Published online: 2019-09-16

Case Report

The Nowhere Stone: Unusually Located Intrahepatic Calculi in a Patient with Low Phospholipid-associated Cholelithiasis Syndrome

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Abstract

Intrahepatic calculi or hepatolithiasis is an uncommon phenomenon which is found in relatively higher rates in eastern Asian countries. Patients usually present with features of cholangitis or intrahepatic abscess and are at risk for developing cholangiocarcinoma. Correct diagnosis and management often pose challenges. A 42-year-old female presented with a history of episodic upper abdominal pain since 8 years. Initial imaging studies showed evidence of biliary calculi, but were confounding in their localization. Magnetic resonance cholangiopancreatography showed two large calculi in the right biliary system proximal to the confluence, along with choledocholithiasis. Endoscopic retrograde cholangiopancreatography and common bile duct clearance were done; however, the patient underwent hepatic sectionectomy as a curative procedure. ABCB4 mutation was detected on DNA analysis and hence aided in making the diagnosis of low phospholipid-associated cholelithiasis. Additional imaging studies are warranted in doubtful cases. Difficult accessibility of the calculi may often limit endoscopic therapeutic options and pave the way for surgical interventions. As there is an increased risk of cholangiocarcinoma in these patients, regular follow-up is essential.

Keywords: *ABCB4, gallstones, hepatolithiasis, intrahepatic calculi, magnetic resonance cholangiopancreatography*

Introduction

Intrahepatic calculi, an uncommon phenomenon, are observed with varying prevalence rates globally, with high rates reported in Eastern Asia and a few South American countries,[1] while Indian data have been sporadic. The reported average morbidity is 0.6%–1.3% in the west, even though Asian studies have shown a trend for reduced prevalence.[2] Multiple etiological factors including diet, nutrition, biliary tract abnormalities, recurrent bacterial and parasitic infections, and immune status have been implicated.[2] In general, affected patients have a prolonged history of recurrent abdominal pain, fever, chills, and jaundice. Intrahepatic calculi occur proximal to the confluence of the right and left hepatic ducts, can be unilobar or bilobar, and show an increased tendency for affliction of the left lobe.[3] Primary calculi are formed *de novo* in the bile ducts, while secondary calculi are often those that migrate retrogradely from the common bile duct (CBD) or the gallbladder (GB). Among the diagnostic modalities, magnetic resonance cholangiopancreatography (MRCP) is often preferred.[4] Endoscopic removal of these calculi is often not easy, and surgical intervention is sometimes required. Longstanding intrahepatic calculi may predispose to cholangiocarcinoma,[5] and hence prompt diagnosis and management is essential.

Access this article online

Quick Response Code:

Website: www.jdeonline.in

DOI: 10.4103/jde.JDE_6_18

Case Report

A 42-year-old married female presented with a history of episodic right upper quadrant and epigastric pain for 8 years; she experienced the pain 3 months after the birth of her only child. There was no family history of biliary or pancreatic disease. She was nondiabetic and had no

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How to cite this article: Suresh I, Lokesh E, Suhas C, Nanaiah A. The nowhere stone: Unusually located intrahepatic calculi in a patient with low phospholipid-associated cholelithiasis syndrome. J Dig Endosc 2019;XX:XX-XX.

history suggestive of steatorrhea. Blood workup revealed leukocytosis, mildly elevated liver transaminases and gamma-glutamyltransferase, dyslipidemia, and elevated levels of serum amylase and lipase [Table 1].

Initial ultrasonogram of the abdomen done elsewhere suggested cholelithiasis and choledocholithiasis [Figure 1]. Contrast-enhanced computed tomography (CECT) of the abdomen suggested relatively large faceted intraluminal ?fundal GB calculi measuring 3.2 cm × 2.2 cm, smaller distal CBD calculi (7 and 8 mm) and dilated CBD (11 mm) with normal intrahepatic biliary radicles [Figure 2]. MRCP/magnetic resonance imaging (MRI) abdomen was done which suggested choledocholithiasis, dilated CBD, no GB calculi and the presence of two calculi in the intrahepatic radicles near the confluence of the hepatic ducts measuring 30 mm × 33 mm and 26 mm × 28 mm, respectively, with surrounding normal liver tissue [Figures 3 and 4].

