Unusual presentation of more common disease/injury

A rare grade III symptomatic Tsunoda class III left lobe hepatolithiasis in a North American woman

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Summary

A 44-year-old Caucasian woman without any identified predisposing factors, presented to her local emergency room with multiple episodes of recurrent ascending cholangitis. She underwent a laparoscopic cholecystectomy several years prior to her admission to the hospital for parenteral antibiotic therapy and she had no personal or family history of hypercholesterolaemia. Transferred to a tertiary hospital for surgical therapy, she underwent a left hepatic resection for a chronically infected left lobe hepatolithiasis (HL) conditioning atrophy of the parenchyma due to obstruction of the biliary tree by multiple large cholesterol stones. HL is a very rare condition in Western countries and its aetiology and predisposing factors are still unclear. We present her symptomatology, diagnostic and therapeutic management and discuss the epidemiology and risk factors of HL, that is, a common condition in South East Asia while exceptional in Caucasian patients who have not travelled in high-prevalence regions.

BACKGROUND

Hepatolithiasis (HL) is defined as the presence of gallstones in the bile ducts located in the liver parenchyma and proximal to the confluence of the right and left hepatic ducts, irrespective of the coexistence of gallstones in the common bile duct (CBD) and/or gallbladder. HL is endemic in Southeast Asia, where its prevalence can be as high as 30–50%.¹ On the contrary, the disease is rare in the West, with a prevalence of only 0.6–1.3%.² Its aetiology is not fully understood and may be classified into two forms:

1. intrahepatic HL where the stones exist only above the confluence and
2. intra-hepatic and extrahepatic HL where the stones are found in the bile duct lumen both proximally and distally to the biliary bifurcation.

Gallstones in HL are of two types: cholesterol stones that represents only 5–13% of cases and calcium bilirubinate stones that represents the remaining 85–95%.³

In Western countries, HL is a very rare disease and most of these patients are of Asian descent. Caucasians, Hispanics and African-American are not prone to develop HL unless they have other risk factors such as biliary strictures causing bile stasis and formation of crystals in the lumen of the biliary tree. In Western countries, Caroli's disease, primary sclerosing cholangitis, cholangiocarcinomas and postoperative strictures are predisposing factors for HL, while in Asia, HL is associated with parasitic infections with *Clonorchis sinensis* and *Ascaris lumbricoides*.⁴ Cholangiocarcinoma has been identified in 8–12% of patients affected by HL and most likely malignant transformation seems to be induced by chronic bacterial infection, bile stasis and mechanical irritation by the stones leading to mucosal hyperplasia and chronic proliferative cholangitis that are premalignant conditions.⁵ In North America, cholesterol stones are the predominant types of stones associated with HL. The left hepatic lobe

is more often affected by HL and the theoretical reason for this is the anatomical acute angle at the junction between the left hepatic duct and the common hepatic duct that can cause some degree of bile stasis.⁶

Untreated, HL can give rise to cholangitis, hepatic abscesses, secondary biliary cirrhosis, atrophy of the liver parenchyma, portal hypertension and cholangiocarcinoma due to chronic inflammation of the bile duct wall.^{7–8} The morbidity and a mortality of patients affected by HL is reported to be 20–30% and 1–10%,^{9–10} respectively.

The clinical and anatomical severity of HL are stratified in IV classes by the Japanese Hepatolithiasis Research Group and by Tsunoda Classification, respectively (tables 1 and 2).¹¹

We describe a rare clinical presentation of a 44-year-old Caucasian woman with recurrent episodes of ascending cholangitis due to intrahepatic HL involving only the left biliary system.

CASE PRESENTATION

A 44-year-old Caucasian woman was referred for assessment to a tertiary university centre due to recurrent episodes of ascending cholangitis presenting with high fever (39.5°C), abdominal pain, nausea, vomiting and hypotension. Her medical and surgical history was remarkable only for previous cholecystectomy, benign breast cyst

Table 1 Clinical severity score of hepatolithiasis by the Japanese Hepatolithiasis Research Group

Grade	Symptoms
I	No symptoms
II	Abdominal pain
III	Transient jaundice or cholangitis
IV	Continuous jaundice, sepsis or presence of cholangiocarcinoma

Table 2 Tsunoda anatomical classification of the severity of hepatolithiasis

Class	Findings
I	No marked dilatation or strictures of intrahepatic ducts
II	Diffuse dilatation of intrahepatic ducts without strictures
III	Unilateral Solitary or multiple cystic dilatation of intrahepatic ducts
IV	Bilateral with strictures

excision, tonsillectomy and haemorrhoidectomy. She denied any health problems during the last few years preceding her current admission to the hospital. Her family history was non-contributory. She was not on any medications and her social history was negative for travelling outside Canada, she smoked 4–5 cigarettes per day and she denied alcohol abuse. She worked as a waitress and she did not follow any specific dietary regimen. Her physical examination was within the normal limits.

