

Diagnosis of Autoimmune Pancreatitis: The Mayo Clinic Experience

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Background & Aims: The Japan Pancreas Society criteria for diagnosis of autoimmune pancreatitis (AIP) mandate presence of characteristic imaging (diffuse pancreatic enlargement with diffusely irregular, narrow pancreatic duct). AIP has unique histologic features associated with infiltration of tissues of affected organs with abundant IgG4-positive cells. We propose expanded diagnostic criteria for AIP with a cohort of histologically confirmed AIP. **Methods:** We reviewed the pancreatic imaging findings on computed tomography scans, serum IgG4 levels, other organ involvement, and response to steroids in 29 consecutive patients who met histologic criteria for AIP. **Results:** Computed tomography scans (n = 22) showed diffuse pancreatic enlargement in 6 (27%) patients; the rest had focal enlargement, distinct mass, normal pancreas, or focal acute pancreatitis. Serum IgG4 level was elevated in 15 of 21 (71%) patients, and other organ involvement (eg, intrahepatic biliary strictures) was noted in 11 of 29 (38%) patients. All 17 patients treated with steroids exhibited resolution/marked improvement of pancreatic/extrapancreatic manifestation. On the basis of this experience we propose that diagnosis of AIP can be made in patients with ≥ 1 of these criteria: (1) diagnostic histology, (2) characteristic imaging on computed tomography and pancreatography with elevated serum IgG4 level, or (3) response to steroid therapy of pancreatic/extrapancreatic manifestations of AIP. Twenty additional patients met expanded diagnostic criteria for AIP, and their demographic and clinical profile was similar to that of the 29 patients meeting histologic criteria. **Conclusions:** AIP defined by histological criteria shows a wide spectrum of radiologic features, with characteristic imaging seen only in a minority. Incorporation of additional features into current diagnostic criteria can identify the full spectrum of clinical presentations of AIP.

Autoimmune pancreatitis (AIP) can be defined as a systemic fibroinflammatory disease that afflicts not only the pancreas but also a variety of other organs including bile duct, salivary glands, the retroperitoneum, and lymph nodes. Organs affected by AIP have a lymphoplasmacytic infiltrate rich in IgG4-positive cells.¹ The inflammatory process responds to steroid therapy.² The diagnosis of AIP currently rests on fulfilling the Japan Pancreas Society's minimal consensus criteria³ (Table 1), which require the presence of characteristic imaging features, that is, a diffusely enlarged sausage-shaped gland and a diffusely irregular, attenuated pancreatic duct (Figure 1).

Histopathologic features of chronic pancreatitis usually encountered in practice do not provide information about its etiology. However, recent studies have shown that pancreatic histology can distinguish AIP from usual chronic pancreatitis and obstructive pancreatitis.⁴⁻⁶ The histology of AIP, termed lymphoplasmacytic sclerosing pancreatitis (LPSP), is characterized by a lymphoplasmacytic infiltrate around small-sized ducts, swirling fibrosis centered around ducts and veins (storiform fibrosis), and obliterative phlebitis wherein the infiltrate surrounds pancreatic venules while sparing arterioles.⁷⁻¹⁰ In addition, pancreatic immunostaining is diagnostic of AIP when it shows abundant IgG4-positive cells,¹¹⁻¹³ and it can distinguish AIP from alcoholic pancreatitis and inflammatory infiltrate surrounding pancreatic cancer.¹⁴ Similarly, other organs involved in AIP also show abundant tissue infiltration with IgG4-positive cells.¹ Thus, histopathology and immunostaining can be used to diagnose AIP.

Abbreviations used in this paper: AIP, autoimmune pancreatitis; CT, computed tomography; HPF, high-power field; LPSP, lymphoplasmacytic sclerosing pancreatitis.

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Table 1. Japanese Pancreas Society Criteria for AIP³

Mandatory criteria
Typical imaging: diffuse enlargement of pancreas along with diffuse (>33%) main pancreatic duct narrowing with an irregular wall
Supportive criteria (at least one)
(1) Serology: autoantibodies, elevated γ -globulins or IgG
(2) Histopathology: lymphoplasmacytic infiltrate and pancreatic fibrosis

A review of literature reveals a number of additional features of AIP not included in the Japanese criteria. These include serologic features, other organ involvement, and response to steroids. Serologic abnormalities in AIP include elevated titers of γ -globulins, IgG, and elevated titers of a variety of antibodies including anti-nuclear antibody, rheumatoid factor, anti-carbonic anhydrase antibody, and antilactoferrin antibody.^{15–17} Recently Hamano et al¹⁸ reported that elevated serum levels of the IgG4 subset of IgG were a sensitive and specific marker of AIP.

