Case Report

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Intrahepatic cholangiocarcinoma with intrahepatic biliary lithiasis arising 47 years after the excision of a congenital biliary dilatation: Report of a case

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Summary **We report a case of intrahepatic cholangiocarcinoma with biliary lithiasis arising 47 years after surgery for a congenital biliary dilatation (CBD). A 62-year-old woman was admitted for the investigation of a liver tumor. She had undergone a choledochoduodenostomy at the age of 15 years for CBD and resection of an extrahepatic bile duct with choledochojejunostomy because of cholangitis at the age of 55 years. An enhanced computed tomography (CT) revealed a liver tumor 50 mm in diameter in the S6 region with surrounding lymph node swelling and intrahepatic metastatic lesions in the S8 region. A drip infusion cholangiographic CT showed biliary lithiases in the left liver. An extended right hepatectomy and lymph node dissection was considered but was abandoned because of suspicions of liver functional insufficiency as a result of biliary lithiasis. She underwent biliary lithotomy through a percutaneous transhepatic cholangioscopy and subsequent systemic chemotherapy.**

Keywords: Intrahepatic cholangiocarcinoma, biliary lithiasis, congenital biliary dilatation

1. Introduction

A significant association between congenital biliary dilatation (CBD) and hepatobiliary malignancies is well known (*1*). According to the literature, 2.5%-28% of CBD cases are associated with malignant biliary tract tumors at the initial presentation (*2*). The cause of this carcinogenesis is presumed to be the reflux of pancreatic juice into the bile duct caused by an anomalous junction of the pancreatobiliary duct. Therefore, for the treatment of CBD, the recommended standard surgical method is the excision of the entire extrahepatic bile duct with a bilioenterostomy to stop the reflux of pancreatic juice, in what is called a "separation-operation". Some patients have been reported to develop intrahepatic cholangiocarcinoma (ICC) at a long interval after treatment as seen in several case reports. Some of these patients have undergone a reoperation to remove the ICC. Ono *et al*. (*3*) investigated the long-term outcomes and late complications after hepaticojejunostomy for a choledochal cyst. In that retrospective study, 56 patients with a choledochal cyst were followed up for more than 10 years after surgery, and two patients (3.6%) and one patient (1.8%) developed ICC and multiple intrahepatic bile duct stones, respectively. However, there have been no reports of ICC with intrahepatic biliary lithiasis in the opposite lobe of the liver arising after the excision of CBD.

2. Case report

A 62-year-old woman was referred to our hospital for the investigation of a large tumor in her liver, detected using computed tomography (CT), after she visited a local hospital complaining of general fatigue, a low-

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grade fever, and back pain. A physical examination performed upon admission disclosed neither jaundice nor a palpable abdominal tumor. When she was 15 years old, she underwent an anastomosis between a dilated common bile duct and the duodenum for CBD, which was classified as type 1 according to the classification of Todani. However, the patient had continued to suffer from intermittent cholangitis. Although imaging examinations revealed no neoplastic lesions in the biliary tract, her pathologic extrahepatic duct was totally excised using a Roux-en-Y choledojejunostomy and a cholecystectomy when she was 55 years old. The excised gallbladder and extrahepatic bile duct showed evidence of neither carcinoma nor pre-carcinogenic findings. She had been well without any symptoms since her last operation until she felt general fatigue and back pain at the age of 62 years. A laboratory test revealed liver dysfunction, and abdominal ultrasonography and CT scanning showed an ill-defined heterogeneous mass, measuring 50 mm, in the right lateral sector.

The patient's laboratory data upon admission to our hospital showed elevated alkaline phosphatise (1,560 IU/L), gamma glutamyl transpeptidase (303 IU/L), and C-reactive protein (10.65 mg/dL), however, total bilirubin was within the normal range (0.3 mg/dL). Serum albumin was low (2.5 g/dL). As for tumor markers, carcinoembryonic antigen was elevated (46.8 ng/mL) and carbohydrate antigen 19-9 was normal (1 U/mL). The indocyanine green (ICG) retention value at 15 min was 10.1%.

