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Case Report

Intrahepatic Cholangiocarcinoma Arising 33 Years After Excision of a Choledochal Cyst: Report of a Case

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We report a case of intrahepatic cholangiocarcinoma arising 33 years after excision of a choledochal cyst. A 61-year-old woman was admitted to our hospital complaining of fever. Thirty-three years ago she had undergone extrahepatic choledochal cystectomy and choledochojejunostomy for a choledochal cyst. Computed tomography showed a tumor in the anterior segment of the liver, extending to the posterior and medial segments and the right portal vein. Intrahepatic biliary stones were seen in the bile ducts. We performed extended right lobectomy. Microscopically, the tumor was cholangiocarcinoma. Most of the tumor area was composed of invasive adenocarcinoma but a carcinoma-*in-situ* component was also observed in some regions including the hilar bile duct, where an intrahepatic biliary stone was seen. This suggests that the cancer development could be related to intrahepatic cholestasis. Patients with choledochal cyst may have to be carefully followed up for more than 30 years even after diversion surgery.

Key words: Cholangiocarcinoma – Choledochal cyst – Cancer development

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According to various reports, 2.5% to 28% of congenital choledochal cysts are associated with malignant biliary tract tumors.[1–4] The regurgitation of pancreatic juice into the bile duct and the accumulation of bile juice in an anomalous pancreatobiliary ductal junction leads to chronic changes and may stimulate genetic alterations in patients with an anomalous pancreatobiliary ductal junction.[1,5–8] Biliary tract carcinoma rarely arises after biliary diversion surgery, such as roux-en-Y hepaticojejunostomy, but the remaining bile duct may predispose to carcinoma development for several years afterward.[1,5] Cases of cancer development in the biliary system more than 10 years after diversion surgery have been reported.[1,5,9–13] However, it is unknown whether such patients had carcinogenic potential for several decades after diversion surgery. Cancer could develop postoperatively due to cholestasis or it could develop *de novo* in patients after diversion surgery, as can occur in healthy individuals. We encountered a rare case of intrahepatic cholangiocarcinoma developing 33 years after excision of a choledochal cyst and we assessed the pathologic findings, focusing on cancer development.

Case Report

A 61-year-old woman was admitted to our hospital complaining of high fever and upper abdominal pain. She had undergone diversion surgery (excision of a choledochal cyst with roux-en-Y hepaticojejunostomy reconstruction) because of a choledochal cyst 33 years previously. Laboratory data on admission were as follows (values in parentheses are normal limits): white blood cell count, 10,300/mm^3 (8900/mm^3); albumin, 2.8 g/dL (3.9 g/dL); alkaline phosphatase, 849 IU/L (320 IU/L); and γ-glutamyl transpeptidase, 256 IU/L (40 IU/L). Hemoglobin, platelet count, prothrombin time, total bilirubin, aspartate aminotransferase, alanine aminotransferase, cholinesterase, lactate dehydrogenase, blood urea nitrogen, and creatinine were all within normal limits. Hepatitis B virus surface antigen and hepatitis B virus e antibody were positive. Hepatitis B virus surface antibody, hepatitis B virus e antigen, and hepatitis C virus antibody were negative. Carcinoembryonic antigen and carbohydrate antigen 19-9 were 16.4 ng/mL (2.5 ng/mL of normal limit) and 18,665 ng/mL (37 ng/mL of normal limit), respectively. Computed tomography showed a hepatic tumor that was roughly 7.5 cm in diameter and whose margin was unclear. The tumor was located mainly in the anterior segment, and was extending to the posterior segment, the medial segment, the caudate lobe, the jejunum around hepaticojejuno-anastomosis, and the right portal vein (Fig. 1a). Intrahepatic biliary stones were observed in the bile ducts of the hilar portion and lateral segment (Fig. 1b). Hilar lymph nodes swelling were also observed. Selective angiography showed an encasement of the right portal vein, the right hepatic artery, and the artery feeding segment 1 (Fig. 1c). A percutaneous transhepatic biliary drainage tube was inserted in the bile duct of segment 3. Cholangiography through the biliary tube showed dilated intrahepatic bile ducts in the left lobe, intrahepatic biliary stones, and a stenosis at the hepaticojejuno-anastomosis (Fig. 1d). Based on these findings, the tumor was diagnosed as cholangiocarcinoma arising in the anterior segment accompanied with extension to the medial and posterior segments and the caudate lobe, metastasis to hilar lymph nodes, vascular invasion to the arteries and the portal vein, and invasion to the hepaticojejuno-anastomosis. No distant metastases were found, and an entire resection was subsequently planned.

