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Hilar biliary cysts in hepatic transplantation. Report of three symptomatic cases and occurrence in resected liver grafts

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Abstract Hilar cysts are infrequent post-transplant biliary tract complications. Thirteen cases were discovered among 493 consecutive liver transplants (2.6 %). Three (0.60 %) were symptomatic (obstructive jaundice) while the other ten were found by systematically searching in the hilum in a series of 129 consecutive, resected grafts at retransplantation or autopsy (n = 54). Two types of cysts were detected: in eight grafts (1.6 %), these were blind unilocular cavities with viscid mucous content, located adjacent to the biliary tract anastomoses. These had been inadvertently created as a result of the sequestered remnant cystic duct after cholecystectomies and biliary tract reconstructions, where a double-barreled common duct and long cystic duct had been present in the donor liver. These mucoceles ranged from 0.5 to 5.5 cm in diameter (median 1.7 cm). The three symptomatic cases were diagnosed by imaging techniques 3.5 years after transplantation; however, this type of cyst was found as early as the 2nd month post-transplantation when detected in lost liver grafts. Five livers (1 %), lost between 5 months and 2.8 years post-transplantation, showed cystically dilated peribiliary glands, sometimes with multilocular, and occasionally multiple, cavities ranging from 0.5 to 2 cm in diameter (median 0.8 cm). This type of cyst was asymptomatic and located adjacent to the left, right, or common hepatic ducts. Threads were found near four cysts, suggesting that surgical injury may have been responsible for obstructing the neck of the glands. With the increasing number of long-term survivors of liver transplantation, unless preventive surgical methods are implemented, the number of symptomatic cysts of these origins can be expected to grow. Transplantation teams should, therefore, be aware of these potential causes of biliary tract complications.

Key words Liver transplantation, biliary cyst · Biliary cysts, liver transplantation

Introduction

Leakages, necroses, perforations, fistulas, bleeding, and stenosis are frequent biliary tract complications after orthotopic liver transplantation (OLT) [8, 11]; however, the development of hilar biliary cysts is rare [2, 4, 9, 17]. Slooff et al. [9] observed 2 so-called retention cysts among 16 surgical biliary complications in their series of 49 OLTs on 46 patients. Resection was required in one cyst and the other was aspirated by repeated percutaneous punctures. Krom et al. [3] described a very dilated and obstructed remnant of the cystic duct that caused a spherical impression on the donor bile duct. Stratta et al. [11] described 2 cystic duct mucoceles among a total of 27 biliary complications after 144 Roux-en-Y choledochojejunostomies.

Table 1 Symptomatic mucoceles of the cystic duct remnant (*CT* computed tomography, *c-c* terminoterminal choledochocholedochostomy, *c-j* choledochojejunostomy)

Case	Donor age, sex	Recipient age, sex	Terminal liver disease	Biliary anastomosis	Previous biliary complications	Time from OLT to diagnosis of mucocele	Symptoms	Diagnosed by	Size (cm)	Associated biliary pathology	Biliary reconstruction	Follow-up
1	35, F	55, M	Alcoholic cirrhosis	c-c	Stricture, lithiasis (day 30)	4.5 years	Cholangitis, obstruction	Percutaneous cholangiogram	1.5	Stricture	c-j	6 months. No biliary complications
2	26, M	40, F	Alcoholic cirrhosis	c-c	Stricture (day 4)	4 years	Obstruction	Percutaneous cholangiogram CT	5.5	None	–	30 days. Died of recurrent alcoholic hepatitis
3	24, M	55, M	HCV posthepatitic cirrhosis	c-c T-tube	No	3.5 years	Obstruction	US Percutaneous cholangiogram	1.7	Stenosis, neuroma	c-c T-tube	6 months. No biliary complications. Periportal hepatitis (anti-HCV +)

Koneru et al. [2] and Zajko et al. [17] described 8 tension mucoceles, identified on transhepatic cholangiograms as extrinsic masses compressing the common hepatic duct, among more than 1800 hepatic grafts (0.44%). Biliary obstruction or cholangitis from 2 weeks to 3.3 years following transplantation was clearly identified in their patients. The authors suggested that cholangiographic features appear to be specific for a mucocele of the graft cystic duct remnant [17].

