

Cross-Reaction Allergic Pancreatitis With Ketoprofen and Flurbiprofen

To the Editor:

A 59-year-old woman had the abrupt onset of shortness of breath, wheezing, nausea, vomiting, and constant pain in the epigastrium that radiated to the flanks 3 hours after she took 1 tablet of flurbiprofen (200 mg) because of severe low back pain. Two years before this current presentation, the patient was admitted at another hospital with acute pancreatitis; at that time, clinical symptoms developed a few hours after she took 1 sachet of ketoprofen (80 mg) with a rapid and complete recovery achieved after a few days. Her previous history also revealed bronchial asthma and hypertension that were controlled with irbesartan, hydrochlorothiazide, spironolactone, and salbutamol on demand; she denied alcohol use, toxic habits, or taking any other medications—including over-the-counter medications—or herbal remedies.

At admission, the patient was fully alert and oriented and afebrile, with normal vital parameters; physical examination yielded normal findings apart from bilateral and diffuse wheezing and a severely tender abdomen with no rebound tenderness and no bowel sounds. Laboratory data showed increased blood levels of amylase (1844 IU/L [reference range, 40–250 IU/L]) and lipase (4189 IU/L [reference range, 23–300 IU/L]); hematologic variables, cholesterol level, triglycerides, electrolytes, and renal and liver function tests were normal as were the results of serological tests for *Mycoplasma* species, viral hepatitis, and other viral infections. Abdominal ultrasonography and contrast-enhanced computed tomography showed a diffusely edematous pancreas and a small filling defect consistent with a nonoccluding thrombus at the branching of the portal and splenic veins; there was a moderate amount of intraperitoneal free fluid with no collateral venous vessels or any direct or indirect evidence of splenic or transmural

intestinal infarction. The gallstone and biliary ducts were normal, and biliary stones or sludge or any other abnormal findings were not found.

Irbesartan, hydrochlorothiazide, and spironolactone were discontinued, and the patient was managed conservatively with bowel rest, intravenous fluids, and inhaled budesonide and tiotropium. On the second day of hospital stay, she was free of wheezing and abdominal pain; physical examination was normal, and blood amylase and lipase values were within the reference range. A rechallenge test was not performed for ethical reasons, and the patient was discharged on the fourth day. At that time, blood pressure was below 140/80 mm Hg, and we decided not to start any antihypertensive therapy. At a follow-up visit 1 month later, she was doing well with no clinical or laboratory evidence of active pancreatic disease; an abdominal computed tomographic scan was normal, and serological tests for *Mycoplasma* species and viruses remained negative. Blood pressure was below 140/80 mm Hg on repeated measurements, although the patient was still not receiving any blood pressure-lowering medications.

In this patient, we documented the recurrence of severe pancreatitis after exposure to ketoprofen and flurbiprofen—2 widely used nonsteroidal anti-inflammatory drugs with a similar chemical structure which share the molecule of propionic acid. As a matter of fact, scoring on the probability scale of Naranjo et al¹ indicates a high probability that both relapses of pancreatitis were drug-related adverse events; there was a clear-cut temporal relationship between taking flurbiprofen or ketoprofen and the onset of clinical symptoms along with elevation of pancreatic enzymes; more important, we did not find any other plausible alternative cause to explain those flares-up of such a severe pancreatitis. She was also receiving irbesartan and hydrochlorothiazide, but this is not a true confounding factor in our opinion. Irbesartan and hydrochlorothiazide are a potential, although rare, cause of pancreatitis;^{2,3} however, our patient was taking those medications for several years and did not ever report

any complaints consistent with an acute or chronic pancreatic disorder, nor laboratory studies showed elevated blood levels of pancreatic enzymes over a follow-up period of more than 5 years, except after exposure to flurbiprofen or ketoprofen.

Allergic or hypersensitivity pancreatitis remains an elusive entity because idiosyncratic or toxic mechanisms are commonly advocated to explain the pathogenesis of most cases of drug-induced pancreatitis.³ Our MEDLINE search yielded no case of pancreatitis related to the use of flurbiprofen and only a few reports of pancreatitis associated with the use of ketoprofen.^{4–7} Those studies attributed the onset of ketoprofen-related pancreatitis to a toxic rather than an immune-mediated mechanism, possibly linked with inhibition of phospholipase-A2 activity and interference with prostaglandin synthesis, which is reasonably the most important mechanism of potential pancreatic injury among people taking nonsteroidal anti-inflammatory drugs. Under this perspective, the cumulative dose could reasonably be the most relevant risk factor.⁸ In contrast, the pathophysiology of pancreatitis seems to be completely different in our patient. The clinical features and course, the onset of symptoms after just a few hours after a single dose of flurbiprofen or ketoprofen was taken, and also the finding of wheezing when she presented with flurbiprofen-related pancreatitis strongly argue in favor of an allergic or hypersensitivity cross-reaction between ketoprofen and flurbiprofen as the underlying mechanism which ultimately triggered the onset of pancreatic injury and inflammation in both episodes. Our patient had a normal eosinophil count and remained afebrile throughout the entire course; however, all these features along with the absence of lymphadenopathy and the negative search for antinuclear and anti-smooth-muscle antibodies do not represent a definite argument against an allergic or immune-mediated mechanism of pancreatic injury in this case. We did not perform sophisticated in vitro immunologic investigations to confirm this hypothesis; however, the clinical data that we provided do consistently support

our view. We also decided against a rechallenge test with flurbiprofen or ketoprofen because of the concern of inducing severe acute pancreatitis.

Clinicians should carefully consider the risk of a severe cross-reaction allergic pancreatitis when planning to use drugs with a similar chemical formula to medications that have been implicated as triggers of a previous episode of drug-induced pancreatitis.

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Establishment and Characterization of a New Cell Line (SPH) Derived From a Pancreatic Ductal Adenocarcinoma

To the Editor:

Pancreatic cancer constitutes approximately 2% of all diagnosed cancers. However, it is the fourth most common cause of cancer death.^{1,2} More than 90% of pancreatic cancers are ductal adenocarcinomas (PDACs), a very aggressive and destructive type of cancer, which is characterized by an extremely poor prognosis, pronounced invasiveness, and rapid progression. Despite progress in understanding of etiology and pathogenesis of pancreatic adenocarcinoma, the 5-year survival of patients with pancreatic cancer remains low.^{3–5} Early diagnosis of carcinoma and discrimination between malignant and benign are difficult. Therefore, it has been considered as the greatest oncological challenge.^{6,7}

The cell lines established from human pancreatic adenocarcinoma are useful and important tools to study its biological properties, find a new tumor marker for early diagnosis, and try a new therapeutic approach.^{8–10} In vitro-cultured cell line is needed for the study of human cancer. Although there are currently a few pancreatic cancer cell lines available commercially, additional cell lines will still be useful to further study the highly aggressive disease. In this regard, we set out to establish a cell line (SPH) derived from the human PDAC and characterize the SPH cells, such as morphology, growth characteristics, chromosome analysis, heterotransplantability, and tumor markers.

