

[CASE REPORT]

Coexisting Type 1 Autoimmune Pancreatitis and Mixed-type Intraductal Papillary Mucinous Neoplasm

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Abstract:

An 84-year-old man was referred to our hospital for a cystic lesion of the pancreatic head, swelling of the pancreatic tail and hilar biliary stricture, resulting in elevated liver enzyme levels. We suspected branch duct-type intraductal papillary mucinous neoplasm (IPMN) and type I autoimmune pancreatitis (AIP) associated with sclerosing cholangitis because of the high serum IgG4 levels. The main pancreatic duct on the tail side of the AIP lesion was moderately dilated. Although the biliary stricture and pancreatic swelling improved after prednisolone treatment, the pancreatic enzyme levels increased rapidly. The entire main pancreatic duct exhibited remarkable dilatation, which led to the diagnosis of mixed-type IPMN. The clinical characteristics of IPMN in the main pancreatic duct appear to have been initially masked by AIP.

Key words: intraductal papillary mucinous neoplasm (IPMN), autoimmune pancreatitis (AIP), sclerosing cholangitis, IgG4

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Introduction

Some studies (1-3) have highlighted the pathological findings of coexisting intraductal papillary mucinous neoplasm (IPMN) and type 1 autoimmune pancreatitis (AIP). However, whether or not the two diseases are closely associated remains unclear.

Thus far, several case reports (4-6) have described the coexistence of branch-duct IPMN (BD-IPMN) and AIP; however, the coexistence of AIP and main-duct IPMN (MD-IPMN) or mixed-type IPMN (MD+BD-IPMN) has been scarcely reported. MD-IPMN is characterized by the marked dilatation of the main pancreatic duct (MPD), whereas narrowing of the MPD is typical of AIP. The imaging findings in cases where these two diseases coexist are therefore curious.

We herein report a case of type I AIP associated with mixed-type IPMN that showed an interesting clinical course and imaging findings.

Case Report

An 84-year-old man without severe illness other than hypertension and hyperlipidemia underwent periodic health examinations. Hepatobiliary enzymes were elevated, and the patient first visited another hospital. Computed tomography (CT) revealed swelling of the pancreatic tail with a capsule-like rim. Areas of low density and isodensity were observed in the arterial and portal phases, respectively, which suggested an inflammatory change rather than pancreatic cancer (Fig. 1). In other parts of the swollen pancreatic tail, the MPD was mild to moderately dilated, and a cystic lesion 22 mm in diameter was observed in the pancreatic head. Intrahepatic bile ducts in the hepatic left lobe were mildly dilated. The patient's serum IgG and IgG4 levels were high.

The patient was referred to our hospital for further examinations and treatment. His laboratory data in the sera were as follows: total bilirubin, 0.7 mg/dL; aspartate aminotransferase, 96 U/L; alanine aminotransferase, 110 U/L; alkaline phosphatase, 999 U/L; γ -glutamyl transpeptidase, 1,403 U/L;

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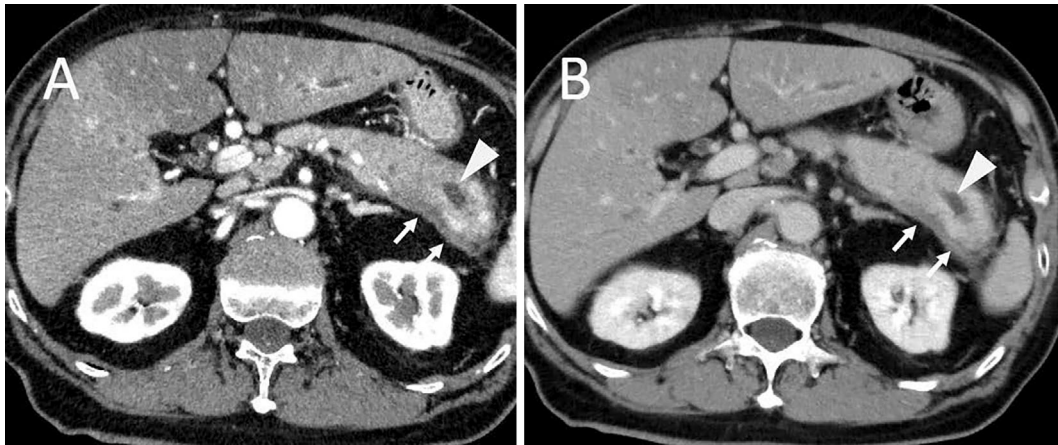


