

[CASE REPORT]

Intraductal Papillary Mucinous Neoplasm with Pancreatogastric Fistula

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Abstract:

We herein report a rare case of intraductal papillary mucinous neoplasm with a pancreatogastric fistula in an elderly Japanese man admitted to our hospital. The pancreatogastric fistula was confirmed using endoscopic retrograde pancreatography via a cannulated guidewire placed in the stomach. Six months after admission, the patient was diagnosed with intraductal papillary mucinous carcinoma. A pancreatogastric fistula is generally a rare complication of intraductal papillary mucinous neoplasm. It was caused by mechanical penetration in this case. Interestingly, we also observed endoscopic and histochemical mucosal changes in the fistula.

Key words: intraductal papillary mucinous neoplasm, intraductal papillary mucinous carcinoma, pancreatogastric fistula, mechanical penetration, endoscopic retrograde cholangiopancreatography

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Introduction

In 1982, Ohashi et al. (1) reported the first four cases of mucus-producing pancreatic carcinoma having a favorable prognosis. After considerable research, the disease concept of intraductal papillary mucinous neoplasm (IPMN) was established in the mid-1990s. In 2006, to clarify the morphological and pathological features, the International Association of Pancreatology proposed an international consensus guideline for the management of IPMN and pancreatic mucinous cystic neoplasm (2). This guideline was revised in 2012 (3) and 2017 (4).

We herein report a rare case of IPMN with a pancreatogastric fistula diagnosed by an endoscopic biopsy and discuss the relationship between IPMN and pancreatogastric fistula. Interestingly, we observed endoscopic and histological mucosal changes in the fistula during its transformation

from intraductal papillary mucinous adenoma (IPMA) to intraductal papillary mucinous carcinoma (IPMC) (5).

Case Report

An 83-year-old Japanese man with a history of prostate cancer who had suffered cerebral infarction 2 months prior was transferred to our hospital for rehabilitation. Laboratory investigations revealed anemia (hemoglobin, 10.8 g/dL) with an elevated platelet count and erythrocyte sedimentation reaction. The carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels in the blood were moderately elevated (439.4 U/mL and 8.6 ng/mL, respectively).

Abdominal ultrasonography revealed a pancreatic tumor. Esophagogastroduodenoscopy (EGD) showed an ulcerative lesion with mucin excretion on the posterior wall of the upper gastric corpus and an enlarged ampulla of Vater with a patulous orifice and mucin excretion. EGD also showed a

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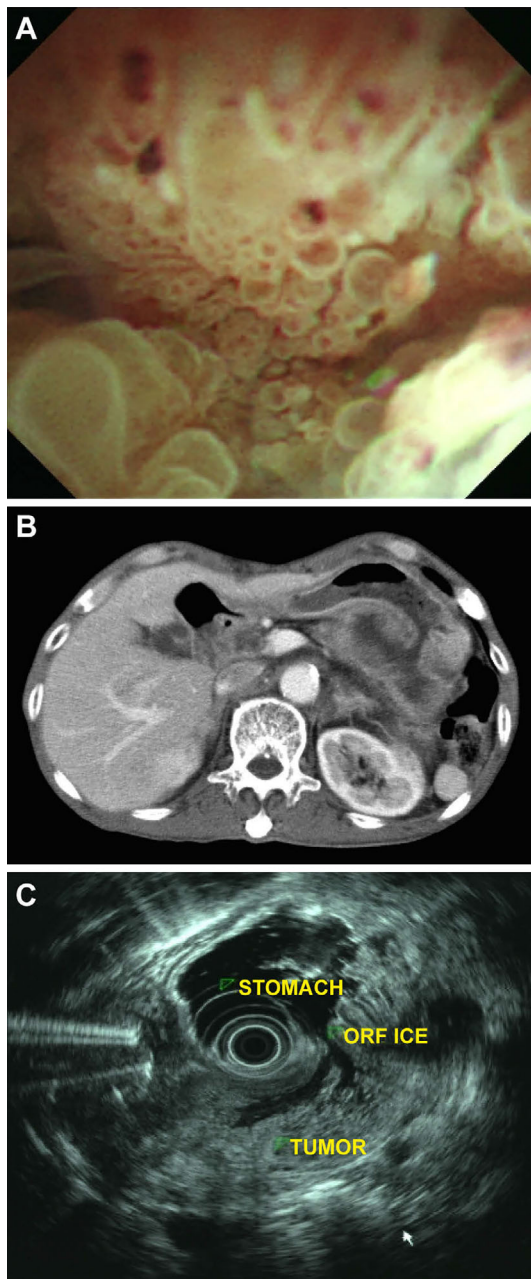


