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Primary cholesterol hepatolithiasis associated with cholangiocellular carcinoma: a case report and literature review

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Running Head: Hepatolithiasis with cholangiocarcinoma

Abstract

Hepatolithiasis associated with cholangiocellular carcinoma is occasionally a calcium bilirubinate stone. Primary cholesterol hepatolithiasis associated with cholangiocellular carcinoma is rare; only 6 cases have been reported in the literature. A 55-year-old man was admitted to our hospital because of an elevated level of carbohydrate antigen 19-9. Various imaging studies demonstrated a mass in the segment VII of the liver. The patient underwent a curative surgical operation. Histopathological examination revealed that it was cholangiocellular carcinoma located in the periphery of the liver. A cholesterol stone was present, encircled by the cholangiocellular carcinoma. Minor inflammatory changes were observed around the stone.

Key Words: Hepatolithiasis; Intrahepatic stones; Intrahepatic calculi; Cholesterol stone; Cholesterol hepatolithiasis; Cholangiocellular carcinoma

Introduction

Primary hepatolithiasis is well known as an endemic disease prevalent in Southeast Asia, including Japan, Korea, China, and Taiwan; it is very rare among Caucasians (1,2). The nature of primary hepatolithiasis is mostly calcium bilirubinate, and some of the stones are cholesterol-rich pigment stones (3). Primary cholesterol hepatolithiasis is extremely rare (4).

Particular cases of primary cholesterol hepatolithiasis of more than 90% cholesterol composition have been reported in Japan (5,6). Hepatolithiasis is occasionally associated with cholangiocellular carcinoma (CCC) (7,8) and the stones of primary hepatolithiasis associated with CCC are calcium bilirubinate stones in almost all reported cases (7,8). Primary cholesterol hepatolithiasis associated with CCC is rare. Herein, we present such a rare case.

Case report

In October 2004, a 55-year-old male was hospitalized because of an elevated level of carbohydrate antigen 19-9 (CA19-9). He had been admitted to our hospital because of liver dysfunction, although he was asymptomatic; he was referred to our department for further examination at age 52. Laboratory data showed that the CA19-9 was 15.3 U/mL (normal range: <37 U/mL). He had been diagnosed as having primary cholesterol hepatolithiasis, on the basis of ultrasonography (US), computed tomography (CT) and endoscopic retrograde cholangiogram (ERC) findings. US demonstrated focally dilated ducts containing highly echogenic material with strong shadowing in the peripheral segments of the liver. However, no wall thickness, stones or debris was seen in the

gallbladder. CT revealed only subtle dilatation of peripheral bile duct. ERC revealed the dilated common bile duct (15 mm in diameter) with filling defects (up to 12 mm in diameter), and intrahepatic cylindrical duct dilatation with internal filling defects in the right anterior subsegmental branch duct of segment VIII of the liver. There was no stricture of the bile duct. He underwent endoscopic sphincterotomy for round whitish-yellow cholesterol stones. These stones contained 95% cholesterol in dry weight, by chemical analysis. A bacteriological study of the intrahepatic bile was negative. He was monitored with laboratory data and **US**, CT at regular intervals. **We continued careful observation as intrahepatic stones remained, and stone fall into the common bile duct was considered likely**. In May 2004, follow-up CT scan revealed a low-density area close to the right adrenal gland in segment VII of the liver (Fig. 1A), **US did not reveal the tumor at this stage, and the abnormal finding was diagnosed as inflammatory granular changes**. Laboratory data showed that the CA19-9 was 50.4 U/mL, and in July the value was increased to 66.5 U/mL. In September 2004, CT scan detected a mass close to the right adrenal gland and diaphragm in segment VII of the liver (Fig. 1B). The mass was associated with the elevation of the CA19-9. He had family history of bile duct stone apparent in his parent and three siblings (Fig. 2). On admission to our hospital, his abdomen was soft; no mass was palpable. Results of laboratory tests were as follows: total bilirubin, 1.8 mg/dL (normal range: 0.2-1.2 mg/dL); direct bilirubin, 0.2 mg/dL (normal range: <0.3 mg/dL); aspartate aminotransferase, 23 IU/L (normal range: 5-40 IU/L); alanine aminotransferase, 23 IU/L (normal range: 4-45 IU/L); aminoalkaline phosphatase, 622 IU/L (normal range: 103-335 IU/L); and white blood cell count, 3,200 / μ L (normal range: 3,500-9,300 / μ L). Tumor marker values were as