We established a human pancreatic carcinoma cell line, designated SPH, from cancerous ascites of a 57-year-old male patient with the pancreas carcinoma (postoperative pathological diagnosis was ductal adenocarcinoma, with tubular pattern). The patient gave informed consent for the use of surgical samples for these investigational and analytical studies. For cytological diagnosis of metastatic malignant ascetic fluid, we confirmed with immunohistochemical staining for CA19-9 (positive) and calretinin (negative), and it was positive.

The cells have been cultured for 32 months and designated SPH. Postoperative pathological diagnosis was ductal adenocarcinoma, with tubular pattern, moderately differentiated type with liver metastasis. Papanicolaou

staining of the cells from metastatic cancerous ascites indicated the clusters of adenocarcinoma cells. The SPH cells had large nucleonic body in nucleus, and nucleus containing 1 or 2 abundant cytoplasm stains faintly, which have histopathologically recognized characteristics of ductal adenocarcinoma of the pancreas. We performed immunohistochemical staining of cultured tumor cells with pancreatic markers such as CA19-9. Tumor-associated antigen levels in the conditioned media are shown in Table 1. The SPH cells produced CA19-9, SPan-1, and DUPAN-2 in the conditioned medium in relatively high levels. The doubling time of the population of the SPH cells was estimated to be about 35 hours. The chromosome analysis of SPH cells at passage 20th showed aneuploidy with a modal chromosome number of 85, distributed from 77 to 91. Karyotype revealed both numerical and structural abnormalities of chromosomes. Using typical G-band karyotype metaphase plate analysis, 6 to 9 types of marker chromosomes were found.

All the tumors transplanted into nude mice grew a tumor when 1×10^7 SPH cells were inoculated. The histological features of these tumors in nude mice were typical ductal adenocarcinoma, which were similar to the original adenocarcinoma of the pancreas.

To be brief, we report here the establishment and characterization of a new human pancreatic carcinoma cell line, designated SPH. We were able to maintain human metastatic PDAC cells in vitro without any interruption. Thus, the SPH cell line is expected to be useful for studying the cell proliferation and the identification of pancreatic carcinoma-associated specific antigens, which may provide a suitable model to study many aspects of pancreatic ductal cell biology, and prognostic markers for metastatic diseases.

TABLE 1. Tumor-Associated Antigen Levels in the Conditioned Media of SPH Cells

Tumor-Associated Antigen	Concentration (U/mL)
CA19-9	450
SPan-1	380
DUPAN-2	270

ACKNOWLEDGMENTS

The authors thank their department colleagues for their helpful discussions and expert technical assistance.

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Endoscopic Ultrasound–Guided Fine-Needle Injection of Immature Dendritic Cells Into Advanced Pancreatic Cancer Refractory to Gemcitabine A Pilot Study

To the Editor:

New therapies for pancreatic cancer are needed to improve its prognosis. Immunotherapy, a novel approach, has been investigated for pancreatic cancer.¹

Dendritic cells (DCs), used in DC vaccine therapy against cancer, are potent antigen-presenting cells for induction of primary T-cell–dependent immune responses.² Many strategies for delivering antigens into DCs have been established in murine models and clinically tried. Synthetic peptide approaches require identification of tumor-specific antigens for individual tumors and demonstration of their recognition by cytotoxic T lymphocytes. However, because cancer has many unknown antigens, antigenic peptides and cytotoxic T-lymphocyte epitopes presented by human pancreatic cancer remain largely unidentified. We intratumorally injected unloaded DCs into pancreatic cancer cells; they acquire and process tumor antigens in situ, migrate to regional lymphoid organs, and initiate a

strong tumor-specific immune response. Such intratumoral injection appears preferable to intravenous or intradermal injections.

Interventional endoscopic ultrasound (EUS) can approach pancreatic cancer cells using EUS-guided fine-needle injection (EUS-FNI) technique.¹ We performed EUS-FNI of DCs to investigate the feasibility, safety, and clinical response of EUS-FNI of unpulsed immature DCs into the pancreatic cancer refractory to systemic administration of gemcitabine. This report of a pilot clinical study to inject unpulsed immature DCs into advanced pancreatic cancer cells is believed to be the first. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committee of Fukushima Medical University. All patients provided informed consent before treatment.

Seven patients had been unsuccessfully treated (gemcitabine) unresectable pancreatic cancer: 7 stage IV patients with multiple liver metastasis and/or artery involvement and 2 with malignant ascites. All patients had histologically proven intraductal adenocarcinoma by EUS-guided fine-needle aspiration. For preparation of DCs, the patients were leukaphoresed to obtain a neutrophil-depleted fraction of peripheral blood mononuclear cells from approximately 6 to 7 L of blood. Countercurrent elutriation was then performed to separate cells into monocyte-rich and lymphocyte-rich fractions and used or cryopreserved as described previously.³ Using granulocyte-macrophage colony-stimulating factor and interleukin

TABLE 1. Results of Intratumoral DCs Injection

Patients			Status Before DCs Injection			Treatment	Response to DCs Injection	
Case	Age, yrs	Sex	Stage	Metastasis	Prior Chemotherapy	(Times of Injection)	Response	Survival After Diagnosis, mo
1	54	Male	IVb	Liver, peritoneum	GEM	4	MR, CA-19-9↓	6
2	54	Male	IVb	Liver	GEM, UFT	21	MR, CA-19-9↓	14
3	52	Male	IVb	Liver	GEM	2	PD, CA-19-9↑	5
4	62	Male	IVb	Liver	GEM, S1	6	PD, CA-19-9↑	7
5	56	Male	IVb	Liver	GEM	3	PD, CA-19-9↑	6
6	42	Female	IVb	Liver, peritoneum	GEM	11	SD, CA-19-9↓	10
7	62	Female	IVa	None	GEM	18	SD, CA-19-9↓	21

4, patients' peripheral monocytes generated immature DCs.⁴ Patients received intratumoral injection of 10 billion or more immature DCs at 2 to 3 sites using EUS-FNI. Five of 7 patients received irradiation therapy before initial EUS-FNI of DCs to induce apoptosis and necrosis and to produce tumor-associated antigens for DC cross-presentation. DC was administered on days 1, 8, and 15. The cycles were repeated every 28 days as much as possible. Physical and laboratory examinations assessed the potential vaccine toxicity. Clinical end points were CA-19-9, tumor response, and survival. Standard clinical response criteria were applied. Complete response was complete regression of all lesions lasting at least 1 month. Partial response (PR) was a greater than 50% decrease of lesions lasting more than 1 month. Mixed response (MR) was a regression of main pancreatic tumors, whereas other lesions remained stable or progressed. Stable disease (SD) was defined as a less than 25% size reduction with no newly developed lesions for more than 1 month. Progressive disease (PD) was defined as increase of more than 25% in the sites of the metastatic lesions or the occurrence of new lesions.