Figure 1. Findings of diagnostic imaging. A: Esophagogastroduodenoscopy showing the papillary tumor with a typical fish egg-like mucosal lesion on the fistula. B: Abdominal enhanced computed tomography showing a cystic lesion of the pancreas and pancreatogastric fistula. C: Endoscopic ultrasonography confirming a pancreatogastric fistula.

fish egg-like mucosal lesion in the fistula (Fig. 1A). Contrast-enhanced computed tomography (CT) showed a low-density non-enhanced mass lesion in the pancreatic body and the tail. In addition, the existence of a pancreatogastric fistula was confirmed (Fig. 1B). Endoscopic ultrasonography revealed concordant findings, including a cystic lesion, the presence of solid tumor and mural lesion, and fistula formation (Fig. 1C).

A pathological examination of the biopsy specimen of the fistula showed irregular papillary proliferation lined with mucus-producing columnar epithelial cells with moderate

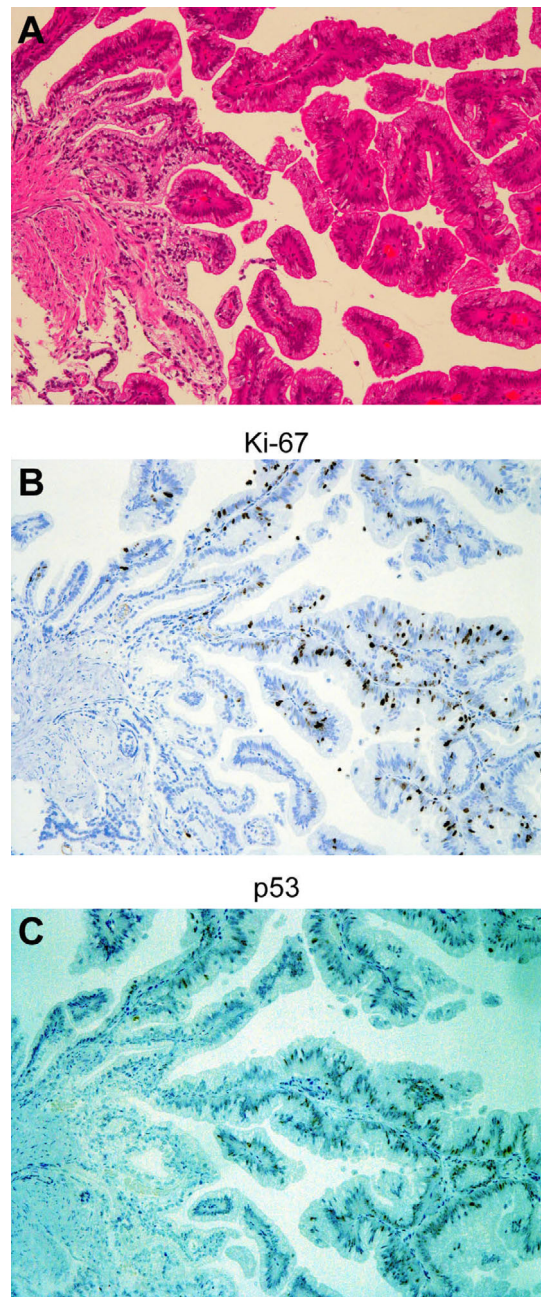


Figure 2. A pathological examination of the initial biopsy specimen. A: Hematoxylin and Eosin staining: low-power microscopy showing a non-invasive intraductal papillary mucinous neoplasm border with the fistula in the stomach. B, C: Immunohistochemical staining revealing that around 30% neoplastic cells were Ki-67-positive (B), and the majority were p53-negative (C).

