Cholangiocarcinoma Derived from Remnant Intrapancreatic Bile Duct Arising 32 Years after Congenital Choledochal Cyst Excision: A Case Report

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Key Words

Congenital choledochal cyst · Remnant intrapancreatic bile duct · Cholangiocarcinoma · Pancreaticobiliary maljunction

Abstract

We report a rare case of a 46-year-old woman with cholangiocarcinoma derived from remnant intrapancreatic bile duct arising 32 years after the excision of a congenital choledochal cyst. She had undergone anastomosis of the choledochal cyst and duodenum at birth, excision of the choledochal cyst and hepaticoduodenostomy with jejunal interposition at 14 years of age as well as the excision of an infectious cyst around the anastomosis site at 21 years of age. At 29 years of age, she was diagnosed with a chronic hepatitis C virus (HCV) infection and was referred to our hospital for treatment. She did not consent to interferon-based therapy against the HCV infection. At 46 years of age, she experienced epigastric discomfort. A dynamic CT revealed multiple tumors in the liver, a tumor in the head of the pancreas as well as lymph node metastases in the mediastinum and abdominal cavity. A liver tumor biopsy revealed adenocarcinoma, and she was clinically diagnosed with cholangiocarcinoma derived from remnant intrapancreatic bile duct with multiple metastasis in the liver

and lymph node metastasis. She requested palliative therapy and eventually died during the treatment course. The autopsy specimen revealed a tumor in the head of the pancreas, and on the basis of local existence and the pattern of metastasis, it was confirmed as cholangiocarcinoma derived from remnant intrapancreatic bile duct. A microscopic examination revealed a poorly differentiated adenocarcinoma. This report provides information on a case of cholangiocarcinoma derived from remnant intrapancreatic bile duct arising after the excision of congenital choledochal cyst that was assessed pathologically.

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Introduction

Congenital choledochal cyst is the local or diffuse dilation of the bile duct. It may cause severe complications such as lithiasis, cholangitis, pancreatitis, and carcinoma. In particular, it is well known that the congenital choledochal cyst has a significant association with cholangiocarcinoma [1]. According to the literature, 2.5–28% of the congenital choledochal cyst cases are associated with malignant biliary duct tumors at initial presentation [2]. Most congenital choledochal cysts are complicated by pancreaticobiliary maljunction [3] and cholestasis, infections, and the countercurrent of pancreatic and bile juice-induced changes in the biliary mucous membrane epithelium. They cause gene mutations, eventually leading to the development of cholangiocarcinoma at a high rate [4]. Therefore, the recommended standard surgical intervention is the excision of the entire extrahepatic bile duct, followed by hepaticoenterostomy to separate the streams of bile and pancreatic juice; this procedure is known as a separation-operation. However, in some patients, biliary cancer develops long after a separation-operation. In order to prevent the development of cancer, careful long-term follow-up is required for patients even after a separation-operation.

Here we report a case of cholangiocarcinoma derived from remnant intrapancreatic bile duct arising 32 years after the excision of a congenital choledochal cyst, with a review of the literature.

Case Report

A 46-year-old woman was referred to our hospital for the investigation of a liver tumor that was previously detected by ultrasonography at a local hospital after she complained of epigastric discomfort. She had previously undergone anastomosis of the choledochal cyst and duodenum for congenital choledochal cysts (Todani type I-a or I-c) at birth, the excision of choledochal cysts and hepaticoduodenostomy with jejunal interposition at 14 years of age, and the excision of an infectious cyst around the anastomosis site at 21 years of age, during which she had also received a blood transfusion. At 29 years of age, she was diagnosed with a chronic hepatitis C virus infection but did not consent to interferon-based therapy and instead, was monitored while taking ursodeoxycholic acid. At 39 years of age, she was transferred to Chiba University Hospital.

