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【 CASE REPORT 】

Mucinous Cystadenocarcinoma of the Pancreas with Cyst Infection in a Male Patient

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Abstract:
Follow-up computed tomography revealed a 40-mm pancreatic tail cyst in a 59-year-old man with type 1 diabetes mellitus. An intraductal papillary mucinous neoplasm was suspected; mucinous cystic neoplasm (MCN) was not considered because the patient was a man. During follow-up, cyst infection occurred but was improved by conservative treatment. At the 24-month follow up examination, cyst nodules had developed, corresponding to an increase in the carbohydrate antigen 19-9 level. Mucinous cystadenocarcinoma (MCC) was diagnosed pathologically based on distal pancreatectomy. A diagnosis of male MCN/MCC is often delayed, which may lead to a poor prognosis. MCN infection is also rare and poorly recognized. We observed an atypical male case of MCN/MCC.

Key words: pancreatic cancer, MCN, MCC, cyst in cyst, male

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Introduction

Mucinous cystic neoplasm (MCN) of the pancreas was first reported by Compagno et al. in 1978 (1). MCN is a relatively rare pancreatic cyst tumor that accounts for 2-5% of exocrine tumors and is predominately found in the body and tail of the pancreas in middle-aged women (2). Morphologically, MCN shows both unilocular and multilocular lesions with a thick fibrous capsule. A small cyst inside the main cyst is observed, which is referred to as "cyst in cyst." This is a useful feature for diagnosing MCN morphologically based on imaging studies. Regarding the pathology of MCN, ovarian-like stroma positive for estrogen receptor (ER) and progesterone receptor (PgR) is mandatory for the diagnosis. As such, MCN is very rare in men. Surgical resection is recommended in all cases of MCN because adenocarcinoma frequently occurs (3). However, a preoperative diagnosis of atypical cases, such as in men and cases of cyst infection, may be more difficult.

Case Report

We herein report a 59-year-old man with mucinous cystadenocarcinoma (MCC). His medical history included type 1 diabetes mellitus, angina pectoris, calculous cholecystitis, and acute pancreatitis due to alcohol consumption. His drinking history consisted of 700 mL of beer daily. There was no history of smoking or allergy. He had no symptoms at the initial diagnosis, and a blood test revealed only slight anemia (Table 1). Computed tomography (CT) revealed a 40-mm multi-locular cyst on the pancreatic tail that did not contain an intra-cystic nodule or cyst. The cysts were adjacent to each other in a "cyst by cyst" manner, so it was diagnosed as an intraductal papillary mucinous neoplasm (IPMN) and followed (Fig. 1).

One year and 7 months after the initial diagnosis, cyst infection was suspected due to the presence of abdominal pain and peri-cystic fat stranding on CT (Fig. 2). The cyst infection improved through conservative treatment with antibiot-

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ics, and the patient was discharged on day 15. Although the cyst had not changed in diameter at two years and two months after the initial diagnosis, two new nodules were found inside the cyst. The nodules showed a low intensity on both T1- and T2-weighted magnetic resonance imaging (MRI) images and high intensity on diffusion-weighted imaging (DWI) (Fig. 3). Magnetic resonance cholangiopancreatography (MRCP) revealed no dilatation of the main pancreatic duct, which did not communicate with the cyst. A 13-mm nodule was found inside the cyst by contrast-enhanced abdominal ultrasonography (Fig. 4). Furthermore, the level of carbohydrate antigen (CA) 19-9 had also increased over time, and malignancy could not be ruled out (Fig. 5). A diagnosis of IPMC was considered preoperatively, and lymphoepithelial cyst (LEC), epidermoid cyst and dermoid cyst were considered as differential diagnoses. Pancreatic mucinous neoplasm was considered unlikely because the patient was a man.

Table 1. Laboratory Data.

