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【 CASE REPORT 】

Type 2 Autoimmune Pancreatitis with Crohn's Disease

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Abstract:
Autoimmune pancreatitis (AIP) is a distinct subtype of pancreatitis, which is classified into type 1 and 2 based on the clinicopathological features. According to the international consensus diagnostic criteria, pancreas resection or core biopsy specimens are recommended to make an accurate histological evaluation. However, the usefulness of endoscopic ultrasonography (EUS) guided fine needle aspiration (FNA) for histological evaluation has also been reported. Furthermore, the simultaneous presentation of type 2 AIP and Crohn's disease (CD) is very rare, especially in the Asian population. Therefore, we herein report a case of type 2 AIP with CD, which was diagnosed using EUS guided FNA with a 22-gauge needle.

Key words: autoimmune pancreatitis, Crohn's disease, endosonography, fine-needle aspiration, inflammatory bowel diseases

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Introduction

Autoimmune pancreatitis (AIP) is a novel disease entity, which is classified into type 1 (lymphoplasmacytic sclerosing pancreatitis; LPSP) and type 2 (idiopathic duct-centric pancreatitis; IDCP) (1). However, the histological confirmation of AIP is challenging because adequate tissue sampling is difficult without performing either a core biopsy or pancreas resection. Recently, the usefulness of endoscopic ultrasonography (EUS)-guided fine needle aspiration (FNA) for histological evaluation has been reported (2, 3).

Type 2 AIP can develop in patients with inflammatory bowel disease (IBD) (4-6). However, in most cases the type of IBD is ulcerative colitis (UC) rather than Crohn's disease (CD). Furthermore, the simultaneous presentation of type 2 AIP and CD is very rare, especially in the Asian population (7, 8). Therefore, we herein report a case of type 2 AIP which simultaneously presented with CD and which was diagnosed using EUS-FNA with a 22-gauge needle.

Case Report

A 20-year-old man was referred to our emergency room complaining of epigastric abdominal pain with acute diarrhea lasting for 2 days. He also had symptoms of nausea, vomiting, and fatigue. His skin did not show any yellowish discoloration, and his body temperature was normal. He did not have any history of alcohol abuse, previous attack of pancreatitis, or other symptoms associated with autoimmune diseases, except for undergoing surgery for the treatment of an anal fistula 5 years earlier.

The laboratory data were as follows: white blood cell count 37,740/mm^3, hemoglobin 13.4 g/dL, hematocrit 41.4%, platelet count 295,000/mm^3, aspartate aminotransferase 38 IU/L, alanine aminotransferase 24 IU/L, alkaline phosphatase 62 IU/L, total bilirubin 1.98 mg/dL, direct bilirubin 0.52 mg/dL, amylase 175 U/L, lipase 175 U/L, total protein 4.65 g/dL, albumin 2.23 g/dL (3.3 to 5.2 g/dL), and C-reactive protein 30.7 mg/dL (0 to <0.05 mg/dL). Abdominal computed tomography (CT) revealed a diffuse enlargement of the pancreas with a peripheral rim and minimal peripancreatic fluid collections (Fig. 1A). Endoscopic retrograde cholangiopancreatography (ERCP) showed focal stricture of the main pancreatic duct (Fig. 2). EUS revealed diffuse pancreatic swelling with hyperechoic ductal wall and prominent side branches of pancreatic duct. Focal stricture and irregularity of pancreatic duct were also identified without any upstream pancreatic duct dilation (Fig. 3). Furthermore, diffuse colonic wall thickening with slight enhance-