Her laboratory data were as follows: elevated carcinoembryonic antigen 730 ng/ml, carbohydrate antigen 19-9: 5,170 U/ml, alpha-fetoprotein 8.2 ng/ml, alpha-fetoprotein-L3 <0.5%, and des-γ-carboxy prothrombin 41 mAU/ml (table 1). An abdominal ultrasonography showed a hypoechoic lesion of 32 mm in diameter in the S6 region of the liver. A dynamic CT of the abdomen revealed a tumor in the head of the pancreas (fig. 1a, b), a nondilated main pancreatic duct, and constricted vessels from the celiac artery to the left hepatic artery. Lymph nodes along the abdominal aorta, celiac artery, and superior mesenteric artery as

well as its branches were swollen (fig. 1c). Many low-density tumors were noted in the liver and several nodes were noted on the pelvic surface of the sacrum; thus, we considered the presence of multiple liver and peritoneal metastases (fig. 1d). On MRI with gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid, the tumors in the liver were hyperintense on diffusion-weighted image and enhanced marginally in the early phase of a dynamic study. A dynamic CT of the breast revealed lymph node swelling in the left supraclavicular fossa, mediastinum, and right cardiophrenic angle. Magnetic resonance cholangiopancreatography of the abdomen did not confirm a dilation of the bile and main pancreatic duct. An upper gastrointestinal endoscopy revealed a reconstruction and bile in the duodenum. Biopsy specimens of the S6 liver tumor indicated adenocarcinoma. Based on these findings and the clinical history, she was diagnosed with cholangiocarcinoma derived from remnant intrapancreatic bile duct with metastasis to the mediastinum and abdominal cavity. She refused aggressive treatment with chemotherapy and chose best supportive care instead. Ultimately, she died because of obstructive jaundice and renal failure 2 months after the diagnosis.

A macroscopic examination of the specimen revealed that the tumor in the head of the pancreas was white, accompanied by bleeding and necrosis (fig. 2a–c). The size of the tumor was 65 × 55 × 55 mm. A pathological examination revealed that it was a poorly differentiated adenocarcinoma with partial well-differentiation; it exhibited mucus production and pancreatic invasion (fig. 2d). A dilation of the main pancreatic duct was not observed. The bile duct anastomosis with interposed jejunum at the portal hilum had no malignant findings. Multiple metastases occupied about 80% of the liver. The tumor had also metastasized to the lung, pleura, peritoneum, and spleen. Lymph node metastasis was located in the pulmonary hilum, splenic hilum, stomach, and duodenum. Based on the location and pattern of metastasis of the tumor, the diagnosis of cholangiocarcinoma derived from remnant intrapancreatic bile duct was confirmed, and this was also considered the cause of death.

Discussion

An excision of the cyst and hepaticojejunostomy, but not cyst-duodenum anastomosis, is now the first choice of treatment for a congenital choledochal cyst because of a high occurrence rate of carcinogenesis [5]. On the other hand, in patients without pancreaticobiliary maljunction and mutual countercurrent of pancreatic juice, surgery is performed to prevent bile accumulation. Although there are articles of cholangiocarcinoma derived from dilated intrahepatic bile duct [6]. Reports on cholangiocarcinoma derived from remnant intrapancreatic bile duct are rare. To the best of our knowledge, there are only 6 other reported cases, which include 1 man and 5 women (average age: 42.7 years, range: 27–68; table 2) [4, 7–11], and all of these patients underwent surgery for intrapancreatic cholangiocarcinoma. Four of 6 cases had postoperative mortality after a short term of 9–16 months (average: 12.3 months). An infectious cyst around the anastomosis site after the operation and a surgical resection as well as the progression of distant metastasis and the fact that surgical excision was not feasible are characteristics of the present case.

In the hyperplasia-dysplasia-carcinoma sequence, the carcinogenetic formation of the congenital choledochal cyst complicated with pancreaticobiliary maljunction is caused by changes in the biliary mucous membrane epithelium, mainly hyperplastic changes, and gene mutations based on chronic inflammation due to cholestasis, infection, and countercurrent of pancreatic and bile juice, inducing repeated damage and the restoration of the biliary mucous membrane epithelium [4]. Furthermore, carcinogenesis after a separation-operation is

caused by the insufficient excision of the dilated bile duct, accompanied by inflow into the remnant intrapancreatic bile duct and the stagnation of pancreatic juice.

A pathological assessment of the patient in the present report revealed that most of the main tumor consisted of poorly differentiated adenocarcinoma with partial well-differentiation. We could not recognize a pathological structure of the common bile duct. The main tumor was protruding from the head of the pancreas and was located in the position of the intrapancreatic bile duct; thus, we diagnosed the patient with cholangiocarcinoma derived from remnant intrapancreatic bile duct. One of the characteristics of this case is that the infectious cyst, which was not completely resected, formed after the separation-operation; we consider this cyst to be the source of the carcinoma.

