

[CASE REPORT]

Metachronous Pancreatic Cancer with Pancreaticobiliary Maljunction Diagnosed Five Years after Cholecystectomy for Gallbladder Cancer, in Which Follow-up Imaging Was Possible Until the Onset of Cancer: A Case Report and Review of the Literature

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Abstract:

Whether or not pancreaticobiliary maljunction (PBM) is a risk factor for pancreatic cancer (PC) is unclear. We present a case of metachronous PC with PBM diagnosed after cholecystectomy for gallbladder cancer, in which follow-up imaging was possible until PC onset. A 63-year-old man who had been diagnosed with gallbladder cancer and had undergone cholecystectomy 5 years earlier developed pancreatitis. Pancreatography revealed PBM, and pancreatic duct brush cytology revealed adenocarcinoma. On reviewing the follow-up images, pancreatic morphological abnormalities, which had not been observed before cholecystectomy, were found to have gradually progressed, suggesting that biliopancreatic reflux led to pancreatic carcinogenesis.

Key words: pancreaticobiliary maljunction, pancreatic cancer, pancreatitis, biliopancreatic reflux

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Introduction

Pancreaticobiliary maljunction (PBM) is a congenital anomaly in which union of the pancreatic and biliary ducts outside the duodenal wall causes pancreaticobiliary reflux (1). Because the long common channel defeats the effect of the sphincter of Oddi in PBM, pancreatobiliary reflux frequently occurs, resulting in a high incidence of biliary tract cancer (BTC). The incidence of BTC in adult patients with PBM without biliary dilatation is 42.4%, and cancer localization in these patients is 88.1% for gallbladder cancer (2). Therefore, cholecystectomy is recommended in patients with PBM without biliary dilatation.

In addition to BTC, pancreatic cancer (PC) associated

with PBM has been reported (3, 4). The incidence of PC in patients with PBM is low, but it has been reported to be 0.8%, which is 49.4 times higher than the incidence of PC in the overall population in Japan (5). The association between biliopancreatic reflux and pancreatic carcinogenesis has been proven in animal experiments (6); however, the cause-and-effect relationship between the two in clinical practice has not been clarified. Thus, whether or not patients with PBM are more susceptible to PC than others remains unclear.

We encountered a case of metachronous PC with PBM that was diagnosed after cholecystectomy for gallbladder cancer. Notably, the pancreas, which had no abnormalities at the time of cholecystectomy, gradually developed morphological changes over the course of five years after cholecys-