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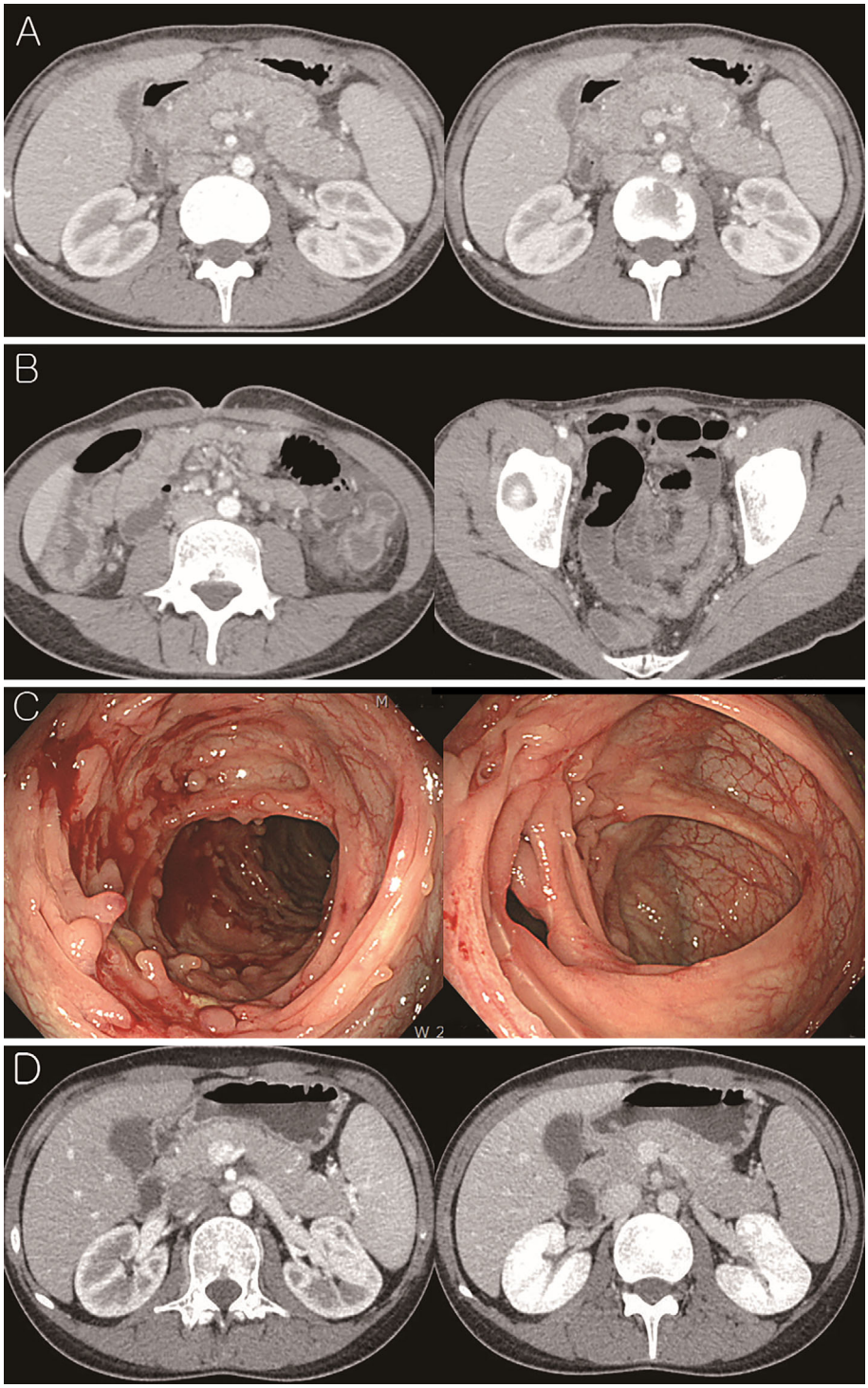

Figure 1. **Axial abdominal computed tomography. A: Diffuse enlargement of the pancreas with a peripheral rim of low attenuation and minimal peripancreatic fluid collections. B: Diffuse colonic wall thickening with slight enhancement from the cecum, including terminal ileum, to hepatic flexure and sigmoid colon. C: Longitudinal ulcers with a cobble stone appearance, pseudopolyps, and patulous ileocecal valve were identified during colonoscopy. D: Diffuse enlargement of the pancreas with peripancreatic fluid collection improved after 2 weeks of treatment with steroids.**

ment was noticed from the cecum, including the terminal ileum, to the site of hepatic flexure on an abdominal CT scan (Fig. 1B). Longitudinal ulcers with a cobble stone appearance, pseudopolyps, and patulous ileocecal valve were identified on colonoscopy (Fig. 1C). A histological examination showed moderate chronic active colitis, which was patchy with non-necrotizing granulomas without any virus-associated changes. To differentiate CD from tuberculosis (TB), and cytomegalovirus (CMV) enterocolitis, we performed additional laboratory tests for mycobacterium and

