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Case report

Multiple hepatic peribiliary cysts with cirrhosis

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Editorial on page 407

Multiple hepatic peribiliary cysts were found in three autopsy cases of patients who had had underlying liver diseases and obstructive jaundice. Macroscopically, the cysts were visible and present exclusively in the hepatic hilum and larger portal tracts. Histologically, the cysts were of varying size and were lined by a single layer of cuboidal or flattened epithelial cells without atypia. Intimate association between the cysts and peribiliary glands was found in the walls of large bile ducts. All three cases were associated with liver cirrhosis in patients with portal hypertension, and two of the patients had also had hepatocellular carcinoma. These findings support the previous assumption that multiple hepatic peribiliary cysts may be closely related to a portal hypertensive condition. Although peribiliary cysts have been considered to be clinically asymptomatic in general, in one of our patients, the cystic dilatation appeared to have been responsible for the progression of obstructive jaundice.

Key words: multiple hilar cysts, peribiliary cyst, portal hypertension, obstructive jaundice

Introduction

Hepatic peribiliary cysts are retention cysts of peribiliary glands located in the hilum of the liver and larger portal tracts. This condition has been reported under the names, "multiple cysts in the hepatic hilum",[1] "hepatic cysts of periductal origin",[2,3] and "multiple hepatic peribiliary cysts",[2,4,5] and is a rather rare condition. This condition was first described by Nakanuma et al.[1] in 1984. According to a study reported by Terada and Nakanuma,[6] multiple peribiliary cysts were identified in 0.26% (three cases with alcoholic cirrhosis) of all autopsied patients (1139 cases) during the period from 1978 to 1988. Recently, we experienced three new autopsy cases of multiple hilar cysts in a relatively short period, (from October 2001 to February 2002). We report here the autopsy findings of these cases. Possible involvement of the cysts in the progression of obstructive jaundice, to some extent, will be discussed.

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Case reports

Clinical summary

Case 1

The first patient was a 78-year-old Japanese man who had a history of jaundice diagnosed at the age of 58, when liver biopsy revealed centrilobular cholestasis with minimal liver damage. Benign recurrent cholestasis, cholestatic viral hepatitis, and drug-induced cholestasis were included in the differential diagnosis then. The jaundice had improved without treatment. The patient occasionally drank approximately 100 ml/day of a Japanese spirit (amount of ethanol, 20–25 g/day). There was no history of blood transfusion. In January 2001, he was admitted to a regional hospital because of jaundice and skin itching. Serum test for hepatitis B virus (HBV) was negative. Serum anti-hepatitis C virus (HCV) was positive, though viral RNA was negative. Aspartate aminotransferase (AST) was 270 IU/l (normal range, 9–32 IU/l); alanine aminotransferase (ALT), 139 IU/l (normal range, 3–33 IU/l); alkaline phosphatase (ALP), 1587 IU/l (normal range 77–207 IU/l); γ-glutamyl transpeptidase (γ-GTP), 200 IU/l (normal range, 4–41 IU/l); total bilirubin (TB), 25.94 mg/dl (normal rang, 0.2–1.2 mg/dl); and direct bilirubin (DB), 17.28 mg/dl (normal range, 0.1–0.7 mg/dl). Serum anti-mitochondrial antibody (AMA) was nega-