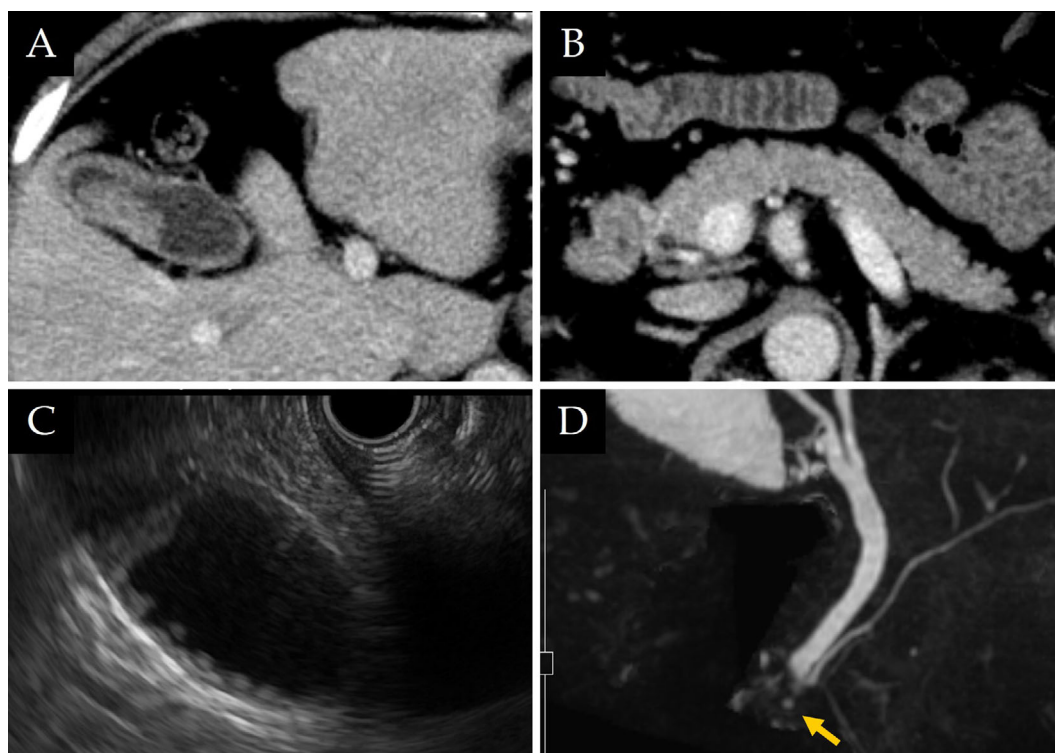


Figure 1. Abdominal contrast-enhanced CT findings at the time of gallbladder cancer diagnosis. A: Mass in the gallbladder. No biliary dilatation was observed. B: No abnormal findings were observed in the pancreas. C: EUS reveals thickening of the hypoechoic layer on the inner side of the gallbladder wall. D: MRCP revealed a structure that appeared to be an abnormally long common duct but lacked ductal continuity and was not recognized as a PBM (arrow).

tectomy, and these abnormalities were observable in follow-up images until the onset of PC. This case report endeavored to clarify the process of pancreatic carcinogenesis in PBM and the importance of always being aware of the possibility of metachronous PC.

Case Report

A 63-year-old man with a history of end-stage renal failure due to diabetic nephropathy was diagnosed with gallbladder cancer secondary to abdominal pain. Contrast-enhanced computed tomography (CT) showed no distant metastasis, lymph node metastasis, liver invasion, or bile duct invasion. No biliary dilatation was observed, and no abnormal findings were found in the pancreas (Fig. 1A-B). Endoscopic ultrasonography (EUS) revealed thickening of the hypoechoic layer on the inner side of the gallbladder wall (Fig. 1C). Magnetic resonance cholangiopancreatography (MRCP) revealed a structure that appeared to be an abnormally long common duct; however, it lacked ductal continuity and was not recognized as a PBM (Fig. 1D). Because endoscopic retrograde cholangiopancreatography (ERCP) was not performed preoperatively, PBM was not observed. He underwent cholecystectomy, and pathology showed pT2, pN0, and stage II according to the 3rd English edition of the Japanese classification of BTCs (7). Non-cancerous areas of the gallbladder mucosa show chronic in-

flammatory and hyperplastic changes. He did not receive adjuvant chemotherapy due to end-stage renal failure and was followed up at another hospital with abdominal plain CT every six months, with no recurrence of gallbladder cancer.

Five years after cholecystectomy, the patient developed appetite loss and was referred to our department with suspected pancreatitis. He had a 20-year history of consuming approximately 50 g of alcohol daily but had abstained from alcohol for the past 10 years, making alcoholic acute pancreatitis unlikely. No weight loss or fatty diarrhea was observed. A physical examination revealed no abdominal tenderness. Laboratory test results revealed elevated pancreatic enzyme levels as follows: amylase, 589 IU/L; lipase, 1,084 IU/L; and trypsin, 19,473 ng/mL (Table 1). There was no notable increase in serum lipid levels, calcium levels, immunoglobulin G4 levels, or tumor markers such as carbohydrate antigen 19-9 or Duke pancreatic monoclonal antigen type 2.

Abdominal contrast-enhanced CT showed stricture of the main pancreatic duct (MPD) in the pancreatic head, dilatation of the upstream MPD, atrophy of the pancreatic body tail, and swelling of the pancreatic tail with increased concentration of the surrounding fatty tissue (Fig. 2A-C). No distinct mass was detected in the pancreatic head on CT. EUS showed that the MPD was interrupted at the pancreatic head, but no obvious mass lesion was identified, suggesting the possibility of early PC (Fig. 3).

Table 1. The Laboratory Test Results at the Time of Referral to Our Department Five Years after Cholecystectomy for Gallbladder Cancer.