Other kinds of biliary cysts can also develop in the hilum of the liver. Nakanuma et al. [7] described cystic lesions of an acquired origin, limited to the hepatic hilum, incidentally found in eight cases of an autopsy series of nontransplanted patients without associated polycystic disease, Caroli disease, or previous cholecystectomy, but with other severe parenchymatous liver diseases. The cysts were the result of dilatation of pre-existing peribiliary glands. In their series, no cysts were found in normal livers. Biliary cysts of this origin in the hilum of nontransplanted livers were found to be the cause of obstructive jaundice in one out of three autopsy cases described by Wanless et al. [16] and in another patient referred to by Stevens et al. [10]. As far as we know, there is no previous report of this kind of cyst in the transplantation setting.

The aims of this study were to report the clinicopathological features of 3 symptomatic cases of hilar biliary cysts among a series of 493 consecutive liver transplants in 418 patients and the morphological characteristics of 10 biliary cysts discovered in a systematic search of the hepatic hilum of 129 failed liver grafts resected at autopsy or at retransplantation.

Case reports (Table 1)

Case 1

OLT with an ABO-compatible liver from a 35-year-old female donor who had died of intracranial hemorrhage was performed in September 1991 on a 51-year-old male patient with terminal cirrhosis caused by chronic alcoholism. Terminoterminal choledochocholedochostomy without a T-Kehr tube was the chosen technique for biliary anastomosis. Protocol immunosuppression was achieved with cyclosporin A (2 mg/kg per day), corticosteroids (2 mg/kg per day), and azathioprine (2 mg/kg per day). The patient was discharged 23 days after transplantation. There were no post-transplant complications except for a steroid-related diabetes mellitus (blood glucose 290–320 mg/100 ml) until January 1992, when jaundice and the results of liver function tests prompted a percutaneous needle biopsy. A late acute rejection, Snover grade 2, was diagnosed, and three steroid boluses were administered. One month later, a further bout of jaundice (bilirubin 5.2 mg/100 ml; normal level < 1) prompted an endoscopic retrograde cholangiopancreatography, and stenosis of the biliary anastomosis and choledocholithiasis were diagnosed. These were treated with endoscopic sphincterotomy, extraction of stones, and dilatation of the stenosis. In April 1996, 4.5 years after transplantation, the patient developed fever (38 °C) and progressive jaundice. Total serum bilirubin rose to 21.6 mg/100 ml, alkaline phosphatase (AP) to 1060 IU/l (normal range 98–280 IU/l), and gamma-glutamyl transpeptidase (GGT) to 415 IU/l (normal range 7–50 IU/l). AST and ALT serum rates were 100 IU/l (normal range 2–40 IU/l) and 211 IU/l (normal range 2–40 IU/l), respectively. Dilatation of the main bile duct was observed on ultrasound, and percutaneous cholangiography showed an impression over the dilated proximal biliary passage, above an anastomotic stenosis (Fig. 1A). Endoscopic dilatation of the stenosis was attempted unsuccessfully and surgery was indicated. At surgery, a cyst, firmly attached to the main biliary duct at the level of the stenosis of the anastomosis, was detected. The cyst (Fig. 1B) and the graft duct were dissected and resected, including the distal section of the dilated donor common bile duct. A chole-

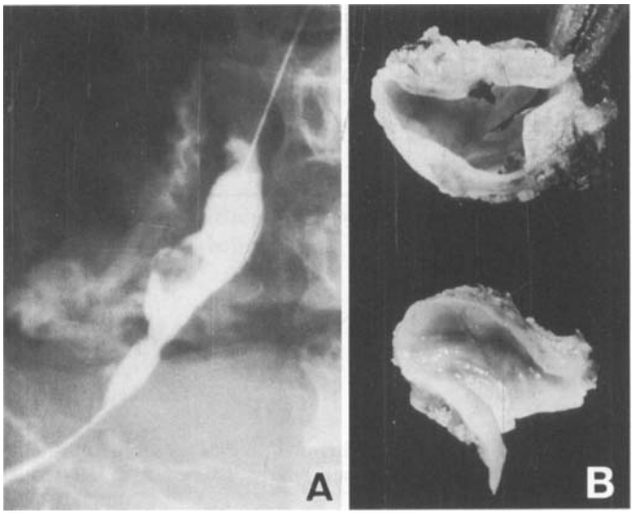

Fig. 1 A, B Case 1: **A** In a posteroanterior cholangiogram, the impression of the biliary cyst over the main biliary duct appears to be located intraluminally. Lithiasis was considered as a differential diagnosis; **B** Macroscopically, the section of the resected cyst shows a shiny, mucosal intraluminal surface after removal of its viscous content