To prevent the development of malignant biliary duct tumors, a complete excision of the extrahepatic bile duct is recommended for patients with congenital choledochal cyst. During bile duct excision from the pancreas side, in principle, it is desirable to completely dissect and not leave the intrapancreatic bile duct above its junction and the main pancreatic duct [12]. And from the liver side, the dilated bile duct should be removed completely. However, there is no clear evidence to determine the excision range for Todani type IV-a intrahepatic bile duct dilatation; thus, further studies are warranted.

In conclusion, the present case indicated that cholangiocarcinoma may develop 32 years after a separation-operation. Thus, a careful long-term follow-up is required even after a separation-operation.

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Statement of Ethics

This study complied with the guidelines for human studies. Informed consent was not obtained because of the retrospective design (case report). The patient's records/information was anonymized to protect the confidentiality of the personal information.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 1. Laboratory data of the patient on admission

Blood cell count	
WBC, / μ l	5,400
RBC, $\times 10^4$ / μ l	422
Hb, g/dl	13.0
Ht, %	37.2
Plt, $\times 10^4$ / μ l	18
Coagulation	
PT-INR	1.01
Tumor markers	
AFP, ng/ml	8.2
AFP-L3, %	<0.5
PIVKA-II, mAU/ml	41
CEA, ng/ml	730.0
CA 19-9, U/ml	5,170.0
Blood chemistry	
TP, g/dl	7.2
Alb, g/dl	3.7
T-BIL, mg/dl	0.8
D-BIL, mg/dl	0.1
AST, IU/l	33
ALT, IU/l	26
LDH, IU/l	262
ALP, IU/l	261
LDH, IU/l	262
γ -GTP, IU/l	79
UN, mg/dl	7
Cre, mg/dl	0.43
Serology	
HBsAg	(–)
HCV-Ab	(+)

WBC = White blood cells; RBC = red blood cells; Hb = hemoglobin; Ht = hematocrit; Plt = platelets; PT-INR = prothrombin time-international normalized ratio; AFP = alpha-fetoprotein; PIVKA-II = protein induced by vitamin K absence or antagonists-II; CEA = carcinoembryonic antigen; CA 19-9 = carbohydrate antigen 19-9; TP = total protein; Alb = albumin; T-BIL = total bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; ALP = alkaline phosphatase; γ -GTP = gamma-glutamyl transferase; UN = urea nitrogen; Cre = creatinine; HBsAg = hepatitis B virus surface antigen; HCV-Ab = hepatitis C virus antibody.

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Table 2. Reported cases of remnant intrapancreatic bile duct carcinoma that developed after resection of the choledochal cyst

Age, years/ gender	Todani classification	Initial operation	Time after biliary reconstruction, years	Operation for cancer	Prognosis/ months	Reference
27/female	IV-a	Ex, Hj	13	PD	Dead/14	[3]
39/female	I-b	Ex, Hj	17	TP	Dead/9	[5]
42/female	–	Ex, Hj	17	PpPD	Alive/60	[6]
39/female	IV-a	Ex, Hj	17	TP	Dead/10	[7]
68/male	I-a	Ex, Hj	8	PD	Dead/16	[8]
41/female	I-b	Ex, Hj	13	PD	Alive/5	[9]
46/female	I-a or I-c	–	32	–	Dead/2	Present case

PD = Pancreaticoduodenectomy; TP = total pancreatectomy; PpPD = pylorus-preserving pancreaticojejunostomy; Ex = excision of the cyst; Hj = hepaticojejunostomy.

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Fig. 1. CT. **a, b** Abdominal CT showing a tumor in the head of the pancreas (**a**, arrow) and multiple tumors in the liver (**b**, arrow). **c** Lymph node swelling was observed in the mediastinum (arrow). **d** Several nodes were noted on the pelvic surface of the sacrum (arrow).

Fig. 2. Pathological findings of the specimen. **a** Gross appearance of the pancreas. **b** The yellow arrow indicates the tumor in the head of the pancreas. **c** The locations of the tumor were presumed to be the intrapancreatic bile duct and main pancreatic duct (MPD). CBD = Common bile duct. **d** The tumor was mainly composed of degenerated and necrotizing, poorly differentiated adenocarcinoma cells.