WBC	7,020 / μ L	TP	7.1 g/dL	TC	589 IU/L
Neut	72.0 %	Albumin	4.0 g/dL	TG	548 IU/L
Eosi	5.3 %	T-Bil	0.4 mg/dL	Lipase	1,084 IU/L
Baso	0.7 %	ALP	77 U/L	Amylase	589 IU/L
Mono	7.0 %	GGT	8 U/L	P-Amylase	548 IU/L
Lymp	15.0 %	AST	8 U/L	Lipase	1,084 IU/L
RBC	4.21 $\times 10^6$ / μ L	ALT	4 U/L	Trypsin	19,473 ng/mL
Hb	13.2 g/dL	LDH	129 U/L	CEA	1.6 ng/mL
Hct	41.2 %	BUN	36 mg/dL	CA19-9	14 U/mL
PLT	135 $\times 10^3$ / μ L	Creatinine	7.86 mg/dL	DUPAN-II	<25 U/mL
PT	99 %	Na	135 mEq/L	IgG4	107 mg/dL
APTT	30.1 s	K	4.7 mEq/L		
		Cl	97 mEq/L		
		Ca	9.5 mg/dL		

WBC: white blood cell, Neut: neutrophil, Eosi: eosinophil, Baso: basophil, Mono: monocyte, Lymp: lymphocyte, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, TP: total protein, T-Bil: total bilirubin, ALP: alkaline phosphatase, GGT: γ -glutamyltransferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, TC: total cholesterol, TG: triglyceride, CEA: carcinoembryonic Antigen, CA19-9: carbohydrate antigen 19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, IgG4: immunoglobulin G4

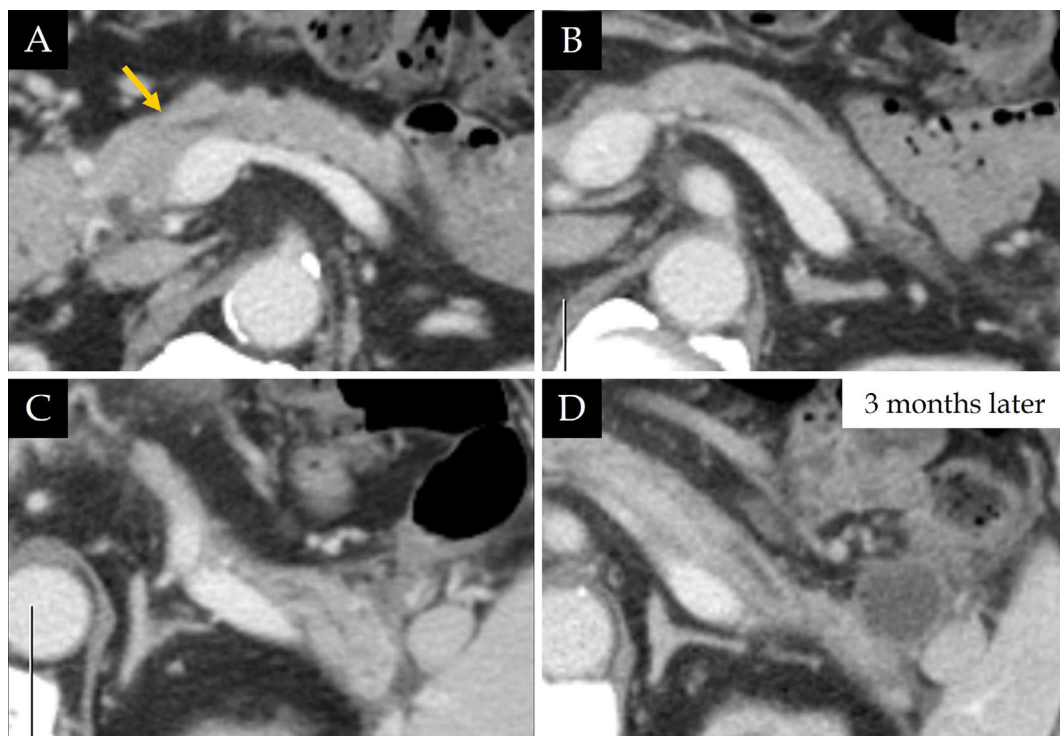


Figure 2. Abdominal contrast-enhanced CT findings at the time of referral to our department five years after cholecystectomy. A: Stricture of the main pancreatic duct (MPD) without a distinct mass in the pancreatic head (arrow). B: Dilatation of the upstream MPD and atrophy of the pancreatic parenchyma in the pancreatic tail. C: Swelling of the pancreatic tail with increased concentration of surrounding fatty tissue. D: An image taken three months later showing the appearance of a pseudo-cyst in the pancreatic tail.

