

[CASE REPORT]

A Diagnostically Challenging Case of Autoimmune Pancreatitis Due to Contamination of the Pathological Specimen with Early Gastric Cancer

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Abstract:

A 73-year-old man with worsened diabetes underwent abdominal computed tomography and was diagnosed with localized enlargement of the pancreatic tail. Based on the suspicion of autoimmune pancreatitis, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed. A cytologic examination showed findings suggestive of adenocarcinoma. Due to discrepancies between the imaging and pathological findings, esophagogastroduodenoscopy was performed. An extensive early gastric cancer lesion was detected in the posterior wall of the gastric corpus. It was therefore likely that puncturing through the tumor resulted in the contamination with cancer tissue. The possibility of a concomitant malignancy should be considered in EUS-FNA, and thorough examinations should be conducted.

Key words: autoimmune pancreatitis (AIP), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), gastric cancer

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Introduction

Autoimmune pancreatitis (AIP), which was first proposed by Yoshida et al. (1) in 1995, is now increasingly recognized as a new disease entity worldwide. According to the 2011 revised version of the diagnostic criteria, AIP can be categorized into definite, probable, and possible cases based on a combined assessment of imaging, hematological, and pathological findings, as well as extrapancreatic lesions and steroid options.

Suspected cases of AIP, especially those with localized pancreatic enlargement, should be differentiated from pancreatic cancer. Several recent case reports of AIP complicated by malignancy have led to an increase in focus on the association between these two conditions. We encountered a

case of AIP with localized pancreatic enlargement in which endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed to rule out pancreatic cancer but which led to an incorrect diagnosis due to contamination of the specimen with early gastric cancer tissue.

In the present study, we compared findings between surgical specimens of the stomach and pathological specimens collected by EUS-FNA and conducted a review of the literature concerning the association between AIP and malignancies.

Case Report

Patient: A 73-year-old man.

Chief complaint: Worsened diabetes control.

History of present illness: He had been prescribed oral

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Table. Laboratory Data.

Blood count		Biochemical examination			
WBC	7,030 / μ L	TP	7.4 g/dL	BUN	21 mg/dL
Hb	14.3 g/dL	Alb	4.1 g/dL	Cr	0.69 mg/dL
Plt	21.5×10^4 / μ L	T-Bil	0.74 mg/dL	Na	140 mEq/L
		AST	25 IU/L	K	4.3 mEq/L
		ALT	23 IU/L	Cl	102 mEq/L
Immune serological examination		LDH	201 IU/L	Ca	8.9 mg/dL
IgG	1,815 mg/dL	γ -GTP	22 IU/L	P	3.2 mg/dL
IgG4	398 mg/dL	ALP	170 IU/L	CRP	0.04 mg/dL
		Amy	107 IU/L	HbA1c	9.1 %
Tumor marker					
CA19-9	34.3 U/mL				
CEA	1.6 ng/mL				

WBC: white blood cells, Hb: hemoglobin, Plt: platelet, IgG: immunoglobulin G, IgG4: immunoglobulin G4, CA19-9: carbohydrate antigen 19-9, CEA: carcinoembryonic antigen, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ -GTP: γ -glutamyltranspeptidase, ALP: alkaline phosphatase, Amy: amylase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, HbA1c: hemoglobin A1c



Figure 1. Abdominal CT findings. Localized enlargement of the pancreatic tail was found, with a band-like rim surrounding the lesion observed at the 70- and 180-second locations. No capsule-like structure, dilatation of the main pancreatic duct, or tumorous lesion was observed. CT: computed tomography

antidiabetics for type 2 diabetes by his previous physician. With rapidly worsening diabetes control, as evidenced by a glycated hemoglobin A1c level of 10.1%, he underwent contrast-enhanced abdominal computed tomography (CT). CT revealed localized enlargement of the distal pancreatic body and fluid retention around the pancreas. Under suspicion of AIP, he was referred to our hospital for a detailed examination.

Medical history: His is currently on oral medications for type 2 diabetes, hypertension, and primary aldosteronism. The patient underwent surgery for right breast cancer at 69 years of age.

Family history: His father had gastric cancer.

Lifestyle: No history of smoking or drinking.

Present illness at the presentation: His height and weight were 166 cm and 65.9 kg, respectively. He had no yellow discoloration of the bulbar conjunctiva or abdominal tenderness. A surgical scar on the right chest and gynecomastia on the left chest were noted. Blood test results at the first presentation showed increased IgG of 1,815 mg/dL and IgG4 of

398 mg/dL. Carbohydrate antigen 19-9 and carcinoembryonic antigen levels were within normal ranges. A high fasting blood glucose level of 188 mg/dL and high HbA1c of 9.1% were noted (Table).

Abdominal CT findings (Fig. 1): Localized enlargement of the pancreatic tail with a band-like rim surrounding the lesion, with no clear capsular structure. No tumorous lesion was observed, nor was any dilatation of the main pancreatic duct noted.