Table 1 shows that all DC injections were tolerated without clinical toxicity. No complication associated with EUS-FNI procedure was noted. The CA-19-9 level decreased in 3 patients; 3 had MRs (2 with malignant ascites). Median survival was 9.9 months, although previous studies reported 8 to 9 months as the mean for chemotherapy patients⁵; patients with peritonitis carcinomatosa face shorter survival. The poor prognosis associated with pancreatic cancer suggests that the response and survival data reported here for intratumoral injection of DCs are encouraging. These data indicate that intratumoral injection of unpulsed DCs into the pancreatic cancer using EUS-guided FNI is safe and can induce some clinical responses in patients with advanced diseases.

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A Pure Invasive Micropapillary Carcinoma of the Pancreatic Head Long Disease-Free Survival After Pancreatoduodenectomy and Adjuvant Chemotherapy With Gemcitabine

To the Editor:

Invasive micropapillary carcinoma (IMPC) first was described in the breast.¹ The tumor cells are grouped in small cluster surrounded by a characteristic

cleft.² This type of cancer nearly always is associated with a poor prognosis and extensive lymph node metastases.³ Invasive micropapillary carcinoma of the ampullopanceatobiliary region has been reported only by Khayyata et al³; moreover, these tumors only rarely showed the clustered pattern exclusively.

We describe clinicopathologic and immunohistochemical features of a pure primary IMPC arising in the pancreatic head. Although we know of no previous report of effective adjuvant chemotherapy for IMPC, our patient's tumor responded completely to adjuvant chemotherapy with gemcitabine.

CASE REPORT

A 67-year-old man presented to another hospital with obstruction of the transverse colon, where a colonic tumor was resected surgically with tumor-free margins. Because intraoperative exploration also disclosed a small area of induration in the gallbladder, cholecystectomy was performed simultaneously. The colonic tumor was macroscopically a type 4 cancer, with no accompanying ulceration. Initial pathological diagnoses were "poorly differentiated adenocarcinoma, so-called linitis plastica type" and "metastasis to the gallbladder." However, because the tumor of the colon differed in appearance from typical colon cancer, this lesion was consistent with the possibility of carcinoma metastasis from another organ. Three months after the first surgical treatment, the patient complained of general malaise and became jaundiced. A pancreatic head tumor was detected by computed tomography (CT), and he was referred to our institution for additional treatment.

Computed tomography showed a nodular tumor in the head of the pancreas and multiple enlarged lymph nodes in the hepatoduodenal ligament. With administration of intravenous contrast material, enhancement of this tumor was poor in the early phase but relatively strong in the delayed phase; the tumor margin was distinct. Magnetic resonance cholangiopancreatography showed expansion of the C-shaped duodenal loop around the pancreatic head. The lowermost common bile duct and main pancreatic duct were obstructed. Liver and lung metastases were not detected. Upper gastrointestinal endoscopy showed an elevated and eroded lesion surrounding the papilla of Vater, and a biopsy specimen from this lesion indicated adenocarcinoma. Initially, we diagnosed the pancreatic tumor as a recurrence of colon cancer representing mainly lymph node metastases, considering

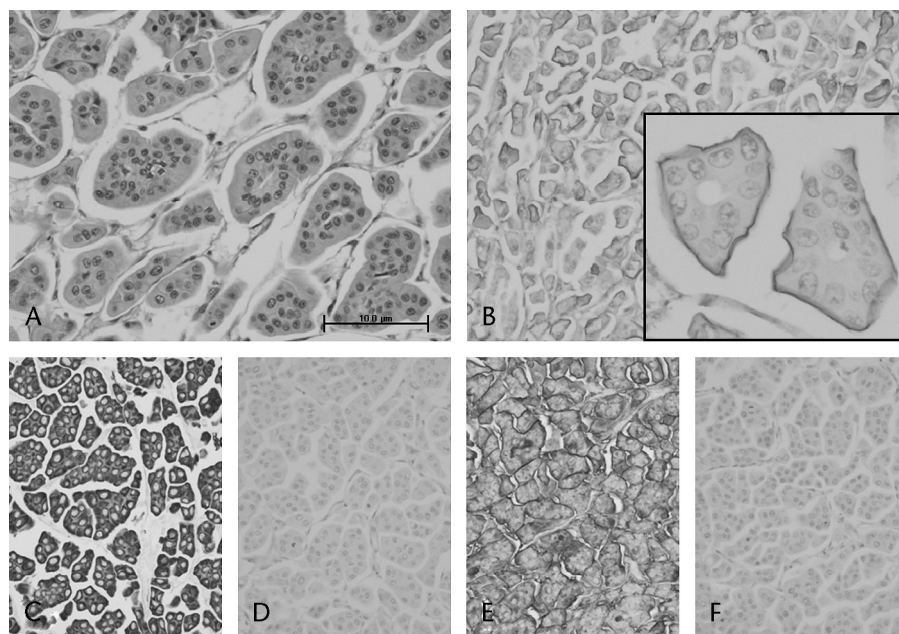


FIGURE 1. Pathological examination. A, The histological pattern of the pancreatic tumor (hematoxylin-eosin, original magnification $\times 200$). B–F, Immunohistochemical analysis for MUC1, CK7, CK20, CA19-9, and CEA (original magnification $\times 100$).

its expansile and nodular pattern of growth. Because these findings argued against further surgical resection, we instead administered cisplatin as a daily intravenous infusion from days 1 to 5 of chemotherapy, followed by cessation for 2 days. We continued this schedule for 1 month, but the disease was progressive and signs of duodenal constriction appeared.

We decided upon palliative resection to reduce gastrointestinal symptoms. With the patient's informed consent, we performed pancreatoduodenectomy, finding tumors in the remaining transverse and sigmoid colon in addition to the pancreatic tumor. We simultaneously performed partial colectomy. The pancreatoduodenal reconstruction method was IIA.