However, as findings were unclear on EUS, PBM could not be suspected. At this point, we recommended that he un-

dergo a further examination with PC in mind, but he refused, so we decided to proceed with follow-up imaging.

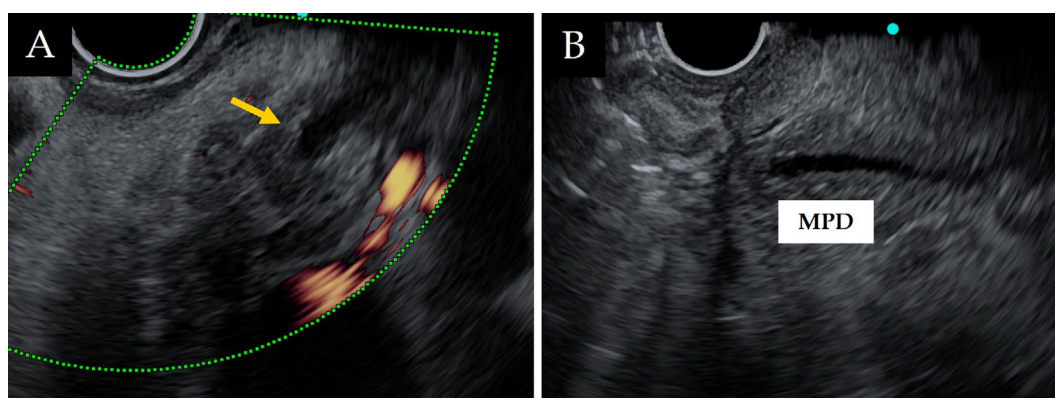


Figure 3. EUS findings at the time of referral to our department five years after cholecystectomy. **A:** The main pancreatic duct (MPD) was interrupted at the pancreatic head (arrow), but no obvious mass lesion was identified. **B:** The common duct was unclear on EUS; therefore, PBM could not be suspected.

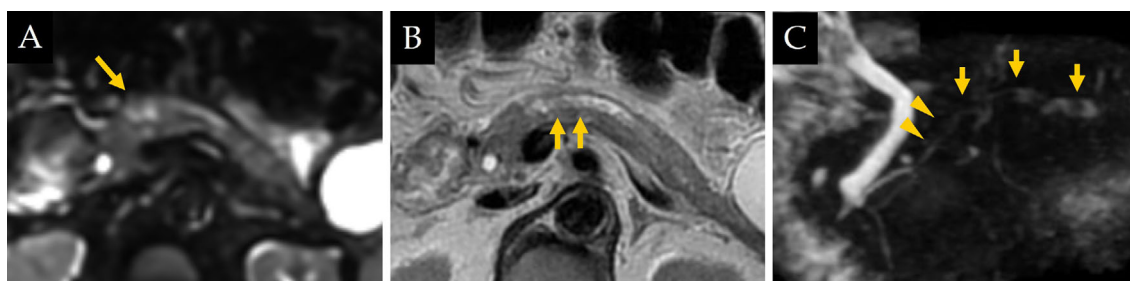


Figure 4. Abdominal MRI findings at the time of referral to our department five years after cholecystectomy. **A:** Diffusion-weighted imaging revealed high intensity at the main pancreatic duct (MPD) in the pancreatic head (arrow). **B:** Multiple protein plugs within the dilated MPD (arrows). **C:** MRCP showed MPD stricture in the pancreatic head (arrowheads), and visualization of the dilated upstream MPD was poor due to protein plugs (arrows).