Magnetic resonance cholangiopancreatography (MRCP) findings (Fig. 2): Slight dilatation of the main pancreatic duct was visualized in the head through to the body but not in the tail of the pancreas.

Endoscopic retrograde cholangiopancreatography (ERCP) findings (Fig. 3): On pancreatography, the pancreatic duct was enhanced up to the tail, with mild wall irregularity and localized irregular narrowing. The diagnosis of pancreatic juice cytology was class II, with no malignant findings.

EUS findings (Fig. 4): Findings suggestive of chronic pancreatitis were observed in the head up to the pancreas.

Narrowing of the main pancreatic duct was noted in the pancreatic tail, with a hypoechoic pattern and irregular inner texture in the parenchyma. Two punctures were made through the stomach into the enlarged portion of the pancreatic tail using a 22-G EXPECT[®] needle (Boston Scientific Corporation, Boston, USA).

Histopathological findings of EUS-FNA specimens (Fig. 5): Cytology revealed aggregations of disarranged and poorly-bound atypical cells, which were suspected of being adenocarcinoma cells of class V. Histology [Hematoxylin and Eosin (HE)-stained] revealed scarce plasma cells, while IgG4 staining showed no significant positive findings. The enlarged cells with densely-stained nuclei were positive for p53 and were thus suspected of being malignant epithelial cells. In this case of suspected AIP, the pathological findings of EUS-FNA specimens suggested adenocarcinoma. The discrepancy between the imaging and pathological findings warranted re-testing. Esophagogastroduodenoscopy (EGD) was performed for screening purposes.

EGD findings (Fig. 6): An almost semi-circumferential type-IIc lesion was found in the upper gastric corpus through to the lesser curvature, to the posterior wall of the gastric angle.

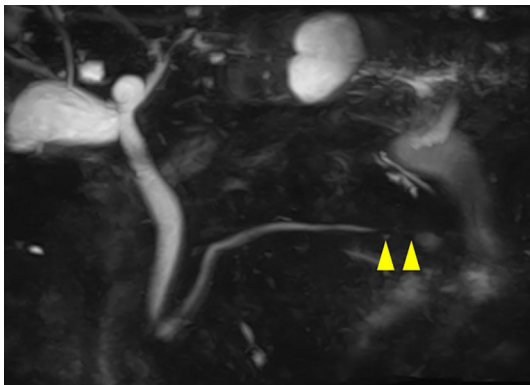


Figure 2. MRCP findings. Slight dilatation of the main pancreatic duct was observed in the head up to the body of the pancreas. The caudal pancreatic duct was not visualized (arrowheads). MRCP: magnetic resonance cholangiopancreatography

Histopathological findings of biopsy specimens (Fig. 6): Well-differentiated tubular adenocarcinoma and papillary adenocarcinoma were observed, with a diagnosis of adenocarcinoma, tub1> pap, group 5.

Positron emission tomography (PET)-CT findings (Fig. 7): No uptake was noted in the stomach, whereas an increased uptake (SUVmax: 4.2-4.8) occurred in the pancreatic tail. Although AIP was strongly suspected, the possibility of the pancreatic lesion being malignant could not be ruled out.

Taken together, these findings led to the diagnosis of early gastric cancer, cType IIc, cT1bN0M0, and cStage IA. Since the tumor had a diameter of ≥ 30 mm and was suspected to be a submucosa cancer, surgery was selected. For the pancreatic lesion, a needle biopsy was to be performed during surgery. Total gastrectomy with D1 lymphadenectomy followed by Roux-en-Y reconstruction was performed.

Histopathological findings of the surgical specimen (Fig. 8): A type-IIc lesion was located 6 cm from the anal end and 3.3 cm from the oral end of the specimen and measured 75×125 mm. Histological findings included adenocarcinoma of tub1>>tub2 proliferating over the mucosa, with ≥ 2 mm submucosal invasion in part. Mild vascular invasion was also noted. The tumor was surrounded by abundant IgG4-positive plasma cells, whereas few IgG4-positive plasma cells were found in the lamina propria in the non-tumor part of the specimen.

Histopathological findings of the pancreatic FNA specimen collected during surgery: No remarkable abnormalities were found.

The pancreatic lesion satisfied the following in the 2011 version of the clinical diagnostic criteria for AIP: Ib, localized enlargement (segmental/focal); II, irregular narrowing of the main pancreatic duct; and III, high serum IgG4 (≥ 135 mg/dL). However, the lesion did not meet the pathological criteria and thus was determined to be probable AIP.

The final diagnosis was early gastric cancer, type IIc, T1 bN0M0, Stage IA, and probable type-1 AIP.