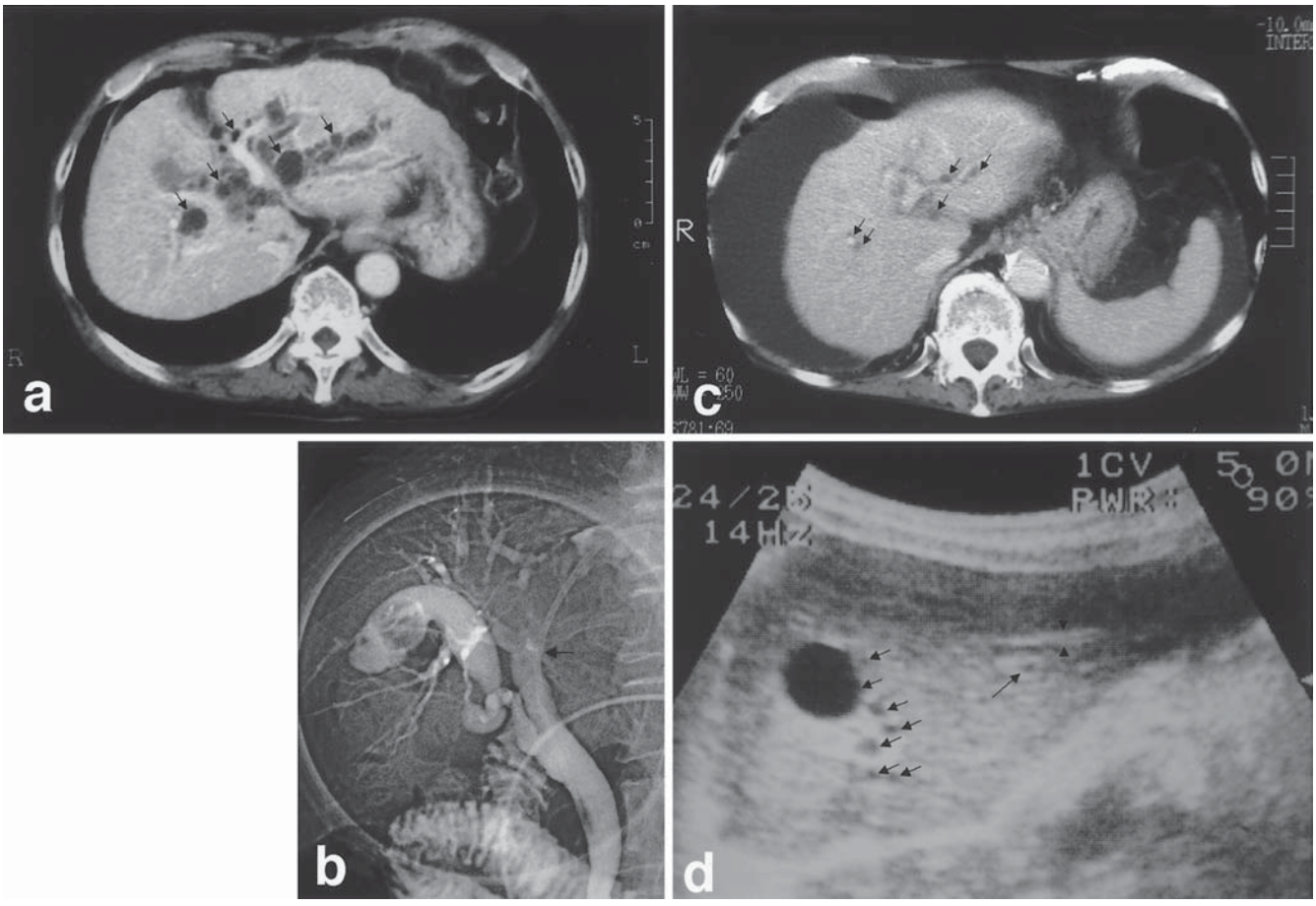

Fig. 1a–d. Imaging findings. **a** Computed tomography (CT) scan in case 1 revealed dilated intrahepatic bile ducts and multiple cystic lesions (*arrows*) in the hepatic hilum and large portal tracts. **b** Cholangiogram from endoscopic nasobiliary drainage (ENBD) tube in case 1 showed abrupt cutoff of the common hepatic duct (*arrow*), approximately 2 cm distal to the bifurcation of the cystic duct, and irregularity of the intrahepatic bile ducts. **c** CT scan in case 2 revealed multiple cystic lesions (*arrows*) in the hepatic hilum and large portal tracts. **d** Ultrasonography (US) in case 2 also demonstrated multiple cystic lesions (*short arrows*) in the hepatic hilum and large portal tracts. *Arrowheads*, bile duct; *long arrow*, portal vein