Figure 1. A: Arterial phase. Swelling in the pancreatic tail is visible as an area of low density on CT. B: The portal phase shows an isodense area. A capsule-like rim surrounding the swollen pancreas (arrows) and MPD dilatation (arrowhead) is visible. CT: computed tomography, MPD: main pancreatic duct

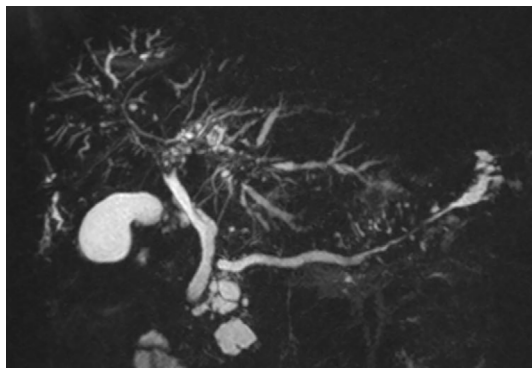


Figure 2. MRCP reveals severe hilar biliary stricture, a multilocular cystic lesion in the pancreatic head, and narrowing of the MPD in the pancreatic tail. On the tail side of the narrowing, MPD dilatation is only slightly noticeable (7 mm). The diameter of the MPD in the pancreatic body is 5 mm. MRCP: magnetic resonance cholangiopancreatography, MPD: main pancreatic duct

amylase, 203 U/L; lipase, 320 U/L; hemoglobin A1c, 6.4%; IgG, 2,933 mg/dL; IgG4, 504 mg/dL; carcinoembryonic antigen, 1.9 ng/mL (normal: <5.0 ng/mL); and cancer antigen 19-9, 23 U/mL (normal: <37 U/mL). Magnetic resonance cholangiopancreatography (MRCP) revealed severe hilar stricture, narrowing of the MPD in the tail, and a multilocular cyst in the pancreatic head (Fig. 2). On the tail side of the swelling, MPD dilatation was only somewhat noticeable (7 mm); thus, we regarded it as poststenotic dilatation. The diameter of the MPD in the body was 5 mm.

The extent of hilar biliary stricture resulted in the abandonment of endoscopic retrograde cholangiography to avoid cholangitis. An endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) for pancreatic tail swelling was performed using a 19-G needle (Expect™; Boston Scientific, Marlborough, USA). Although the specimen was fibrotic, plasmacyte infiltration was scarce (Fig. 3). No find-

ings suggested the presence of malignancy. Although the pathological findings were not typical, we diagnosed this case as definite type 1 AIP associated with IgG4-related sclerosing cholangitis based on the international consensus diagnostic criteria for AIP (7). The cystic lesion of the pancreatic head was regarded as BD-IPMN.

We administered prednisolone at a dose of 30 mg/day. Insulin administration was also initiated for the associated diabetes mellitus aggravated by steroid use. On day 7 after treatment initiation, hepatobiliary enzyme levels were decreased; however, the pancreatic enzyme levels were markedly increased (amylase 899 U/L, lipase 3,039 U/L) despite a lack of symptoms. MRCP revealed an improvement in hilar biliary stricture and the dilatation of the entire MPD, especially in the tail (Fig. 4); the findings on CT were similar.

Although the patient did not report abdominal pain, oral feeding was discontinued because of excessively high pancreatic enzyme levels. Pancreatic enzyme levels subsequently decreased; however, after the resumption of meals, the levels again increased. The maximum levels of amylase and lipase were 2,517 U/L, and 6,200 U/L, respectively (day 20). This process continued for six weeks; however, ultimately, the pancreatic enzyme levels returned to normal or were slightly elevated.

One month after steroid treatment, MRCP and CT showed further progression of MPD dilatation, although biliary stricture and pancreatic tail swelling notably improved (Fig. 5). As mixed-type IPMN was suspected, endoscopic retrograde cholangiopancreatography was performed on day 32. Mucus discharge from the enlarged orifice of the major papilla was confirmed. Intraductal ultrasonography revealed a large amount of mucus in the MPD; however, a protruded lesion was not visible (Fig. 6). Pancreatic juice cytology resulted in a class II diagnosis.