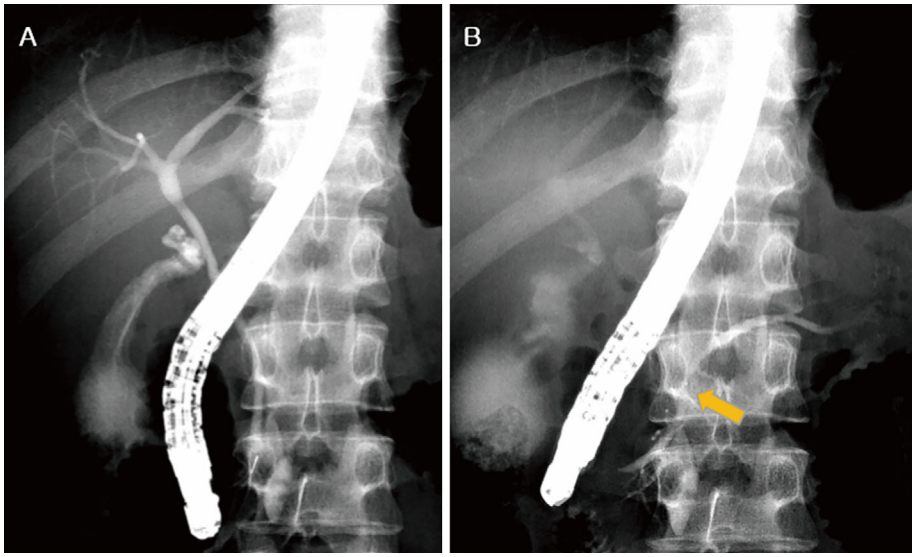

Figure 2. **Endoscopic retrograde cholangiopancreatography. A: Normal cholangiography. B: Focal stricture of the main pancreatic duct around pancreas neck portion was identified on pancreatography.**

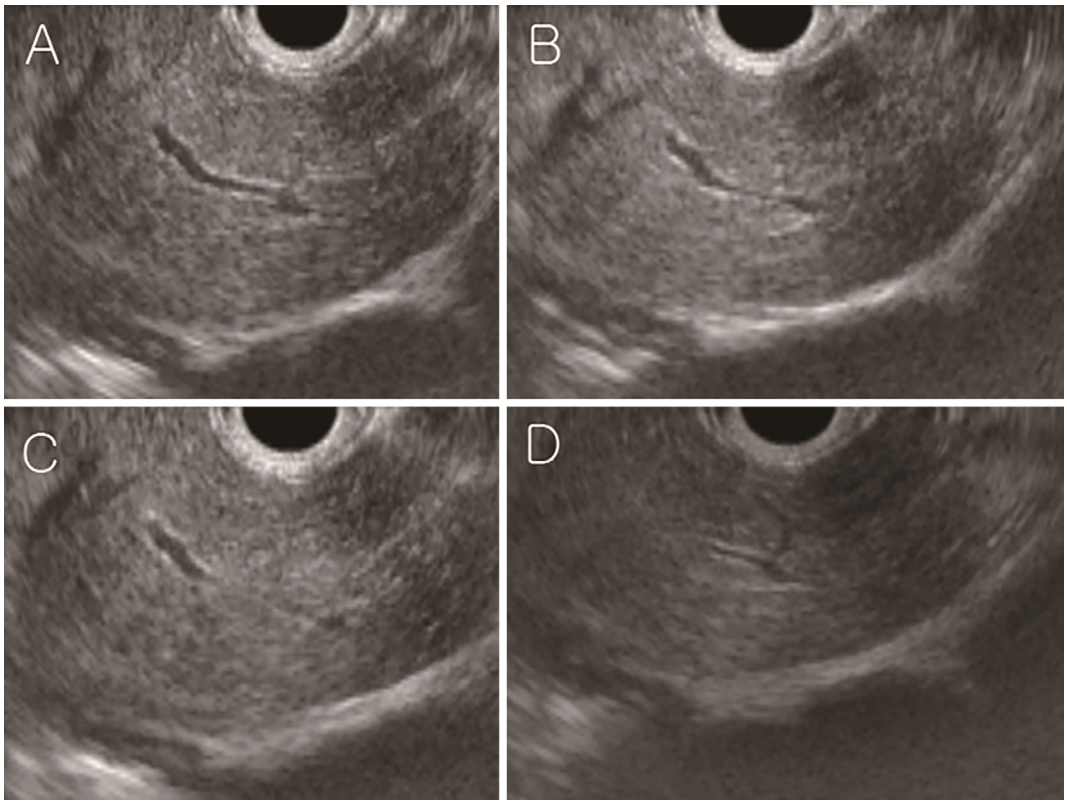

Figure 3. **Endoscopic ultrasonography. A: Hyperechoic ductal wall. B: Irregularity of the pancreatic duct. C: Focal stricture of the pancreatic duct without any upstream pancreatic duct dilation. D: Prominent side branches of the pancreatic duct.**