Since the possibility of the pancreatic lesion being malignant could not be ruled out, careful postoperative follow-up was performed with CT and a scheduled repeat of EUS-

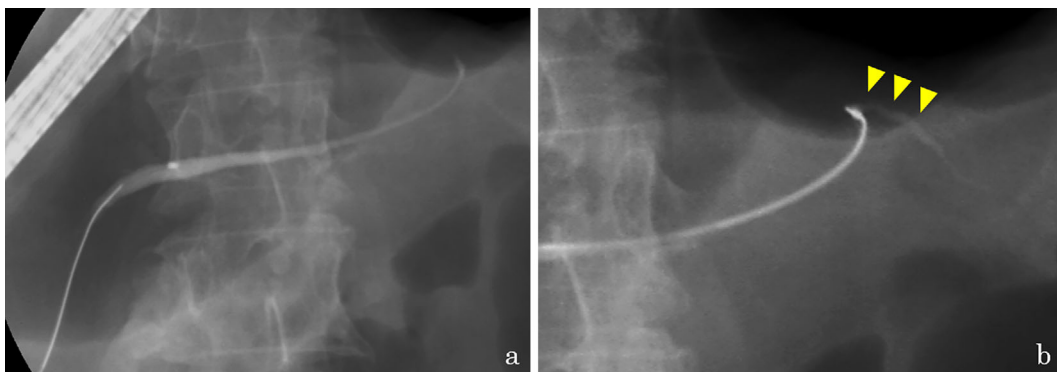


Figure 3. ERCP findings. Mild irregularity and irregular narrowing of the caudal pancreatic duct wall were observed (arrowheads). ERCP: endoscopic retrograde cholangiopancreatography

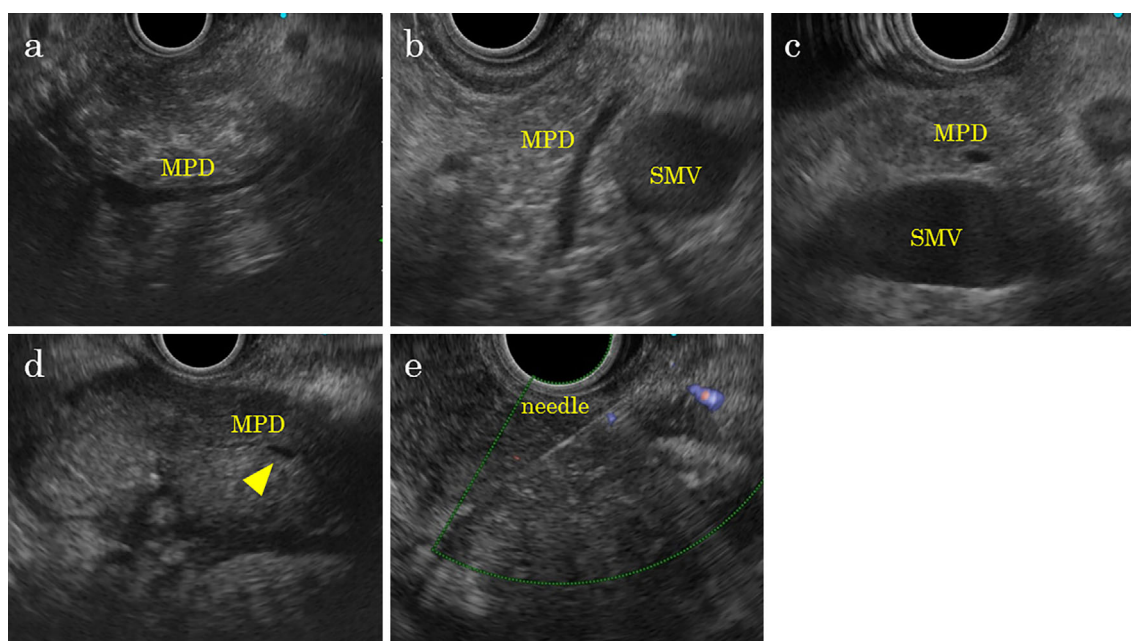


Figure 4. EUS and EUS-FNA images. **a:** Pancreatic head, **b:** Transition from the pancreatic head to the body, **c:** Pancreatic body, **d:** Pancreatic tail, and **e:** EUS-FNA to the pancreatic tail. The parenchyma of the pancreatic head to the body showed findings suggestive of chronic inflammation, such as non-honeycombing lobularity, while the parenchyma of the distal body to the tail showed a heterogeneous hypoechoic pattern with an irregular inner texture. The main pancreatic duct was neither narrowed nor dilated in the head until the body of the pancreas but was narrowed in the tail (**d:** arrowhead). EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration, MPD: main pancreatic duct, SMV: superior mesenteric vein

FNA. EUS performed four months after surgery revealed reduced irregularity of the pancreatic parenchymal texture compared to the previous session. The EUS-FNA specimen from the pancreatic tail was cytologically diagnosed as class I and histologically showed infiltration of only a few inflammatory cells.