tive. Abdominal computed tomography (CT) demonstrated dilated intrahepatic bile ducts and multiple cystic lesions in the hepatic hilum and large portal tracts (Fig. 1a). Primary sclerosing cholangitis was suspected by cholangiogram from an endoscopic nasobiliary drainage (ENBD) tube, which disclosed abrupt cutoff of the common hepatic duct approximately 2 cm distal to the bifurcation of the cystic duct, and also showed diffuse irregularity of the left intrahepatic duct and obstruction of the right intrahepatic duct (Fig. 1b). Gastric fiberscopy revealed an early gastric carcinoma. The patient received only conservative therapy, and was discharged in April 2001. In June 2001, he was readmitted because of purulent cholangitis associated with disseminated intravascular coagulation. Platelet transfusion and administration of antibiotics transiently alleviated the symptoms; however, obstructive jaundice progressed and the liver function gradually deteriorated. Hepatic encephalopathy, systemic edema, ascites, and malnutrition developed, and the patient died in October 2001.

Case 2

The second patient was a 77-year-old Japanese man who had a history of blood transfusion. There was no history of alcohol abuse. Serum tests for HBV and HCV were negative. The patient had taken acetaminophen for a common cold in December 1993, and then jaundice and liver dysfunction developed. In July 1994, he was admitted to the Miyazaki Medical College Hospital. AST was 237 IU/l; ALT, 173 IU/l; ALP, 1829 IU/l; γ-GTP, 156 IU/l; TB, 9.0 mg/dl; and DB, 5.7 mg/dl. Abdominal CT and ultrasonography (US) demonstrated multiple liver cysts in segments 2 and 7 (Fig. 1c,d). Primary biliary cirrhosis (PBC), stage II, was suspected by liver biopsy, though AMA was negative. On the other

hand, his past history suggested drug (acetaminophen)-induced hepatitis. Administration of steroid and ursodeoxycholic acid transiently improved the liver function. In February 2001, accumulation of ascites was observed, which was diminished after administration of diuretics and albumin. In October 2001, the liver function rapidly deteriorated and the patient died of hepatic failure, possibly due to drug-induced hepatic injury or PBC.

Case 3

The third patient was a 70-year-old man who had been diagnosed with liver cirrhosis of HCV etiology. Test for HBV was negative. Hepatocellular carcinoma was found in 1998, and transarterial chemoembolization (TACE) was performed seven times until 2000. However, no further TACE had been done since then, because the vessel used was impaired. Beginning in 2002, jaundice developed, and the patient was admitted to a regional hospital. AST was 179 IU/l; ALT, 93 IU/l; ALP, 1302 IU/l; γ-GTP, 541 IU/l; TB, 20.1 mg/dl; and DB, 14.1 mg/dl. Abdominal CT suggested obstructive jaundice due to massive hepatocellular carcinoma in the hepatic hilum. Accumulation of ascites and malnutrition developed, and the patient died of hepatic failure in February 2002.

Autopsy findings

In case 1, the liver, weighing 630 g, was atrophic, associated with cirrhosis. Segment 8 contained a tumor nodule (moderately differentiated hepatocellular carcinoma), which measured 35 mm × 30 mm, associated with tumor rupture, and segment 6 contained two small nodules of well-differentiated hepatocellular carcinoma. Multiple serous cysts were present in the hilum and also in the large portal tracts, approximately 3–4 cm distal from the bifurcation of the common hepatic duct (Fig. 2a). The cysts were of various sizes, ranging from 1 mm to 20 mm in diameter, and were filled with serous fluid. The lumina of the proximal common hepatic duct and intrahepatic ducts were narrowed by these cysts (Fig. 2c). The lining of the cyst lumen was not bile-stained, in contrast to the lining of the adjacent bile ducts. Despite the clinical assumption of primary sclerosing cholangitis, diagnostic evidence of this condition could not be found histologically. Therefore, the diffuse irregularity of the intrahepatic ducts and the cutoff of the common hepatic duct, which were observed clinically by cholangiogram, appeared to have been caused by the multiple cysts. Other pathological findings included esophageal varices, splenomegaly, and ascites (6 l).