CMV infection as follows: interferon-gamma release assay and TB-polymerase change reaction with biopsied tissue specimens were negative. In addition, a cytomegalovirus (CMV) antigenemia assay and immunohistochemistry with biopsied tissue specimens were negative. However, the tissue was positive for anti-*Saccharomyces cerevisiae* antibodies although it was negative for perinuclear anti-neutrophil cytoplasmic antibodies. Fecal calprotectin was highly elevated with 714.4 μg/g. Samples were positive for lupus anticoagulant and rheumatoid factors, but negative for antinuclear antibody were found. IgG and IgG subtype IV were 1,048 (normal range 700-1,600 mg/dL) mg/dL and 9.4 mg/dL (normal range 3.92-86.4 mg/dL), respectively. EUS-FNA with a 22-gauge needle (Echotip Ultra®; Cook Medical,

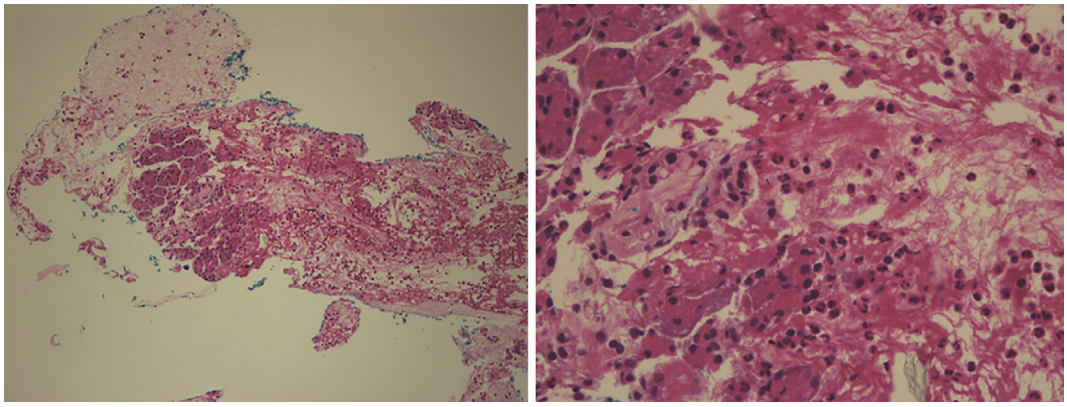

Figure 4. **An endoscopic ultrasonography guided fine needle aspiration biopsy showed the presence of granulocytic acinar infiltrate without any IgG4-positive cells.**

Bloomington, USA) was performed for pathologic evaluation, and the target portion of EUS-FNA was pancreas body, because AIP was suspected to be diffusely involved through the pancreas. The presence of granulocytic acinar infiltrate was observed without any IgG4-positive cells (Fig. 4). Under a suspicion of CD with type 2 AIP, steroid therapy was started with a dose of 40 mg/day, after which the symptoms quickly improved. Moreover, the peripancreatic fluid collections nearly resolved on a follow-up CT scan, at 2 weeks after the start of treatment (Fig. 1D). Considering these findings, the final diagnosis was type 2 AIP with CD. The patient has been closely followed-up and he has maintained a state of remission.

Discussion

Since a large-caliber cutting biopsy needle [19-gauge needle with a tissue tray and sliding sheath; Trucut biopsy (TCB) needle] was introduced to the EUS-FNA procedure in 2005 (9), several reports regarding the usefulness of EUS-FNA for the diagnosis of AIP have been published (10-12). In 2012, Iwashita et al. also reported that the conventional 19-gauge needle was safe and reliable for performing a histologic analysis of AIP (13). Furthermore, the possibility of using a 22-gauge needle for the diagnosis of AIP was reported by Kanno et al. in 2012 (14). After that, the usefulness of EUS-FNA with 22-gauge needle was demonstrated by a multicenter prospective study in 2016 (15).