Abdominal CT performed four months after surgery revealed no obvious recurrence/metastasis of gastric cancer. Although these findings were improved compared to the previous session, the low-density area in the pancreatic tail was still present and was suspected to be an AIP lesion.

Discussion

AIP is a disease concept proposed by a Japanese group in 1995 (1) and defined as pancreatitis with suspected autoimmune etiology. Based on the International Consensus Diagnostic Criteria (ICDC), which were established as the universal diagnostic criteria in 2011, AIP is further classified into types 1 and 2 (2). Type-1 AIP is histologically equivalent to lymphoplasmacytic sclerosing pancreatitis (LPSP) and characterized by the marked infiltration of lymphocytes/plasma cells, infiltration of IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. As the serum IgG4 level is observed to be high in many cases, AIP is considered a pancreatic lesion of IgG4-related diseases. In Japan, most cases of AIP are diagnosed as type 1, and its incidence

is increasing with the increasing acceptance of the disease concept (3). Type-2 AIP accounts for about 40% of cases in the West and is histologically equivalent to idiopathic duct-centric chronic pancreatitis (IDCP), which forms a characteristic granulocytic epithelial lesion (GEL). Type-2 AIP has no specific serum marker and does not form any extrapancreatic lesions.

AIP is often detected in patients with upper abdominal discomfort, increased hepatobiliary enzymes, obstructive jaundice due to biliary stricture or diabetes, or as a differential diagnosis to pancreatic or bile duct cancer. It may also be detected in patients with diffuse pancreatic enlargement on ultrasonography. It is associated with a mostly hypoechoic characteristic lesion with a “sausage-like” appearance. The diffuse pancreatic enlargement can also be observed on CT. An endoscopic retrograde pancreatogram reveals narrowed ducts, and in particular, irregular narrowing of the main pancreatic duct. Although the presence of localized ductal narrowing or dilatation may complicate the differentiation from pancreatic cancer or tumor-forming pancreatitis, the differential diagnosis is important due to the prognosis and treatment strategy being totally different.

Even though AIP can be a difficult differential diagnosis of pancreatic cancer, it can also coexist with pancreatic cancer. Pancreatic cancer was detected in 2.7%, 0.9%, and 4.8% of patients with AIP, as reported by Hirano et al. (4), Ghazale et al. (5), and Ikeura et al. (6), respectively. Aside