Intraoperative findings were more or less consistent with the preoperative diagnosis. The tumor was located mainly in the anterior segment and extended to the posterior and medial segments, caudate lobe, jejunum around the hepaticjejuno-anastomosis, and right portal vein. The right hepatic artery seemed to be involved in the tumor. During surgery, we detected invasion of the tumor into the diaphragm. We performed extended right lobectomy with combined resection of the jejunum loop and diaphragm. The origin site of the right portal vein was sutured after its combined resection. The remnant bile duct of the left lobe was reanastomosed to the newly constructed jejunal loop in roux-en-Y style. The patient was discharged from our hospital 2 months after surgery. Although the patient received postoperative chemotherapy using S-1, recurrence was found around the portal vein on computed tomography 9 months after surgery. The chemotherapy regimen was then changed from S-1 to gemcitabine, but the patient showed almost no response to gemcitabine and died 13 months after surgery.

The resected specimen contained a tumor, 5.6 × 4.7 cm in diameter, which appears as a yellowish-white firm mass without capsule formation (Fig. 2a). The tumor spread was mainly in the anterior segment including the hilar bile duct around the choledochojejunostomy anastomosis, which had been constructed 33 years prior, and extending to the diaphragm. Microscopically, the tumor consisted of

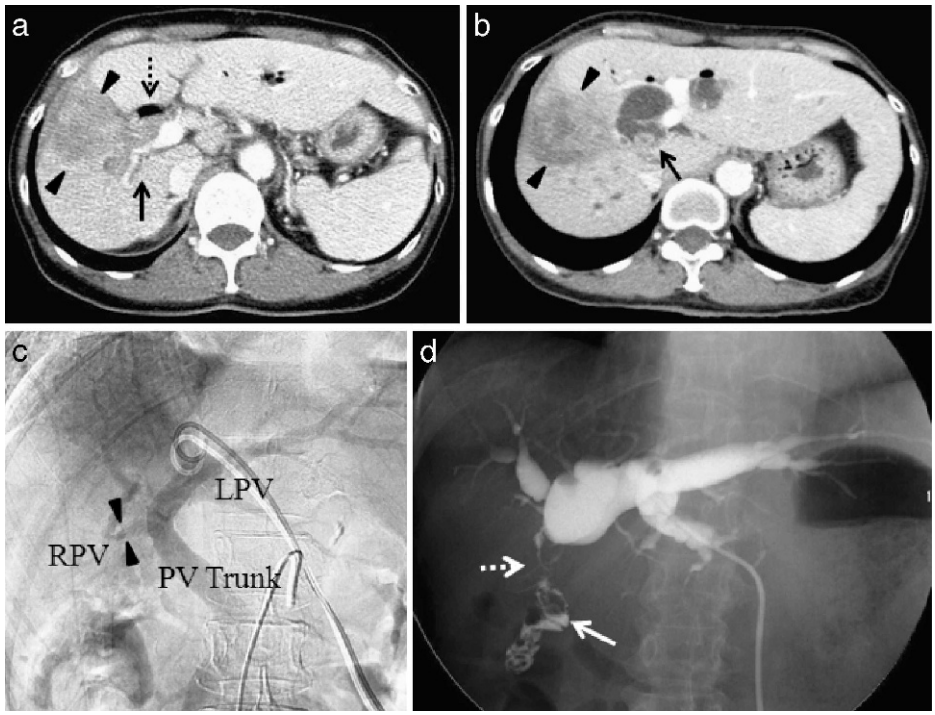

Fig. 1 Preoperative imaging diagnosis. (a) Contrast-enhanced computed tomography findings. A tumor in the anterior segment of the liver is extending to the posterior and medial segments. An arrow indicates the right portal vein encasement. A broken arrow indicates the jejunum, which is anastomosed to the hilar bile duct. (b) Contrast-enhanced computed tomography findings. An intrahepatic biliary stone is seen in the hilar bile duct. (c) Angiography findings in the portal phase. Encasement is seen in the right portal vein. (d) Cholangiography through the percutaneous transhepatic biliary drainage tube inserted in the bile duct of segment 3. An arrow indicates the jejunum loop. A broken arrow indicates a stenosis at the hepaticojejuno-anastomosis.

irregular glandular structures with intraluminal mucin, indicating that the tumor was cholangiocellular carcinoma (well-to-moderately differentiated type) (Fig. 2b–d). Most of the tumor area was composed of invasive adenocarcinoma, and a carcinoma-*in-situ* component was also seen in some of the peripheral areas and in the hilar area around the choledochojejunostomy anastomosis. The hilar bile duct contained an intrahepatic biliary stone. There were tumor invasions into the right portal vein, middle hepatic vein, jejunum loop, and diaphragm, but not into the right hepatic artery. There were metastases in the hilar lymph nodes.