Biochemistry			Complete blood count		
Alb	(g/dL)	4	WBC	(10^2/μL)	7.2
BUN	(mg/dL)	13.1	RBC	(10^4/μL)	441
Cre	(mg/dL)	0.76	Hb	(g/dL)	12.9
eGFR	(mL/min)	82.5	Plt	(104/μL)	21.2
Na	(mM/L)	145			
Cl	(mM/L)	109	Tumor maker		
K	(mM/L)	3.9	CA19-9	(U/mL)	9
AST	(IU/L)	13	CEA	(ng/mL)	4
ALT	(IU/L)	9	DU-PAN-2	(U/mL)	27
γGTP	(IU/L)	18	SPAN-1	(U/mL)	15.6

Alb: albumin, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, Na: natrium, Cl: chlorine, K: kalium, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: γ-glutamyl transpeptidase, WBC:white blood cell, RBC: red blood cell, Hb:hemoglobin, Plt: platelet, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, DUPAN-2: duke pancreatic monoclonal antigen type 2, Span-1: s-pancreas-1 antigen

After obtaining the patient's informed consent, distal pancreatectomy was performed two years and two months after the initial diagnosis. A macroscopic examination of the surgical specimen revealed a 32×28-mm cyst containing a papillary nodule (Fig. 6A). The cyst contained a copious amount of mucin, suggesting MCN or IPMN macroscopically. The level of mucus amylase was normal at 63 U/L, but the CA19-9 level in the cyst was high at 521 U/mL. Microscopically, the cyst had thick fibrous wall and a papillary-growing tumor inside (Fig. 6B). The tumor cells exhibited eosinophilic cytoplasm with irregularly spaced, enlarged and roundish nuclei (Fig. 6D). The tumor invasion was observed as tubular adenocarcinoma (Fig. 6E, F). The cyst wall contained abundant spindle-shaped stromal cells growing in fascicles, which were immunohistochemically positive for ER, PgR and smooth muscle actin (SMA), suggesting that they were ovarian-like stroma (Fig. 7). We also conducted a somatic mutation analysis of G-protein αs (*GNAS*) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), as described previously (4). We analyzed

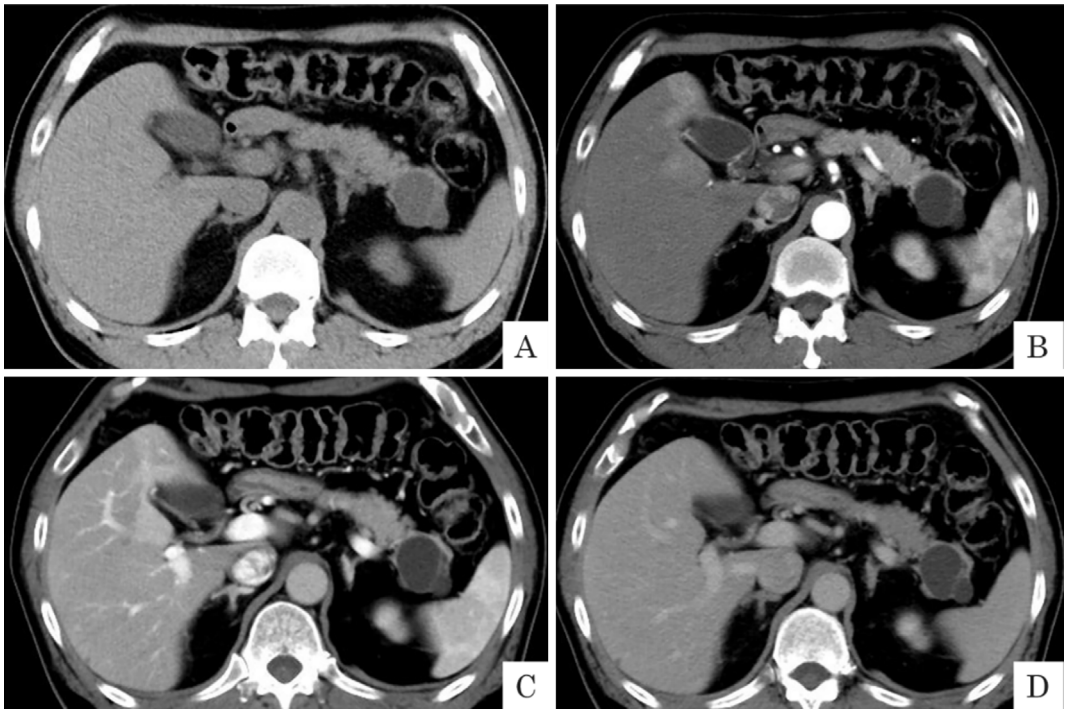

Figure 1. Initial CT images showing a 40-mm multilocular cyst on the pancreatic tail. A) Unenhanced CT image showing a multilocular cyst on the pancreatic tail. B) Arterial-phase CT image showing a multilocular cyst with no enhancement. C, D) Venous-phase CT image showing a multilocular cyst with slight contrast enhancement of the cyst septa.