An abdominal enhanced CT examination performed at our hospital revealed an ill-defined tumor, 5 cm in diameter, originating from the right lateral sector of the liver and extending to the porta hepatis (Figure 1). Bile duct dilatation of the right lateral caudate, and left lateral branches was also apparent. Coronal reconstruction of the CT examination data revealed a pancreaticobiliary maljunction and dilatation in the residual intrapancreatic bile duct (Figure 2).

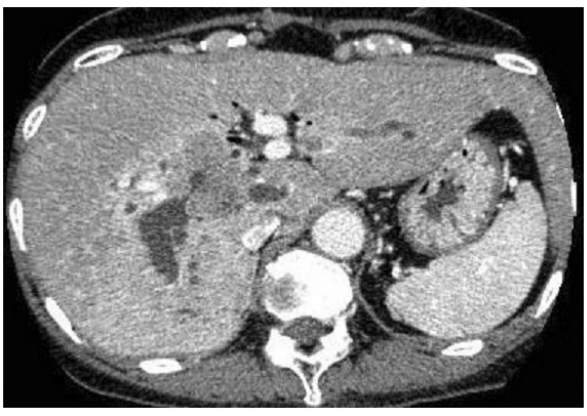

Figure 1. Enhanced abdominal CT showed a dense tumor, 5 cm in diameter, in the right lobe of the liver, extending into the porta hepatis.

Gadoxetic acid disodium-enhanced magnetic resonance imaging (MRI) revealed an intrahepatic metastatic lesion in segment 8 of Couinaud (Figure 3).

Drip infusion cholangiographic (DIC)-CT using meglumine iotroxate revealed diffuse peripheral dilatation of the intrahepatic bile duct in both hemilivers with narrowing proximal portions. In the biliary tracts of the right hepatic lobe, excretion of contrast-enhanced media was not observed. Many intrahepatic biliary stones in segment 2 and 3 were also observed (Figure 4).

The patient was diagnosed as having ICC in the right liver with intrahepatic biliary lithiasis in the left liver arising 47 years after an initial bilioenteric anastomosis for CBD. An extended right hepatectomy with regional lymph node dissection was initially suggested. However, liver volumetry revealed that the future remnant liver corresponded to 40% of the total liver parenchyma, and we suspected that the function of the future remnant left lateral section was insufficient because it was impaired as a result of the numerous intrahepatic biliary stones. Additionally, a hepaticojejunostomy was thought to be inappropriate

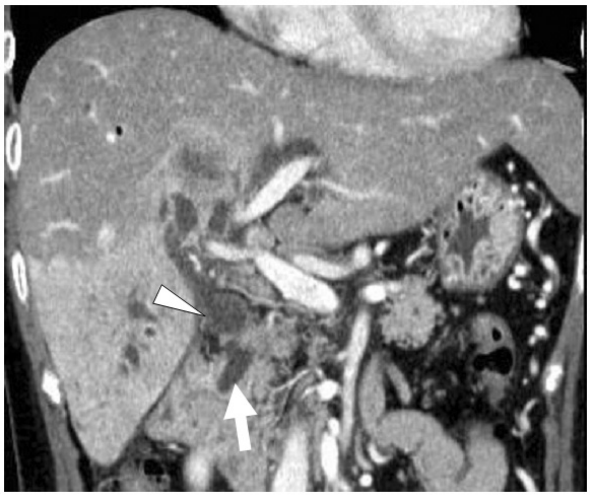

Figure 2. Coronal view CT showed pancreaticobiliary maljunction (white arrow) and dilatation in the residual intrapancreatic bile duct (white arrowhead).

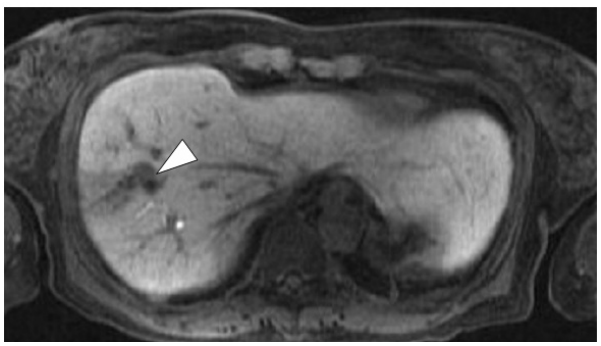

Figure 3. Gadoxetic acid-enhanced MRI showed that there was an intrahepatic metastatic lesion in the right anterior superior segment (white arrowhead).

