Strategy to differentiate autoimmune pancreatitis from pancreas cancer

Kensuke Takuma, Terumi Kamisawa, Rajesh Gopalakrishna, Seiichi Hara, Taku Tabata, Yoshihiko Inaba, Naoto Egawa, Yoshinori Igarashi

Kensuke Takuma, Terumi Kamisawa, Rajesh Gopalakrishna, Seiichi Hara, Taku Tabata, Yoshihiko Inaba, Naoto Egawa, Yoshinori Igarashi

Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo 113-8677, Japan
Yoshinori Igarashi, Department of Gastroenterology and Hepatology, Omori Medical Center, Toho University School of Medicine, Tokyo 143-8541, Japan

Author contributions: Takuma K and Kamisawa T contributed equally to this work and wrote the manuscript; Gopalakrishna R, Hara S, Tabata T, Inaba Y, Egawa N, and Igarashi Y collected the data.

Correspondence to: Terumi Kamisawa, MD, PhD, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan. kamisawa@ckj.com
Telephone: +81-3-38232101 Fax: +81-3-38241552
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Abstract

Autoimmune pancreatitis (AIP) is a newly described entity of pancreatitis in which the pathogenesis appears to involve autoimmune mechanisms. Based on histological and immunohistochemical examinations of various organs of AIP patients, AIP appears to be a pancreatic lesion reflecting a systemic “IgG4-related sclerosing disease”. Clinically, AIP patients and patients with pancreatic cancer share many features, such as preponderance of elderly males, frequent initial symptom of painless jaundice, development of new-onset diabetes mellitus, and elevated levels of serum tumor markers. It is of uppermost importance not to misdiagnose AIP as pancreatic cancer. Since there is currently no diagnostic serological marker for AIP, and approach to the pancreas for histological examination is generally difficult, AIP is diagnosed using a combination of clinical, serological, morphological, and histopathological features. Findings suggesting AIP rather than pancreatic cancer include: fluctuating obstructive jaundice; elevated serum IgG4 levels; diffuse enlargement of the pancreas; delayed enhancement of the enlarged pancreas and presence of a capsule-like rim on dynamic computed tomography; low apparent diffusion coefficient values on diffusion-weighted magnetic resonance image; irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography; less upstream dilatation of the main pancreatic duct on magnetic resonance cholangiopancreatography, presence of other organ involvement such as bilateral salivary gland swelling, retroperitoneal fibrosis and hilar or intrahepatic sclerosing cholangitis; negative work-up for malignancy including endoscopic ultrasound-guided fine needle aspiration; and steroid responsiveness. Since AIP responds dramatically to steroid therapy, accurate diagnosis of AIP can avoid unnecessary laparotomy or pancreatic resection.

Key words: Autoimmune pancreatitis; Pancreatic cancer; Endoscopic retrograde cholangiopancreatography; Magnetic resonance cholangiopancreatography

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a recently described entity of pancreatitis in which the pathogenesis appears...
to involve autoimmune mechanisms\textsuperscript{[1,2]}. Characteristic histopathological findings in AIP patients in Japan include dense infiltration of T lymphocytes and IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis in the pancreas; this form is termed lymphoplasmacytic sclerosing pancreatitis (LPSP)\textsuperscript{[3-5]}. Recently, another AIP variant having different histological findings has been described. It is called idiopathic duct-centric pancreatitis (IDCP), and is rare in Japan but more prevalent in Europe and the United States\textsuperscript{[6,7]}. Clinically, AIP patients and those with pancreatic cancer have many features in common, such as painless jaundice, development of new-onset diabetes mellitus (DM), and elevated levels of serum tumor markers. In both populations there is preponderance of elderly males. In North America, about 2.5% of pancreaticoduodenectomies were performed in AIP patients following a mistaken diagnosis of pancreatic cancer\textsuperscript{[8]}. Since AIP responds extremely well to steroid therapy, it is of utmost importance that it be differentiated from pancreatic cancer to avoid unnecessary laparotomy or pancreatic resection.

Other prominent features of AIP include a variety of extrapancreatic complications. Patients frequently have significantly elevated serum IgG4 levels\textsuperscript{[9,10]}. Currently, AIP is recognized as a pancreatic lesion of IgG4-related systemic disease\textsuperscript{[11,12]}. In this review, we will summarize clinicopathological features of AIP and describe a strategy to differentiate it from pancreatic cancer.