Although we did not obtain pathological evidence of malignancy, surgery appeared to be appropriate for MD or mixed-type IPMN (8). However, the patient refused surgery

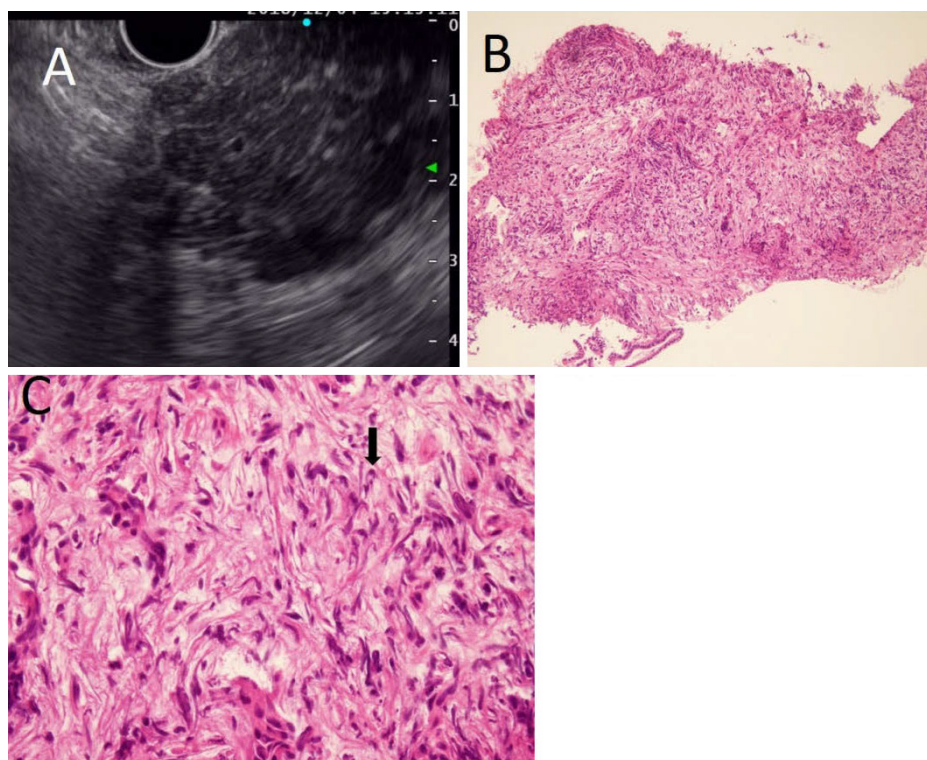


Figure 3. A: EUS reveals pancreatic swelling as a hypoechoic area with scattered hyperechoic spots, which is consistent with AIP. B: The specimen obtained by EUS-FNAB was fibrotic; however, lymphoplasmacytic infiltration is scarce [Hematoxylin and Eosin (H&E) staining, $\times 40$]. There is no definite finding suggestive of storiform fibrosis or obliterative phlebitis. IgG4 immunostaining is performed; however, significant findings are not obtained, likely due to the small number of lymphoplasmacytes. C: A single plasmacyte (arrow) is visible in this view (H&E staining, $\times 100$). EUS: endoscopic ultrasound, AIP: autoimmune pancreatitis, FNAB: fine-needle aspiration biopsy

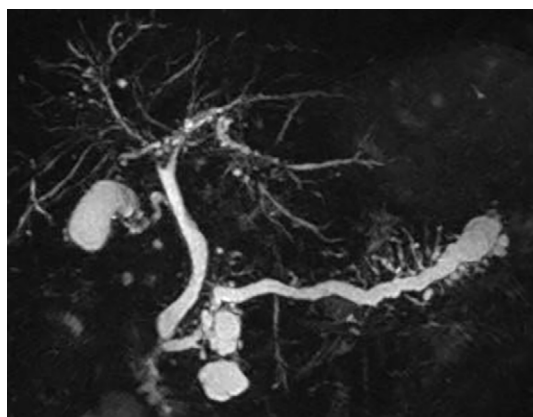


Figure 4. MRCP (day 7: 7 days after initiating steroid treatment) reveals the improvement of hilar biliary stricture and the dilatation of the MPD, especially in the pancreatic tail. The diameter of the MPD in the body and tail is 7 and 13 mm, respectively. MRCP: magnetic resonance cholangiopancreatography, MPD: main pancreatic duct

because of his old age, frailness, and lack of symptoms; therefore, he was followed up with prednisolone maintenance therapy at a dose of 5 mg/day for AIP only. Eighteen months later, arterial-phase CT revealed a low-density area 27 mm in diameter in the pancreatic neck. This lesion be-

came isodense in the portal phase (Fig. 7). We again performed an EUS-FNAB; the result was similar to that of the first EUS-FNAB, showing fibrotic tissue with limited lymphoplasmacytic infiltration. Although AIP recurrence was suspected, the patient refused an increase in the dose of prednisolone because of a lack of symptoms, and careful observation has been continued.