In case 2, the liver, weighing 470 g, was hard and severely atrophic, associated with biliary cirrhosis. The liver parenchyma had a yellowish-green color and contained no tumor nodule. In the hepatic hilum and large portal tracts, there were multiple cysts, containing serous fluid, around the intrahepatic ducts (Fig. 2b). Histologically, severe bile stasis accompanying bile infarcts and fibrosis was observed in the liver parenchyma. Paucity of the interlobular bile ducts was noted around 60% of the portal tracts. In addition to the above findings, dilatation, with bile stasis, of relatively large intrahepatic bile ducts was also observed, suggesting the possible coexistence of an obstructive disease of the large bile duct. Indeed, many peribiliary cysts (<1 mm to 20 mm), containing serous fluid, were found in the hilum and larger portal tracts, occasionally resulting in narrowing of the bile duct lumen (Fig. 2d). The cysts did not communicate with the bile ducts. A small (5 mm in diameter) cyst was also formed in the wall of the common bile duct, protruding into the lumen. On the other hand, no cystic lesion was observed in the hepatic parenchyma or peripheral portal tracts. There were varices in the esophagus, stomach, and anal region. Ascites accumulation (6 l) was also noted. Other pathological findings included ductular dilatation of esophageal glands (Fig. 3a) and panlobular emphysema.

In case 3, the liver, weighing 1370 g, contained numerous tumor nodules, associated with liver cirrhosis. The largest nodule was present near the hilum, associated with central necrosis and numerous satellite tumor nodules. Histologically, the tumor was a poorly differentiated hepatocellular carcinoma. The main tumor nodule completely occluded the intrahepatic bile duct at the hilum, associated with dilatation of the peripheral intrahepatic bile ducts. In the larger portal tracts proximal to the main tumor nodule, many peribiliary cysts were formed (Fig. 2e). The size of the cysts ranged from 2 mm to 10 mm. The cysts contained serous fluid and were without apparent communication with the bile duct system. Other pathological findings included esophageal and gastric varices, splenomegaly, ascites (3.5 l), pancreatic cyst (Fig. 3b), enteritis cystica profunda (Fig. 3c), and panlobular emphysema.

There was no apparent portal vein thrombosis in any of our three patients.

Histopathology of the multiple hepatic peribiliary cysts

In all cases, the hilar cysts of the liver were peribiliary cysts lined by a single layer of columnar, cuboidal, or flattened epithelial cells. They were of varying sizes, from microscopic dilatation of the periductal elements to transitional-sized and macroscopic cysts. Outside the lining epithelium there was loose connective tissue accompanied by a mild chronic inflammatory infiltrate. Clusters of typical, small peribiliary glands were intimately associated with the cysts. Some of the cysts were