dochojejunostomy to a Roux limb was performed. Cyst wall histology showed a mucous-secreting epithelium lining fibromuscular tissue. Fibrosis and some inflammatory infiltration were seen in the stenotic perianastomotic tissue.

Case 2

OLT with an ABO-compatible graft from a 26-year-old male who died of cranioencephalic trauma was performed on a 40-year-old female patient with terminal alcoholic cirrhosis (Child grade C) in May 1992. Terminoterminal choledochocholedochostomy without a T-Kehr tube was the chosen technique for biliary anastomosis. Protocol immunosuppression was achieved with cyclosporin A (2 mg/kg per day), corticosteroids (2 mg/kg per day), and azathioprine (2 mg/kg per day). The patient developed jaundice and results were altered in liver function tests (AST 174 IU/l, ALT 391 IU/l, AP 316 IU/l, GGT 654 IU/l, and bilirubin 48.3 mg/dl) on post-transplantation day 4. Dilatation of the intra- and extrahepatic biliary tract was observed by ultrasound, and stenosis of the biliary anastomosis was visualized by endoscopic retrograde cholangiography. Surgical resection of the 1.5-cm stenosed biliary duct was performed, and a terminoterminal choledochocholedochostomy without a T-Kehr tube was reconstructed. Serum bilirubin levels progressively decreased and the patient was discharged on post-transplantation day 35. The patient did well until January 1994, when liver function tests showed AST 136 IU/l, ALT 284 IU/l, AP 160 IU/l, GGT 425 IU/l, and bilirubin 2.2 mg/dl. Moderate macrovacuolar steatosis, centrilobular sclerosis, disseminated acidophilic bodies, and mild lobular inflammation with some neutrophilic leukocytes were seen during histological examination of a percutaneous liver biopsy. Alcoholic injury was suspected, but the patient denied recidivistic alcohol ingestion. She was lost to follow-up for the next 2 years.

The patient was admitted to the hospital for the last time in May 1996, 4 years post-transplantation, with ascites and elevations in hepatic and renal function tests [AST 84 IU/l, ALT 32 IU/l, AP 129 IU/l, GGT 137 IU/l, bilirubin 14.6 mg/dl, and creatinine 4 mg/l (normal level < 1.2mg/l)]. Serum antibodies for HBV and HCV were negative. A liver biopsy showed alcoholic hepatitis, Gerber and Popper grade IV/V, with extensive pericellular fibrosis and moderate macrovacuolar steatosis, Mallory hyalin, and intense cholestasis. Intense ductular proliferation was seen in the periseptal and periportal parenchyma interfaces, and associated extrahepatic biliary obstruction was suspected. Computed tomography showed dilatation of the biliary tract and a large extrinsic cyst compressing and displacing the common bile duct graft (Fig. 2A). A percutaneous transhepatic cholangiogram showed a biliary stenosis with a filiform lumen due to an extrinsic mass (Fig. 2B). A permanent transhepatic biliary catheter was placed in the suprastenotic dilated duct. Over the next few days the patient experienced temporospatial disorientation and multiple ecchymoses. Ascites increased, with a progressive breakdown of liver and renal functions.