follows: carcinoembryonic antigen, 1.8 ng/mL (normal range: 1.0-6.5 ng/mL); CA19-9, 144.7 U/mL. US showed a dimly demarcated non-uniform mass, about 25-mm in diameter, with a highly echogenic material with strong shadowing, measuring about 5 mm in segment VII of the liver. Portal phase-enhanced CT revealed a parenchymal low-attenuated mass of 27 × 24-mm in the segment VII of the liver. The tumor was well-demarcated, except for a portion attached to the right adrenal gland and diaphragm (Fig. 1C). ERC revealed an interruption of the segment VII duct of the liver, and intrahepatic cylindrical duct dilatation with internal filling defects in the VIII duct (Fig. 3). Right hepatectomy and cholecystectomy with concomitant resection of the right adrenal gland and diaphragm were performed with the preoperative diagnosis of primary cholesterol hepatolithiasis associated with CCC. Gross appearance of the resected specimen was a white nodular mass, measuring 25 × 23-mm, with a cholesterol stone, measuring 6 × 5-mm in the marginal segment VII of the liver (Fig. 4A). Histopathological examination revealed moderately to poorly differentiated adenocarcinoma (Fig. 4B) with infiltration into the right adrenal glands (Fig. 4C). Vascular and perineural invasion was noted. A crystalloid pattern was observed in the structure of the stones, showing the characteristics of cholesterol stone (Fig. 4D). The inflammatory and fibrotic changes around the bile duct wall were scanty (Fig. 4D). A few tiny cholesterol stones were scattered in the peripheral intrahepatic bile ducts, at different locations. The postoperative course was uneventful. The level of CA19-9 gradually lowered to the normal range. However, his serum CA19-9 level was elevated to 56.8 U/mL in July 2005. He relapsed into disease 10 months after the surgical operation, and was diagnosed as having peritoneal carcinomatosis at laparotomy for

observation. The patient has been surviving for 25 months after the surgical operation, treated with systemic combination chemotherapy (gemcitabine and cisplatin). His serum CA19-9 level has gradually lowered to 41.9 U/mL, although it has not reached the normal range.

Discussion

We herein described a case of primary cholesterol hepatolithiasis associated with CCC. Primary cholesterol hepatolithiasis should be regarded as a different clinical entity from primary calcium bilirubinate hepatolithiasis of long-standing chronic inflammation which has a close relationship with bile stasis and bacterial infection (5,9). It is presumed that the formation of primary cholesterol hepatolithiasis requires both the secretion of supersaturated bile and the presence of bile stasis (10). Stricture of the bile duct is related to bile stasis, and stone formation usually occurs in the dilated bile duct in the periphery of the stricture. In the present case, neither a definite stricture of the bile duct nor bacterial infection of the bile duct was present. Hepatolithiasis associated with CCC is almost always calcium bilirubinate hepatolithiasis (7,8). In CCC associated with calcium bilirubinate hepatolithiasis, the stones are closely situated within or adjacent to the CCC, suggesting an etiological role of hepatolithiasis in carcinomatous transformation (7,8). An association of CCC with primary cholesterol hepatolithiasis is very rare. There have been only six cases of primary cholesterol hepatolithiasis associated with CCC (11-15) prior to the present case (Table1). Terada et al (13) and we observed a minimal degree or absence of chronic inflammatory changes in the surrounding of the bile duct. Kondo et al(5) pointed to the different pathogenesis of

primary cholesterol hepatolithiasis compared with primary calcium bilirubinate hepatolithiasis. It is speculated that primary cholesterol hepatolithiasis has little association with bile stasis and bacterial infection. It is recently discussed that metabolic factors are accidentally related to the mechanism of stone formation in primary cholesterol hepatolithiasis (16). In the present case, it seems probable that congenital factors since the patient's family history showed incidences of cholesterol stone as well as acquired factors acted synergistically in the genesis and growth of cholesterol hepatolithiasis. From the fact that primary cholesterol hepatolithiasis and CCC were found in the same segment of the liver, the former could be related to the latter in this case. While Chijikawa Chijiwa et al (15) discussed association rates of CCC with primary cholesterol hepatolithiasis, the risk of CCC is thought to be even higher in patients with primary calcium bilirubinate hepatolithiasis than those with primary cholesterol hepatolithiasis (7,8). However, the exact causal relationship between the presence of cholesterol stones and CCC remains unclear.