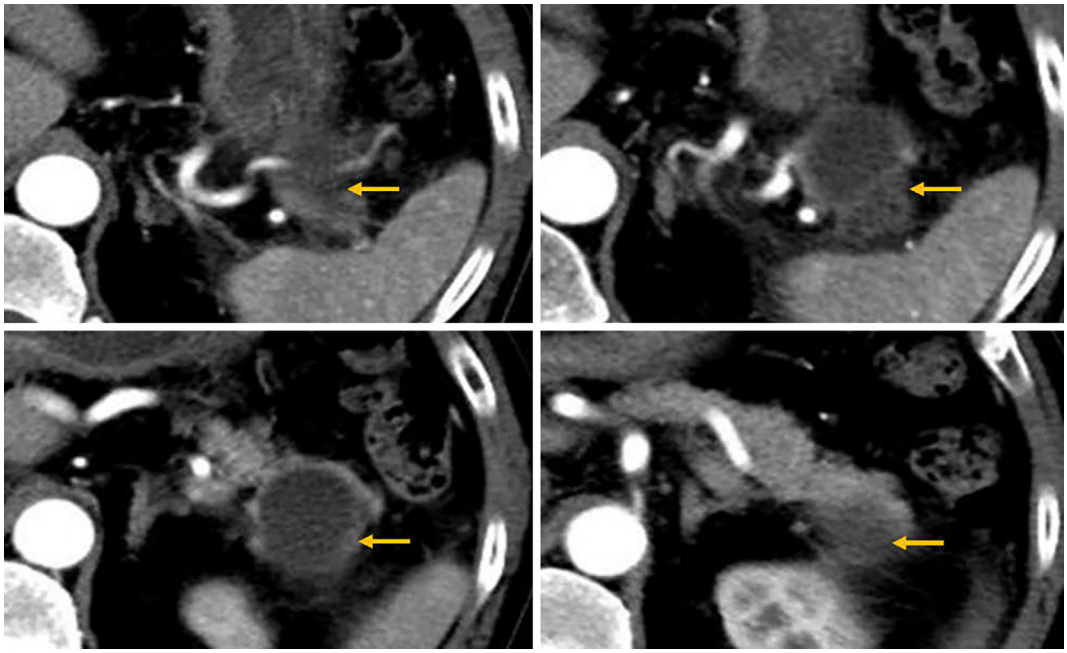

Figure 2. **CT image after 1 year and 7 months showing peri-cystic fat stranding (arrow).**

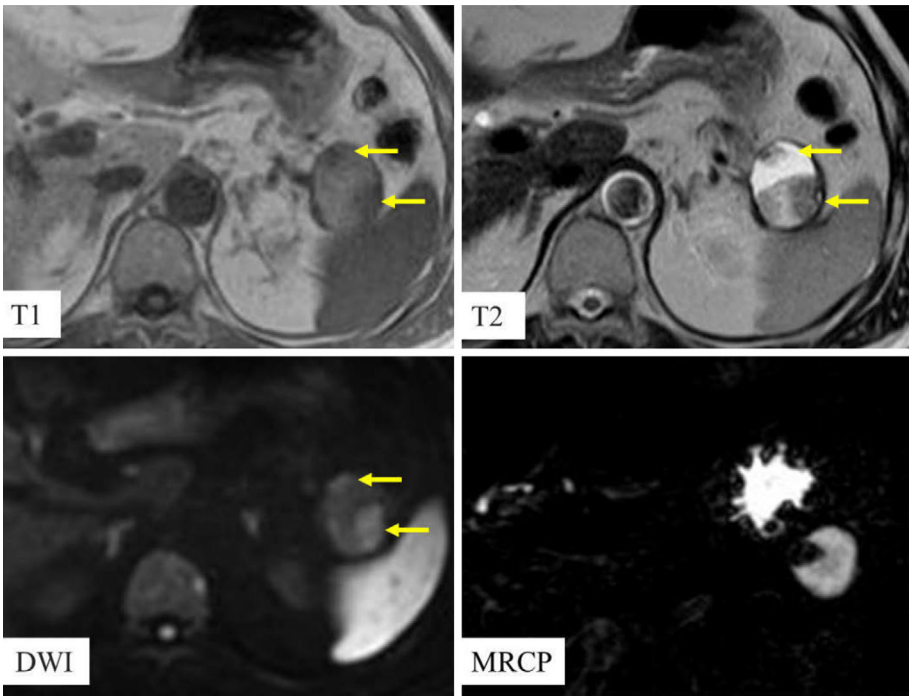

Figure 3. **MRI scan acquired before surgery. Nodules showing a low intensity on both T1WI and T2WI and a high intensity on DWI (arrow). DWI: diffusion weighted imaging, MRCP: magnetic resonance cholangiopancreatography**