Abdominal contrast-enhanced CT three months later showed that dilatation of the MPD had worsened, and a pseudocyst appeared in the pancreatic tail (Fig. 2D). Magnetic resonance imaging revealed a high intensity at the MPD stricture on diffusion-weighted imaging and multiple protein plugs within the dilated MPD (Fig. 4A-B). MRCP showed MPD stricture in the pancreatic head, and visualization of the dilated upstream MPD was poor owing to the presence of protein plugs (Fig. 4C). During ERCP, contrast medium was simultaneously injected into both the MPD and the common bile duct, and their confluence appeared to be located outside the duodenal wall (Fig. 5A). Although an abnormally long common duct could not be clearly visualized, the distance from the papilla to the confluence was 10 mm, which was considered to be a type B PBM (non-stenotic type), as proposed by the Japanese Study Group on Pancreaticobiliary Maljunction (8) (Fig. 5B). The MPD was irregularly narrowed at the pancreatic head and a large number of protein plugs were found in the dilated MPD (Fig. 5C). Brushing cytology of the narrowed area of the pancreatic head revealed adenocarcinoma (Fig. 6).

On reviewing the CT images taken every six months after cholecystectomy, it was found that the pancreas was slightly

enlarged until one year after surgery, after which it began to undergo atrophic changes (Fig. 7A-C). Stricture of the MPD in the pancreatic head where adenocarcinoma was detected by brush cytology, and dilatation of the upstream MPD was first detected on contrast-enhanced CT five years after cholecystectomy (Fig. 7D). A detailed evaluation of the CT reconstruction images taken at the time of the PC diagnosis showed that the confluence of the MPD and common bile duct was located outside the duodenal wall, and an abnormal common duct measuring ≥ 10 mm in length was identified within the duodenal wall, which was unclear on ERCP (Fig. 7E).

The patient was advised to undergo surgery; however, he declined. One year after the patient was referred to our department, the cancer in the pancreatic head grew to form a mass. ERCP was performed to place a pancreatic duct stent for obstructive pancreatitis, and the bile amylase level measured at that time was only slightly elevated at 363 IU/L.

Discussion

This case presented with metachronous PC with PBM diagnosed after cholecystectomy for gallbladder cancer, for

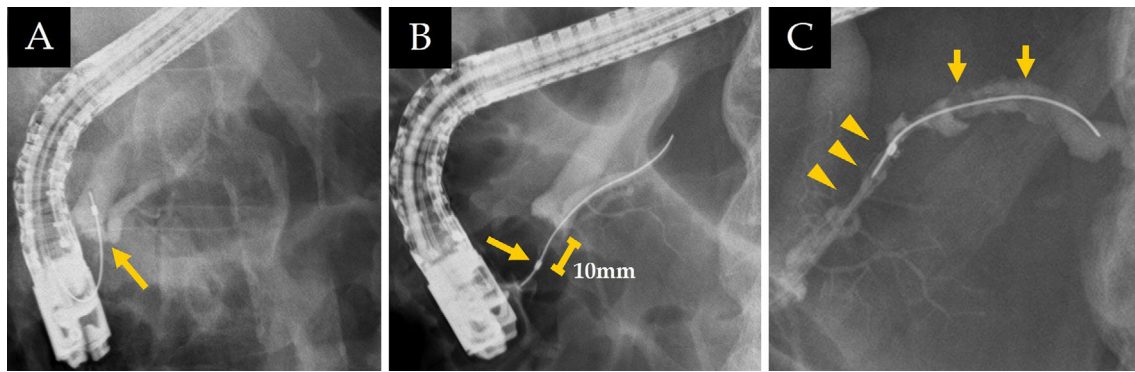


Figure 5. ERCP findings. A: Contrast medium was simultaneously injected into both the main pancreatic duct (MPD) and the common bile duct, and their confluence appeared to be located outside the duodenal wall. B: Although an abnormally long common duct could not be clearly visualized, the distance from the papilla, where the tip of the catheter was located (arrow), to the confluence was approximately 10 mm, which was considered a pancreaticobiliary maljunction (PBM). C: Irregularly narrowed MPD at the pancreatic head (arrowheads) and protein plugs in the dilated MPD (arrows).