Complication with CCC could occur, as in the present case, during the follow-up of primary cholesterol hepatolithiasis, not necessarily that of primary calcium bilirubinate hepatolithiasis; thus careful follow-up is indispensable. Particularly if CT shows a new low-density area or tendency of enlargement of a low-density area during the follow-up of primary cholesterol hepatolithiasis, complication with CCC should be considered and close examination should be performed.

In conclusion, we reported a rare case of primary cholesterol hepatolithiasis associated with peripheral cholangiocellular carcinoma.

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intrahepatic cholesterol stones, including immunohistochemical staining against apolipoprotein A-1. *Hepatology* 17:531-7,1993.

Figure&Legends

Figure 1

A: In May, 2004, CT revealed initially a small low-density area in the periphery of segment VII of the liver (*arrow*). The lesion was attached to the low density area (*arrowhead*), which was diagnosed as cholesterol hepatothiasis with the bile duct dilataion.

B: In September 2004, follow-up CT demonstrated a slight extension of the lesion (*arrows*).

C: In October 2004, ongoing follow-up CT revealed a heterogeneously low-density area of 27 × 24 mm in the peripheral segment VII of the liver (*broken arrows*).

Figure 2

□, male; ○, female; GCS, Gallbladder cholesterol stones; GS, Gallbladder stones; CBDS, common bile duct stones; PCHL, Primary cholesterol hepatothiasis; CBDCS, Common bile duct cholesterol stones; CCC, Cholangiocellular carcinoma

The patient's father had a history of operation for GCS (by chemical analysis) at age 69, and died of other disease at age 92. His mother, now 95 years old, had operation for GCS (by chemical analysis) at another hospital at age 69. His eldest brother, now 69 years old, had operation for GS and CBDS at another hospital at age 65. His second eldest brother, now 67 years old, is being under observation in our department for PCHL (by chemical analysis); he has undergone cholelithiasis for CBDCS (by chemical analysis) by endoscopic sphincterotomy at present age. His fourth elder brother is now

under observation by his nearby doctor for GS.

Figure 3

Endoscopic retrograde cholangiogram revealed an interruption of segment VII duct (*arrow*), and filling defects in the segment VIII duct (*arrowheads*), with cylindrical dilatation localized just at the stone-bearing part of the intrahepatic bile duct.

Figure 4

A: A gross appearance of a white nodular mass (*arrow*) with a cholesterol stone (*arrowheads*) in the marginal segment VII of the liver.

B: Photomicrograph of the resected specimen, showing that the tumor was moderately to poorly differentiated adenocarcinoma (H&E; original magnification 100 ×).

C: Photomicrograph of the resected specimen, showing that the tumor had invaded the adrenal gland (*arrows*) (H&E; original magnification 100 ×).

D: Photomicrograph of the resected specimen, showing a crystalloid pattern in the structure of the stone, and that the surrounding bile duct wall was scanty of inflammation or fibrosis (H&E; original magnification 100 ×).

