, increases bile secretion, potentializes the action of MDR3, reduces the quantity of hydrophobic bile acids and increases hydrophilic through the intracellular signalization regulation[6]. The effect on symptomatology is fast, even though it is not possible to visualize the effects as quickly in image exams because the cellular damage is caused by the inflammation generated by the micro crystals and not due to the formation of large calculi[6]. This treatment works for the majority of patients and should be used long term, even after the symptoms disappear. It is not known if it should be done for the rest of the patient's life[15]. The current perspective for LPAC is that new treatment should be able to induce an increase in the activity of gene ABCB4[6].

Concerning surgical treatment, the patient was subjected to a cholecystectomy in one of the first acute pancreatitis episodes attributed to a bile cause. When compared to the literature, the removal of the gallbladder because of the presence of lithiasis which caused pain was seen in 90% of LPAC cases[6]. There are other situations that demand interventional treatments, like patients with inflammation and abscess due to the dilation of intrahepatic biliary ducts by biliary calculi. In these cases the draining via percutaneous, endoscopic or surgical treatment with partial hepatectomy[6]. In case of complications that may cause terminal hepatocellular insufficiency, liver transplant must be performed[6].

The low availability of hepatic phosphatidylcholine, a phospholipid necessary in the formation of lipoprotein secretion, reduces serum level of high

density lipoprotein (HDL) and very low density lipoproteins (VLDL) through the inhibition of hepatic secretion and increase of the serum capture of these particles[16]. Although the deficiency of this enzyme has been recently associated with the progression of liver and heart diseases more studies are needed to clarify this aspect of the disease[16]. 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[4,15].

Upon LPAC suspicion as the cause of intrahepatic cholelithiasis, it is necessary to check for differential diagnosis that may point out to other diseases known for causing bile duct inflammation, such as Caroli's disease and primary sclerosing cholangitis[9].

Conclusion

Although LPAC syndrome is not very frequent in literature, it must be remembered as a diagnostic hypothesis in biliary colic and pancreatitis caused by bile, which reoccurs even after cholecystectomy or manifests in young patients who don't display the expected risk factors for these diseases.

References

1. Rosmorduc O, Poupon R, Hermelin B. MDR3 gene defect in adults with symptomatic intrahepatic and gallbladder cholesterol cholelithiasis. Gastroenterology. 2001; 120(6):1459–67.
2. Dong C, Condat B, Picon-Coste M, Chrétien Y, Potier P, Noblinski B, et al. Low-phospholipid-associated cholelithiasis syndrome: prevalence, clinical features, and comorbidities. JHEP Rep. 2021;3(2):100201.
3. Pasmant E, Goussard P, Baranes L, Laurendeau I, Quentin S, Ponsot P, et al. First description of ABCB4 gene deletions in familial low phospholipid-associated cholelithiasis and oral contraceptives-induced cholestasis. Eur J Hum Genet. 2012; 20(3):277–82.
4. Poupon R, Rosmorduc O, Boëlle PY, Chrétien Y, Corpechot C, Chazouillères O, et al. Genotype-phenotype relationships in the low-phospholipid-associated cholelithiasis syndrome: a study of 156 consecutive patients. Hepatology. 2013; 58(3):1105–10.
5. Nayagam JS, Williamson C, Joshi D, Thompson RJ. Review article: liver disease in adults with variants in the cholestasis-related genes ABCB11, ABCB4 and ATP8B1. Aliment Pharmacol Ther. 2020; 52(11–12):1628–39.
6. Goubault P, Brunel T, Rode A, Bancel B, Mohkam K, Mabrut JY. Low-Phospholipid Associated Cholelithiasis (LPAC) syndrome: a synthetic review. J Visc Surg. 2019; 156(4):319–28.
7. Condat B, Zanditenas D, Barbu V, Hauuy M-P, Parfait B, El Naggar A, et al. Prevalence of low phospholipid-associated cholelithiasis in young female patients. Dig Liver Dis. 2013; 45(11):915–9.
8. Rosmorduc O, Hermelin B, Boelle P, Parc R, Taboury J, Poupon R. ABCB4 gene mutation—associated cholelithiasis in adults. Gastroenterology. 2003;125(2):452–9.
9. Rosmorduc O, Poupon R. Low phospholipid associated cholelithiasis: association with mutation in the MDR3/ABCB4 gene. Orphanet J Rare Dis. 2007; 2(1):29.
10. Erlinger S. Low phospholipid-associated cholestasis and cholelithiasis. Clin Res Hepatol Gastroenterol. 2012; 36:S36–40.
11. Wang G-J, Gao C-F, Wei D, Wang C, Ding S-Q. Acute pancreatitis: etiology and common pathogenesis. World J Gastroenterol. 2009;15(12):1427.
12. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol. 2007; 5(6):648-61.
13. Nitsche C, Maertin S, Scheiber J, Ritter CA, Lerch MM, Mayerle J. Drug-induced pancreatitis. Curr Gastroenterol Rep. 2012; 14(2):131–8.
14. Garg R, Rustagi T. Management of hypertriglyceridemia induced acute pancreatitis. Biomed Res Int. 2018; 2018:4721357.
15. Gille N, Karila-Cohen P, Goujon G, Konstantinou D, Rekik S, Bécheur H, et al. Low phospholipid-associated cholelithiasis syndrome: A rare cause of acute pancreatitis that should not be neglected. World J Hepatol. 2020; 12(6):312–22.
16. Cole LK, Vance JE, Vance DE. Phosphatidylcholine biosynthesis and lipoprotein metabolism. Biochim Biophys Acta. 2012; 1821(5):754–61.

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