Macroscopically, the tumor of the pancreas measured $45 \times 55 \times 35$ mm, had a soft consistency, and was whitish to gray on cut section. The histological pattern was characterized by small round to ovoid micropapillary tumor cell clusters without fibrovascular cores, lying within clefts. In most areas, the micropapillary clusters were closely packed, with scant intervening stroma. The cells had fairly abundant acidophilic cytoplasm and showed moderate nuclear atypia (Fig. 1A). Focal lymphatic invasion was marked, and venous invasion was moderate. No area of typical adenocarcinoma was seen, with the tumor consisting purely of IMPC. Tumors of the colon and gallbladder showed the same findings limited to the submucosa, a pattern compatible with metastases from the pancreatic tumor.

Mucin 1 (MUC1) immunostaining was prominent and diffuse along the surfaces

of cell clusters facing the stroma (Fig. 1B). Immunohistochemically, the tumor was positive for cytokeratin (CK) 7 (Fig. 1C) and negative for CK20 (Fig. 1D). Tumor cells were positive for carbohydrate antigen 19-9 (CA19-9) (Fig. 1E) and negative for carcinoembryonic antigen (CEA) (Fig. 1F).

Adjuvant systemic chemotherapy with gemcitabine was begun on the 40th postoperative day as a biweekly intravenous infusion of gemcitabine for 30 minutes (900 mg/m^2), with outpatient administration 36 courses. We examined for recurrence by CT every 3 months. At 42 months after surgical resection, the patient was well with no sign of recurrence when he died suddenly of accidental trauma. No neoplastic lesions were detected in other organs such as breast, lung, or urinary tract throughout the course.

DISCUSSION

We report a unique case of a patient with a pure pancreatic IMPC. After he received gemcitabine as adjuvant chemotherapy after pancreatoduodenectomy, he survived disease-free for more than 3 years.

Invasive micropapillary carcinomas have been associated with a high degree of aggressiveness, arising in various organs including breast, urinary bladder, lung, and colon, manifested by advanced stage at presentation, massive lymph node metastasis, and extensive lymphatic and vascular invasion. Ampullopapillary IMPCs have

been reported to account for 4.1% of the carcinomas in this region.³ The extent of the micropapillary component in primary tumors has been classified by Khayyata et al³ as focal (20%–50% of the tumor), predominant (51%–80%), or diffuse (>80%). Finding the diffuse type to be very rare, those authors reported only 2 such cases originating from the pancreas and 2 others originating from the periampullary region. Our case, a pure IMPC without areas of typical adenocarcinoma of the pancreas, needed to be distinguished from an IMPC that had metastasized to this region from another organ; IMPC can be pure in metastases even when this pattern is only focally present in the primary tumor. Moreover, the IMPC morphology is not specific for any anatomic location.

In cases with periampullary origin, liver injury from biliary tract obstruction should be evident even at an early stage. In our case, liver injury was not apparent until a tumor mass in the pancreatic head could be demonstrated by CT.

In addition to clinical information, immunohistochemical stains such as CK7 and CK20 can be helpful in identifying the primary tumor site, because the CK7/CK20 immunohistochemical staining pattern is usually retained in both the primary IMPC and metastatic

foci.^{2,4} Invasive micropapillary carcinoma of the breast, lung, and parotid gland all are CK7⁺/CK20⁻, as is micropapillary transitional cell carcinoma. Invasive micropapillary carcinomas of the colon, however, are CK7⁻/CK20⁺, as are typical colonic cancers. In our case, the pancreatic tumor and the presumable metastatic tumors in the colon and gallbladder all were CK7⁺/CK20⁻. In addition, the tumors of colon and gallbladder had the same morphology as the pancreatic lesion as well as a distribution limited to the submucosa. These findings indicated that the colon and gallbladder tumors had metastasized from the pancreatic tumor.

MUC1, a glycoprotein normally located at the apical cell surface of normal glandular epithelium, has an important physiological role in the maintenance of lumina and an inhibitory role in tumor cell-stroma interaction. In *in vitro* studies, increasing MUC1 expression was associated with decreased adhesion between adjacent cells and between cells and the extracellular matrix.⁵ In typical carcinomas of the pancreas, increased expression of MUC1 was associated with low-grade cytological features and good prognosis, whereas aberrant expression, such as intracytoplasmic localization, was associated with poor outcome independently of tumor differentiation.⁶ In our case, MUC1 expression in neoplastic cell clusters present in the surface facing the stroma as a narrow band of staining; significant lymphotropism was observed. Invasive micropapillary carcinoma, then, shows reversal of cellular polarity in an "inside-out" growth pattern where the surfaces of tumor cells that face the stroma acquire apical secretory properties. This has been demonstrated in earlier studies by electron microscopy⁷ as well as immunohistochemical staining for MUC1.⁸ MUC1, then, may be an important factor in the detachment of cells from the stroma, contributing to a micropapillary morphology as well as facilitating spread of cells by dissection of the stroma.

Gemcitabine (difluorodeoxycytidine) is a nucleoside analogue that is highly effective against typical pancreatic cancer.⁹ Gemcitabine was effective even in our IMPC case. Because this tumor originated from the pan-

creas, it may have retained some properties of typical pancreatic carcinoma, as verified by the CK7/CK20 immunohistochemical staining pattern. Characteristics of this tumor shared in common with typical pancreatic carcinoma may have rendered it sensitive to gemcitabine, permitting disease-free survival for more than 3 years.

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Successful Resection of Lung Metastases From Intraductal Papillary Mucinous Neoplasm

To the Editor:

We report here a patient with intraductal papillary mucinous neoplasm (IPMN), who was surgically treated for 2 synchronous lung metastases. To our knowledge, this is the first article on the resection of the lung metastases from IPMN. Because IPMN has recently come to be known, this type of tumor is likely to increase in number.