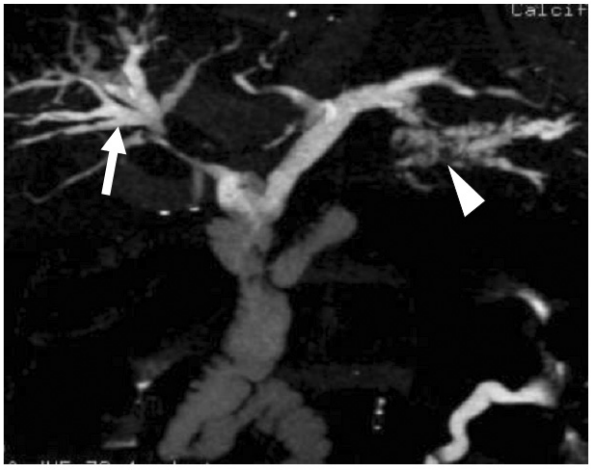

Figure 4. DIC CT showed that intrahepatic bile ducts in the anterosuperior segment of the right hepatic lobe were dilated (white arrow) and several intrahepatic biliary stones were present in the lateral segment of the left hepatic lobe (white arrowhead).

until all the intrahepatic stones in the future liver remnant, which were thought to be too numerous to remove during surgery, could be removed.

The patient was referred to gastroenterologists to undergo chemotherapy and lithotomy. Following an initial percutaneous transhepatic biliary drainage, the drainage tube was changed several times to a larger-sized one. Then, several lithotomy sessions were performed using a radiological procedure, although several small intrahepatic stones persisted. In parallel with the lithotomy procedures, systemic chemotherapy was planned. The scheduled protocol was as follows: therapy drip infusion of gemcitabine at a dose of 1,400 mg bi-weekly and oral intake of S-1 at a dose of 100 mg/day for 14 days followed by a 14-day rest interval. The systemic chemotherapy was started 12 days after the initial biliary drainage; however, the scheduled therapy was frequently discontinued because of episodes of acute cholangitis or tube dislocation, and gemcitabine was only administered 4 times during 4 months after the initial biliary drainage. A CT scan performed at 5 months after the initial biliary drainage revealed tumor progression in terms of number and size as well as multiple hepatic abscess foci. Although antibiotics were administered, the inflammation did not improve and the patient further developed pulmonary embolization. She died 5 and a half months after the initial biliary drainage, *i.e.*, 7 months after the diagnosis of the intrahepatic cholangiocarcinoma. An autopsy was not performed because of the family's wishes.

3. Discussion

Irwin and Morison described the first reported malignancy associated with CBD in 1944 (*4*). To date, lengthy and repeated reflux episodes of pancreatic juice into the bile duct *via* pancreaticobiliary maljunction have been considered to play an important role in the development of malignant transformations (*5*). Mutations of K-ras and other genes have been implicated, as well as the reflux of pancreatic juice associated with pancreaticobiliary maljunction (*6*). Therefore, once a diagnosis of CBD has been made, early radical surgery is recommended. However, a tendency toward carcinoma development or a precancerous condition in the biliary tree induced by exposure to carcinogens, such as reflux of small intestinal juice, appears to remain after surgery, especially when a pathologic duct is left untouched. Indeed, Kobayashi *et al.* analyzed the relative risks of biliary tract cancer before and after the excision of a congenital choledochal cyst and concluded that the relative risk in patients who underwent this operation was still higher than that of the general population, although it decreased by approximately 50% after surgery (*7*). This result suggested that the epithelium of the residual bile duct wall may have already progressed to a precancerous stage at the time of surgery and that genetic changes may have taken place or continued during the postoperative period. Additionally, biliary-enteric anastomosis is thought to be a possible risk factor for the development of ICC after surgery for benign diseases (*8*). Tocci *et al.* reported that the incidence of ICC after hepaticojejunostomy was 1.9%, with an interval of 11-18 years (*9*). Eleftheliadis *et al.* examined the histological findings of bile duct epithelium obtained by choledochoscopic biopsy from 9 patients at 1-12 years after a choledochoduodenostomy; they detected hyperplasia, pseudopyloric gland metaplasia, and intestinal metaplasia, features that are frequently found in the epithelium adjacent to gallbladder cancer and are regarded as the basis of carcinogenesis (*10*).