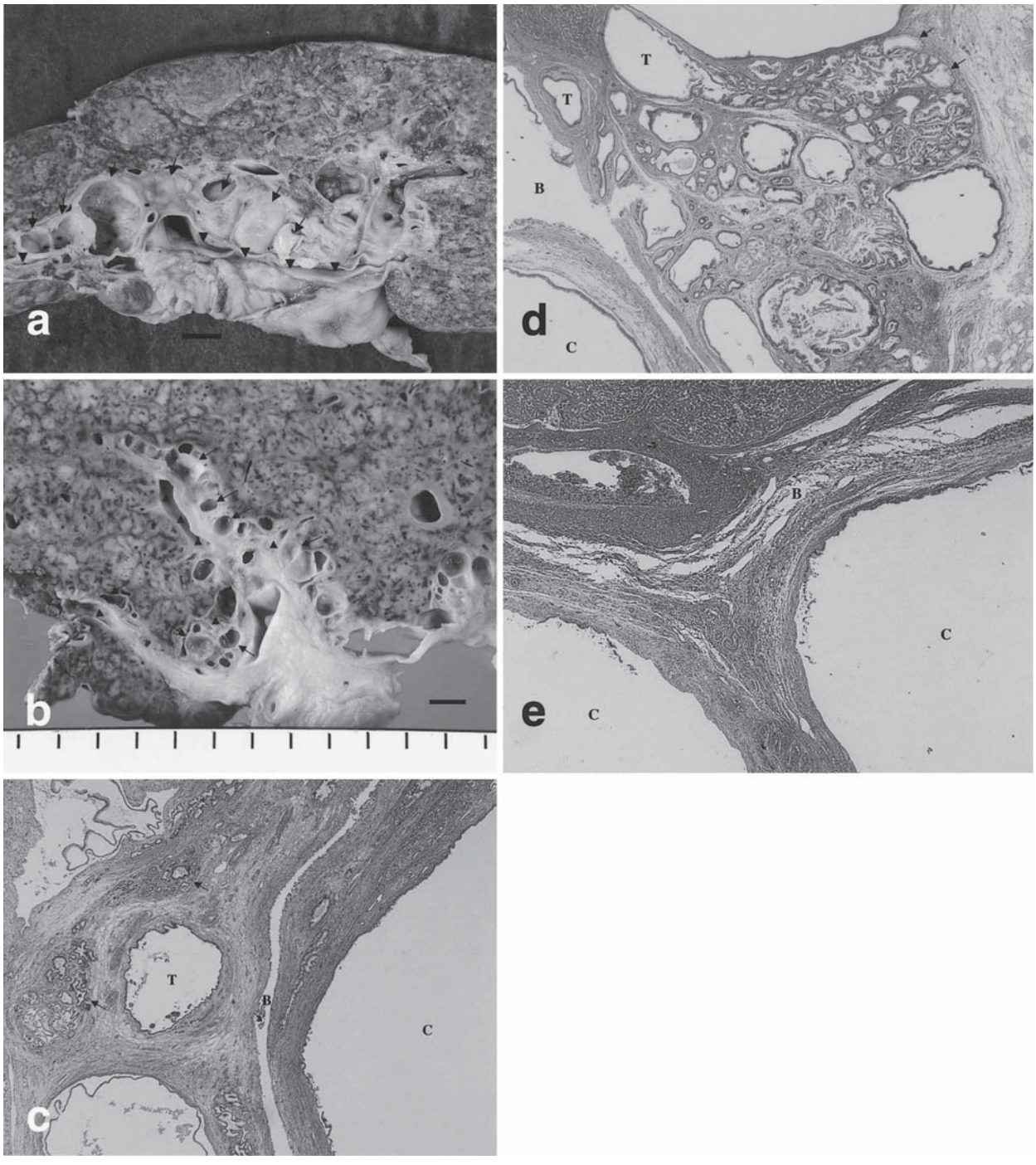

Fig. 2a–e. Macroscopic and microscopic findings of the liver. **a** Macroscopic findings in case 1. Multiple cysts of various sizes, containing serous fluid, were present in the hepatic hilum and large portal tracts approximately 3–4 cm distal from the bifurcation of the common hepatic duct. The intrahepatic ducts (*arrowheads*) were compressed by peribiliary cysts (*arrows*). **b** Macroscopic findings in case 2. In the hepatic hilum and large portal tracts, there were multiple cysts of various sizes (*arrows*), containing serous fluid, around the intrahepatic ducts (*arrowheads*). **c** Microscopic findings in case 1. A large peribiliary cyst (*C*) compressed the intrahepatic duct (*B*). There was a transition between the peribiliary cysts and the peribiliary glands (*arrows*), suggesting that the peribiliary cysts arose from preexisting intrahepatic peribiliary glands. **d** Microscopic findings in case 2. A macroscopic cyst (*C*) was seen adjacent to the intrahepatic bile ducts (*B*). Microscopic dilatations of the peribiliary glands (*arrows*) and transitional-sized cysts (*T*) were also noted. Macroscopic cysts, peribiliary glands, and transitional-sized cysts were intermixed. **e** Microscopic findings in case 3. There were macroscopic cysts (*C*) along the intrahepatic ducts (*B*). **a** and **b**, *bar*, 1 cm; **c**, **d**, **e** H&E, ×12.5