While type 1 and type 2 AIP are combined under the same disease category, there are significant differences between the two subtypes. Type 1 AIP belongs to the disease spectrum of IgG4-related diseases and involves other organs, such as bile duct, kidney, or lymph nodes, whereas type 2 AIP has a strong association with IBD. The common clinical presentation of type 2 AIP is acute pancreatitis, whereas painless obstructive jaundice is the common presentation in type 1 AIP. IgG4 is a well-known serological marker for type 1 AIP, whereas there is no definite serological marker for type 2 AIP. Furthermore, while the age of affected patients is relatively young in type 2 AIP, the elderly with a mean age of about 60 years are usually affected by type 1 AIP.

Although the understanding of AIP has progressively expanded, the incidence and prevalence of AIP associated with IBD was insufficient, especially in AIP with CD. Generally, type 2 AIP is uncommon in Asian countries. However, recently published multicenter survey from Japan demonstrated that the proportion of type 2 AIP was 29%, showing outcome that is comparable to that of Western countries (16). Therefore, the regional distribution of AIP might similar between the countries and the discrepancy might result from unfamiliarity and/or an underdiagnosis of type 2 AIP because type 2 AIP usually has a mild clinical course.

Recently, a multicenter study from 23 centers in Europe with an average follow-up duration of 5.7 years, was published revealing the clinical features of AIP associated with IBD (17). Among 91 patients with AIP and IBD, 33 (36%) patients had AIP with CD and 31 (34%) patients relapsed at least once during the follow-up and finally endocrine and exocrine pancreatic insufficiency was observed in 12% and 19%, respectively. Furthermore, patients with AIP with CD have been reported to have a more inflammatory behavior, less perianal disease, and more colectomies than controls, whereas there were no cases demonstrating colorectal or pancreatic cancer. These results are in line with previous studies of an increased severity of IBD, but no increased cancer risk (18, 19). Regarding the occurrence of AIP in IBD patients, it was reported that AIP preceded IBD in about 20%, was synchronous in 26%, and occurred after IBD in 54%. The activity of IBD therefore increases at the time of AIP occurrence (17).

The mechanism of AIP occurrence in IBD patients is unclear, in regard to whether IBD is merely an immune-medicated association, a true extrapancreatic manifestation of AIP or an extraintestinal manifestation of IBD. Recently, Ravi et al. suggested that IBD may represent an extrapancreatic manifestation of AIP based on the fact that IgG4 positive cells was identified on colon biopsy (19). Furthermore, about 70% of AIP patients were found to demonstrate an active disease state of IBD at the time of AIP diagnosis. More-

over, interleukin (IL)-8 overexpression was identified in the crypt epithelium of ulcerative colitis and in the duct/ductular epithelium of type 2 AIP, suggesting that there is a possible cross-linking immunologic mechanism in AIP and IBD development (20).

Moreover, the diagnosis of AIP remains challenging, and there several different diagnostic criteria from Asia, Europe, and North America (21, 22). For the development of universally accepted criteria, the International Consensus of Diagnostic Criteria (ICDC) suggested five cardinal features of AIP based on pancreatic parenchymal imaging, pancreatic ductal imaging verified by endoscopic retrograde pancreatography, serology, and other organ involvement, histology of the pancreas from a core biopsy, and steroid responsiveness. The five criteria were fulfilled in our case: 1) diffuse pancreatic enlargement with delayed enhancement; 2) focal narrowing of the pancreatic duct without any marked upstream dilatation on endoscopic pancreatography; 3) other organ involvement in CD; 4) a histological finding of granulocytic acinar infiltrate without any IgG4-positive cells; and 5) positive steroid responsiveness. Consequently, this case was diagnosed with definite type 2 AIP.

In our case, the stricture and irregularity of the pancreatic duct is localized, despite the presence of diffuse pancreatic swelling. One possible explanation is that the occurrence of acute pancreatitis as the initial presentation in type 2 AIP may be not indicate AIP itself, but instead may represent the disease sequelae of pancreatic duct stricture from AIP, which causes to acute pancreatitis by some obstructive mechanism resulting the onset of diffuse pancreatic swelling. This potential hypothesis was also mentioned by Hart el al. (7), although further studies and cases are needed to support this hypothesis with confidence.

Recently, a therapeutic algorithm for AIP has been proposed by international consensus for the treatment of autoimmune pancreatitis in 2017 (23). According to this algorithm, steroids are the first-line agent for remission induction unless there is any contraindication to administer steroids, and steroids are well-known to be remission induction agents of CD, while it is ineffective for the maintenance of disease remission (24). In this case, AIP simultaneously presented with CD. Therefore, steroids were selected for remission induction for both AIP and CD.