Table 1: Investigations

Parameters	Values
Hb	11.6 g%
TC	13,970 cells/mm^3
DC	N(78) L(10)
Platelet count	2.8 lakhs/mm^3
Peripheral smear	Normocytic normochromic
ESR	40 mm (1st h)
INR	1.06
Total bilirubin	1.7 mg/dL
Direct bilirubin	0.9 mg/dL
Total protein	
Albumin	3.83 g/dL
A/G ratio	
SGOT	31 IU/L
SGPT	47 IU/L
ALP	254 IU/L
GGT	53 U/L
HIV, HBsAg, Anti HCV	Negative
Serum amylase	103 U/L
Serum lipase	218 U/L
TC	242
Triglycerides	184
HDL	37
LDL	140
Hepatic bile phospholipid	0.7 g/L
Hepatic bile cholesterol	7.4 g/L
DNA analysis	Missense mutation in ABCB4 gene

Hb=Hemoglobin, ESR=Erythrocyte sedimentation rate, INR=International normalized ratio, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase, ALP=Alkaline phosphatase, GGT=Gamma-glutamyl transpeptidase, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, TC=Total cholesterol, DC=Differential Count

Endoscopic retrograde cholangiopancreatography was done during which the distal CBD calculi were extracted, and it was also ascertained that the larger calculi were present in the right system, above the

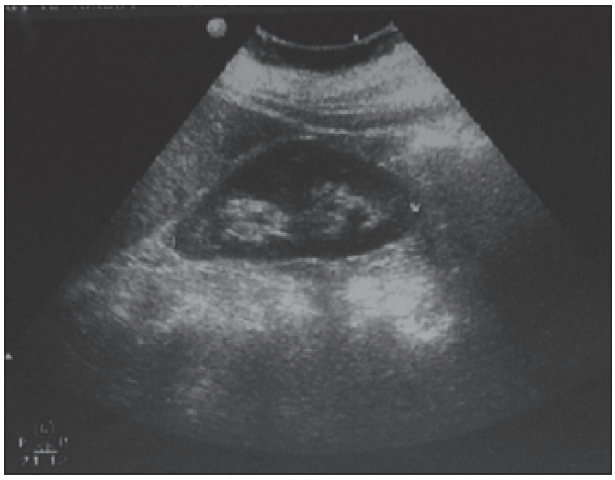

Figure 1: Ultrasonography abdomen

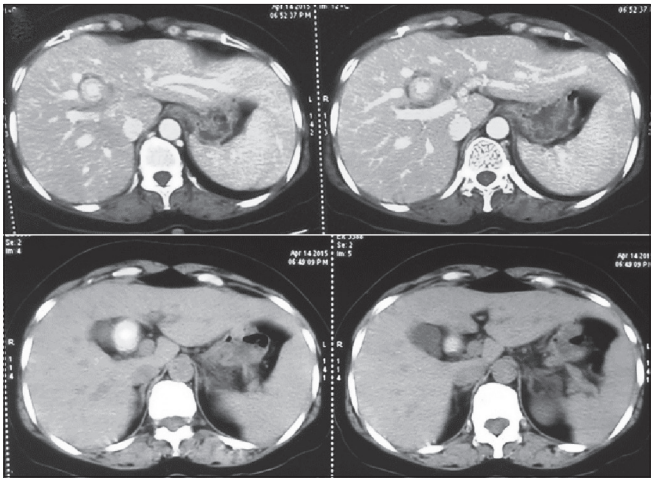

Figure 2: Contrast-enhanced computed tomography abdomen showing calculi

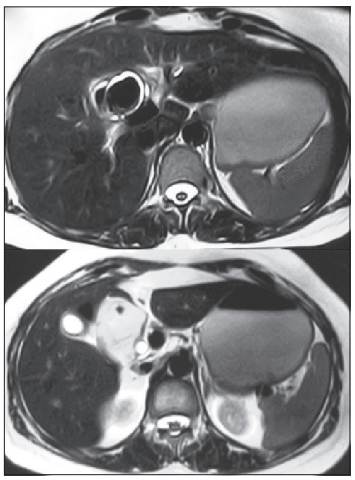

Figure 3: Magnetic resonance imaging abdomen

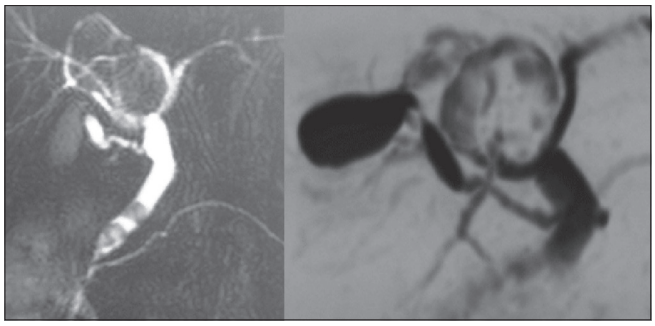

Figure 4: Magnetic resonance cholangiopancreatography showing calculi in common bile duct and proximal to biliary confluence

biliary confluence [Figure 5]. Aspirated bile showed low levels of phospholipids and hence a possibility of low-phospholipid-associated cholelithiasis was entertained.