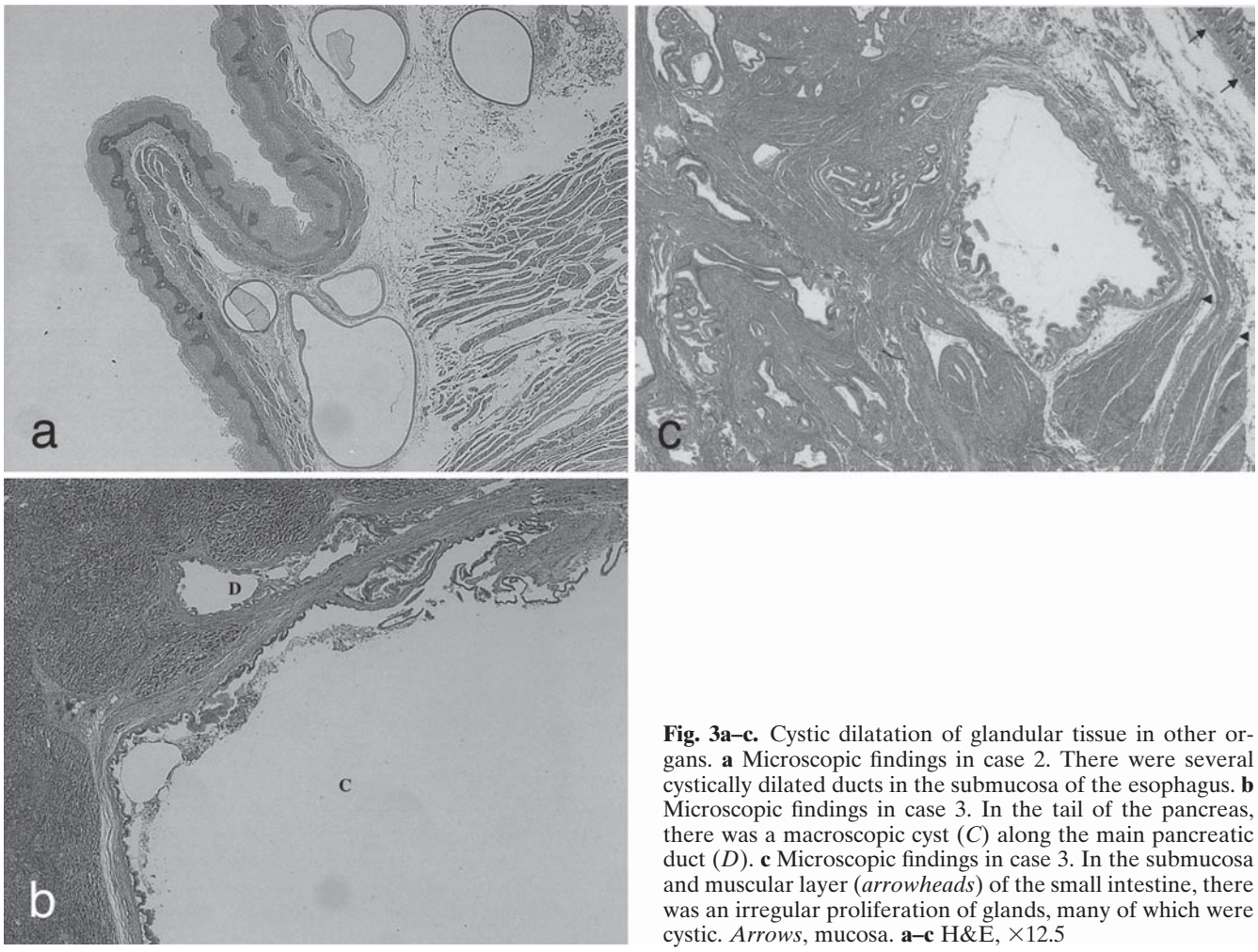

Fig. 3a–c. Cystic dilatation of glandular tissue in other organs. **a** Microscopic findings in case 2. There were several cystically dilated ducts in the submucosa of the esophagus. **b** Microscopic findings in case 3. In the tail of the pancreas, there was a macroscopic cyst (*C*) along the main pancreatic duct (*D*). **c** Microscopic findings in case 3. In the submucosa and muscular layer (*arrowheads*) of the small intestine, there was an irregular proliferation of glands, many of which were cystic. *Arrows*, mucosa. **a–c** H&E, ×12.5

adjacent to the large intrahepatic bile duct and occasionally compressed the bile ducts. Secondary dilatation of the biliary tree, associated with cholestasis, was considered in case 1, and was suspected in case 2.

Discussion

To date fewer than 60 cases of multiple hepatic peribiliary cysts have been reported in the English-language literature.[1–14] This is a rare condition, and the incidence of this disease was 0.26% in all autopsy patients (1139 cases).[6] We experienced three cases of multiple peribiliary cysts in a relatively short period (from October 2001 to February 2002). Our three cases during 5 months may be a rare experience; however, these abnormalities may be overlooked because of the observer's unawareness. Indeed, microscopic dilatations of the periductal glands were reported to be present relatively frequently in cirrhotic livers.[6]

Generally, multiple hepatic peribiliary cysts are considered to be clinically harmless. However, to date, three cases have been reported in which the patients showed clinical symptoms such as obstructive jaundice, due to the cysts (Table 1). The first case was reported in 1987 by Wanless et al.,[3] in an alcoholic patient who presented with jaundice and died of liver failure. Endoscopic retrograde cholangiography (ERC) showed cutoff of both hepatic ducts. Baron et al.[5] reported a retrospective imaging-pathologic correlation study of 12 cases of multiple hepatic peribiliary cysts, and 1 case showed obstructive jaundice caused by a large cyst compressing the biliary duct. Stevens et al.