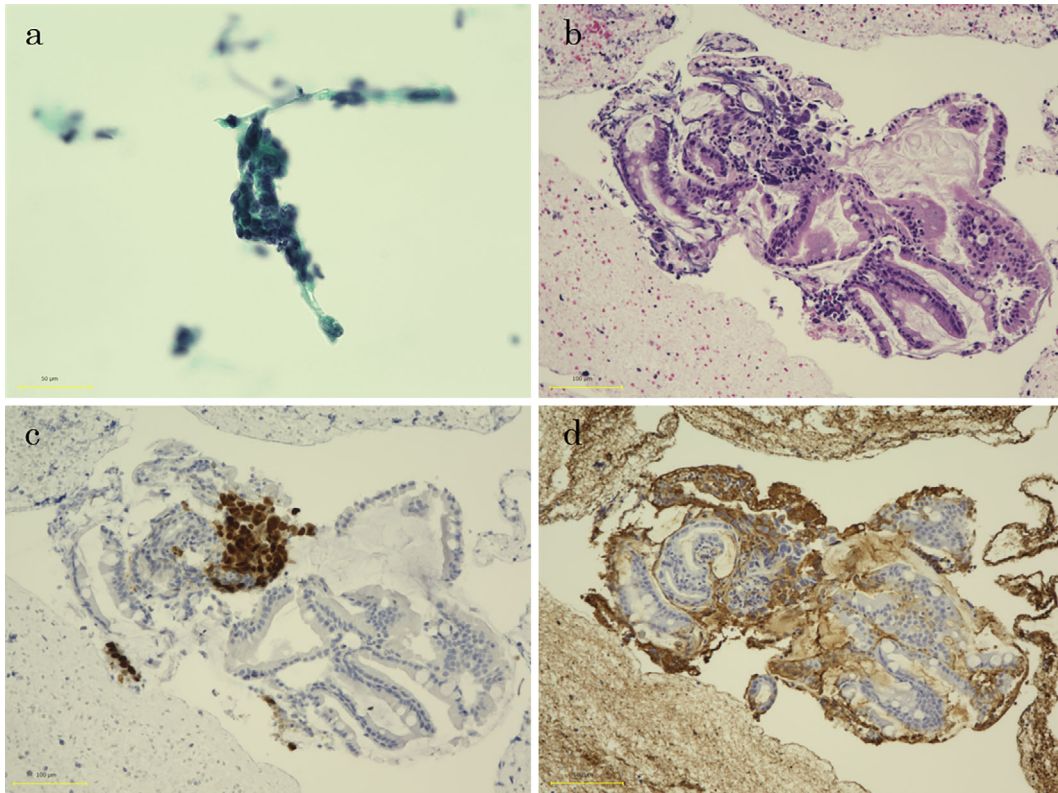


Figure 5. Pathological specimens. a: Papanicolaou-stained image showing aggregations of atypical cells suspected of being adenocarcinoma cells. b: Hematoxylin and Eosin-stained image showing scarce plasma cells and some enlarged cells with densely-stained nuclei. c: The enlarged cells with densely-stained nuclei were positive for p53 and thus were suspected of being epithelial malignant cells. d: IgG4 staining revealed no significant findings.

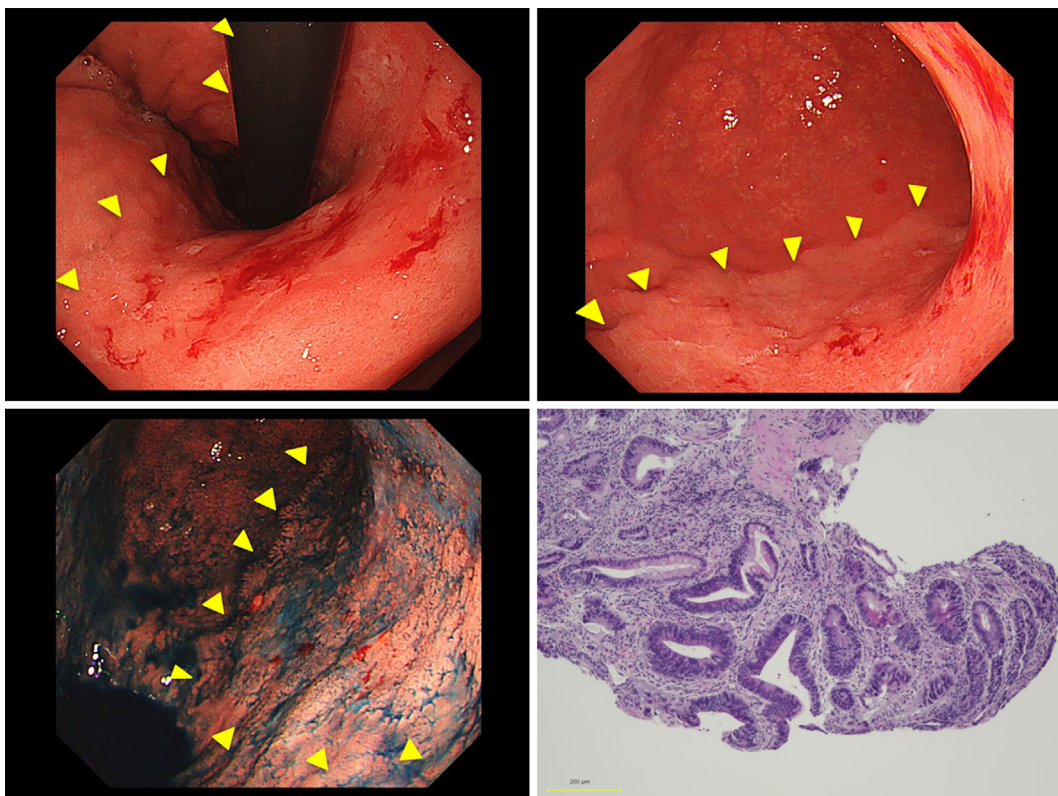


Figure 6. An almost semi-circumferential type-IIc lesion was found in the upper gastric corpus through to the lesser curvature, to the posterior wall of the gastric angle (arrowheads). The pathological diagnosis of the biopsy specimen was adenocarcinoma, tub1>pap.

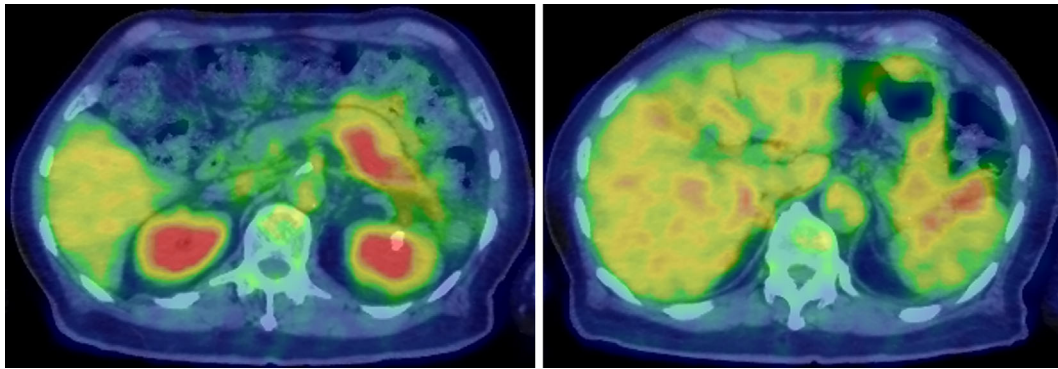


Figure 7. An FDG-PET image showing an increased uptake (SUVmax: 4.2-4.8) in the pancreatic tail and no uptake in the stomach. FDG-PET: fluorodeoxyglucose-positron emission tomography, SUVmax: maximum standardized uptake value