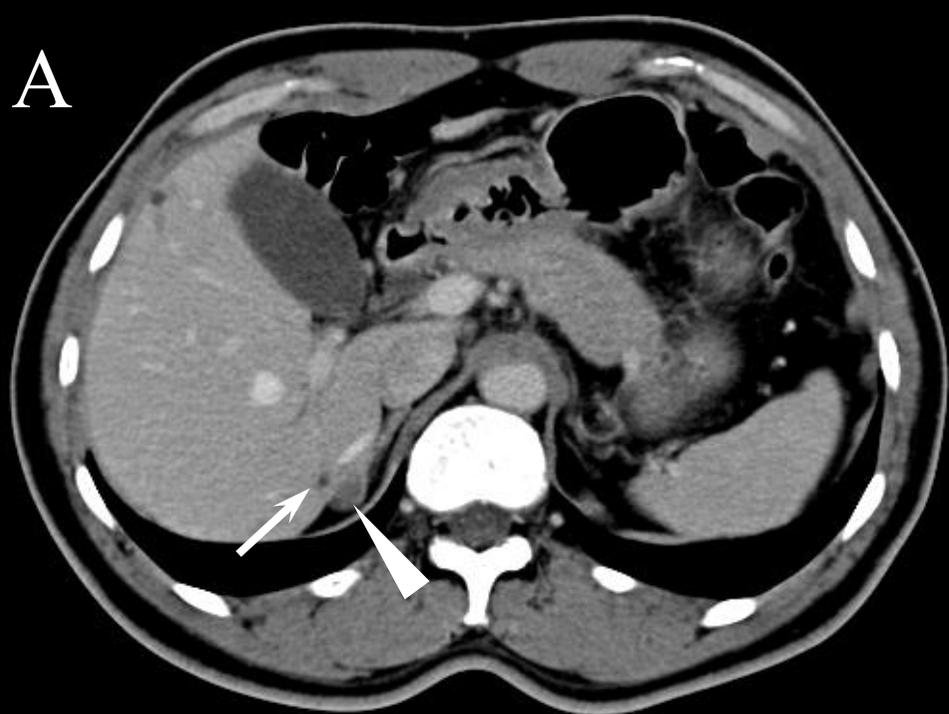
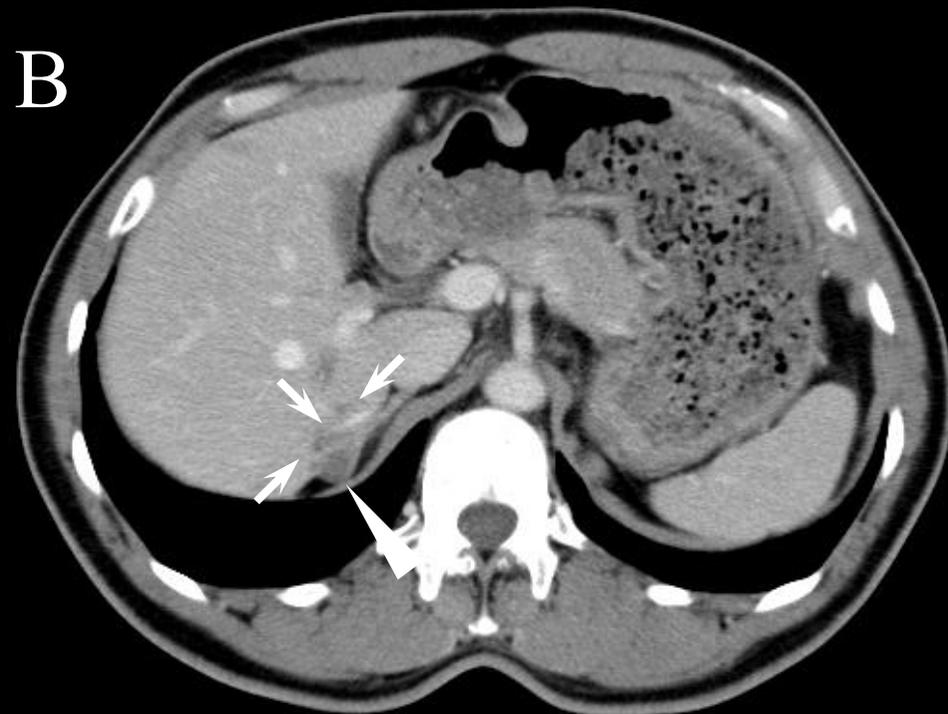