cellular atypia (Fig. 2A). Mucin (MUC)1, MUC5AC, and MUC6 were highly expressed on the papillary portion of the tumor, but MUC2 and caudal type homeobox 2 (CDX2) proteins were undetected. In the papillary portion of the tumor, the Ki-67 expression was mild, and the p53 expression was scarce (Fig. 2B, C). Furthermore, endoscopic retrograde cholangiopancreatography showed a dilated main pancreatic duct with leakage of contrast medium into the gastric corpus (Fig. 3A). In addition, the pancreatogastric fistula was con-

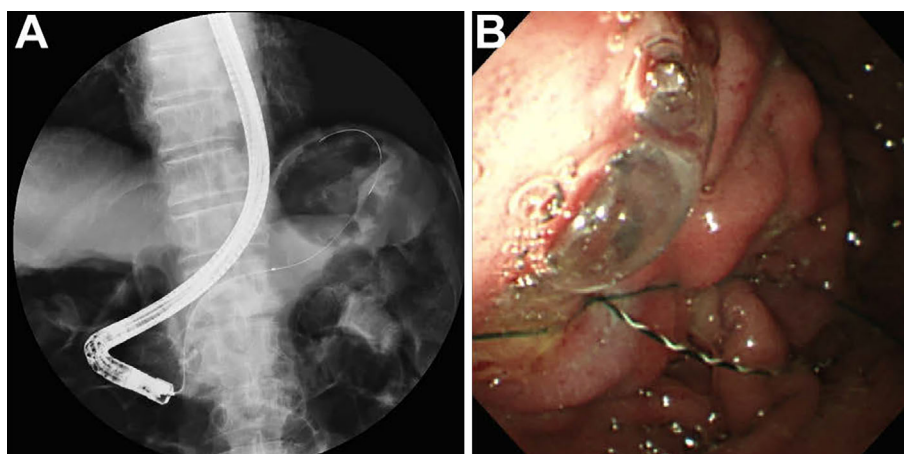


Figure 3. Findings of endoscopic retrograde cholangiopancreatography. **A:** Endoscopic retrograde cholangiopancreatography showing the main pancreatic duct and pancreaticogastrophic fistula. A guidewire was inserted into the stomach via the pancreaticogastrophic fistula. **B:** Endoscopically confirmed guidewire placement in the stomach.

(Day 220)

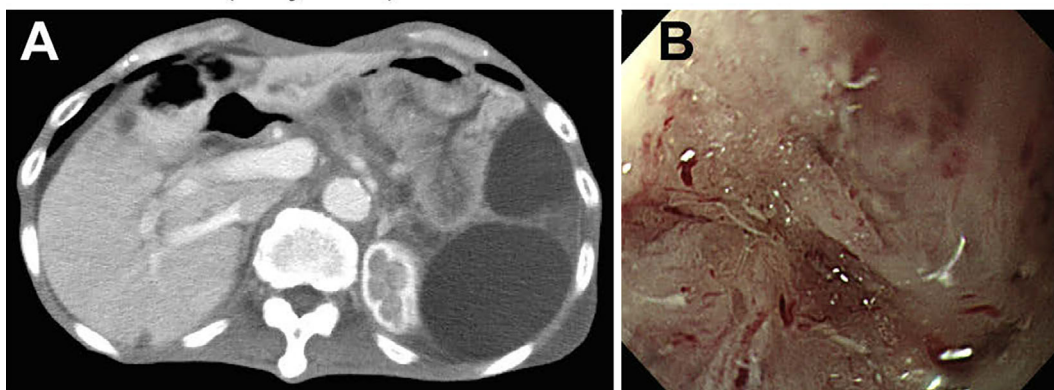


Figure 4. Follow-up imaging findings. **A:** Abdominal computed tomography showing gradual enlargement of the pancreaticogastrophic fistula and pancreatic cystic lesion during follow-up. In addition, there were several metastatic lesions in the liver along with dilatation of the intrahepatic bile duct. **B:** Compared with the previous esophagogastroduodenoscopy findings, the mucous membrane was irregular, and the fish egg-like appearance of the fistula had disappeared.

firmed using endoscopic retrograde pancreatography through a cannulated guidewire placed inside the stomach (Fig. 3B).