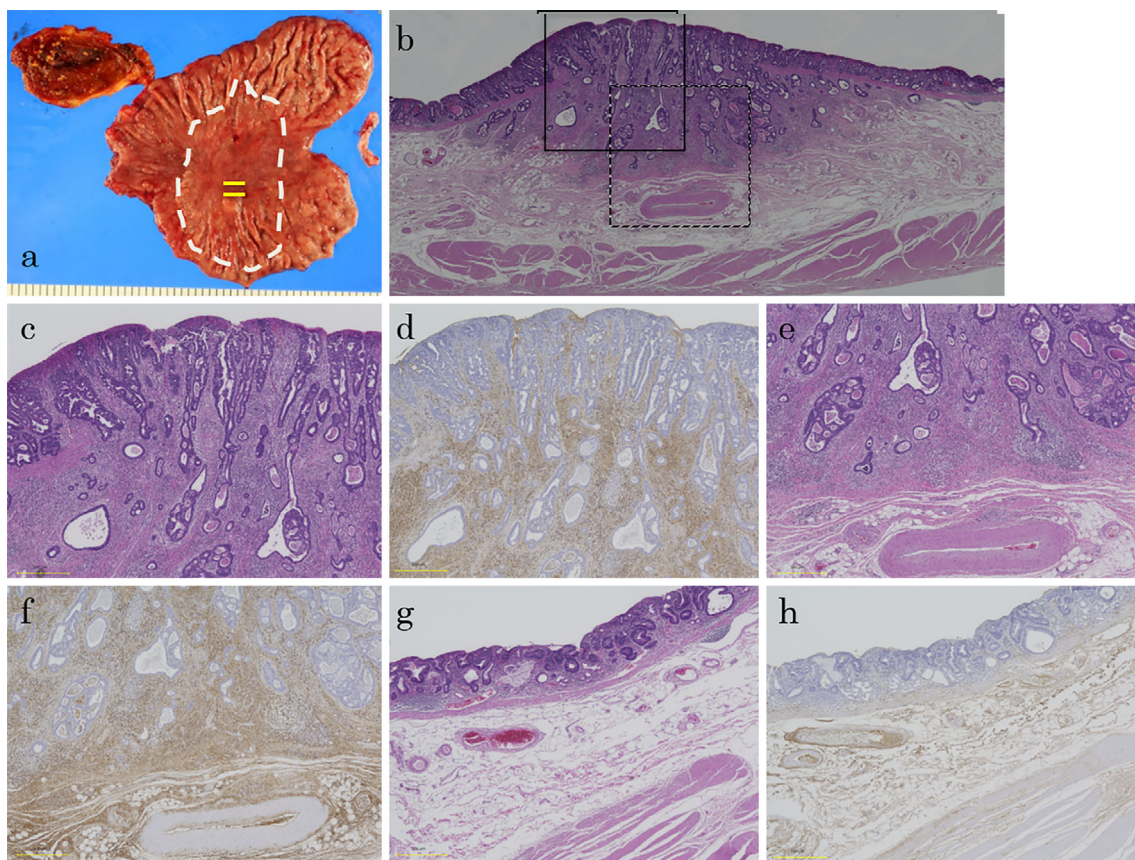


Figure 8. a: Surgical specimen containing extensive type-IIc lesion (white dotted line) with an SM2 lesion in part (yellow line). b: A loupe image of the SM2 site. c: The rectangular area surrounded by the black solid line in (b) showing adenocarcinoma of tub1>>tub2, proliferating over the mucosa, with invasion into the muscularis mucosae and the submucosa in part. d: The IgG4-stained version of (c) showing abundant IgG4-positive plasma cells in the lamina propria through to the submucosa. e: The rectangular area surrounded by the black dotted line in (b) showing SM2 invasion. f: The IgG4-stained version of (e) showing abundant IgG4-positive plasma cells in the submucosa. g and h: HE and IgG4-stained continuous sections from the non-tumor part of the specimen, showing almost no IgG4-positive plasma cells in the lamina propria or submucosa. HE: Hematoxylin and Eosin

from these limited case reports on AIP complicated by pancreatic cancer, however, there is insufficient scientific evidence regarding the association between AIP and pancreatic cancer. Notably, though, Kamisawa et al. (7) detected a de-

fect in the *Kras* gene in the pancreas, common bile duct, and gallbladder epithelium of AIP patients, while Gupta et al. (8) found a high prevalence of pancreatic intraepithelial neoplastic (PanIN) lesions in AIP. These observations sug-