the tumor cells of the papillary nodule using a pair of primers (i) for exon 8 of *GNAS*: TTGGTGAGATCCATTGACCTCAATTT (left) and TGAATGTCAAGAAACCATGATCTCTGTT (right), (ii) for exon 9 of *GNAS*: GACATTCACCCCAGTCCCTCTGG (left), GAACAGCCAAG CCCACAGCA (right), and (iii) for exon 2 of *KRAS*: CTGG TGGAGTATTTGATAGT (left), CTCATGAAAATGGTCAG AGAAACCT (right). It was revealed that this tumor was *GNAS* wild and *KRAS* mutated (G12D). These findings led to a diagnosis of invasive MCC of the pancreas (pT1bN0M 0, stage IA).

The patient was followed for 10 months after resection; during this period, recurrence did not occur. This study was approved by the Ethics Committee of Juntendo University, Tokyo, Japan, on August 2018 and was performed according to the Declaration of Helsinki.

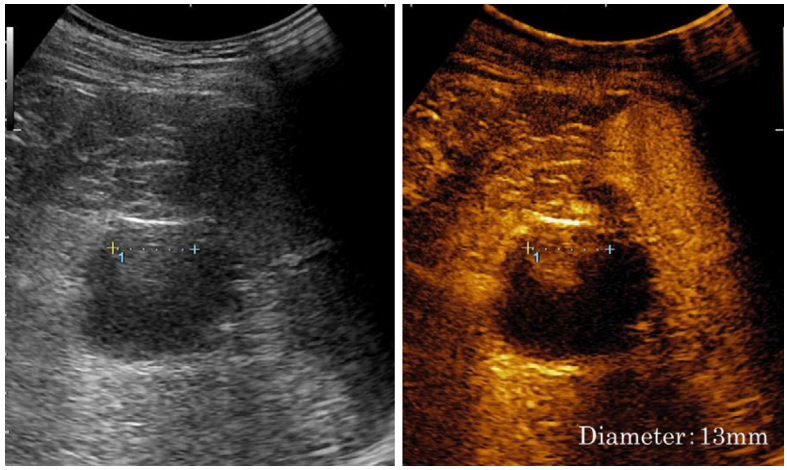

Figure 4. **Contrast-enhanced ultrasonography performed before surgery. The nodule is located in the cyst and shows enhancement.**

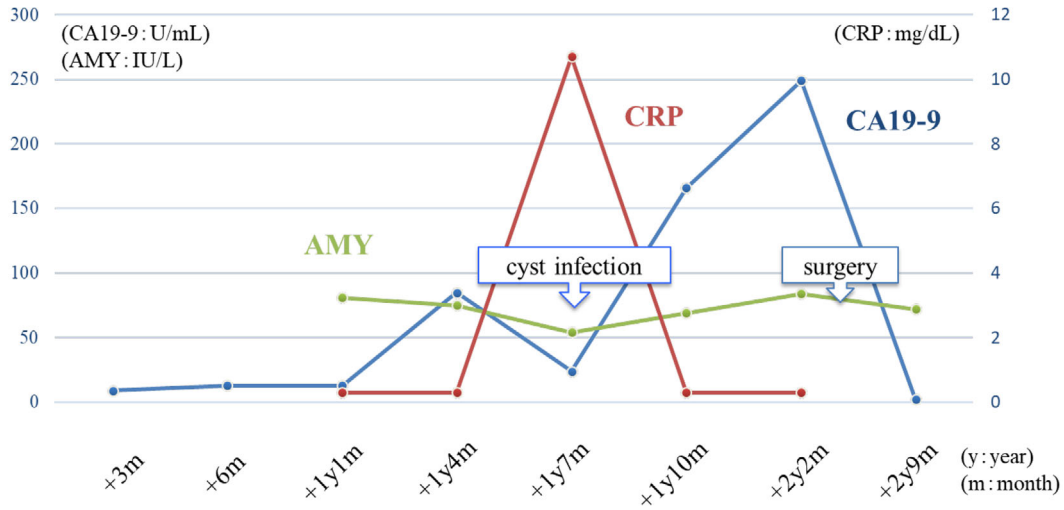

Figure 5. **Transitive graph of the amylase (AMY), CRP and CA19-9 levels. CRP: C-reactive protein, CA19-9: carbohydrate antigen 19-9**