[7] presented a case of obstructive jaundice, in which endoscopic retrograde cholangiopancreatogram (ERCP) showed marked diffuse irregularity with areas of both stricture and dilatation in the common hepatic duct and intrahepatic ducts by the cysts. All our three patients (cases 1–3) showed obstructive jaundice, and, in case 1, the formation of peribiliary cysts was considered to be responsible for

Table 1. Symptomatic cases of multiple hepatic peribiliary cysts (MHPC)

Author	Age (years)/Sex	Symptoms	Images	Clinical diagnosis	Pathological diagnosis
Wanless et al.[3]	64/M	Obstructive jaundice Ascites Ankle edema	US, CT, cholangiogram: dilated intrahepatic bile ducts ERC: abrupt cutoff of both hepatic duct lumina just proximal to the bifurcation of the common hepatic ducts	2 Years after renal transplantation; drug (azathioprine)-induced liver dysfunction	MHPC (size, <0.1–1.2 cm) Portal fibrosis Bile duct proliferation Origanized thrombus in a portal vein
Baron et al.[5]	69/F	Obstructive jaundice	CT: Numerous large cysts adjacent to enhancing portal venous branches Cholangiogram: narrowing of right and left hepatic ducts, and dilated proximal ducts in the right and left lobes	Severe cirrhosis	MHPC (size, 0.2–2.5 cm) Liver cirrhosis (micronodular type)
Stevens et al.[7]	73/M	Obstructive jaundice Gynecomastia Spider angiomata Palmar erythema	US: ascites and multiple dilated intrahepatic bile ducts ERCP: diffuse irregularity, stricture, and dilatation at the common bile duct bifurcation and in the intrahepatic ducts	Alcoholic hepatitis Cholangiocarcinoma	MHPC (size, 0.2–1.2 cm) Cholestasis Liver cirrhosis No evidence of alcoholic hepatitis
Case 1 in the present report	78/M	Obstructive jaundice	CT: dilated intrahepatic bile ducts and multiple cystic lesions in the hepatic hilum Cholangiogram: abrupt cutoff of the common hepatic duct approximately 2 cm distal to the bifurcation of the cystic duct Diffuse irregularity of the left intrahepatic duct and obstruction of the right intrahepatic duct	Primary sclerosing cholangitis, likely	MHPC (size, 0.1–2 cm) Liver cirrhosis Hepatocellular carcinoma