**AUTOIMMUNE PANCREATITIS**

**Clinical features**

AIP occurs predominantly in elderly males\textsuperscript{[12,13]}. Typical presentation with severe abdominal pain and clinically acute pancreatitis is rare; the major presenting complaint is painless obstructive jaundice due to associated sclerosing cholangitis. Failure of pancreatic exocrine or endocrine function is frequently seen. Up to 50% of AIP patients present with glucose intolerance. The diagnoses of DM and AIP are made simultaneously in many cases, but some patients experience exacerbation of preexisting DM with the onset of AIP\textsuperscript{[12,11]}. In addition to symptoms resulting from pancreatic involvement, AIP patients often have other complications, such as biliary stricture and thickening of the gallbladder wall, swelling of salivary and lacrimal glands, and a retroperitoneal mass. Histological features in these other anatomical locations include dense fibrosis with abundant infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis. We have observed these features in the periportal area of the liver, gastric mucosa, colonic mucosa, dermis, lymph nodes, and bone marrow of AIP patients\textsuperscript{[11,13,14]}. Based on histological and immunohistochemical examinations of various organs of AIP patients, we proposed that a novel clinicopathological entity, an “IgG4-related sclerosing disease”\textsuperscript{[11,13]} should be described.

IgG4-related sclerosing disease is a systemic disease affecting multiple organs with tissue fibrosis and obliterative phlebitis. We suggest that AIP appears to be a pancreatic lesion reflecting a systemic IgG4-related sclerosing disease, which can be manifest elsewhere to varying degree. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (Figure 1)\textsuperscript{[12,11,13]}. These extrapancreatic lesions can be synchronous or metachronous\textsuperscript{[13]}

**Histopathological features**

Histological pancreatic findings in AIP patients with LPSP are characterized by dense infiltration of T lymphocytes and IgG4-positive plasma cells and storiform fibrosis. Obliterative phlebitis is frequently detected. The pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration, but the ductal epithelium is usually preserved\textsuperscript{[11,3]}. American and European pathologists have described another unique histological pattern in AIP, which they have termed IDCP\textsuperscript{[15]} or AIP with granulocyte epithelial lesion (GEL)\textsuperscript{[16]}. Neutrophilic infiltration in the epithelium of pancreatic ducts is a characteristic feature of IDCP; this is not seen in LPSP. Infiltration of IgG4-positive plasma cells and obliterative phlebitis are uncommon in IDCP\textsuperscript{[14,16,17]}. IDCP is seen mostly in Western countries, but it appears uncommon in Asia\textsuperscript{[18,17]}. LPSP and IDCP are regarded as two distinct subtypes of AIP, and it has been proposed that LPSP be called “type 1 AIP” and IDCP “type 2 AIP”\textsuperscript{[18,16,17]}.

**Diagnostic criteria for AIP**

Since there is currently no diagnostic serological marker for AIP, and approach to the pancreas for histological examination is generally difficult, AIP is currently diagnosed on the basis of presence of a combination of abnormalities unique to AIP. The Japanese clinical diagnostic criteria for AIP were revised in 2006\textsuperscript{[19]}. In 2006, new diagnostic criteria for AIP were proposed in Korea\textsuperscript{[20]} and the United States\textsuperscript{[21]}. In 2008, Asian diagnostic criteria for AIP were published by Japanese and Korean pancreateologists\textsuperscript{[22]}.
In 2011, international consensus diagnostic criteria for AIP were proposed. According to these, AIP is classified into type 1 and 2. Five cardinal features of AIP are used: imaging of pancreatic parenchyma and ducts; serology; other organ involvement; pancreatic histology; and an optional criterion of response to steroid therapy. Each feature is categorized as a level 1 or 2 finding, depending on the diagnostic reliability. The diagnosis of type 1 and type 2 AIP can be definitive or probable (Tables 1 and 2).

**Treatment and prognosis**

A multicenter study for steroid treatment of AIP was performed in Japan in 2009, and Japanese consensus guidelines for treatment of AIP were proposed in 2010. According to the guidelines, steroid treatment is a standard therapy for AIP, as it is usually effective clinically, serologically, and radiologically in these patients, including for extrapancreatic lesions. It is most important to distinguish AIP from pancreatic cancer before starting steroid therapy. Indications for steroid therapy are symptoms such as obstructive jaundice, abdominal pain, and hydronephrosis. Before beginning steroid therapy, jaundice is usually managed by endoscopic or transhepatic biliary drainage in patients with obstructive jaundice, and the blood glucose level should be controlled with insulin in patients with DM. Initially, oral prednisolone (0.6 mg/
secondary to pancreatic cancer typically progresses steadily, whereas the jaundice of AIP in IgG4-related sclerosing disease sometimes fluctuates or, in rare cases, improves spontaneously \[2,11,28\].

**Serum IgG4 levels**

AIP patients frequently have significantly elevated serum IgG4 levels \[29\]. In our series of 39 patients \[39\], the median level was 301.5 mg/dL, and 30 (77%) had levels greater than 135 mg/dL. On the other hand, the median level was 34.0 mg/dL in 114 pancreatic cancer patients. However, 5 of these had levels \(\geq 135\) mg/mL; therefore, elevation of serum IgG4 levels alone cannot rule out pancreatic cancer. According to Ghazale et al. \[31\], serum IgG4 levels were elevated in 13/135 (10%) of pancreatic cancer patients; however, only 1% had IgG4 levels \(> 280\) mg/dL, compared with 53% of AIP patients.