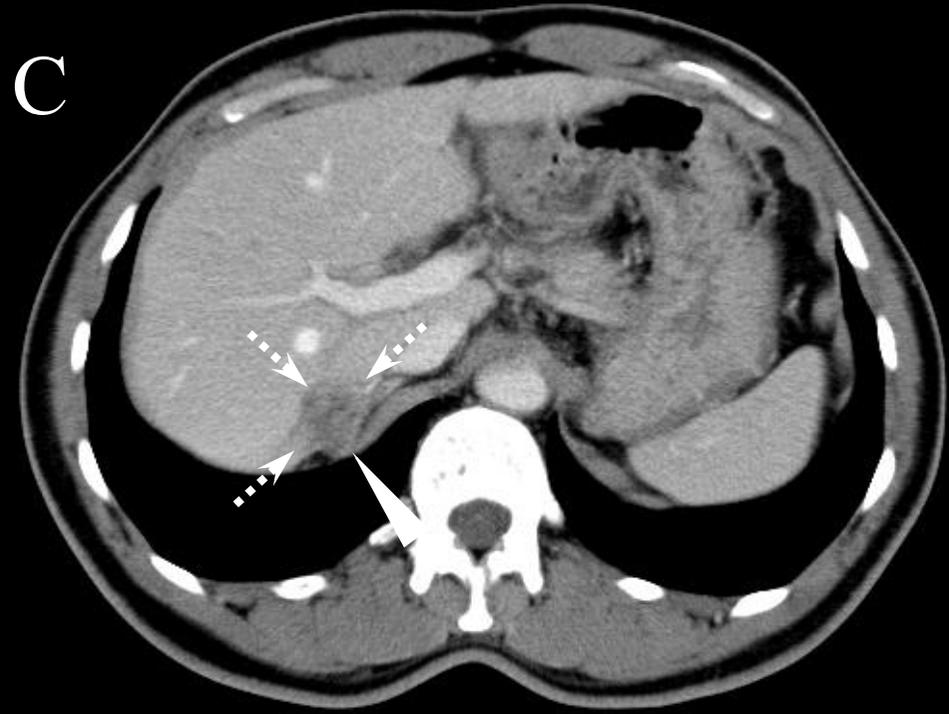
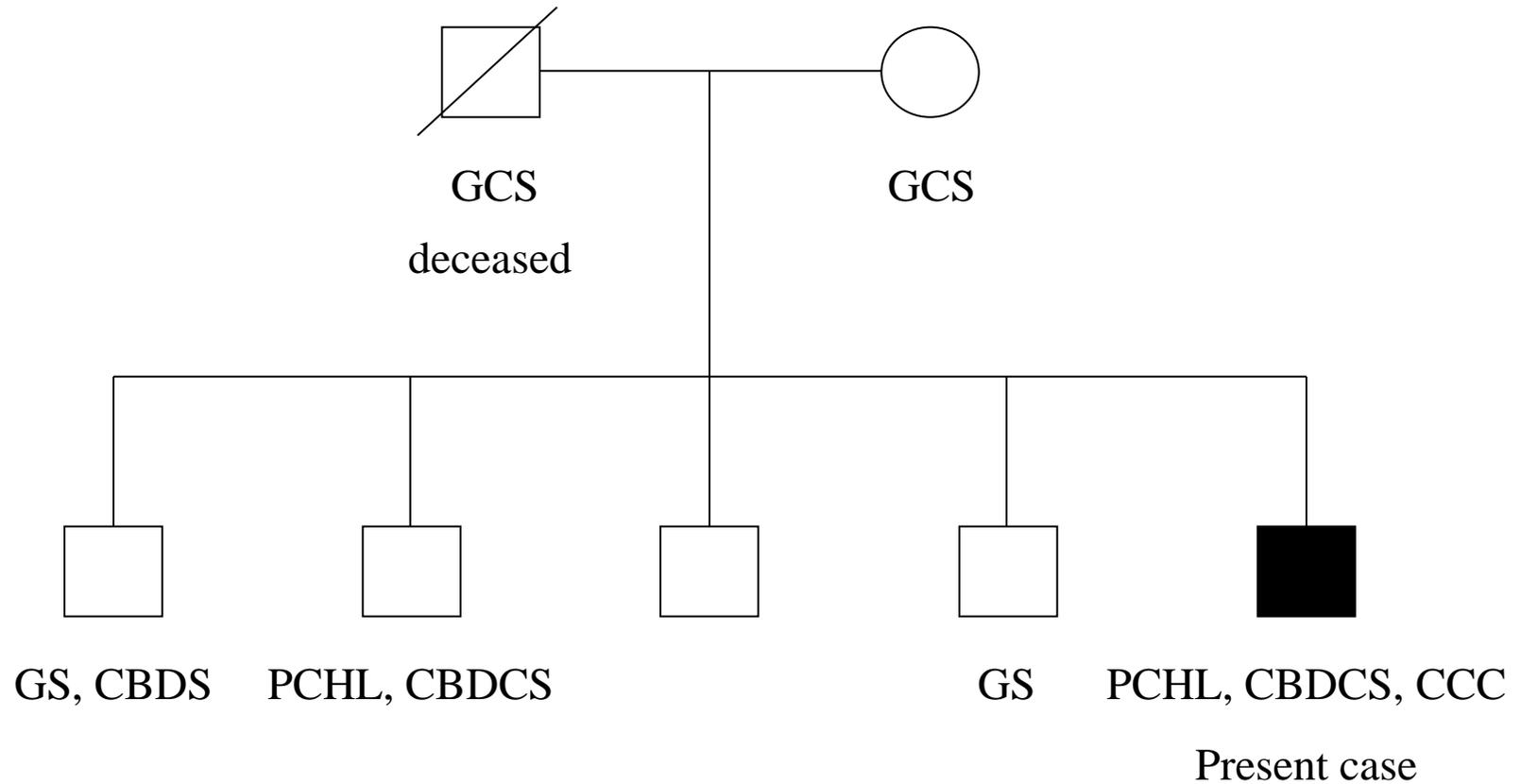