Hepatobiliary surgery consult was sought, and she was advised surgery. The patient preferred to get her surgery done abroad, and hence traveled to the United States, where she underwent systematic extended right posterior sectionectomy involving complete S6 + partial S5 resection and cholecystectomy after an unsuccessful attempt at cholangioscopic lithotripsy because of ductal kinking and poor accessibility. The patient also was not willing for a trial of mechanical lithotripsy. The operated specimen of the GB did not show the presence of calculi or malignancy, while the resected hepatic segment showed the presence of two cholesterol-rich pigment calculi measuring 30 mm × 32 mm × and 25 mm × 28 mm, respectively, in the secondary biliary ducts. DNA analysis revealed mutation of the ABCB4 gene. Postoperatively, she recovered well and was discharged after 12 days. The patient returned to us after 2 months. She was given ursodeoxycholic acid and remained asymptomatic on follow-up after 12 months; repeat CECT did not show the development of any new lesions. This report emphasizes the uncommon nature of this condition, the diagnostic dilemma it poses, treatment options available, and the value of genetic analysis in aiding the diagnosis.

Discussion

The diagnosis and treatment planning of intrahepatic calculi has significantly improved with the introduction of advanced imaging modalities. Ultrasound serves as the first point of imaging in many centers, but as often is the case, is dependent on the operator experience and equipment. The presence of large intrahepatic calculi can be confounding and warrants additional advanced imaging techniques such as CECT or MRI/MRCP. Endoscopic ultrasound is another modality, but may be better at demonstrating calculi in the left biliary system

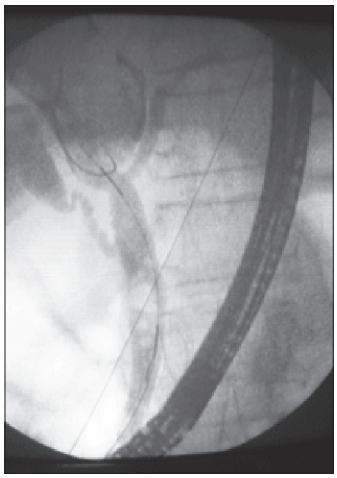

Figure 5: Endoscopic retrograde cholangiopancreatography cholangiography

than the right. Cholangiographic assessment remains the most accurate diagnostic procedure.[6]

In our patient, the initial imaging studies (ultrasonography and CECT) conveyed a picture of cholelithiasis with choledocholithiasis, with the sonologist suspecting a folded-up GB. MRI/MRCP was able to delineate the lesion better and was able to localize it proximal to the biliary confluence. The management strategy and patient counseling would have been different had we been steadfast with the initial diagnosis. The locus of the calculi also presents a point of interest in this patient, since the involvement of the secondary radicles in the right biliary system occurs less commonly than the left.[7] In contrast to literature reporting a higher likelihood of the previous cholecystectomy in patients with right hepatic involvement,[7] the patient in this case had no history of surgery.

Endoscopic or percutaneous treatment with or without lithotripsy is frequently used in the management of this condition by choledochoscopy and surgery. Extraction of all intra- and extrahepatic calculi, removal of atrophic liver segments, biliary strictures, areas with poor biliary drainage, etc., are the main goals of therapy.[8] Patients are at risk for developing cholangiocarcinoma due to the chronic inflammatory process, and liver resection remains the only treatment option in many cases.

Many studies have reported interesting histopathological findings in the resected hepatic segments – including evidence of Caroli's disease, periductal fibrosis, hepatic atrophy, cirrhosis, and chronic cholangiohepatitis.[7] In our patient, the resected liver segment showed hepatic atrophic changes, which were not picked up by any imaging studies. A few Indian studies have emphasized the need for surgical intervention in difficult cases along with a multidisciplinary approach.[9,10]

Regular follow-up with ultrasound or CT is recommended to analyze calculi reformation and the development of liver disease.

Conclusion

Intrahepatic calculi present diagnostic as well as management-related challenges. Additional imaging studies are warranted in doubtful cases. Difficult accessibility of the calculi may often limit endoscopic therapeutic options and pave the way for surgical interventions. Formation of the primary calculi is often associated with genetic mutations. As there is an increased risk of cholangiocarcinoma in these patients, regular follow-up is essential.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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