Discussion

MCNs are multilocular mucin-producing tumors that tend to differentiate into gastric, intestinal, bile duct and pancreatic epithelia. The World Health Organization (WHO) defines MCNs as tumors with ovarian-like stroma in a thick cyst wall (5). Epidemiologically, MCNs often occur in the body and tail of the pancreas in women 40-50 years old (6). A few male cases of MCN (approximately 0-8.5% of all cases) have been reported (7-10). Regarding the malignant potential, a large cyst diameter and the presence of nodules therein have been identified as risk factors for malignant transformation of MCN (7). A review of surgically resected and unresected cases indicated that cysts less than 40 mm in size not containing a mural nodule tended to be considered benign and so were observed rather than resected (11, 12). However, the literature regarding MCNs should be interpreted with caution, as MCNs and IPMNs were considered to be the same entity before the International Consensus Guidelines were published in 2006 (13).

Fifteen male cases of MCN have been reported in PubMed, including the present case (Table 2) (7, 14-23). The mean age was 49 years, all cysts were located in the body or tail of the pancreas, and all had ovarian-like stroma. The mean size of the cysts was 45 mm, and 2 cysts (14%) had components of microinvasive carcinoma. Although there are few male cases of MCN in the literature, Ethun et al. reported a rate of adenocarcinoma and high-grade dysplasia in these cases of 39%, which is higher than that in women (24). They also speculated that the low detection rate of male MCN might be attributed to its high malignant potential in men (24). The mean tumor size in male cases of MCN, including the present patient, is 45 mm, which is smaller than that for all of the MCN cases reported by Yamao et al. (7).

Our patient was a middle-aged man, and the cyst was located in the tail of the pancreas. Additionally, the cyst di-

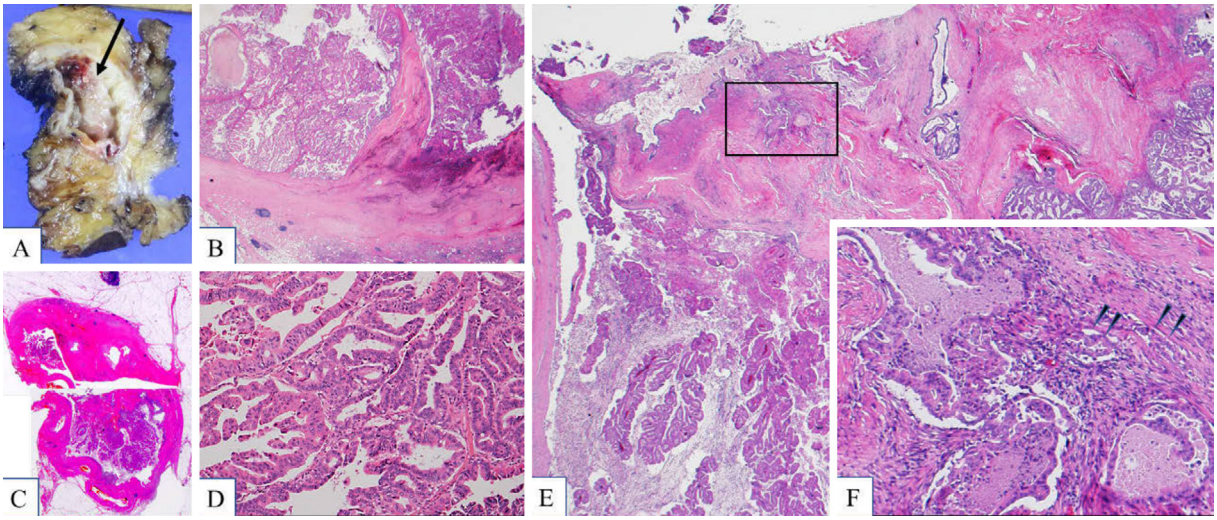

Figure 6. **Pathological findings. (A) The resected pancreas cyst revealed a papillary and whitish nodule inside (arrow). (B, C) Microscopically, the cyst had relatively thick fibrous wall and a nodule inside (B: original magnification ×12.5, C: Loupe image). (D) A closer view showed a papillary-growing tumor inside the cyst (original magnification ×100). (E, F) Invasive tubular adenocarcinoma was associated with MCN (arrowheads) (E: original magnification ×12.5, F: original magnification ×100). B-F: Hematoxylin and Eosin staining. MCN: mucinous cystic neoplasm**