Based on these findings, the patient was diagnosed with IPMN (low-intermediate grade dysplasia; main pancreatic duct type and pancreatobiliary type) along with fistula formation in the stomach. Because of the presence of dementia and limitation of daily living activities, the patient was followed up closely without any treatment.

Six months after admission, follow-up contrast-enhanced CT (Fig. 4A), EGDS (Fig. 4B), and a biopsy were performed. EGDS showed an irregular or non-structured mucous membrane on the fistula with loss of the fish egg-like appearance. The second biopsy demonstrated a papillary tumor similar to the previous one but with increased Ki-67 and p53 labeling indices and increased cellular atypia (Fig. 5). Six months after admission, the patient was histologically diagnosed with IPMC. Although there was no

histopathological evidence of malignancy in the first biopsy, we suspected malignancy at the beginning of admission because of the rapidly progressive course over several months and the presence of liver metastasis on contrast-enhanced CT (Fig. 4). It was suggested that the biopsied portion of the tumor in the interior of the fistula had been invaded and replaced with pre-existing IPMC. By day 190, the disease had gradually worsened, and the CA19-9 level had rapidly increased from 439.4 to 3,199 U/mL. Although the definitive findings of invasive carcinoma could not be confirmed by the second biopsied specimen, we diagnosed him with IPMN with associated invasive carcinoma because of the increased tumor marker levels and the presence of liver metastasis and regional adenopathy.

The patient ultimately died eight months after admission from multiple organ failure aggravated by IPMN with associated invasive carcinoma.

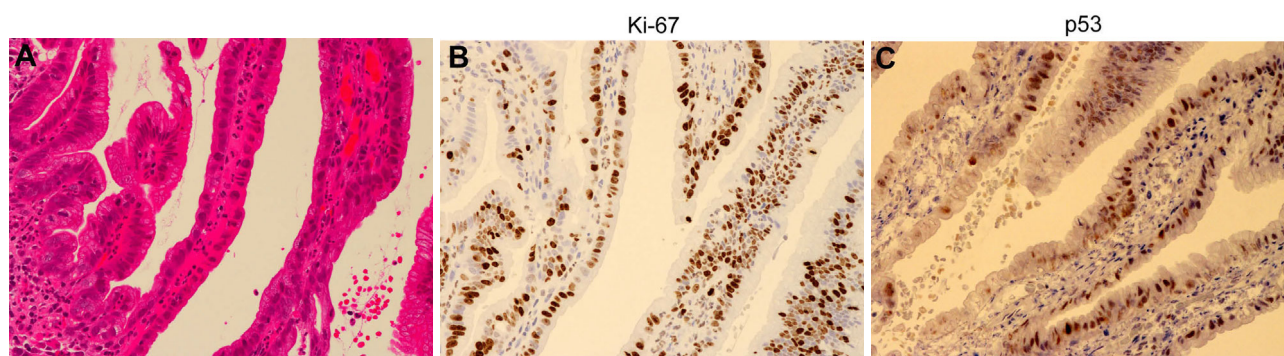


Figure 5. A pathological examination of the second biopsy specimen. **A: Hematoxylin and Eosin staining: high-power microscopy showing an invasive intraductal papillary mucinous carcinoma with a fistula in the stomach. B: Immunohistochemically, around 70% of the neoplastic cells showed Ki-67 expression. C: Immunohistochemically, around 40% of the neoplastic cells showed p53 expression.**

Table. Clinical Features of Previously Reported Intraductal Papillary Mucinous Neoplasm with Pancreatogastric Fistula.