A 73-year-old Japanese woman was diagnosed as lung tumors in a general health examination in September 2004. A postcontrast computed tomography (CT) scan disclosed two 1.5-cm-sized masses in the left lung, and bronchoscopy made the diagnosis of a well-differentiated adenocarcinoma. Routine laboratory studies were within normal limits, including the serum levels of CEA and CA19-9. Abdominal CT scan disclosed an 8.0-cm-sized tumor in the pancreas tail, and endoscopic retrograde pancreatography confirmed mucin excreting from the major papilla with a cytological diagnosis of highly suspicious malignancy. In January 2005, we performed a distal pancreatectomy with splenectomy under the diagnosis of IPMN, followed by left lobectomy for metastatic lung cancer in February 2005. Histopathologically, IPMN had both components of carcinoma and adenoma (Fig. 1). Immunohistochemistry of thyroid transcription factor 1 and surfactant apoprotein showed negativity of both tumor cells of the pancreas and the lung. Only tumor cells of carcinoma exhibited reactivity for mucin 1 (MUC-1) glycoprotein (Fig. 1C), whereas tumor cells of adenoma alone revealed positive expression for MUC-2 glycoprotein

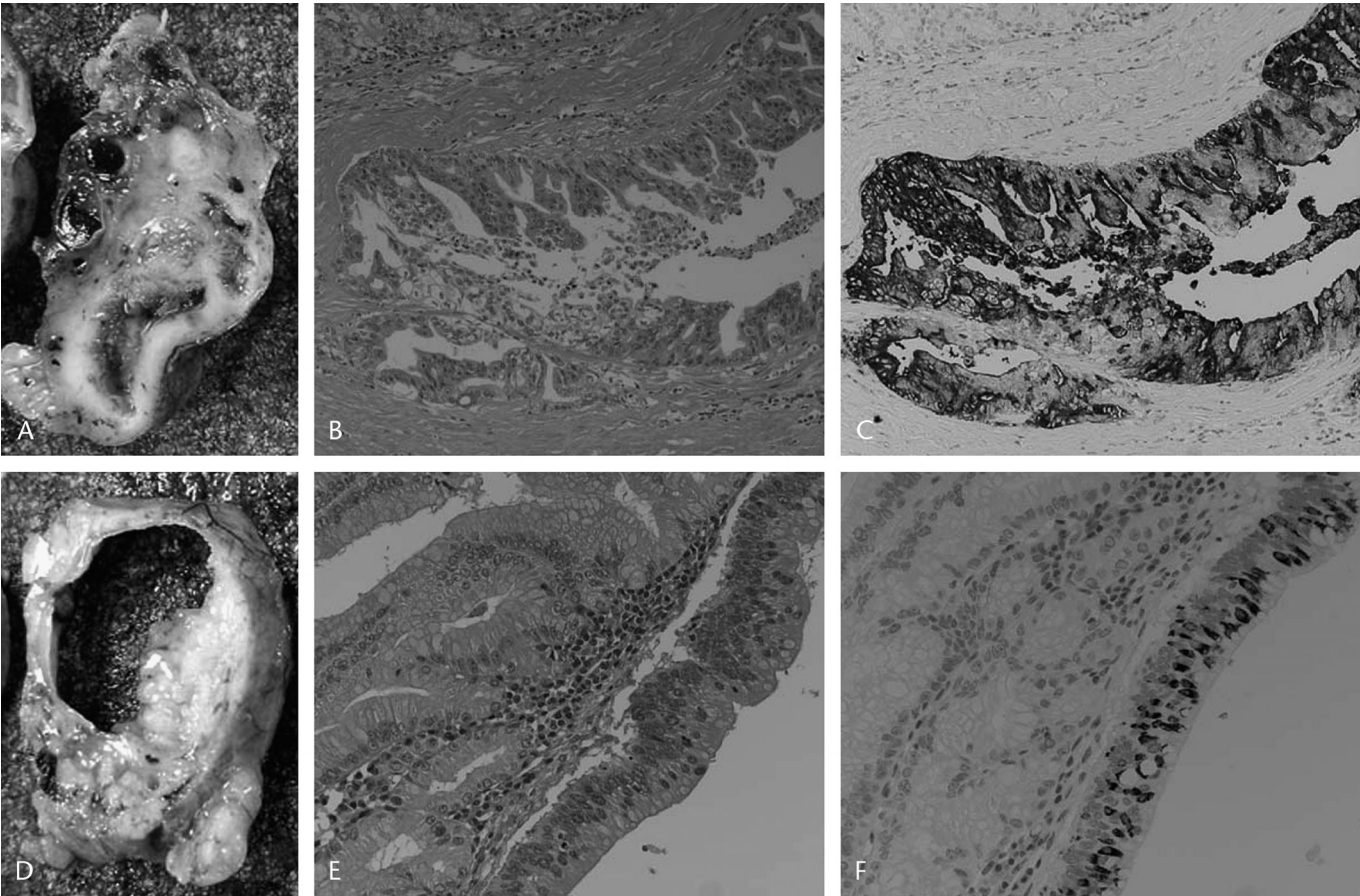


FIGURE 1. A, Cross-section of carcinoma area of IPMN. B, Hematoxylin-eosin staining of carcinoma (original magnification $\times 20$). C, Immunohistochemically, the cytoplasm of carcinoma cells exhibited reactivity for MUC-1. D, Cross-section of adenoma area of IPMN. E, Hematoxylin-eosin staining of adenoma ($\times 20$). F, Immunohistochemistry showed the positivity of adenoma cells for MUC-2.

(Fig. 1F). Tumor cells of lung metastases also showed positive for MUC-1 but negative for MUC-2. Therefore, the tumor was finally diagnosed as IPMN and its lung metastases. The patient had a satisfactory postoperative course and left our hospital in March 2005. She has been followed up on an outpatient basis without chemotherapy. As of December 2006,

she remained well without recurrence, 22 months after her initial operation. Recently, there have been some reports that MUC-1 mucin is related to the prognosis of IPMN.¹ Yonezawa et al² reported that the invasive growth areas of intraductal papillary mucinous tumor acquire a characteristic of MUC-1 mucin expression that is usually seen in

IDC. Sato et al³ provided evidence that MUC-1 mucin promotes pulmonary metastasis of a human pancreatic cancer cell line S2-013 in a nude mouse model. Our case revealed positivity for MUC-1 only in the invasive carcinoma areas of pancreas and lung metastases. Based on this evidence, it was proved that the invasive carcinoma area stained with

TABLE 1. Reported Cases of Lung Resections for Lung Metastases From Pancreas Tumor

Reference	Age (y) and Sex	Histological Diagnosis	Operation for Primary Tumor	Interval From Primary Resection to Metastasis (mo)	Number of Lung Metastases	Tumor Marker	Survival Time After Lung Resection
Baba et al ⁷	48/male	Moderately differentiated adenocarcinoma	Distal pancreatectomy	0	1	CEA: 504	Alive after 59 mo
Itoh et al ⁸	66/female	Papillary carcinoma	Total pancreatectomy	108	4	CA19-9: 785	Alive after 60 mo
Shimada et al ⁹	76/female	Unknown (invasive pancreas cancer)	Pancreaticoduodenectomy	61	1	CA19-9: 61	Alive after 48 mo
Natsume et al (present study)	73/female	IPMN	Distal pancreatectomy	0	2	Normal	Alive after 22 mo