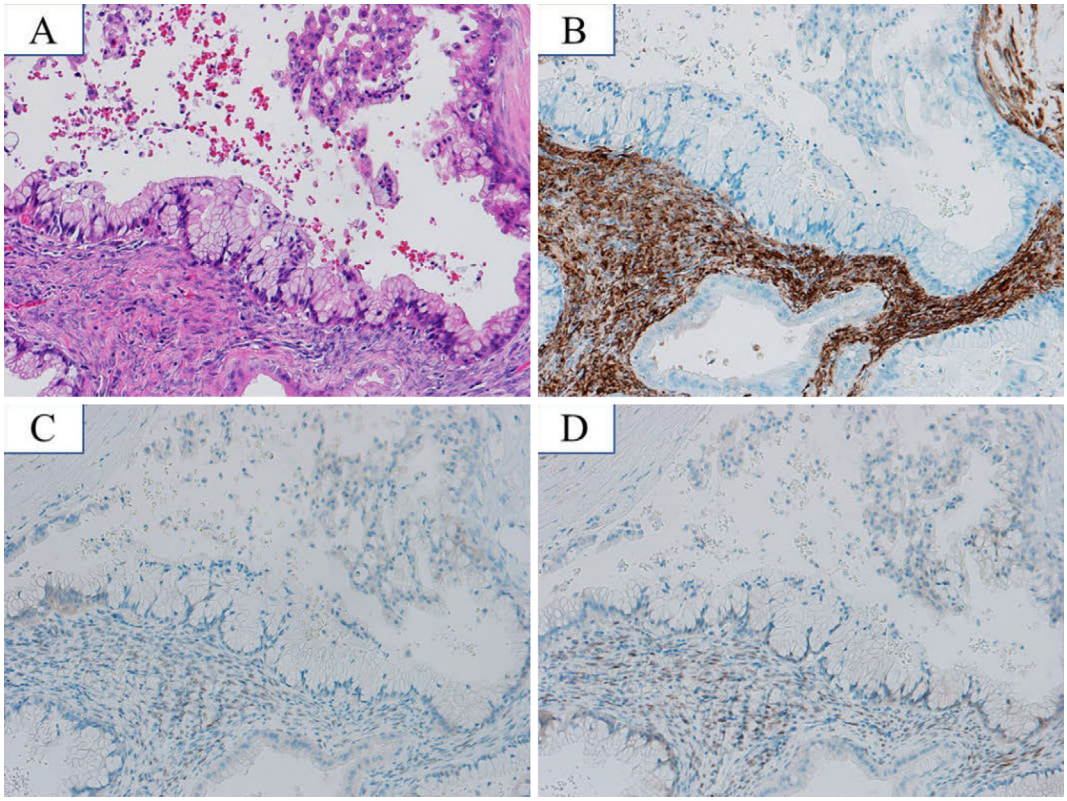

Figure 7. **Ovarian-like stroma. Spindle-shaped stromal cells were seen at the cyst wall and septum (A) and were immunohistochemically positive for SMA (B), ER (C) and PgR (D). A: Hematoxylin and Eosin staining, B: immunohistochemistry for SMA, C: immunohistochemistry for ER, D: immunohistochemistry for PgR (A-D: original magnification, ×100). SMA: smooth muscle actin, ER: estrogen receptor, PgR: progesterone receptor**

ameter did not increase over time, but nodules appeared on the cyst wall after the cyst had become infected. This case had an atypical clinical course due to the absence of a thick capsule-like ovarian-like stroma on CT and the occurrence of cyst infection. Furthermore, the tumor size did not increase over time and, because the patient was male, we did

Table 2. Fifteen Cases of Male MCNs have been Reported in PubMed Including This Case.