The patient died of liver and renal failure 4 years after transplantation. An autopsy was performed and a cyst, 5.5 cm in diameter with viscid fluid inside, was found to be compressing the common biliary duct (Fig. 2C). Hemorrhagic gastritis and hemorrhage

Fig. 2 A–C Case 2: **A** Computed tomography shows a hilar cyst (*arrows*); **B** Extrinsic compression of the common bile duct and dilatation of the proximal biliary passages are seen in the cholangiogram; **C** Photograph of the hepatic hilum at autopsy. The cyst (*) is adjacent to the distal main duct (*between arrows*)

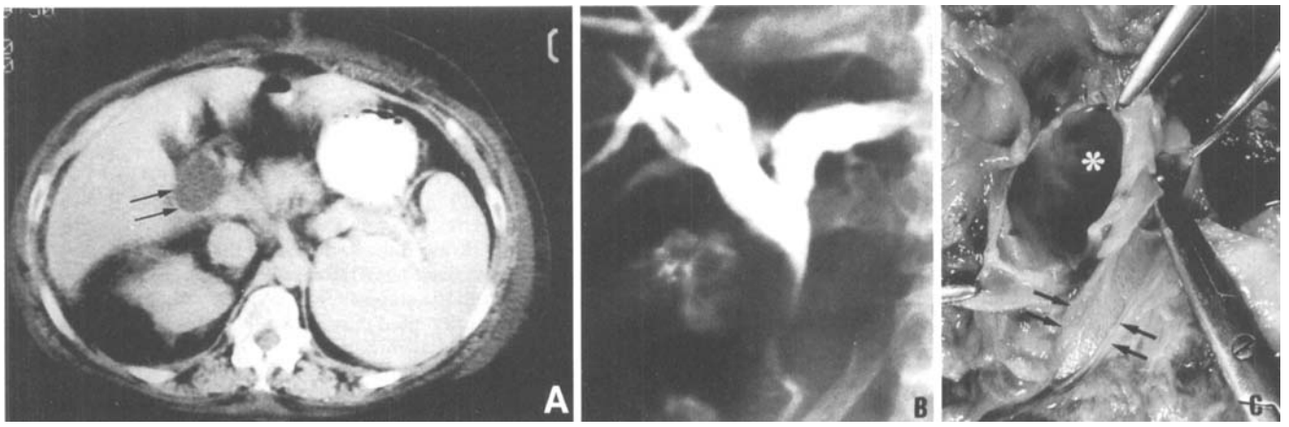

Table 2 Asymptomatic mucoceles of the cystic duct remnant in resected liver grafts (*HCC* hepatocellular carcinoma, *c-c* terminoterminal choledochocholedochostomy

Case	Donor age, sex	Recipient age, sex	ABO compatibility	Terminal liver disease	Biliary anastomosis	Time from OLT to resection	Graft failure	Size (cm)	Associated biliary pathology
4	36, M	37, M	Yes	HBV cirrhosis HCC	c-c T-tube	17 months	Recurrence of HBV cirrhosis	2	None
5	34, F	54, M	Yes	HCV cirrhosis	c-c	5 months	Kaposi's sarcoma	0.5	None
6	18, M	43, F	Yes	Alcoholic cirrhosis	c-c	2 months	No. Died of intracranial hemorrhage	0.8	Fistula, biliary leak, lithiasis
7	53, M	43, M	Yes	Cryptogenic cirrhosis	c-c	2.8 years	Hepatic artery thrombosis	0.8	Ischemic cholangitis, biliary leak, lithiasis
8	32, M	30, M	Yes	HBV and HDV cirrhosis	c-c T-tube	18 months	Chronic rejection	1	None

in the posterior cranial fossa were additional autopsy findings. Threads were seen in the wall of the cyst, and their histological sections showed a cuboid mucosecretor epithelium lining a fibromuscular tissue.