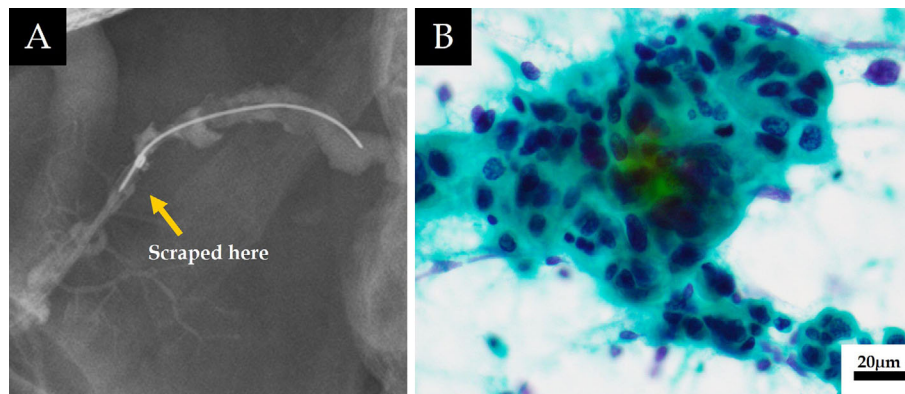


Figure 6. Brushing cytology of the narrowed area. A: Arrow indicates the areas scraped with a brush. B: Cytology revealed adenocarcinoma. Bar=20 μ m.

which follow-up imaging was possible until the onset of PC.

According to a nationwide survey of 2,561 cases between 1990 and 2007 reported by the Japanese Study Group on Pancreaticobiliary Maljunction, the incidence of BTC associated with PBM in adults was reported to be 21.6% in PBM patients with biliary dilatation and 42.4% in patients with PBM without biliary dilatation, which is 1,000 to 3,000 times higher than vital statistics data from the Ministry of Health, Labor and Welfare (9). In PBM, the function of the sphincter of Oddi does not reach confluence because of its long common channel. This abnormality results in reciprocal reflux of bile and pancreatic juices depending on the pressure gradient. However, because the pressure in the pancreatic duct is normally higher than that in the biliary duct, pancreatobiliary reflux occurs easily (10). The mechanism of carcinogenesis in the biliary tract is presumed to be as follows: pancreatic enzymes hydrolyze lecithin in bile, and the resulting lysolecithin causes tissue damage to the bile duct epithelium. Accumulation of this epithelial damage leads to changes, such as hyperplasia and metaplasia, which induce K-ras and p53 mutations (11-14).

There are fewer reported cases of PC associated with PBM than BTC, but the incidence of PC is 0.8%, which is 49.4 times higher than the incidence of PC in the overall population in Japan (5). In a report summarizing 41 cases of PC associated with PBM, there were 5 cases with synchronous double cancers, 2 with synchronous triple cancers, 6 with metachronous double cancers, and 1 with metachronous triple cancers of the pancreas and biliary tract (15). We reviewed and summarized case reports of double cancer of the pancreas and biliary tract with PBM, written in English (Table 2) (16-22). BTC preceded PC in all metachronous cases. PC associated with PBM is characterized by its frequent location in the pancreatic head, and its histological type is more likely to be intraductal papillary adenocarcinoma than conventional PC (15).

Regarding the mechanism of PC associated with PBM, Adachi et al. reported in animal experiments that exposure of the pancreatic duct to bile enhances the cell proliferation activity of the MPD epithelium, resulting in a high incidence of PC (6). It is speculated that biliopancreatic reflux due to cholestasis, cholangitis, and protein plugs in the com-