MUC-1 metastasized to the lung. It is necessary to distinguish the lung tumors from primary lung cancer. Both tumors of the pancreas and the lung in our case showed negative expression for immunohistochemical staining with thyroid transcription factor 1 and surfactant apoprotein. Thyroid transcription factor 1 has 96% positivity in primary lung cancer but all negative in pancreas cancer, and SP-A has 73% positivity in primary lung cancer.⁴ To our knowledge, only 4 cases including ours who underwent surgeries for lung metastases from IPMN or pancreatic cancer have been reported in the English and Japanese literature (Table 1). The histological types were pancreas cancer in 3 patients and IPMN in our patient alone. All cases as well as ours had reportedly survived after resection of lung metastasis. Two patients had a solitary lung metastasis, and our patient had 2 metastases. One case had 4 metastases, but the longer interval from primary resection to metastasis may have been associated with their favorable outcome. Because our case was pancreas cancer arising from IPMN, we might have been able to resect the lung despite 2 metastases, resulting in favorable survival. There have been no reports on resection of lung metastasis from IPMN. As IPMN has recently been come to be known,^{5,6} this type of tumor will have a likelihood to be more frequently reported.

In conclusion, we presented a rare case of successful resection of lung metastases from IPMN; however, lung metastases from IPMN has not been analyzed precisely. Further study of lung metastasis from IPMN using immunohistochemical staining will help us elucidate the neoplasm.

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Acute Pancreatitis Secondary to Metastatic Lobular Breast Carcinoma Report of a Case and Review of the Literature

To the Editor:

Acute pancreatitis secondary to pancreatic metastases is unusual. We present a case of smoldering pancreatitis clinically consistent with biliary pancreatitis; however, at autopsy, the inflammation was associated with diffusely infiltrating breast cancer that was not seen on computed tomography (CT) or endoscopic ultrasound (EUS). In our review of the literature, this is the first reported case of acute pancreatitis secondary to metastatic breast cancer.

CASE REPORT

A 66-year-old woman with severe ischemic cardiomyopathy and diabetes was admitted with acute pancreatitis. On ultrasound, there was a small stone in the gallbladder. The CT scan revealed evidence of pancreatitis, a questionable mass in the head of the pancreas, and mild intrahepatic and common bile duct (CBD) dilation. Endoscopic retrograde cholangiopancreatography (ERCP) was unsuccessful because of failure to visualize the papilla because of extensive edema and luminal narrowing in the second portion of the duodenum. A magnetic resonance cholangiopancreatography was not possible because the patient had a pacemaker. She responded to conservative therapy and was discharged on total parenteral nutrition (TPN).

A follow-up CT scan showed persistent inflammation in the head of the pancreas, and she was referred to our institution for EUS to further evaluate the possible mass in the head of the pancreas. There was sludge in the gallbladder and CBD. The main pancreatic duct was dilated from the tail to the neck; however, no mass was seen in the head of the pancreas, and fine needle aspiration was not performed.

The TPN was continued with a plan for repeat ERCP with clearance of the bile duct. Although her liver enzymes decreased, her amylase and lipase remained elevated. The ERCP was again unsuccessful because of duodenal edema and narrowing, so a percutaneous transhepatic catheter was inserted. Unfortunately, she developed fungemia and progressive multisystem organ failure, and care was withdrawn.

At autopsy, there was marked induration and edema at the head of the pancreas, and the pancreatic duct was obstructed and mechanically tethered at the neck with distal pancreatic ductal dilation. Grossly, there were no masses or evidence of cancer. The gallbladder wall was focally necrotic, but there were no gallstones or sludge. The CBD measured 1.2 cm, and there were no stones or sludge.

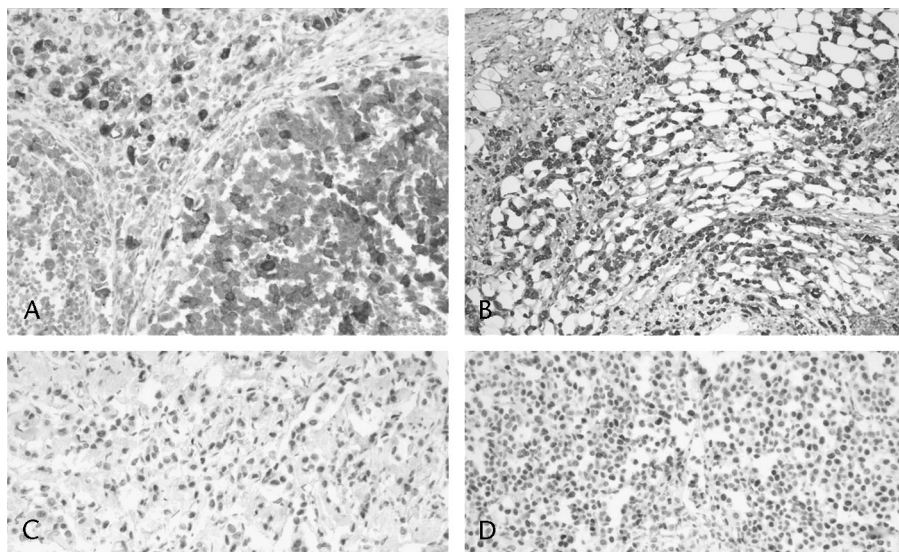


FIGURE 1. The tumor is positive for gross cystic disease fluid protein (A), mammoglobin (B), estrogen (C), and progesterone (D)—all specific immunohistochemical markers for breast cancer.

Microscopic examination of the pancreas revealed inflammation and infiltrating metastatic and poorly differentiated adenocarcinoma with focal signet ring features. The cancer cells diffusely insinuated the pancreatic parenchyma and surrounding soft tissues in a single file pattern without forming a discrete mass. Immunohistochemical stains were strongly positive for gross cystic disease fluid protein, mammoglobin, estrogen receptor, and progesterone receptor, which are all specific for breast cancer (Fig. 1) and confirmed the diagnosis of metastatic lobular breast carcinoma to the pancreas. The patient had no history of breast cancer; because of autopsy limitations, examination of the breast tissue was not performed.

DISCUSSION

This case is interesting for several reasons. First, breast cancer rarely metastasizes to the pancreas. Second, metastasis-induced pancreatitis is extremely rare; to our knowledge, acute pancreatitis secondary to breast cancer has never been reported. Third, most pancreatic metastases are well circumscribed on EUS.