Case 3

OLT with an ABO-compatible graft from a 24-year-old male who had died of cranioencephalic trauma was performed on a 55-year-old male patient with terminal HCV cirrhosis (Child grade C) in August 1992. Terminoterminal choledochocholedochostomy with a T-Kehr tube was the chosen technique for biliary anastomosis. Protocol immunosuppression was achieved with cyclosporin A (2 mg/kg per day), corticosteroids (2 mg/kg per day), and azathioprine (2 mg/kg per day). He was discharged 18 days after transplantation with normal liver function tests. In October 1994 (post-transplantation day 774), liver function control tests showed AST 320 IU/l, ALT 477 IU/l, AP 795 IU/l, GGT 725 IU/l, prothrombin activity 100%, and bilirubin 3.3 mg/dl. A percutaneous liver biopsy showed moderate lobular and mild periportal hepatitis. Serum antibodies to HCV (ELISA) were positive. The results of liver function tests in December 1995 were as follows: AST 63 IU/l, ALT 180 IU/l, AP 910 IU/l, GGT 698 IU/l, and bilirubin 4.7 mg/dl. Liver biopsy showed periportal hepatitis with incomplete fibrous septa and centrilobular cholestasis. Mild extrahepatic dilatation of the biliary tract was seen on ultrasound exploration. Over the next 6 months jaundice slowly progressed. The results of further liver function tests in June 1996 were: AST 67 IU/l, ALT 154 IU/l, AP 1103 IU/l, GGT 1391 IU/l, and bilirubin 12.4 mg/dl. Transparietal cholangiography showed main biliary duct stenosis and dilatation of the proximal extrahepatic ducts and intrahepatic biliary ducts. A catheter was placed in a dilated intrahepatic duct for drainage. Fifteen days later surgery was performed and a cyst, 1.7 cm in diameter and surrounded by inflammatory tissue and causing stricture, was located at the level of the biliary anastomosis. Cyst and biliary anastomosis were resected, and a new terminal choledochocholedochostomy was reconstructed with a T-Kehr tube externalized through the recipient choledochostomy. Histological examination showed an infiltrating traumatic hilar neuroma obstructing the main bile duct. Threads were seen encased in the neuromatous proliferation [1]. The cyst wall showed a mucosecretor epithelium lining the fibromuscular tissue. No biliary complication developed within a 6-month follow-up period.

Materials and methods

In our OLT program, 493 consecutive liver transplantations were performed on 418 patients over a 10-year period (1986–1996). A total of 137 deaths and 75 retransplantations were the result. Some 129 specimens were obtained from these grafts, either at resection of the donor liver, prior to retransplantation, or at autopsy ($n = 54$), and they were systematically searched for hilar cysts. The cause of graft failure was established through clinicopathological analysis, including review of patient charts and histopathological examination of the resected liver grafts.

Previously described systematic examination of the hilum [1] was performed in all cases. Briefly, after fixation in 10% formalin, a rectangular block was obtained that included the hilum and its mesenchymal bifurcation into the parenchyma. This was serially sectioned from left to right into parallel 2- to 3-mm vertical sections that were embedded in paraffin and routinely processed. The sections were stained with hematoxylin-eosin. When a cyst of more than 0.5 cm in diameter was found macro- or microscopically, additional sections were obtained for staining with Masson trichromic and periodic acid-Schiff (PAS). These were considered to be cystic stump cysts when they were located very distally, near the surgical section or the biliary anastomosis, and when they were seen to have their own, microscopically well-defined wall (dense, parallel collagen fibers, including some muscular fibers in interstitial tissue). Cysts without these features were classified as glandular in origin, and their location and possible multiloculation and/or multiplicity was recorded. A search for pericyst threads was done on histological slides. Demographic and other pretransplant clinicopathological characteristics of the ten patients with biliary cysts in their grafts are shown in Tables 2 and 3.

Table 3 Cysts of peribiliary glands in resected liver grafts (*c-c* terminoterminal choledochocholedochostomy, *c-j* choledochojejunostomy)

Case	Donor age, sex	Recipient age, sex	ABO compatibility	Terminal liver disease	Biliary anastomosis	Time from OLT to resection	Graft failure	Size (cm)	Location	Number of cysts	Multiloculation	Threads	Associated biliary pathology
A	16, F	43, F	Yes	Fulminant hepatitis	c-c t-tube	7 months	Fulminant hepatitis	1	Common hepatic duct	1	No	Yes	Lithiasis
B	7, M	4, M	O to A	Hepatic artery thrombosis in previous graft	c-j	6 months	Hepatic artery thrombosis	0.6	Right and left hepatic ducts	2	No	Yes	None
C	45, M	17, F	Yes	Wilson's disease and HBV cirrhosis	c-c	2.3 years	HBV cirrhosis recurrence	1	Right hepatic duct	1	Yes	Yes	None
D	17, M	51, M	Yes	Alcoholic cirrhosis	c-c	4 months	Chronic rejection	0.5	Right hepatic duct	3	Yes	No	None
E	34, F	9, M	O to B	Fulminant hepatitis	c-j	3 months	Hepatic artery thrombosis	0.9	Right hepatic duct	1	Yes	Yes	None

Results

Ten of the 129 resected grafts (7.8%) had asymptomatic biliary cysts in the hilum, and the incidence was 2.6% in the whole series (493 OLTs), including the three symptomatic cases.