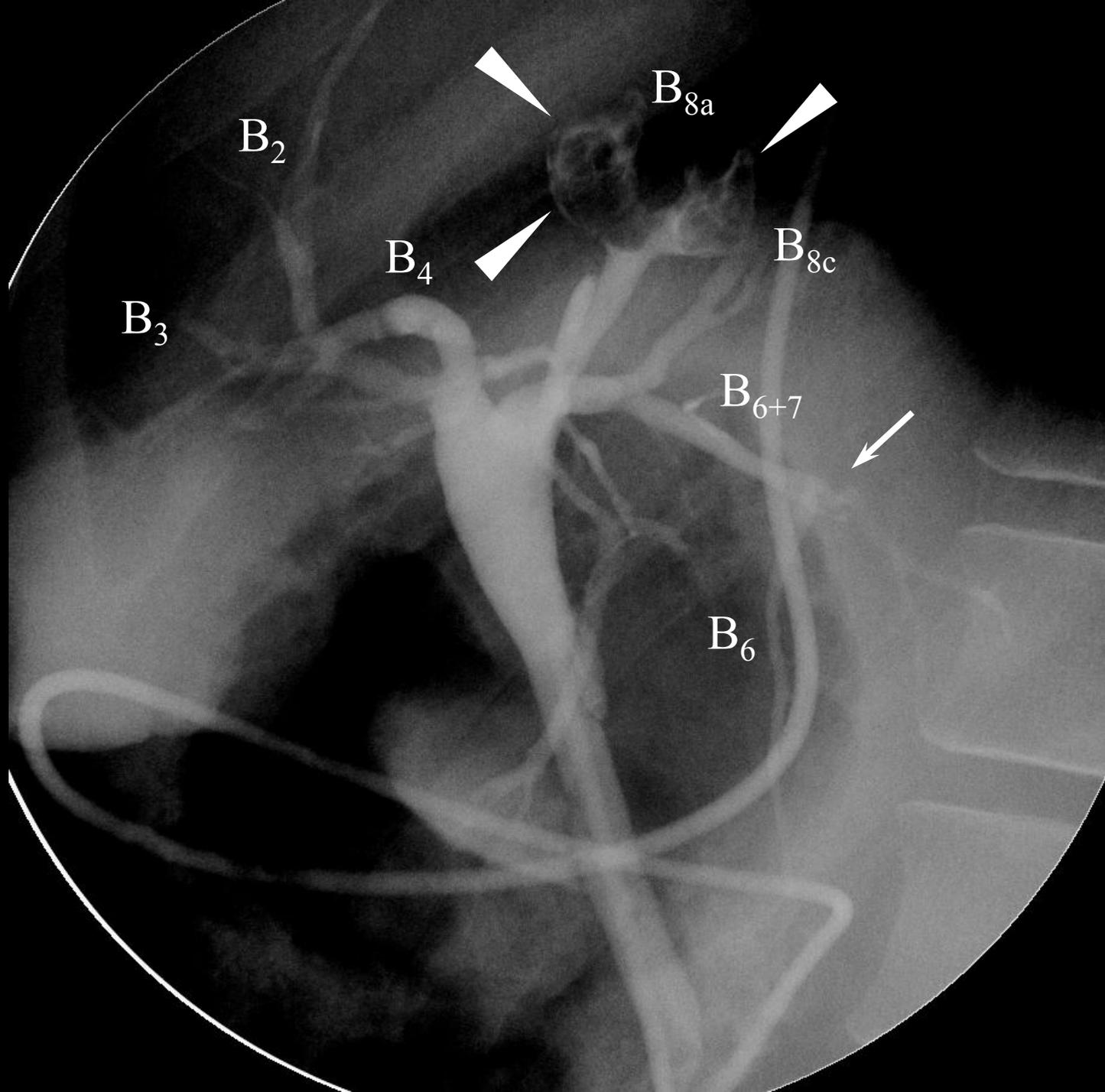
A**B****C**