Pancreatic metastases account for 2% of all pancreatic tumors.¹ Renal cell carcinoma is the most common tumor to metastasize to the pancreas.² In the 8 published series looking at the role of EUS for pancreatic metastasis, 39 cases (45%) were from renal cell carcinoma.³

The pancreas is rarely the site of breast cancer metastases.^{1,4,5} Typically, pancreatic metastases from breast carcinoma present years after initial diagnosis, and the usual presenting symptom in these cases is obstructive jaundice.⁴ Lobular carcinoma (as in our case) seems to be the most common type of breast cancer to metastasize to the pancreas,^{1,4} although metastatic ductal carcinoma has also been reported.⁶

Pancreatic metastasis is seldom the initial presentation of cancer and even more rarely causes acute pancreatitis.⁷ The most common tumor to cause acute pancreatitis is small cell carcinoma of the lung. Lymphoma, gastric carcinoma, and melanoma have also been described as causing acute pancreatitis. Acute pancreatitis in the setting of breast cancer has been reported; however, in these cases, the causes of pancreatitis were hypercalcemia⁸ or chemotherapeutic agents.⁹ Acute pancreatitis secondary to breast cancer metastasis has not been reported.

Typically, metastatic lesions to the pancreas are well circumscribed on EUS. In a retrospective multicenter study comparing EUS features of pancreatic metastases with primary tumors, 24 patients were identified as having definite metastases, and 10 were from renal cell carcinoma.² None of the patients had metastases from breast

cancer. Only 4% of the primary tumors had well-defined margins, compared with 46% of metastatic lesions.² Twenty-one (88%) were solid. In another retrospective study of 16 lesions in 7 patients (isolated lesion in 6 and 10 lesions in 1 patient), 15 of the 16 had well-defined borders.¹⁰

Imaging alone is not useful in distinguishing primary from metastatic tumors. Cytomorphology alone may be sufficient for renal cell carcinoma, small cell carcinoma of the lung, hepatocellular carcinoma, and melanoma because of characteristic cytological features.² Immunohistochemistry can be useful in other cases where cytological features cannot reliably distinguish between types of tumors, such as in breast, colorectal, and prostate cancers.² In this case, histological features such as "Indian filing" and signet ring features were highly suspicious for metastatic breast cancer, but immunohistochemistry helped establish a definitive diagnosis.

Our patient's clinical presentation was consistent clinically with smoldering biliary pancreatitis. This was a difficult case because laboratory parameters were confounded by sepsis, magnetic resonance cholangiopancreatography and ERCP were not possible, and EUS demonstrated the presence of sludge after the patient had been on TPN for 1 month. Both CT and EUS did not diagnose the presence of an underlying malignancy. However, on postmortem examination, there was no sludge, and the cause of pancreatic inflammation was a poorly differentiated and diffusely infiltrating lobular breast carcinoma involving the head of the pancreas with perineural and vascular invasion. To our knowledge, this is the first reported case of acute pancreatitis secondary to metastatic breast cancer.

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Intraductal Papillary Mucinous Neoplasms of the Pancreas With Anomalous Union of the Pancreaticobiliary Ducts

To the Editor:

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a well-characterized group of intraductal mucin-producing cystic neoplasms of the pancreas, being reported with increasing frequency.¹ IPMN has a spectrum of cellular atypia ranging from adenoma to invasive carcinoma. However, the etiologic risk factors and pathogenesis remain to be defined. Anomalous union of the pancreaticobiliary ducts (AUPBD) is defined as union of common bile duct and pancreatic duct outside the duodenum and is usually characterized by a long common chan-

nel.² AUPBD has been regarded as a predisposing factor to various pancreaticobiliary disorders such as choledochal cyst,² biliary cancer,³ and pancreatitis.⁴ However, evidence of association between AUPBD and pancreatic neoplasms is limited.⁴ We experienced 3 cases of IPMNs associated with AUPBD.

CASE 1

A 58-year-old man was referred to our hospital because of a pancreatic mass detected on abdominal computed tomography (CT). The patient had a recurrent history of pancreatitis. Abdominal CT revealed a cystic mass in the body of the pancreas, with dilatation of adjacent main pancreatic duct. On magnetic resonance cholangiopancreatography (MRCP), in addition to the cystic mass on the pancreas, a biliary-pancreatic common channel (Kimura type II) measuring about 15 mm in length was seen (Fig. 1A). The patient underwent a distal pancreatectomy with splenectomy. A cystic mass measuring 2 × 1.5 × 1 cm communicating with the main pancreatic duct was seen in the pancreatic body. Histologically, tall columnar mucin-containing epithelial cells with moderate dysplasia lining the dilated ducts were seen. The epithelium formed papillary structures. The final diagnosis was IPMN with moderate dysplasia.

CASE 2

A 64-year-old man was admitted to our hospital because of a pancreatic mass. A diagnosis of cystic neoplasm of the pancreas had been made 7 years earlier by ultrasonography during a routine checkup. He declined surgical intervention of the mass and had been regularly followed up. A cystic mass was seen in the head of the pancreas with dilatation of the pancreatic duct on CT. The patient underwent a pylorus-preserving pancreaticoduodenectomy. A cystic mass measuring 2.5 × 1.5 × 1.5 cm was involving the head and the uncinate process of the pancreas. A pancreatico-biliary type (Kimura type I) AUPBD could be seen (Fig. 1B). Histologically, the tumor was IPMN with moderate dysplasia.

CASE 3

A 50-year-old woman was admitted to our hospital because of jaundice that had begun 1 week earlier. The patient had undergone a cholecystectomy with wedge resection of the liver and dissection of lymph nodes 8 years earlier because of gallbladder cancer. Intraoperative cholangiography

revealed an AUPBD. The patient had been followed up regularly, without evidence of cancer recurrence. Physical examination was unremarkable except for jaundice and a previous operative scar of the abdomen. Her total bilirubin level was 6.2 mg/dL. CT of the abdomen revealed a mass with rim-like peripheral enhancement in the common bile duct and dilatation of the main pancreatic duct. Endoscopic retrograde nasobiliary drainage was performed for the relief of jaundice. Ten days after endoscopic retrograde nasobiliary drainage, MRCP was performed, revealing a filling defect in the proximal main pancreatic duct and dilatation of the upstream main pancreatic duct. The filling defect was compressing common bile duct and a pancreatico-biliary type (Kimura type I) AUPBD was noticed.