Discussion

Exactly describing the prevalence of pancreatic cystic lesions remains challenging because it varies among studies, likely due to differences in modalities, definitions of cystic lesions, and study subjects' characteristics. For reference, 1 study at an institute of preventive medical care using magnetic resonance imaging that analyzed 2,803 people found that the prevalence of pancreatic cysts in individuals without a history of symptoms of pancreatic disease was approximately 2.5% (0.15% in the case of cysts exceeding 2 cm in diameter); this rate increased with age, reaching 10% in persons ≥ 70 years old (9). Another similar study analyzing 5,296 cases reported a prevalence rate of 13.7% for pancreatic cysts (10). In both studies, the majority of the cystic lesions appeared to be BD-IPMNs. The exact prevalence of MD-IPMN is also unknown; however, most cases of IPMN

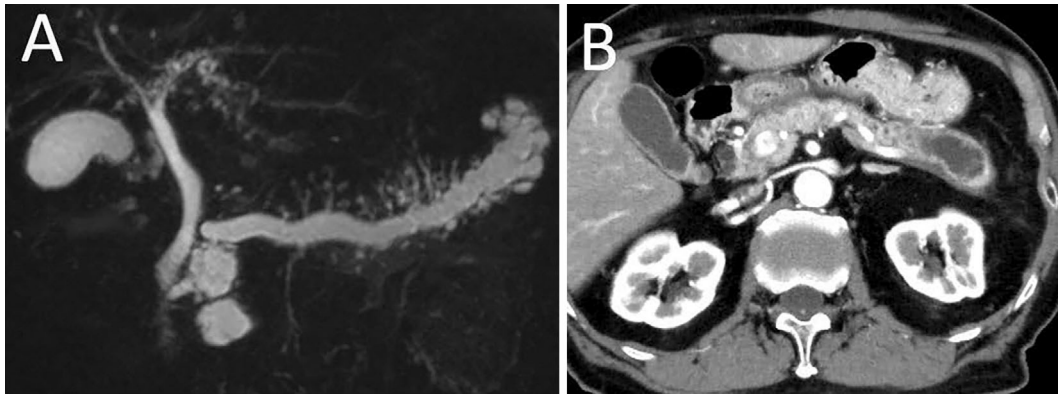


Figure 5. A: MRCP (day 30) reveals further improvement of the hilar biliary stricture and further aggravation of MPD dilatation. The diameter of the MPD in the body and tail is 11 and 14 mm, respectively. B: CT (day 30) reveals the disappearance of the pancreatic swelling and the aggravation of MPD dilatation. MRCP: magnetic resonance cholangiopancreatography, CT: computed tomography, MPD: main pancreatic duct

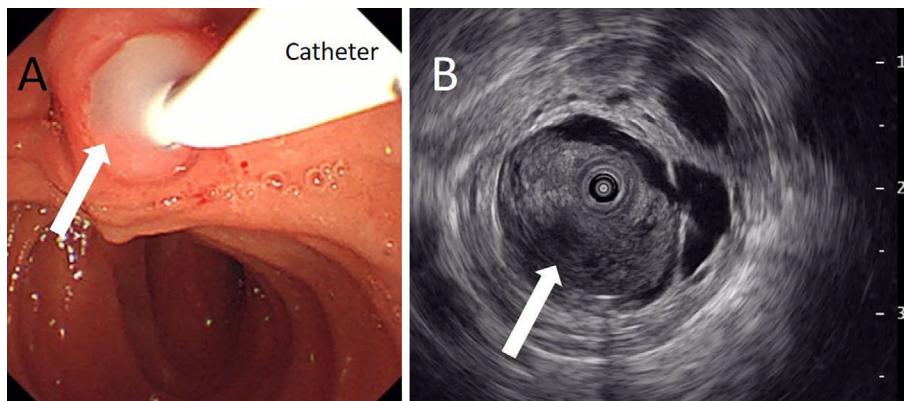


Figure 6. A: Mucus (arrow) discharge is visible from the enlarged orifice of the major papilla. B: IDUS of the MPD reveals a large amount of mucus (arrow); however, no protruding lesion is observed. IDUS: intraductal ultrasonography, MPD: main pancreatic duct