Discussion

The incidence of hepatobiliary malignancies associated with congenital biliary dilation is reported to range from 2.5% to 28%.[1–4] Although the underlying mechanism of carcinogenesis in such cases has not been fully elucidated, it is presumed to be the reflux of pancreatic juice into the bile duct and the accumulation of mixed bile in the biliary system caused by an anomalous junction of the pancreaticobiliary duct. To prevent the development of biliary carcinoma, the entire extrahepatic bile duct is excised, and hepaticoenterostomy has been recommended because it separates bile from pancreatic juice flow. However, some patients have been reported to develop biliary cancer long after this operation. Our search of the English and Japanese language literature found 8 case reports describing biliary cancer arising after surgery with an interval of more than 10 years after diversion surgery (Table 1).[1,5,9–13] The 9 patients, including our own, consisted of 3 men and 6 women, and they ranged in age from 27–61 years. The tumor was resected in 5 patients and was not resected in 4 patients. The cancer development sites were the hepatic duct at the anastomotic site in 1 patient, intrapancreatic remnant choledochal cyst in 1, and intrahepatic bile duct in 7 patients. The longest period between the primary operation and the development of cancer was 34 years. Our patient

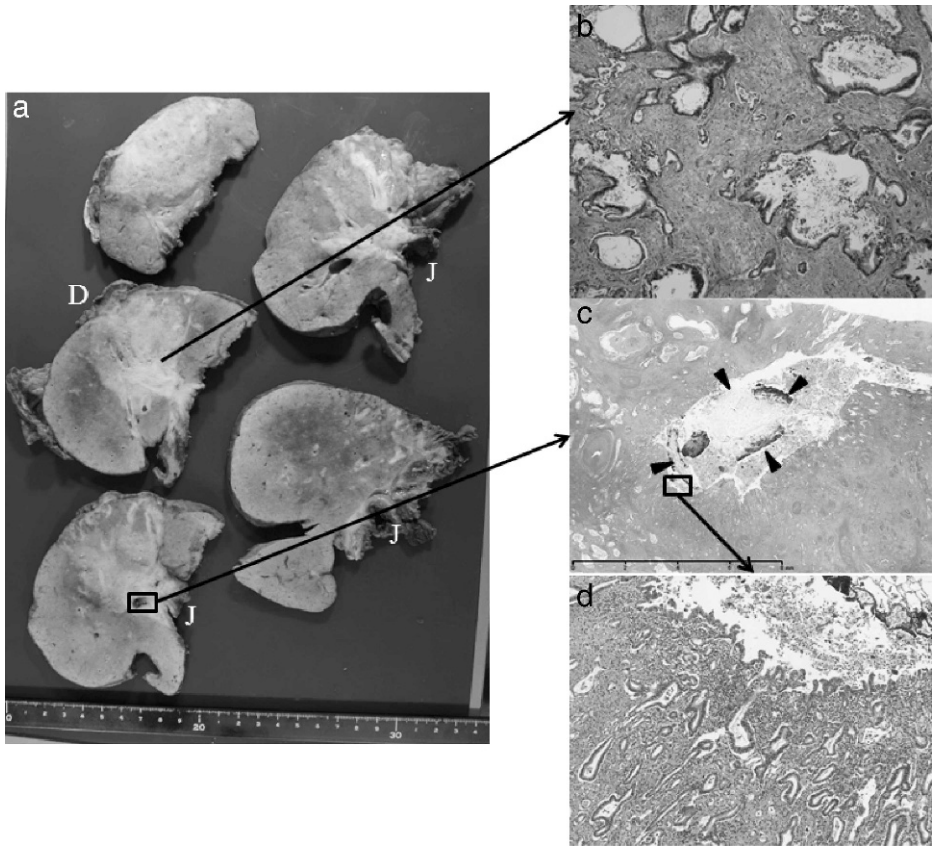

Fig. 2 Macroscopic and microscopic findings of the resected specimen. (a) Macroscopic findings. D, diaphragm; J, jejunum. (b) Histopathologic findings of the invasive adenocarcinoma area. H&E (×10). (c) A loupe observation of the hilar bile duct. H&E. A biliary stone is indicated by small arrowheads. (d) A magnified finding of the area in (c). Both invasive adenocarcinoma and carcinoma-*in-situ* components are seen. H&E. (×10).

also developed cholangiocarcinoma more than 30 years after diversion surgery, which was the second longest interval among the reported cases.