Five cases were unilocular dilatations of the cystic duct remnant (Table 2) and were discovered macroscopically. These were found to contain transparent viscose fluid (mucoceles), they were detected adjacent to the choledochocholedochostomy, and they had an average diameter of 1.0 cm (range 0.5–2.0 cm). Their corresponding grafts were lost between the 2nd and 33rd months (median 15th month) post-transplantation. In no case was loss of the graft attributed to a biliary pathology (Table 2), although two were associated with perianastomotic leakage, secondary to transmural ischemia (coagulative pigmented necrosis) of the wall of the main duct. In one, lost as a result of late thrombosis of the hepatic artery, ischemia of the larger extra- and intrabiliary ducts was severe, and biliary sludge was abundant. Microscopically, the cysts were lined with a columnar or cuboidal PAS-positive epithelium.

Five cases showed cystic cavities near the bifurcation of the common hepatic duct with a diameter greater than 0.5 cm (Table 3). The three largest (0.9, 1.0, and 1.0 cm) were macroscopically observed when liver hila were serially sectioned, and their cavities showed mucous fluid. The remaining two were detected on the histological slides; they had a median diameter of 0.8 cm (range 0.5–1.0 cm). Microscopically, they were located near the wall of the large bile ducts: one at the common hepatic duct, one at the right hepatic duct, and three at the left hepatic duct. Three were isolated cavities. Two cases showed several cavities in a row, and these were considered dilatations of adjacent glands (Fig. 3A). Multiloculation was seen in three cysts, suggesting multiple dilatation of contiguous acini of the same gland. Frequently, lobules of the peribiliary gland were noted around these, revealing varying degrees of cystic luminal dilatations. Suture threads were observed very near the cyst in four cases (Fig. 3B). All five were lined with a flattened, cuboidal epithelium. Absent or very mild staining of the apical cytoplasm was seen using the PAS method. Mild chronic inflammatory infiltrates were found adjacent to their wall. Only one case was associated with another biliary complication (lithiasis).

Discussion

The prevalence of biliary tract complications after transplantation is reported as ranging between 13% and 19% [5, 8, 11]. Biliary cysts in liver graft hila have been infrequently observed [9, 17]. Of the 493 consecutive liver transplants (2.6%) in our study, 13 showed cysts, but only 3 cases were symptomatic (0.60%). A 0.8% prevalence for this complication has previously been reported [11]. The other ten cysts were located after a systematic search was carried out on 129 failed liver grafts.