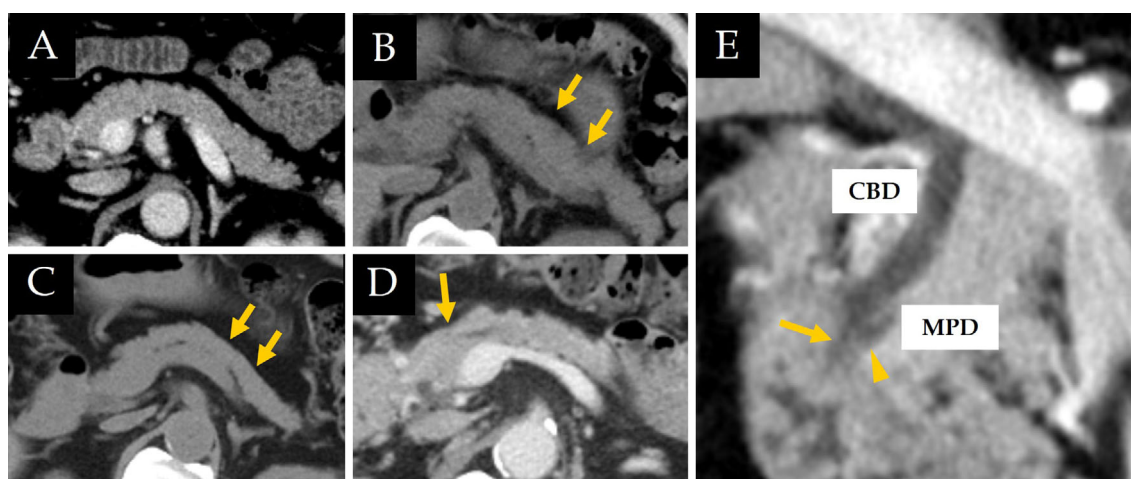


Figure 7. Time series of CT images. A: The pancreas was normal before cholecystectomy. B: One year later, the pancreas was slightly enlarged (arrows). C: Three years later, the pancreas showed atrophic changes (arrows). D: Five years later, stricture of the main pancreatic duct (MPD) in the pancreatic head where adenocarcinoma was detected by brushing cytology, and dilatation of the upstream MPD was first detected (arrow). E: A detailed evaluation of the CT reconstruction image showing that the confluence of the MPD and common bile duct (CBD) was located outside the duodenal wall (arrowhead), and an abnormally long common duct was identified within the duodenal wall (arrow), which was unclear on ERCP.

Table 2. Summary of the Eight Case Reports of Double Cancer of the Pancreas and Biliary Tract with PBM Written in English.

Ref	Age/sex	BD	Locus of PC	Locus of BTC	Onset of PC and BTC	Treatment	Survival time (month)
(16)	46F	Dilated	Head	GB	Synchronous	HPD	≥10mo. alive
(17)	68F	Dilated	Head	GB, CBD	Metachronous (45mo.)	Cholecystectomy → bisegmentectomy → PD	≥12mo. alive
(18)	58M	Dilated	Whole pancreatic duct	GB, CBD	Synchronous	Extended cholecystectomy+TP	30mo. alive
(19)	76F	Not dilated	Head	GB	Metachronous (7mo.)	Cholecystectomy, choledochectomy, and Roux-en-Y choledochojejunostomy → chemo.	Unknown
(20)	22F	Dilated	Head	Hepatic duct	Synchronous	Supportive care	24mo. death
(21)	67F	Dilated	Head	GB, bile duct	Synchronous	PD+extended cholecystectomy	14mo. alive
(22)	72F	Dilated	Head	GB	Synchronous	SSPPD+extended cholecystectomy	8mo. alive

BD: biliary dilatation, BTC: biliary tract cancer, CBD: common bile duct, chemo: chemotherapy, F: female, GB: gallbladder, HPD: hepatopancreaticoduodenectomy, M: male, mo.: months, PD: pancreaticoduodenectomy, Ref: reference, SSPPD: subtotal stomach-preserving pancreaticoduodenectomy, PC: pancreatic cancer, TP: total pancreatectomy

mon channel leads to chronic pancreatitis, which then causes the hyperplasia-dysplasia-carcinoma sequence (23). However, whether or not biliopancreatic reflux is involved in pancreatic carcinogenesis in human PBM has not been thoroughly investigated.