**Computed tomography imaging**

Diffuse enlargement of the pancreas and effacement of the lobular contour of the pancreas, the so-called “sausage-like” appearance, is a typical finding in AIP, and is rarely seen in pancreatic cancer (Figure 2). On delayed-phase of dynamic computed tomography and magnetic resonance imaging (MRI), enhancement of an enlarged pancreas is characteristic of AIP. As fibroinflammatory changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, is specifically detected in some AIP patients \[32-34\].

**Diffusion weighted MRI**

The clinical utility of diffusion weighted MRI (DW-MRI) for differentiating AIP from pancreatic cancer was reported \[35\]. AIP and pancreatic cancer were detected as high signal intensity areas. However, the high signal-intensity areas were found to be diffuse, solitary, and multiple in AIP patients, whereas all patients with pancreatic cancer had solitary areas. Additionally, the apparent diffusion coefficient (ADC) values were significantly lower in AIP than in pancreatic cancer patients or in individuals with a normal pancreas. Morphological differences seen in high signal intensity areas on DW-MRI and ADC values may prove useful to help distinguish AIP from pancreatic cancer.

**Endoscopic retrograde cholangiopancreatography**

Irregular narrowing of the main pancreatic duct (MPD) on endoscopic retrograde cholangiopancreatography (ERCP) is a characteristic radiological feature of AIP, and is mandatory for meeting the Japanese diagnostic criteria for AIP \[36\]. In our study \[31\], comparing the ERCPs of AIP and pancreatic head cancer patients, MPD findings that were highly suggestive of the former included no obstruction, skipped lesions, side branch derivation from the narrowed portion, narrowed portion \(> 3\) cm long, and a maximum diameter of \(< 5\) mm upstream (Figure 3). The histopathological differences around the ducts represent the different pancreaticographic findings between AIP and pancreatic cancer (PC). Infiltrating cancer cells cause scirrhous changes, destroy ductal epithelium, and

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**Figure 2** Dynamic computed tomography of an autoimmune pancreatitis patient showing well-enhanced enlargement of the pancreas.
frequently obstruct main and branch ducts.

**Magnetic resonance cholangiopancreatography**

Since magnetic resonance cholangiopancreatography (MRCP) has become popular as a non-invasive method for obtaining high quality images of the pancreaticobiliary tree, it is becoming preferable to diagnostic ERCP in many cases. However, the narrowest MPD seen on ERCP cannot be visualized by MRCP due to the inferior resolution of MRCP compared with ERCP, so distinguishing between narrowing of the MPD in AIP and stenosis of the MPD in pancreatic cancer is not possible. However, less upstream dilatation of the MPD on MRCP suggests AIP rather than pancreatic cancer. Furthermore, MRCP is useful for judging response to steroid therapy.

**Other organ involvements**

Presence of other organ involvements such as bilateral salivary gland swelling, retroperitoneal fibrosis and hilar or intrahepatic sclerosing cholangitis is highly suggestive of AIP rather than pancreatic cancer.

On 18F-Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET), pancreatic FDG uptake is observed in both, but abnormal extrapancreatic uptake, such as extensive lymph nodes or swollen salivary glands, is highly suggestive of AIP.

**Endoscopic ultrasound-guided fine needle aspiration**

In some cases, when diagnosis is difficult, especially when segmental-type AIP is involved, histopathological examination is necessary. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is useful to either diagnose or rule out pancreatic cancer. However, definitive diagnosis of AIP is sometimes difficult by EUS-FNA, because of the small sample size obtained. Therefore, EUS-guided core biopsy is recommended. Positive IgG4-immunostaining in biopsy specimens taken from the major duodenal papilla supports a diagnosis of AIP.

**Steroid responsiveness**

There is reversible improvement of AIP with oral steroid therapy. In patients with typical radiological findings highly suggestive of AIP, a diagnosis cannot be made, according to Japanese criteria, if there are no histological features and negative laboratory tests. Although it can be diagnostic, a steroid diagnostic trial is not generally recommended; it should only be performed with extreme caution by pancreatologists in carefully selected patients after obtaining negative results from a thorough work-up for pancreatic cancer, including EUS-FNA.

**CONCLUSION**

For an elderly male presenting with obstructive jaundice and a pancreatic mass, AIP should be considered as a differential diagnosis to avoid performance of unnecessary surgery for presumed pancreatic cancer. As it is sometimes difficult to obtain adequate biopsy material from the pancreas, AIP is currently diagnosed based on careful consideration of a combination of characteristic clinical, serological, morphological, and histopathological features.

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