Figure2. Pedigree of the five brothers with the bile duct stones





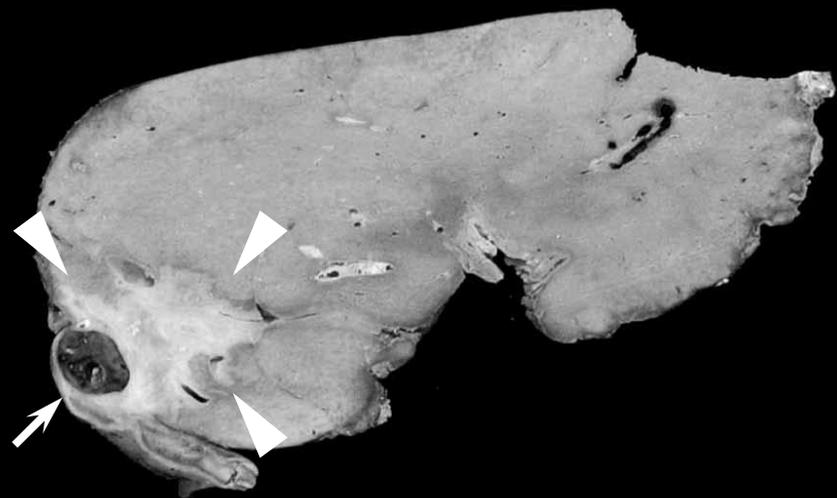
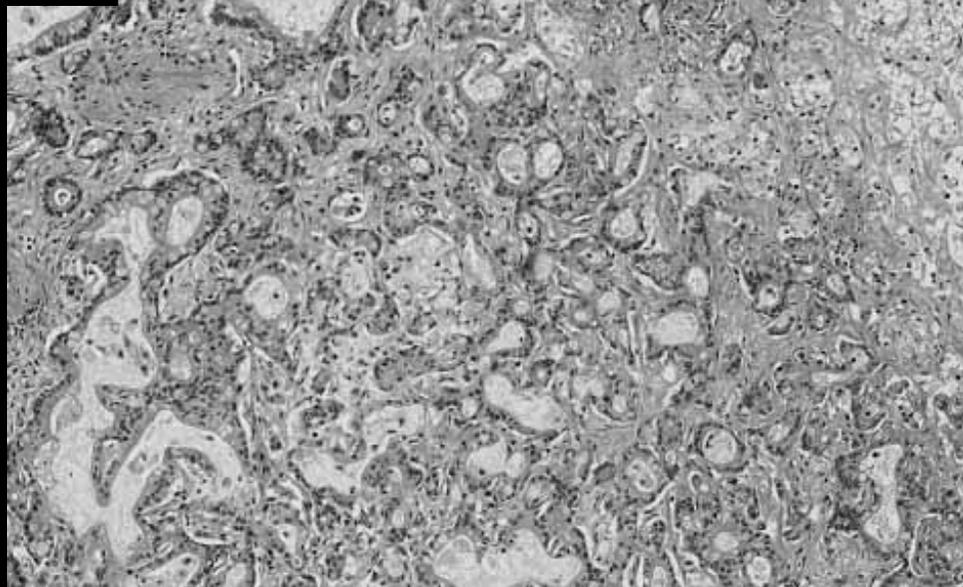
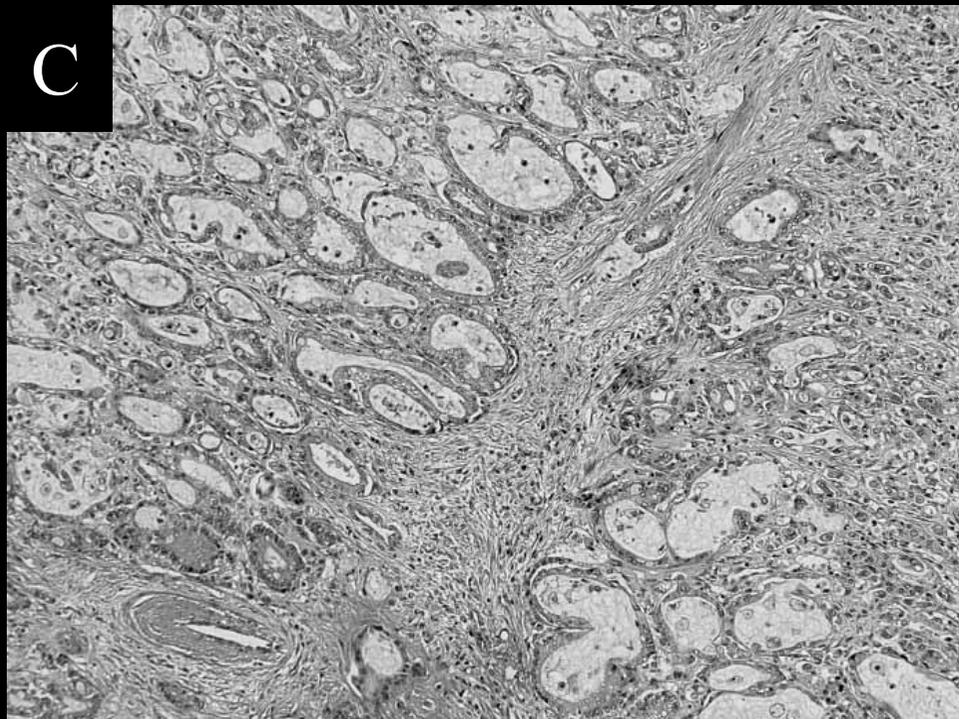
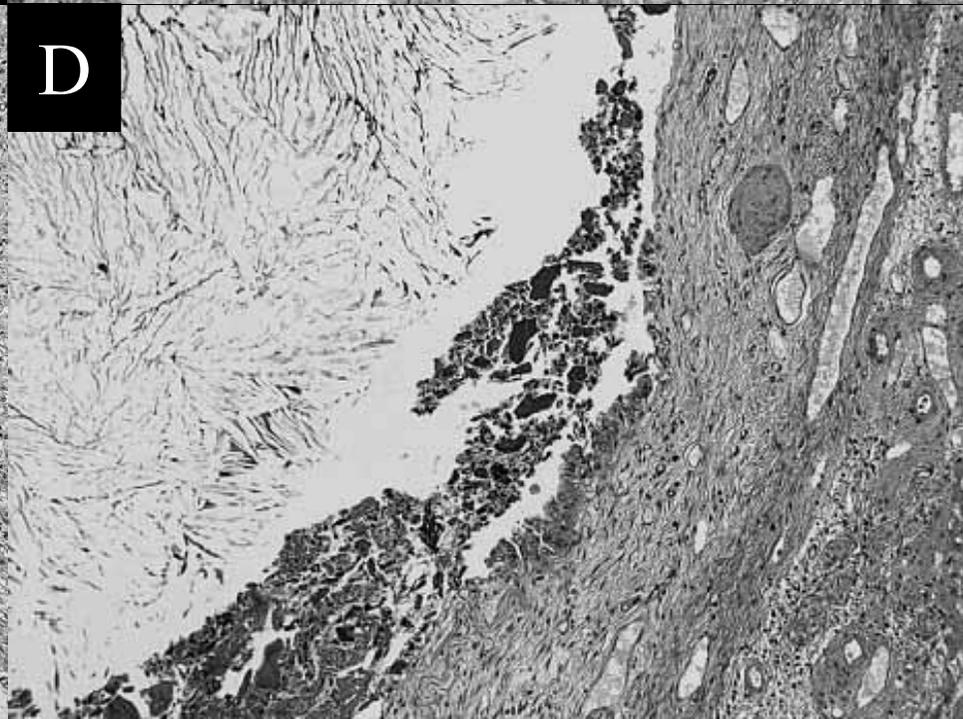
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Table 1. Reported cases of primary cholesterol hepatolithiasis associated with cholangiocellular carcinoma