Case No	Reference No	Age	Gender	invasion	IPMN type	IPMN type	Pathology	location	Fistula invasion	Organ(except stomach)	prognosis (Months)	Dead or Alive
1	9	74	M	-	unknown	NM	pap AC	pt	+	-	12	D
2	13	75	M	-	unknown	NM	pap A	ph,pb	-	-	24	A
3	12	72	F	-	unknown	NM	pap B	pb,pt	-	-	36	A
4	10	70	F	-	intestinal type	Convine	pap B	ph	-	duodenum	36	A
5	11	79	F	-(maybe)	unknown	NM	NM	ph	-	-	NM	A
6	8	79	M	-	unknown	NM	pap A	ph	-	duodenum	18	A
7	7	84	M	+	unknown	NM	pap tub AC	ph,pb	NM	duodenum (bulb & 2nd)	13	A
8	6	72	F	-	intestinal type	Main	pap AC	pb	-	-	9	D
9	6	61	F	+	intestinal type	Branch	col pap AC	pb,pt	-	-	27	D
10	6	70	M	+	intestinal type	Main	col pap AC	ph,pb,pt	-	duodenum	1	D
11	6	69	M	+	intestinal type	Main	col pap AC	pb,pt	+	duodenum	20	D
12	6	50	F	+	Pancreatobiliary type	Branch	tub pap AC	ph	+	duodenum, colon	12	D
13	6	83	M	NM	intestinal type	Branch	col AC	ph,pb,pt	NM	duodenum	2	D
14	6	83	M	NM	intestinal type	Main	pap AC	pt	NM	duodenum, choledochus	2	D
15	6	83	M	NM	intestinal type	Main	pap AC	pb	NM	duodenum, choledochus	110	D
16	present case	83	M	-	Pancreatobiliary type	Main	pap B	ph,pb,pt	-	-	8	D

AC: adenocarcinoma, A: adenoma, B: border line, pap: papillary mucinous, col: colloid, tub: tubular, ph: pancreatic head, pb: pancreatic body, pt: pancreatic tail, NM: not mentioned

Discussion

To our knowledge, there have been 8 published reports comprising 15 cases of IPMN with pancreatogastric fistulas (Table) (6-13). Koizumi et al. (12) reported that the duodenum (24 cases, 59%), common bile duct (21 cases, 51%), and stomach (7 cases, 17%) were the organs most frequently affected by fistula formation. Kobayashi et al. (6) observed fistula in other organs in 18 of 274 (6.6%) patients, 10 of whom had main-duct IPMN, 8 branch-duct IPMN, and 8 pancreatogastric formation. Given the CT and endoscopic ultrasonography findings, our case had main-duct IPMN with a pancreatogastric fistula. Kobayashi et al. (6) noted

mucin-marker expression, and 94% of IPMN cases with pancreatogastric fistula had intestinal-type tumors. According to the immunohistological staining findings, the present case was one of pancreatobiliary type tumor, which is rare among cases of IPMN with pancreatogastric fistulas.

Two factors have been reported to contribute to the pathogenesis of fistula formation, namely direct tumor invasion and increased mechanical force caused by elevated pressure in the pancreatic duct (6, 14). However, some studies have reported that 41-67% of patients with pancreatogastric fistula had mechanical penetration without tumor invasion around the fistula (6, 16). In the present case, we believe that the mechanical force contributed to fistula formation because there was scant evidence of malignancy or invasion

around the fistula.

The 5-year survival rates in patients with non-invasive and invasive IPMN have been reported to be 85-100% and 25-65%, respectively (17, 18). Furthermore, the 5-year survival rates in patients with non-invasive papillary adenocarcinoma, all types of IPMC, and common-type pancreatic carcinoma have been shown to be 100%, 71%, and 10%, respectively (6). Therefore, the prognosis of non-invasive IPMN is more favorable than that of invasive IPMN. However, in the same study, the median survival duration of all IPMN patients with fistula formation was 16 months (6), and they had a worse prognosis than those with IPMC. In our case, despite the absence of the characteristics of IPMC in the initial biopsy, the high CA19-9 expression, rapid progression, and solid component on CT images were suggestive of IPMC somewhere else in the pancreas.

In conclusion, we report a rare case of pancreatobiliary-type IPMN with pancreatogastric fistula. Reports of IPMN with pancreatogastric fistulas are rare, but we have described the changes in the endoscopic, pathologic, and clinical characteristics of IPMN over the natural course of such a case.

We could not obtain informed consent from the patient's relatives after his death because the patient had no relatives, this being a welfare case. We were also unable to obtain informed consent while the patient was alive because of ethical concerns.

The authors state that they have no Conflict of Interest (COI).

Hideaki Takahashi and Yasushi Adachi contributed equally to this work.

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