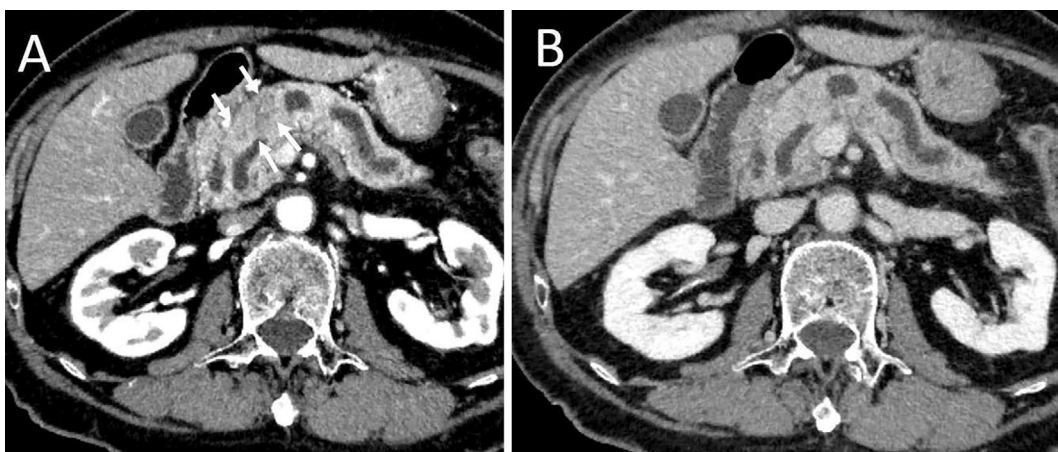


Figure 7. A: Arterial phase. An area of low density with a diameter of 27 mm is observed at the pancreatic neck on CT. B: The portal phase reveals an area of isodensity. CT: computed tomography

appear to be BD-IPMN. According to 2 reports from the University of Tokyo, <2% of individuals with IPMN had dilated MPDs (≥ 10 mm) (10, 11).

The prevalence rate of AIP in Japan is 0.0046% according to a 2011 national survey (12). Thus, in theory, the coexistence of AIP and MD or mixed-type IPMN is expected to

be exceptionally rare, and indeed, only a few studies have reported the coexistence of AIP and IPMN (4-6). IPMN was BD type in most previous reports. Tabata et al. previously reported the only case of the coexistence of AIP and mixed-type IPMN (1). In their case, segmental stenosis of MPD was confirmed by endoscopic retrograde cholangiopancreatography on the proximal side of the dilated MPD due to IPMN. Although pancreatic swelling or a mass lesion suggestive of AIP was not recognized, the serum IgG4 level was very high (627 mg/dL). Pancreatic juice cytology was negative; however, distal pancreatectomy was performed because pancreatic ductal cancer with IPMN could not be completely ruled out. Thus, AIP was eventually diagnosed by pathological findings. To our knowledge, our case is the first reported occurrence of coexisting AIP and MD or mixed-type IPMN diagnosed without surgical pancreatic resection.

Upon encountering this case, we suspected AIP associated with BD-IPMN because of the presence of a multilocular cystic lesion in the pancreatic head. As we did not consider the possibility of mixed-type IPMN, the dilatation of the MPD on the tail side of the AIP lesion was assumed to be poststenotic, although it exceeded the extent for AIP, in which poststenotic dilatation is usually <5 mm in diameter (13).

One week after initiating prednisolone treatment, pancreatic enzymes levels increased rapidly despite improvements in the levels of hepatobiliary enzymes, which was unique to this case. We suspected pancreatitis had occurred due to steroid use or as a complication of the EUS-FNAB that had been performed two days before starting prednisolone; however, the MRCP and CT findings led us to suspect mixed-type IPMN. Since the dilatation of the MPD was more remarkable in the pancreatic tail than in the pancreatic body and head, the main lesion appeared to occur in the tail.