This case is unique in that type 2 AIP simultaneously presented with CD and was diagnosed using EUS-FNA with a 22-gauge needle based on the ICDC criteria.

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

References

1. 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.
2. Kanno A, Masamune A, Fujishima F, et al. Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study. Gastrointest Endosc **84**: 797-804, 2016.
3. Iwashita T, Yasuda I, Doi S, et al. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol **10**: 316-322, 2012.
4. Pitchumoni CS, Chari S. Ulcerative colitis and autoimmune pancreatitis. J Clin Gastroenterol **47**: 469-470, 2013.
5. Kanno A, Nishimori I, Masamune A, et al. Nationwide epidemiological survey of autoimmune pancreatitis in Japan. Pancreas **41**: 835-839, 2012.
6. Kamisawa T, Kim MH, Liao WC, et al. Clinical characteristics of 327 Asian patients with autoimmune pancreatitis based on Asian diagnostic criteria. Pancreas **40**: 200-205, 2011.
7. Hart PA, Levy MJ, Smyrk TC, et al. Clinical profiles and outcomes in idiopathic duct-centric chronic pancreatitis (type 2 autoimmune pancreatitis): the Mayo Clinic experience. Gut **65**: 1702-1709, 2016.
8. Ueki T, Kawamoto K, Otsuka Y, et al. Prevalence and clinicopathological features of autoimmune pancreatitis in Japanese patients with inflammatory bowel disease. Pancreas **44**: 434-440, 2015.
9. Levy MJ, Reddy RP, Wiersema MJ, et al. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc **61**: 467-472, 2005.
10. Mizuno N, Bhatia V, Hosoda W, et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. J Gastroenterol **44**: 742-750, 2009.
11. Imai K, Matsubayashi H, Fukutomi A, Uesaka K, Sasaki K, Ono H. Endoscopic ultrasonography-guided fine needle aspiration biopsy using 22-gauge needle in diagnosis of autoimmune pancreatitis. Dig Liver Dis **43**: 869-874, 2011.
12. Levy MJ, Smyrk TC, Takahashi N, Zhang L, Chari ST. Idiopathic duct-centric pancreatitis: disease description and endoscopic ultrasonography-guided trucut biopsy diagnosis. Pancreatology **11**: 76-80, 2011.
13. Iwashita T, Yasuda I, Doi S, et al. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol **10**: 316-322, 2012.
14. Kanno A, Ishida K, Hamada S, et al. Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. Gastrointest Endosc **76**: 594-602, 2012.
15. Kanno A, Masamune A, Fujishima F, et al. Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study. Gastrointest Endosc **84**: 797-804, 2016.
16. Notohara K, Nishimori I, Mizuno N, et al. Clinicopathological features of type 2 autoimmune pancreatitis in japan: results of a multicenter survey. Pancreas **44**: 1072-1077, 2015.
17. Lorenzo D, Maire F, Stefanescu C, et al. Features of autoimmune pancreatitis associated with inflammatory bowel diseases. Clin Gastroenterol Hepatol **16**: 59-67, 2018.
18. Hart PA, Law RJ, Dierkhising RA, Smyrk TC, Takahashi N, Chari ST. Risk of cancer in autoimmune pancreatitis: a case-control study and review of the literature. Pancreas **43**: 417-421, 2014.
19. Ravi K, Chari ST, Vege SS, Sandborn WJ, Smyrk TC, Loftus EV Jr. Inflammatory bowel disease in the setting of autoimmune pancreatitis. Inflamm Bowel Dis **15**: 1326-1330, 2009.
20. Ku Y, Hong SM, Fujikura K, et al. IL-8 expression in granulocytic epithelial lesions of idiopathic duct-centric pancreatitis (type 2 autoimmune pancreatitis). Am J Surg Pathol **41**: 1129-1138, 2017.
21. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. J Gastroenterol **42**(Suppl 18): 39-41, 2007.

22. Otsuki M, Chung JB, Okazaki K, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol **43**: 403-408, 2008.
23. Okazaki K, Chari ST, Frulloni L, et al. International consensus for the treatment of autoimmune pancreatitis. Pancreatology **17**: 1-6, 2017.
24. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut **63**: 1381-1392, 2014.