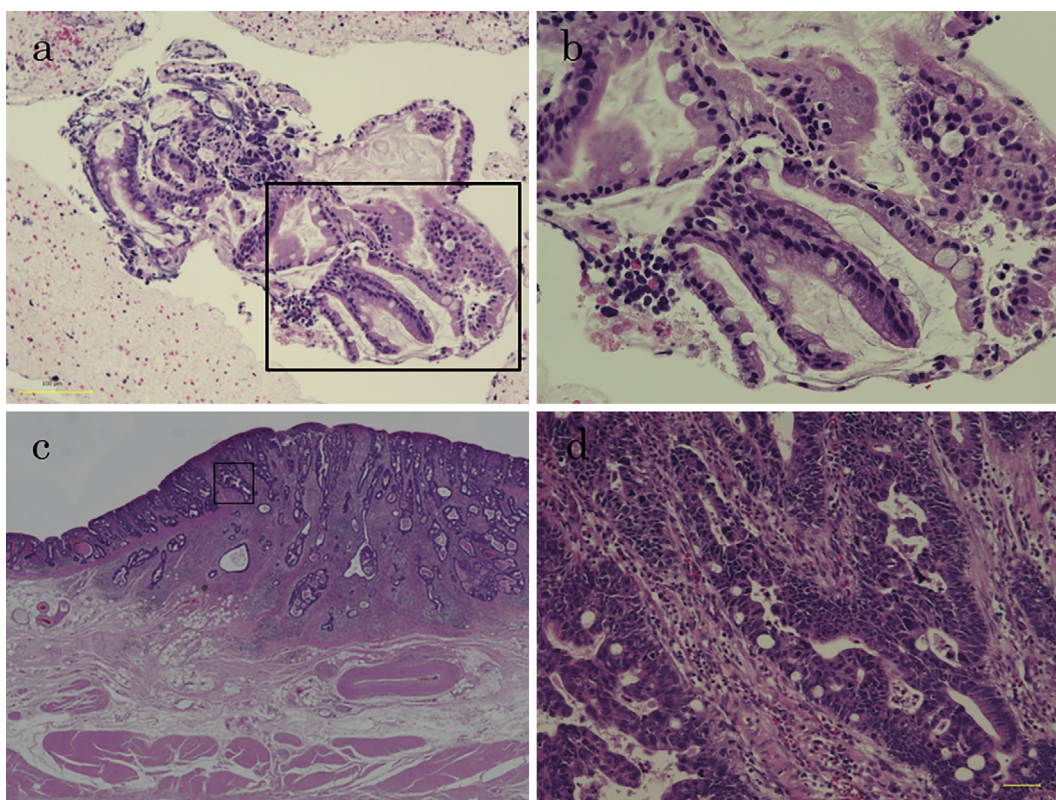


Figure 9. a: HE-stained pathological specimen collected by EUS-FNA of the pancreatic lesion (the same specimen as that in Fig. 5b). b: The rectangular area surrounded by the black solid line in (a) showing goblet cells as well as enlarged cells with densely-stained nuclei. c: A loupe image of the surgical specimen of the stomach (the same specimen as that in Fig. 8b). d: The rectangular area surrounded by the black solid line in (c) showing proliferating adenocarcinoma of tub1>>tub2 and the goblet cells. HE: Hematoxylin and Eosin, EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration

gest that, in addition to chronic pancreatitis, which is a known risk factor for pancreatic cancer, AIP may also be risk factor for pancreatic cancer.

To establish the diagnosis of AIP by EUS-FNA, both the differentiation from pancreatic cancer and the confirmation of AIP are required. Regarding the differentiation of AIP from pancreatic cancer, Imai et al. (9) reported that FNA with a 22-G needle resulted in an accurate benign-malignant differentiation in $\geq 90\%$ of cases. Ogura et al. (10), on the other hand, showed that the addition of a Kras analysis to cytology/histology resulted in an improved differentiation accuracy between AIP and pancreatic cancer compared to cytology/histology alone, with a maintained specificity of 100% and improved sensitivity of 93% (87% without a Kras analysis). For the diagnosis of AIP, Kanno et al. (11) suggested that a 22-G needle was sufficient; however, the diagnostic requirement for type-1 AIP (lymphocyte/plasma cell infiltration, obliterative phlebitis, storiform fibrosis, and infiltration of abundant IgG4-positive plasma cells) was only observed in 92%, 16%, 80%, and 36% of all type-1 AIP patients, respectively. This suggests a high prevalence of lymphocyte/plasma cell infiltration and fibrosis and low prevalence of obliterative phlebitis and infiltration of IgG4-positive plasma cells in AIP. For the detection of obliterative

phlebitis, Miyabe et al. (12) demonstrated the effectiveness of Elastic van Gieson (EVG) staining in detecting lesions from a small specimen. Regarding the diagnosis of type-2 AIP, GEL, a characteristic finding of type-2 AIP, has only been reported in a single patient encountered by Kanno et al. (11), suggesting the difficulty in diagnosing these lesions based on EUS-FNA findings alone at present. The present case was also diagnosed as a probable case because the pathological diagnostic criteria were not met by either the EUS-FNA or the surgical specimen.