Reference numbers	Age	Location	Diameter (mm)	Clinical Symptoms	Preoperative Diagnosis	Surgical Procedure	Histopathology	CA19-9 U/mL (serum)
14	43	Tail	40	Weight Loss	Pseudocyst	SPDP	Adenoma	N/A
15	-	-	-	-	-	-	Adenoma	N/A
16	73	Tail	60	no	Epidermoid Cyst	DP	Adenoma	2
17	25	Tail	50	Abdominal Pain	BD-IPMN	DP	Adenoma	N/A
18	28	Body-Tail	40	Abdominal Pain	PDAC	SPDP	Adenoma	N/A
19	39	Tail	63	Back Pain	BD-IPMN	DP	Adenoma	N/A
7	26	Body-Tail	-	-	-	DP	Adenocarcinoma, invasive	N/A
	36	Body-Tail	-	-	-	DP	Adenoma	N/A
	72	Body-Tail	-	-	-	DP	Adenoma	N/A
20	65	Body-Tail	49	None	BD-IPMN	DP	Adenoma	N/A
21	48	Tail	47	None	Cystic Tumor	DP	Adenoma	N/A
22	55	Tail	30	Appetite Loss	-	DP	Adenoma	1,505
23	50	Tail	51	None	BD-IPMN	DP	Adenoma	N/A
	73	Tail	25	None	LEC	Spleen-Preserving DP SSPPD	Adenoma	156
This case	59	Tail	40	None	IPMN	DP	Adenocarcinoma, invasive	249

SPDP: spleen-preserving distal pancreatectomy, DP: distal pancreatectomy, BD-IPMN: branch-duct intaductal papillary mucinous neoplasm, PDAC: pancreatic ductal adenocarcinoma, LEC: lymphoepithelial cyst, SSPPD: subtotal stomach preserving pancreatoduodenectomy, N/A: not applicant

not suspect MCN. In rare cases of a large size tumor and cyst infection, drainage or surgical resection is typically employed, but this case improved with antibiotic therapy. Regarding IPMNs, cyst infection may indicate high-grade dysplasia, where an association between symptom severity and malignancy of IPMN has been demonstrated (25). Although inflammatory reactions can be identified based on an elevated C-reactive protein (CRP) level, hyperamylasemia was not evident in this case. We also found a *KRAS* mutation at codon 12 (exon 2), whereas the *GNAS* at codon 201 (exon 8) and exon 9 were wild-type. MCNs have been reported to frequently harbor *KRAS* mutations at codon 12 but not *GNAS* mutations (26-28). The molecular status of the present case therefore seems compatible with MCN.

We considered three sets of international guidelines pertaining to the treatment of male cases of MCN. According to the guidelines of the International Association of Pancreatology (IAP), MCN should be surgically resected at the time of the definitive diagnosis (6). The European Society for Medical Oncology (ESMO) guidelines state that although surgery is the treatment of choice, tumors <40 mm in diameter can be closely observed instead (29). In the American Gastroenterological Association (AGA) guidelines, IPMN and MCN are not distinguished. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is used in MCN cases involving pancreatic duct dilation, a cyst size ≥3 cm, and the presence of nodules in the cyst (30). A high intensity of DWI helped diagnose some nodules in the cyst in the present case. However, Sandrasegaran et al. reported that the apparent diffusion coefficient (ADC) alone was not found to be useful for differentiating malignant from non-malignant lesions or IPMN from MCN (31). Additionally, that study included only nine cases of MCN; therefore, a large-scale study limited to MCN cases is needed. Recently, a multicenter Japanese study reported 5 factors with the potential to predict malignancy in MCN: age ≥56 years old, high serum carcinoembryonic antigen (CEA) and CA19-9 levels, tumor size ≥51 mm, and the presence of mural nodules (32). Regarding atypical cases of MCN, especially those involving men or small-sized nodules, a diagnosis using the IAP and ESMO guidelines is difficult. An early diagnosis is more important in men than in women because the rate of invasive carcinoma is higher in men than in women. In cases that are difficult to diagnose by imaging, EUS-FNA can be used, as described in the AGA guidelines; for this reason, the use of this diagnostic modality may increase in the future (30). The CA19-9 level in the cyst was high in this case; such tumor markers in the cyst fluid, as revealed by EUS-FNA, may facilitate the diagnosis (22).

The management of this case was complicated by not performing EUS or an EUS-FNA examination at the time of the initial diagnosis, as it is difficult to detect the cyst-in-cyst structure using other modalities. In Japan, most pancreatic cystic lesions are diagnosed based on imaging studies to avoid tumor cell dissemination.

In conclusion, we encountered a male case of MCN showing an atypical clinical course, including infection. The patient showed a poor prognosis due to the delayed diagno-

sis. The infection suggested a malignant lesions similar to IPMN.

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

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