Author	Age	Gender	Symptoms	Location of the BDS	Location of the CCC	Tumor size (mm)	Treatment procedures	Pathological diagnosis	Outcome	Length of Follow-up
Case 1 ¹¹	62	M	Epigastric pain	R	R	35	ND	Pap	Dead *	1 mo
Case 2 ¹²	41	F	Rt.hypo	Lat	Lat	23	Lateral segmentectomy	Mod-por	Dead	6 mo
Case 3 ¹³	69	M	Rt.hypo Abdominal fullness	Bil	Lat	20	ND	Pap	Dead *	4 mo
Case 4 ¹⁴	51	M	Fever Epigastric pain	Lat	S ₃	20	Lateral segmentectomy	Well	Alive	ND
Case 5 ¹⁵	ND	F	ND	L	Lat-med-hilar	ND	PTBD & Radiation	ND	Dead	4 mo
Case 6 ¹⁵	ND	M	ND	L	Lat	ND	PTBD	ND	Dead	1 mo
Present case	55	M	None	Bil	S ₇	25 × 23	Right hepatectomy	Mod-por	Alive	25 mo

ND, Not described; *BDS*, Bile duct stones; *CCC*, Cholangiocellular carcinoma; *Rt. hypo*, Right hypochondralgia; *R*, Right lobes of the liver; *Lat*, Lateral segment of the liver; *Bil*, Bilateral lobes of the liver; *L*, Left lobe of the liver; *S₃*, Segment III of the liver; *med*, medial lobe of the liver; *hilar*, Hilum of the liver; *S₇*, Segment VII of the liver; *Pap*, Papillary adenocarcinoma; *Mod-por*, Moderately to poorly differentiated adenocarcinoma; *Well*, Well differentiated adenocarcinoma; *An autopsy was performed.