To address the possibility of contamination of the EUS-FNA specimen with gastric cancer tissue, we compared the findings from the EUS-FNA specimen with those from the surgical specimen of the stomach, taking into consideration the possibility that the EUS-FNA specimen had been collected by puncturing through the site of early gastric cancer. The EUS-FNA specimen contained no pancreatic glandular cells and showed atrophied duct-like structure with scattered goblet cells; the histological findings were suggestive of intestinal metaplasia of the stomach (Fig. 9b). The presence of atypical ducts in some areas also suggested well-differentiated adenocarcinoma. These findings were again compared to those from the surgical specimen of the stomach (Fig. 9d), revealing a high similarity between both. It is

therefore likely that the EUS-FNA specimen was contaminated with gastric cancer tissue.

There are increasing numbers of case reports of AIP complicated by various malignancies, including-but not limited to-pancreatic cancer. Yamamoto et al. (13) analyzed 105 cases of IgG4-related diseases, including 10 cases of AIP, and found an increased risk of malignancy in this population. Shiokawa et al. (14) analyzed 108 cases of AIP and reported a relative risk of malignancy of 4.9 in patients with AIP. They identified a total of 18 malignant lesions, with gastric cancer being the most common in 7 patients. There are two suggested mechanisms underlying the association between malignancy and autoimmune diseases (15). One is referred to as inflammation-related carcinogenesis, where autoimmune-related persistent inflammation induces malignancy. In such cases, the duration of autoimmune disease appears to be important. In general, an increased risk of solid cancer through inflammation-related carcinogenesis is observed only after 7 to 10 years of suffering from autoimmune disease. Thus, carcinogenesis through this mechanism appears to require a long duration. The other mechanism involves the induction of autoimmune disease by malignancy as a paraneoplastic syndrome. This association has been suggested based on a high risk of malignancy within one year of an autoimmune disease diagnosis based on the pathological features, indicating that a malignant tumor tends to be surrounded by abundant IgG4-positive plasma cells, and the reduced recurrence rate of AIP after steroid therapy in patients who have undergone treatment for malignancy. The pathological feature of a malignant tumor being surrounded by abundant IgG4-positive plasma cells is considered characteristic of "AIP complicated by malignancy". The present patient also showed abundant IgG4-positive plasma cells around the tumor and few such cells in the non-tumor part of the specimen, a finding suggestive of "AIP complicated by malignancy".

In our patient, no new tumorous lesions were detected in the pancreas by CT or EUS-FNA during follow-up, after the completion of gastric cancer treatment. There was also no findings suggestive of recurrence in other parts of the body. EUS revealed improved irregularity of the texture of the pancreatic lesion, suggesting that the lesion was an inflammatory change. A pathological examination also showed no findings suggestive of malignancy or those characteristic of AIP. With no findings suggestive of pancreatic cancer observed during re-testing, the diagnosis remained "probable AIP".

Although it is difficult to diagnose AIP based on pathological findings, EUS-FNA is still effective for differentiating between AIP and pancreatic cancer. Unlike the recently developed direct-view EUS scopes, convex-type EUS scopes generally have an anterior oblique view and are not suited for a regular examination or an examination of the puncture site. In the present case, an extensive type-IIc early gastric cancer lesion was observed at the puncture site. An oblique-view scope should be sufficient to detect advanced gastric

cancer lesions before puncturing but may be insufficient to detect early gastric cancer lesions, such as the type-IIc lesion observed in the present case. Our search of the PubMed and Ichushi databases for case reports of EUS-FNA performed through a tumor, as was done in the present case, failed to extract any such reports. While there seem to be rare cases in which an extensive early gastric cancer lesion was present along the puncture route, as in the present case, there have been some cases of AIP complicated by malignancies, most commonly by gastric cancer. In order to avoid puncturing through a tumor and to facilitate the early detection of malignancies, such as gastric cancer, we recommend pre-EUS screening using a direct-view scope.

The present case requires careful follow-up to monitor for possible dissemination and seeding of gastric cancer.

Conclusion

We encountered a case of AIP in which the presence of an early gastric cancer lesion along the puncture route for EUS-FNA complicated the diagnosis. Although cases like the one presented here seem to be rare, we must be aware of the possibility of concomitant malignancies in AIP, and detailed examinations should be performed.

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

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