INVESTIGATIONS

During one of the recurrent episodes of ascending cholangitis requiring admission to the local hospital for intravenous fluid resuscitation and parenteral antibiotic therapy, she had elevated white blood cell count ($17.2 \times 10^9/l$; normal range $4.5\text{--}11.0 \times 10^9/l$), serum alkaline phosphatase (ALP) (135 U/l; normal range 32–92 U/l) and gamma glutamyl transferase (GGT) (383 U/l, normal range 7–50 U/l) levels.

During the period when her episodes of ascending cholangitis were in complete remission, her leucocytosis and serum ALP and GGT returned within the normal limits including serum tumour markers carcinoembryonic antigen, CA-19.9 and α -feto protein. A transabdominal ultrasound (US) revealed several echogenic foci at the inferior left lobe of the liver in association with marked left intrahepatic biliary dilatation suggesting an obstructive lesion near the left hepatic duct. A MR cholangiopancreatography (MRCP) (figure 1) showed prominent dilatation of the left hepatic duct and its branches with multiple filling defects consistent with intraductal stones. Three discrete enhancing central lesions (one in segment 2 measuring 1.3×2 cm, one in segment 4A measuring 1.5×1.2 cm and one in segment 7 measuring 2×3 cm) were identified. The left lobe of the liver appeared atrophic. The right bile duct system and the common bile duct were normal in size and did not contain any filling defects suggestive for intrahepatic stones. The pancreas and the pancreatic duct appeared unremarkable and no lymphadenopathies were identified.

An endoscopic retrograde cholangiopancreatography (ERCP) (figure 2) was performed with the intent of crushing the stones and clear the left biliary system without success.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of HL includes

- Benign causes
 - Cholelithiasis
 - Primary sclerosing cholangitis
 - Primary biliary cirrhosis
 - Mirizzi's syndrome
 - Choledochal cyst
 - Caroli disease

Figure 1 Sagittal view of the preoperative abdominal MR cholangiopancreatography (MRCP) showing prominent dilatation of the left hepatic duct and cystic dilatations of the secondary branches of the left biliary system containing multiple filling defects consistent with stones (white arrow) (A). The coronal view of the T1 MRCP shows dilatation of the left biliary system associated with atrophy of the left hepatic lobe. Atrophy of the hepatic parenchyma involved by hepatolithiasis is common in patients affected by long-term biliary obstruction (B).

2. Malignant causes

- Intrahepatic cholangiocarcinoma
- Extrahepatic cholangiocarcinoma
- Locally advanced hepatocellular carcinoma
- Metastatic liver disease

TREATMENT

The patient underwent an exploratory laparotomy and intraoperative US. The right hepatic lobe was normal in size, shape and consistency, while the left lateral segment was atrophic. Intraoperative US revealed multiple large cholesterol stones located predominantly in the main left bile duct (figure 3) and a left hepatic lobectomy was performed.

OUTCOME AND FOLLOW-UP

The patient had an uneventful operative and post-operative course and was discharged home on the fourth

Figure 2 Endoscopic retrograde cholangiopancreatography (ERCP) images showing marked dilatation of the left intrahepatic duct and branches with multiple large stones (white arrows).

postoperative day. During her hospital stay, serum cholesterol and triglyceride levels were obtained after the patient was restarted on her regular solid diet. The serum lipid profile was within the normal limits. A detailed familiar history for hyperlipidaemia was investigated without any positive findings. Three months after her surgical therapy, the patient was seen at the surgical outpatient clinics and she reported that her symptoms were completely resolved and the patient seemed completely recovered.