Pancreatic enzyme levels were likely elevated by the occlusion of the MPD with mucus. As AIP was alleviated, the activity of IPMN in the MPD might have been intensified. Despite elevated pancreatic enzyme levels, the patient did not show any symptoms. Even after the patient was discharged, we occasionally observed elevation of the pancreatic enzyme levels; however, he has never complained of symptoms.

The treatment for MD-IPMN with a dilated MPD (≥ 10 mm) is pancreatectomy in principle, regardless of the findings of pancreatic juice cytology (8). The dilatation of the MPD was more noticeable in the pancreatic tail than pancreatic head and body in our case, whereas a cystic lesion was observed in the pancreatic head. Total pancreatectomy might have been an option; however, we considered this approach to be too invasive given the patient's old age (8, 14, 15). Had the patient not refused surgical treatment, we would have performed distal pancreatectomy.

The diagnosis of this case was challenging because AIP masked the imaging findings characteristic of IPMN in the MPD. It is important to take note of atypical MPD dilatation when suspecting AIP, as well as the paradoxical transition of the pancreatic enzymes after steroid treatment.

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

References

1. Tabata T, Kamisawa T, Hara S, et al. Intraductal papillary mucinous neoplasm of the pancreas and IgG4-related disease: A coincidental association. *Pancreatol* **13**: 379-383, 2013.
2. Hedayat AA, Lisovsky M, Suriawinata AA, et al. Association of IgG4 response and autoimmune pancreatitis with intraductal papillary-mucinous neoplasms. *Pancreatol* **17**: 263-266, 2017.
3. Bateman AC, Culver EL, Sommerlad M, et al. Intraduct papillary mucinous neoplasm of the pancreas: A tumour linked with IgG4-related disease? *J Clin Pathol* **66**: 671-675, 2013.
4. Urata T, Naito Y, Izumi Y, et al. Localized type 1 autoimmune pancreatitis superimposed upon preexisting intraductal papillary mucinous neoplasms. *World J Gastroenterol* **19**: 9127-9132, 2013.
5. Koshita S, Noda Y, Ito K, et al. Branch duct intraductal papillary mucinous neoplasms of the pancreas involving type 1 localized autoimmune pancreatitis with normal serum IgG4 levels successfully diagnosed by endoscopic ultrasound-guided fine-needle aspiration and treated without pancreatic surgery. *Intern Med* **56**: 1163-1167, 2017.
6. Naitoh I, Nakazawa T, Notohara K, et al. Intraductal papillary mucinous neoplasm associated with autoimmune pancreatitis. *Pancreas* **42**: 552-554, 2013.
7. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: Guidelines of the International Association of Pancreatology. *Pancreas* **40**: 352-358, 2011.
8. Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatol* **17**: 738-753, 2017.
9. de Jong K, Nio CY, Mearadji B, et al. Disappointing interobserver agreement among radiologists for a classifying diagnosis of pancreatic cysts using magnetic resonance imaging. *Pancreas* **41**: 278-282, 2012.
10. Mizuno S, Isayama H, Nakai Y, et al. Prevalence of pancreatic cystic lesions is associated with diabetes mellitus and obesity: An analysis of 5296 individuals who underwent a preventive medical examination. *Pancreas* **46**: 801-805, 2017.
11. Oyama H, Tada M, Takagi K, Tateishi K, et al. Long-term risk of malignancy in branch-duct intraductal papillary mucinous neoplasms. *Gastroenterology* **158**: 226-237, 2020.
12. Kanno A, Nishimori I, Masamune A, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan. *Pancreas* **41**: 835-839, 2012.
13. Wakabayashi T, Kawaura Y, Satomura Y, et al. Clinical study of chronic pancreatitis with focal irregular narrowing of the main pancreatic duct and mass formation: Comparison with chronic pancreatitis showing diffuse irregular narrowing of the main pancreatic duct. *Pancreas* **25**: 283-9, 2002.
14. Crippa S, Tamburrino D, Partelli S, et al. Total pancreatectomy: Indications, different timing, and perioperative and long-term outcomes. *Surgery* **149**: 79-86, 2011.
15. Stauffer JA, Nguyen JH, Heckman MG, et al. Patient outcomes after total pancreatectomy: a single centre contemporary experience. *HPB (Oxford)* **11**: 483-492, 2009.

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