In the present case, the patient was diagnosed with PBM for the first time five years after cholecystectomy for gallbladder cancer due to imaging findings of pancreatitis and concomitant PC. Although the abnormally long common duct was unclear on ERCP, the CT reconstruction image revealed confluence of the MPD and common bile duct outside the duodenal wall and an abnormally long common

duct, leading to the diagnosis of PBM. As previously reported (23), the reason for the unclear visualization of the common duct on ERCP was thought to be the inflammatory changes accompanied by protein plugs in the common duct. The reason why high bile amylase levels, which are typical of PBM, were not observed in this case is thought to be that biliopancreatic reflux occurred after cholecystectomy and that exocrine pancreatic function was impaired due to PC and pancreatitis. Because the bile amylase level was not measured at the time of initial ERCP, when the pancreatic morphology was normal, but nearly one year after the diagnosis of PC, when the pancreas had undergone atrophic

changes, it is possible that the exocrine pancreatic function had already declined at that point.

Since the long common duct is unclear on ERCP, high bile amylase levels would provide relatively strong support for the diagnosis of PBM; however, this was lacking in the present case. Therefore, this case may not be one of PBM but rather a high confluence of pancreaticobiliary ducts; both are common pathological conditions that cause biliopancreatic reflux. In the present case, ERCP was not performed at the time of the diagnosis of gallbladder cancer, so the presence of biliopancreatic reflux was noticed later; however, it is possible that it could have been detected a little earlier based on the findings of thickening of the hypoechoic layer on the inner side of the gallbladder wall on EUS and hyperplastic changes in the gallbladder mucosa in the resected specimen, both of which are common in PBM (17).

No morphological abnormalities were found in the pancreas when gallbladder cancer was diagnosed; however, after cholecystectomy, the pancreas was temporarily enlarged and then gradually atrophied. At the same time, we found dilatation of the MPD and a large number of protein plugs in it, which is consistent with the changes that occur with biliopancreatic reflux in PBM that have been reported in the past (24, 25). Acute pancreatitis associated with PBM is often considered clinically transient and mild in most cases (2); in the present case, no abdominal pain or severe hyperamylasemia was observed in the five years following cholecystectomy. In addition, follow-up imaging was performed only with plain CT due to end-stage renal failure, which delayed the detection of changes in pancreatic morphology over time.

The mechanism by which pancreatitis progressed over the five-year period in our case is thought to be primarily due to the removal of the gallbladder, which had stored bile, causing the pressure in the biliary duct to exceed that in the pancreatic duct, resulting in biliopancreatic reflux. After cholecystectomy, bile is stored in the common bile duct instead of the gallbladder, and physiological dilatation of the common bile duct is often observed (26). However, in the present case, no bile duct dilatation was observed, even after surgery, suggesting that bile had flowed into the pancreatic duct. Of note, there have been some reports of PC occurring after biliary tract reconstruction or biliopancreatic undiversion in patients with PBM without biliary dilatation (15, 19). Although biliary diversion surgery eliminates biliopancreatic reflux and reduces the risk of developing PC, if the surgery is performed in adulthood, the pancreatic duct epithelium may already have been damaged by carcinogenic initiators, which poses a risk of developing PC. In addition, the present patient had a 20-year history of consuming approximately 50 g of alcohol daily up to 10 years ago, and it cannot be denied that this may have caused accumulated damage to the pancreas. Although whether or not pancreatitis had occurred before cholecystectomy in this case is unclear, the morphological changes in the pancreas over these

five years are of great interest in elucidating the mechanism of pancreatic inflammatory carcinogenesis after cholecystectomy in patients with PBM. As this patient refused surgical resection for PC, diagnosing PC at an early stage would not have affected the prognosis. However, by suspecting the presence of PBM at the same time as diagnosing gallbladder cancer and focusing on morphological changes in the pancreas after cholecystectomy for PBM, metachronous PC can be detected at an early stage.

In conclusion, we encountered a case of metachronous PC with PBM diagnosed after cholecystectomy for gallbladder cancer, in which follow-up imaging was possible until the PC onset. PBM is closely associated with pancreatitis caused by biliopancreatic reflux and is suspected to be associated with PC. Although the diagnosis of PBM is uncertain, this case is valuable in understanding the process of pancreatic carcinogenesis due to biliopancreatic reflux and recognizing the importance of always being aware of metachronous PC. Patients with PBM should be closely monitored for the development of PC after biliary tract surgery and receive appropriate imaging follow-up.

The author states that he has no Conflict of Interest (COI).

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