The patient underwent a pylorus-preserving pancreaticoduodenectomy. Grossly, a polypoid mass measuring 1.2 × 1.0 × 1.0 cm was seen in the main pancreatic duct. AUPBD was also seen. Histologically, the tumor was a papillary carcinoma invading parenchyma of the pancreas (Fig. 1C). The final diagnosis was invasive intraductal papillary mucinous carcinoma of the pancreas with scant mucin production.

DISCUSSION

From January 1993 to December 2004, a total of 91 patients were pathologically confirmed of IPMN in our institution. Of the 91 patients, 3 patients had AUPBD. Two patients had only IPMN, whereas one patient (case 3) had gallbladder cancer 8 years before the diagnosis of IPMN. The concept of mucin-producing neoplasms of the pancreas was first proposed in 1982 by Ohhashi et al.⁵ IPMNs have been reported with increasing frequency in recent years.¹ Improved imaging of the pancreas, increased awareness and understanding of the disease, and a real increase in the incidence may explain such increase in epidemiological expansion.⁶ AUPBD is a rare condition that predisposes to various pancreaticobiliary disorders. In a nationwide study from South Korea that enrolled 10,243 patients who underwent ERCP during a period of 40 months, 740 patients were considered suitable for evaluation of AUPBD. Of these patients, 30 patients had AUPBD.⁷ The gallbladder cancer diagnosed 8 years earlier in case 3 may be attributed to the AUPBD. Because the hydropressure within the pancreatic

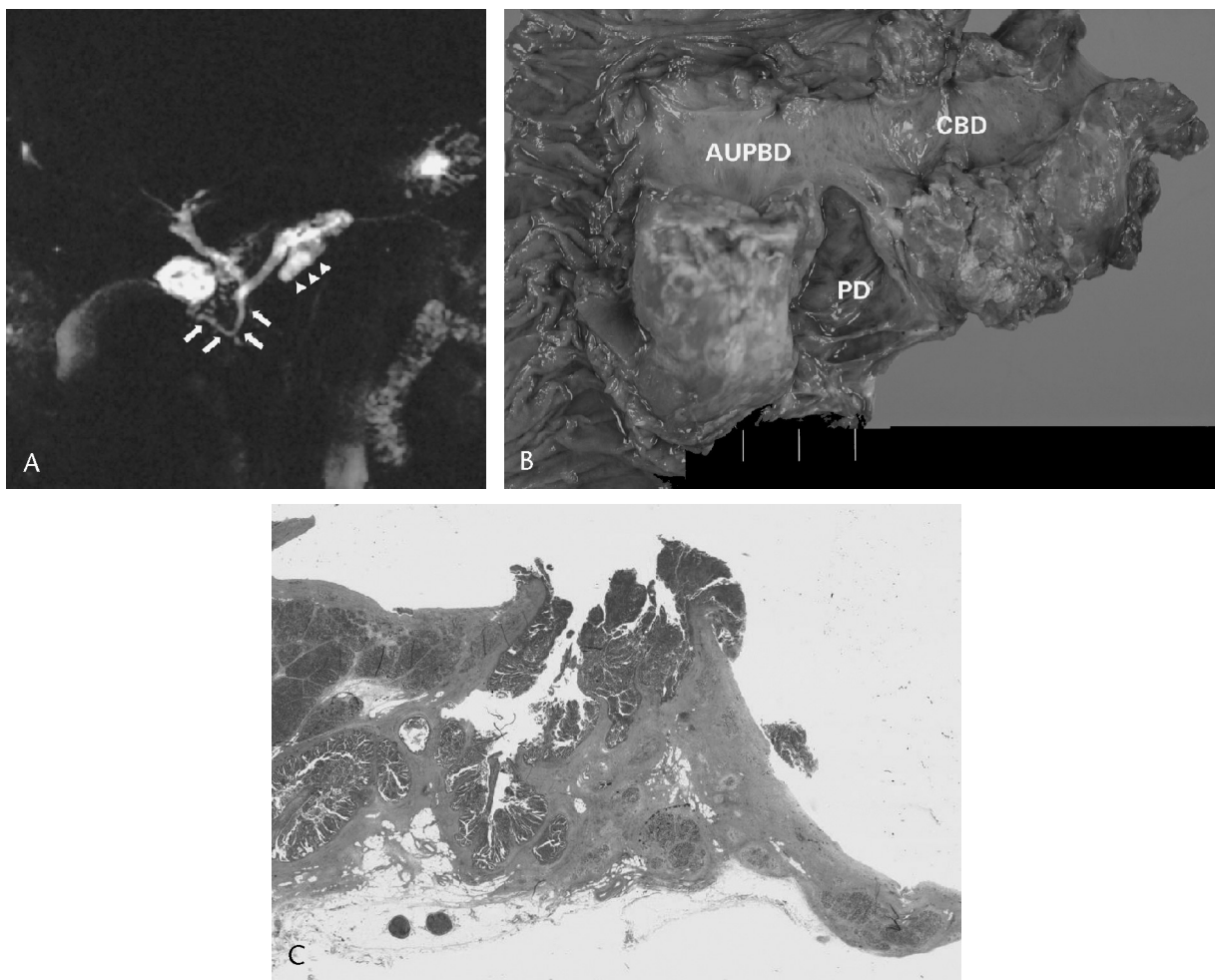


FIGURE 1. A, MRCP of case 1 demonstrating a biliary-pancreatic AUPBD (arrows). A cystic mass is seen at the body of the pancreas (arrowheads). B, Gross specimen of case 2. A pancreatico-biliary type AUPBD is seen on the resected specimen. Each segment on the ruler indicates 10 mm. CBD indicates common bile duct; PD, pancreatic duct. C, Photomicrograph of the resected specimen of case 3. The tumor cells are forming papillary structures and invading parenchyma of the pancreas (hematoxylin-eosin stain, original magnification $\times 1$).

duct is higher than that within the bile duct,⁸ bile reflux into the pancreatic duct may be unusual. However, bile may reflux into the pancreatic duct in patients with AUPBD in some situations, such as bile stasis in the choledochal cyst or common channel and cholangitis, activating pancreatic enzymes and causing pancreatitis. But whether the IPMNs can be attributed to AUPBD remains a question. A few cases of pancreatic ductal adenocarcinoma with AUPBD have been reported.^{4,9} There is only one report of IPMN with AUPBD to date.¹⁰ Relationship between AUPBD and pancreatic ductal adenocarcinoma or IPMN still remains to be defined. It may be a coincidental occurrence of an anomaly and a disease. It is also

possible that biliopancreatic reflux causes pancreatic ductal adenocarcinoma or IPMN.

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