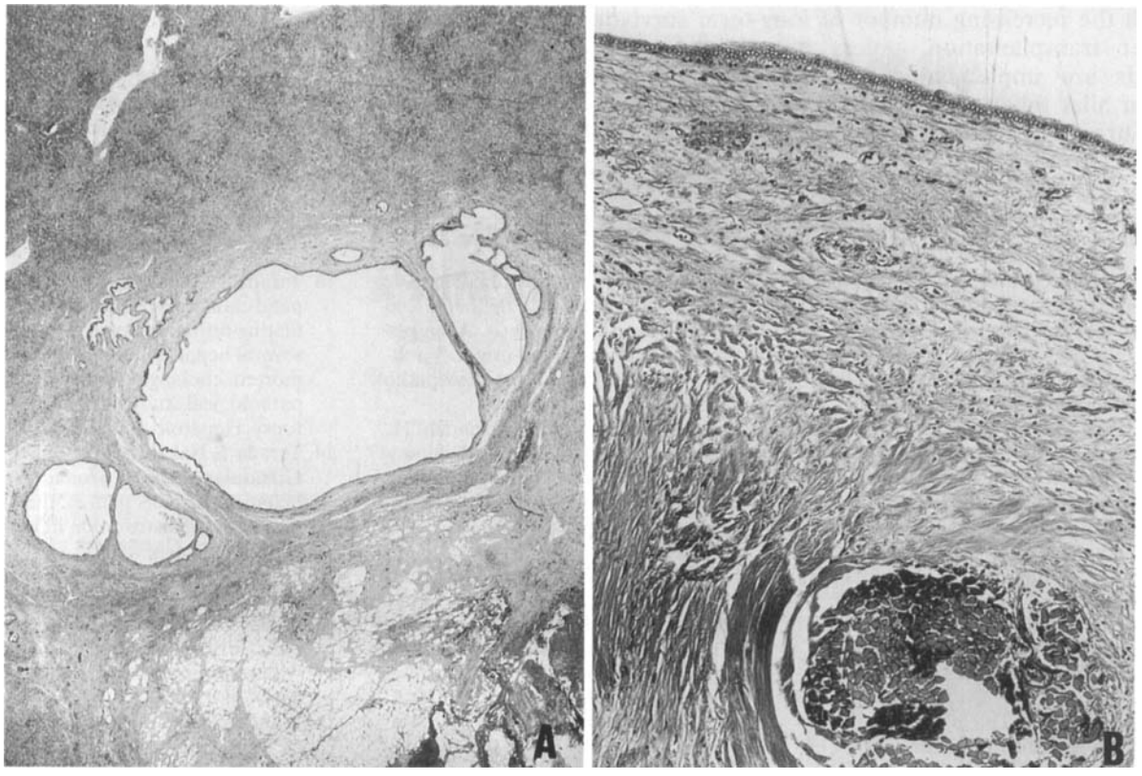

Fig. 3 A Multiloculation and multiplicity in a cyst of periductal gland origin (PAS-diastase × 25). **B** The epithelia are cuboidal. Fibers of a surgical thread can be seen in the wall (*bottom*; H&E, × 100)

Two types of biliary cysts were discovered. The first type has previously been described as a retention cyst [9], or mucocele [2, 3, 11, 17]. When the cystic duct descends for a considerable distance before emptying into the common bile duct, retention of a long remnant may occur after graft cholecystectomy, and the anastomotic suture may create a blind cavity. Persistent mucosecretions by their epithelial lining cells cause dilatation of the mucocele-type of hilar biliary cyst. A total of eight mucoceles were diagnosed in this series, giving a prevalence of 1.6% in our transplants. A long latent period with no symptoms is needed to attain sufficient size to cause obstruction with or without associated cholangitis. Symptoms began 3.5 years after transplantation in this series; however, this kind of cyst could be discovered as early as the 2nd post-transplant month by systematic searching. Four of these eight mucoceles were associated with other biliary tract complications (Tables 1, 2). This association may be indicative of technical difficulties in initial biliary tract reconstructions. Double-barreled common ducts and cystic ducts are found in about 20% of all cases [4, 6], and in a few of these patients this is a true transmural fusion. These anomalies cannot be reliably recognized during cholecystectomy, except with surgical cholangiography. Resection of the entire cystic duct, or excision of the common septum when necessary, has been recommended to prevent this type of hilar cyst [2].

A second type of hilar cyst was observed in five failed livers (1%). This type was similar to the cysts found incidentally in autopsy cases by Nakanuma et al. [7]. Seromucous intramural and extramural glands are found in the walls of the main biliary ducts. These peribiliary glands are found in the highest density in the walls of the right and left hepatic ducts [14]. Cysts in nontransplanted livers have been shown to originate in these glands [7, 16]. Obstructive jaundice caused by cysts of this origin has also been observed [10, 16]. This kind of cyst can be visualized on ultrasound and cholangiography [12, 13, 15]. Nakanuma et. al. [7] found cyst development to be associated with circulatory disturbance of the portal venous system. No portal thromboses were discovered in these five cases. The development of peribiliary cysts in the transplant setting could be related to surgical injury to the liver graft hilum. In this series, this type of cyst was frequently accompanied by suture remnants. Inflammatory response and reparative fibrosis may narrow and obstruct the neck of periductal glands.

With the increasing number of long-term survivors of liver transplantation, unless preventive surgical methods are implemented, additional symptomatic cases of hilar biliary cysts may be expected in the future. Surgeons, radiologists, and pathologists should be made aware of this potential cause of biliary complication.

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