DISCUSSION

HL is a distinct disease entity characterised by de novo formation of stones in the intrahepatic ducts. It presents clinically with repeated attacks of acute bacterial cholangitis with subsequent formation of further stones and strictures in the biliary system. The disease was first

described in 1930 by Digby from Hong Kong and it came to be known as recurrent pyogenic cholangitis.¹² It is prevalent in Southeast Asia, but rare in Western countries. The aetiology of HL is poorly understood, but genetic, dietary and environmental factors are thought to be contributory. In Asia, malnutrition and low socioeconomic conditions are associated with higher incidence of intrahepatic stones whereas in Western countries no specific risk factors have been identified. In general, intrahepatic stone formation is most commonly associated with bile stasis caused by postoperative strictures, sclerosing cholangitis, Caroli's disease or neoplasms that result in biliary stasis.¹³ Intrahepatic stones occur more commonly in the fifth and sixth decades of life and do not demonstrate a gender preference.^{14 15} Concomitant intrahepatic and extrahepatic stones occur commonly in older age groups (seventh and eighth decades)³ and are found in approximately 70% of all HL cases.¹⁵ HL is more frequent in the left lobe because the left hepatic duct coalesces with the CBD at an acute angle which tends to induce bile stasis when associated with biliary strictures.¹⁵

Symptoms of HL may include epigastric or right upper quadrant abdominal pain, jaundice and fever, thus representing the clinical picture of acute cholangitis. Pyogenic cholangitis may occur and may be complicated by formation of hepatic abscess and biliary sepsis in severe cases. Morbidity is primarily related to recurrent cholangitis and the development of secondary sclerosing cholangitis, biliary strictures, parenchymal atrophy, liver abscesses and sepsis. Migration of intrahepatic stones into the extrahepatic biliary tree may cause gallstone pancreatitis.

The association of cholangiocarcinoma with HL is well recognised and its prevalence in patients with HL is 2.4–10%.¹³ The percentage of cholangiocarcinoma patients with concomitant HL has been reported to be in the range of 17–27%.¹⁶

Non-invasive imaging modalities such as US,¹⁷ CT¹⁸ and MRI/MRCP¹⁶ accurately depict the normal anatomy and the presence of intrahepatic stones. In obstructive jaundice, MRCP has accuracy of 96–100% and sensitivity, specificity and accuracy of 97%, 99% and 98%, respectively.³ Despite the excellent diagnostic qualities of modern MRI and multidetector CT scans, the gold standard diagnostic test in HL remains the ERCP or percutaneous transhepatic cholangiography (PTC) that have a sensitivity of almost 100% and can be used to extract stones if their size and location allows it.³

Therapeutic options include the non-surgical approach, surgical treatment, and a combination of the two.^{7 9} The non-surgical approach to HL consists of the extraction of calculi under radiological (PTC with/without lithotripsy or access through a T-tube) or endoscopic (transduodenal papillotomy with or without lithotripsy) control.⁹

Although more invasive, hepatic resection of the affected parenchyma is very effective^{5 19} and it is probably the best therapeutic option, as it achieves the best long-term results with 85–95% therapeutic success in suitable candidates.^{7 20}

Recurrence of HL continues to be the most serious problem, although this has decreased from 60% to 15% at the present time, possibly due to the increase in number of patients treated with hepatectomies and also for the significant improvement of non-surgical techniques that

Figure 3 Postoperative picture of segments 2, 3 and 4 (left hepatic lobe) after being resected. The left lobe appears atrophic with the left biliary duct characterised by significant thickening of its walls (black arrow) due to the chronic inflammatory insult of the impacted cholesterol stones. After opening the main left biliary duct, multiple stones were extracted and displayed in front of the surgical resection margins of the liver. The largest stones measured 3.2 cm in diameter and most of the stones had calcified nuclei but were quite friable in their periphery (white arrow).

allow the disruption and extraction of stones diagnosed in early stage.²¹

In summary, HL remains a prevalent disease of the biliary system in East-Asian countries whereas it is a very rare disease in Western populations. Because of it is often characterised by recurrent episodes of cholangitis, obstructive jaundice and chronic inflammation of the biliary tree, it can be a challenging diagnostic and therapeutic condition especially in Western countries where it is still a very rare disease. Hepatic resection of the involved parenchyma allows the removal of intrahepatic stones and the biliary system leading to long-term resolution of the symptoms and prevention of malignant transformation of the biliary system due to the chronic inflammatory insult caused by the presence of stones and concomitant infection.

Learning points

- ▶ Hepatolithiasis (HL) is a very rare conditions in Western countries.
- ▶ Stones in the intrahepatic ducts are more common in the left lobe than in the right system.
- ▶ Stones in Western countries are usually made of cholesterol whereas stones in Asian countries are usually made of calcium bilirubinate.
- ▶ Atrophy of the liver parenchyma affected by chronic biliary occlusion is often a radiological finding associated with cystic dilatation of the intrahepatic bile ducts.
- ▶ Surgical therapy is often the best curative therapy in patients affected by HL affecting only one lobe.
- ▶ Cholangiocarcinoma associated with HL is diagnosed in 8–12% of patients and it is a very poor prognostic factor.

Competing interests None.

Patient consent Obtained.

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