US, ultrasonography; CT, computed tomography; ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatogram

the obstructive jaundice, which, in combination with preexisting cirrhosis, led to the hepatic failure. Also, in case 2, the multiple peribiliary cysts may have contributed to the progression of the obstructive jaundice during the end stage. In case 3, the obstructive jaundice resulted from complete occlusion of the intrahepatic bile duct by a tumor nodule. Duct narrowing by these cysts was also observed in case 3, though the obstructive jaundice was not directly caused by this factor. Our experience and previous reports indicate that these cysts are not entirely harmless and could cause obstructive jaundice, leading to hepatic failure in combination with preexisting liver disease.[3,5,7]

In clinical practice, it appears that the hepatic peribiliary cyst is still a poorly recognized condition. With the clinical images and its progressive nature, multiple hepatic peribiliary cysts can be misdiagnosed as cholangiocellular carcinoma or primary sclerosing cholangitis.[7] The antemortem images in our case 1 and 2 revealed multiple cystic lesions in the liver. However, compression of the bile ducts by the cysts was not observed clinically. From the findings of the images, case 1 was misdiagnosed as having primary sclerosing cholangitis. In case 3, the cystic lesions could not be identified in the antemortem images. Because of the possible progressive nature and harmful outcome of multiple hepatic peribiliary cysts,[3,5,7,15] clinicians should pay more attention to this disease. Recent studies have indicated that T2-weighted magnetic resonance (MR) images and cholangiographic contrast-enhanced CT scans can lead to a definitive diagnosis of peribiliary cysts.[5]

The definite pathogenesis of multiple hepatic peribiliary cysts is unclear at present. In the previous literature, inflammation or circulatory disturbance in the liver was discussed as one of the possible pathogenic factors.[1–3,6,16] Most of the previously reported cases, as well as the present cases, were in patients who showed portal hypertension associated with severe underlying liver diseases, so circulatory disturbance in the liver seems to be related to the pathogenesis of these cysts. Although several cases in the previous reports were associated with occluding portal venous thromboembolism,[1,3,8] no apparent portal venous thromboembolism could be identified in the present cases. Inflammation or hepatic ischemia due to a portal hypertensive state may lead to glandular obstruction, resulting in cyst formation. Genetic factor(s) may also be involved in the pathogenesis of the cyst formation. This possibility is particularly interesting in the previously reported cases in patients without underlying circulatory disturbance.[10,11,13,14] In the present patients, case 2 and case 3 showed microscopic or macroscopic cystic dilatations of glands in other organs (e.g., ductular dilatation of esophageal glands, pancreatic cyst, enteritis cystica profunda), which may reflect the possibility of genetic susceptibility to cystic change in the ducts and tubules in these patients.

In summary, we have described three new autopsy cases of multiple hepatic peribiliary cysts, including one symptomatic cases. Although peribiliary cysts have been considered to be clinically harmless, there is a possibility that this condition eventually results in serious obstructive jaundice. Therefore, in addition to being a pathological curiosity, this condition may be clinically significant.

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