Uno *et al.* reported several patients with intrahepatic cholelithiasis developing long after the primary excision of the choledochal cysts (*11*). Some authors have reported a high mutagenic activity of stones from patients with cystic conditions of the biliary tract, a phenomenon that has not been observed in the gallstones of patients without cystic biliary disease (*12*). Postoperative stenosis at the site of a hepaticojejunostomy, congenital remnant stenosis, and repeated cholangitis of the intrahepatic bile duct seem to lead to bile stasis and intrahepatic lithiasis and may be a high-risk factor for carcinogenesis. In the present case, when the patient was diagnosed as having ICC in the right lobe of the liver, multiple intrahepatic bile stones were noted in the opposite lobe of the liver. Thereafter, the patient was thought to be a poor candidate for a radical hepatectomy because the remnant liver volume would be too small, considering the possible insufficient functional reserve of the future liver remnant.

Our search of English and Japanese language

Table 1. Reports of intrahepatic cholangiocarcinoma developing after surgery for congenital biliary dilatation

No.	Age	Gender	Year after resection	Site of cancer development	Treatment	Year	*Ref.*
1	58	F	7	Left lobe	Death before surgery	1972	(*13*)
2	38	F	17	?	Death before surgery	1982	(*14*)
3	33	M	20	Right lobe	Unresected	1992	(*15*)
4	?	?	2	Right lobe	Resected	1994	(*16*)
5	29	M	3	Bilateral lobe	Unresected	1996	(*17*)
6	18	F	2.4	Left lobe	Death before surgery	1999	(*7*)
7	52	F	10	Right lobe	Resected	2000	(*18*)
8	46	M	26	Left lobe	Unresected	2004	(*19*)
9	44	M	34	Left lobe	Resected	2007	(*2*)
10	26	M	26	Left lobe	Resected	2008	(*20*)
11	62	F	47	Right lobe	Unresected	2010	Present case

literature found ten case reports describing ICC after surgery for a congenital choledochal cyst (Table 1). The 11 patients, including our own, consisted of 5 men, 5 women, and 1 unknown patient ranging in age from 18 to 62 years. The present case was the oldest of the reported patients with ICC after the excision of CBD. The median period between the primary operation and the development of ICC was 14.0 years, ranging from 2 to 47 years. The lesions were located in the left hemiliver in 5 patients, the right hemiliver in 4 patients, bilateral hemilivers in 1 patient, and 1 unknown. ICC was resected successfully in only 4 of these patients. Three died of the disease before hepatectomy. Although Ono *et al*. previously reported one case of multiple peripheral lithiases secondary to generation of ICC (*20*), the current report is the first case of ICC with intrahepatic biliary lithiasis in the opposite lobe arising after the excision of CBD to our knowledge. In the former case hemihepatectomy with re-reconstruction by hepaticojejunostomy was successfully performed, while in the present patient, the ICC was not resected because of the appearance of hepatic insufficiency in the future remnant liver volume and biliary lithiasis. As for the difference of the carcinogenic mechanism between this case and past-reported cases, high mutagenic activity of stones could have been associated with the occurrence of the ICC. The postoperative periodic enhanced CT at her local hospital could never detect the intrahepatic biliary lithiasis. Firstly the magnetic resonance cholangiography (MRCP) and DIC CT at our institution revealed numerous biliary lithiasis in the left liver. So it can be said that we should take extra care not to narrow the biliary-enteric anastmosis at the time of the excision of CBD. In addition to the enhanced CT, we may have to sometimes use MRCP or DIC CT to check for the formation of biliary lithiasis.

There is no established effective chemotherapeutic regimen for locally advanced ICC, and we believe that aggressive surgical resection is essential for improving the long-term survival in patients with ICC. In conclusion, careful long-term periodic check-ups should be encouraged for patients with CBD to ensure the early detection of new lesions including malignancy and lithiasis even after definitive surgery, since ICC is characterized by few distinct clinical symptoms until the disease has become severely advanced.

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