There are several possibilities as to why cancer develops after such a long interval (more than 10 years) following diversion surgery for choledochal cyst. First, the epithelium of the remnant bile duct wall may have already progressed to a precancerous stage at the time of surgery, and that carcinogenetic changes may have continued during the postoperative period.[5] Second,

Table 1 Patients in whom bile duct cancer developed more than 10 years after choledochal cystectomy

No.	Sex	Age	Interval after surgery	Site of carcinoma development	Resectability	Year/	author	Journal
1	F	52	10 y	Anterior segment	Resected	2001/	Goto	J Gastroenterol[1]
2	F	27	12 y	Intrapancreatic BD	Resected	1986/	Yoshikawa	Am J Gastroenterol[9]
3	F	41	16 y	Intrahepatic BD	Unresected	1992/	Choen	Australas Radiol[10]
4	F	38	17 y	Intrahepatic BD	Resected	1982/	Chaudhuri	Arch Surg[11]
5	F	35	19 y	Hepatic hilar BD	Died before surgery	1999/	Kobayashi	Surgery[5]
6	M	33	>20 y	Right lobe	Unresected	1992/	Choen	Australas Radiol[10]
7	M	46	26 y	Medial segment	Unresected	2004/	Suzuki	Jpn J Gastroenterol Surg[12]
8	M	44	34 y	Left lobe	Resected	2009/	Shimamura	Surg Today[13]
9	F	61	33 y	Right lobe	Resected	2011/	present case	

BD, bile duct.

the existence of stenosis at the anastomosis site or narrow segment in the intrahepatic bile duct may independently induce carcinogenesis even if there was no progression to a precancerous stage at the time of diversion surgery.[8,13] Last, cancer can develop *de novo* in the general population. Our patient underwent diversion surgery in our institute 33 years before the discovery of advanced cancer, but detailed medical records, including preoperative status of the biliary system (*e.g.*, Todani's classification of the choledochal cyst),[14] were not preserved. Because she had not undergone long-term medical follow-up, the postoperative existence of stenosis at the anastomosis site or narrow segment in the intrahepatic bile duct had not been examined. However, the following pathologic findings are noteworthy: (1) an intrahepatic biliary stone was found in the hilar bile duct around the choledochojejunostomy anastomosis, (2) the tumor was composed of not only invasive adenocarcinoma but also a carcinoma-*in-situ* component, and (3) the carcinoma area including carcinoma-*in-situ* was spreading from the hilar portion to the periphery. These pathologic findings suggested that cancer development could be attributed to postoperative initiation rather than *de novo* development. We assume that there had been long-term biliary stasis after the diversion surgery due to anastomotic stenosis and/or the intrahepatic biliary stone, that the long-term biliary stasis led to the development of a regional carcinoma-*in-situ* mainly in the anterior segment, and that invasive adenocarcinoma finally occurred and formed a mass in the carcinoma-*in-situ* region. It is possible that a precancerous condition, such as low grade biliary intraepithelial neoplasia, had already taken place before the diversion surgery, and that this precancerous potential also contributed to cancer development.

The debate on carcinogenetic initiation after diversion surgery in patients with choledochal cyst is clinically of great interest, because it has not been determined how long those patients should be followed-up after surgery. We understand that follow-up of such patients using imaging devices and blood examination over their lifetime would expose patients to repeated invasive procedures and would be costly. However, because our patient had not undergone long-term medical follow-up, the cancer had already progressed to an advanced stage at the time of discovery. The operation had to be invasive to resect the advanced cancer entirely, and resultant survival was almost 1 year. We believe that all patients who have undergone choledochal cystectomy should be assessed to determine their present status, even if the surgery was performed several decades prior and a sufficient record as to preoperative and postoperative biliary status is not preserved. If a stenosis at the anastomosis site, a narrow segment in the intrahepatic bile duct, or an intrahepatic biliary stone is found, treatment for improving biliary stasis or strict follow-up using imaging devices and blood examination may be necessary, as suggested in past reports.[8,13] We may have to accept biannual examination of enhanced computed tomography and blood test in the patients with potential risk. If the patient has no abnormalities related to the presence of intrahepatic cholestasis, the necessity for long-term follow-up is unknown, but we believe that lifelong follow-up is still an option for confirming a patient's current condition after diversion surgery. Annual examination of ultrasound is almost noninvasive and may be informative for the routine condition check.

We reported a rare case of intrahepatic cholangiocarcinoma arising 33 years after excision of a choledochal cyst. We assessed the histopathologic characteristics and considered the possibility that the cancer development was related to past pancreatic juice regurgitation or intrahepatic cholestasis. Consideration of these factors for patients who develop biliary cancer long after diversion surgery for choledochal cyst may provide valuable insight as to the ideal method and interval for postoperative follow-up.

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