AIP has been traditionally described as being “associated” with a number of disorders such as primary sclerosing cholangitis, Sjögren’s syndrome, and retroperitoneal fibrosis.¹⁹ However, more recent studies suggest that these “associations” are in fact manifestations of AIP that mimic other well-described diseases. The common thread that links these manifestations is the finding of tissue infiltration with abundant IgG4-positive cells,^{11,13,20} a characteristic that distinguishes them from the diseases they mimic. The pancreatic and extrapancreatic manifestations of AIP respond, often dramatically, to steroid therapy, whereas the

Table 2. Diagnostic Criteria for AIP (The HISORt Criteria): Definitions

Category	Criteria
Histology	At least one of the following: (1) Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis (LPSP) (2) Lymphoplasmacytic infiltrate with storiform fibrosis showing abundant (≥ 10 cells/HPF) IgG4-positive cells (Figure 1)
Pancreatic imaging	Typical: diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct (Figure 2) Others ^a : Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; or pancreatitis
Serology	Elevated serum IgG4 level (normal, 8–140 mg/dL)
Other organ involvement ^b	Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
Response to steroid therapy ^c	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy (Figure 3)

^aWith negative work-up for known etiologies for pancreatic disease, especially pancreatic/biliary cancer.

^bRadiologic evidence of organ involvement can be confirmed by biopsy showing lymphoplasmacytic infiltrate with abundant IgG4-positive cells or its resolution/improvement with steroid therapy.

^cSteroid therapy should be given only to patients with negative work-up for known etiologies for pancreatic disease and only to those in whom response can be objectively assessed. It should not be used as a substitute for a thorough search for etiology.

diseases they mimic do not. The typical example of this steroid responsiveness is seen in sclerosing cholangitis-like biliary strictures in AIP, which respond to steroid therapy,^{21,22} whereas typical primary sclerosing cholangitis does not.²³

Since 1999 we have maintained a prospective database of patients investigated for AIP. From this database we identified 29 patients who met histologic criteria for AIP. We describe the histologic, clinical, serologic, and imaging features of these patients and report their response to steroids. On the basis of this experience, we propose new diagnostic criteria for AIP and describe the features of 20 additional patients who met alternate (non-histologic) criteria for AIP.

Methods

The study was approved by the Mayo Foundation Institutional Review Board.

Patients

From a database of patients suspected or diagnosed to have AIP, prospectively maintained since 1999 by one of the

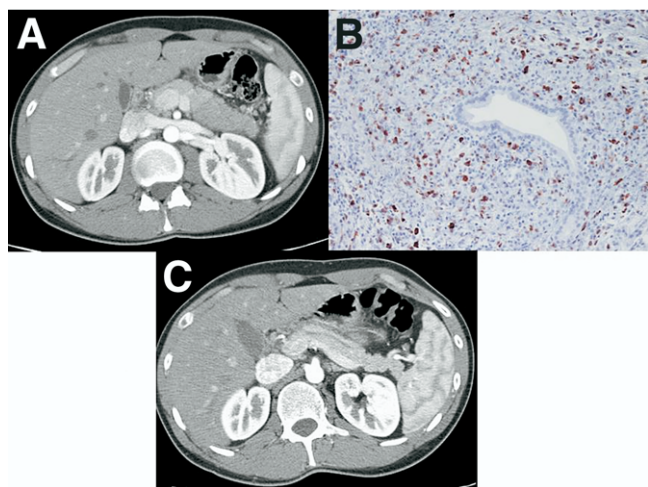


Figure 1. Diagnostic group A: diagnostic histology. Low-density lesion is seen in the tail of the pancreas (A) with elevated serum IgG4 (450 mg/dL). A core biopsy of the pancreas shows lymphoplasmacytic infiltrate with abundant IgG4-positive cells on immunostaining (B). After prednisone therapy there is resolution of the changes in the pancreatic tail with development of mild atrophy (C).

authors (S.T.C.), we identified 29 patients who met histologic criteria for AIP (Table 2). We noted their demographic data and clinical presentation at onset and diagnosis. We also noted the presence of 5 criteria pertaining to histology, imaging, serology, other organ involvement, and response to steroid therapy as defined in Table 2 (the HISORT Criteria).

Pancreatic Histology and Immunostaining

The resection specimens and core biopsies of the 29 patients were reviewed by a single pathologist (T.C.S.). For tissue immunostaining, monoclonal anti-human IgG4 antibody (Zymed, San Francisco, CA) was applied to 4- μ m thick sections by using standard immunohistochemical techniques. Peroxidase activity was visualized by applying diaminobenzidine solution containing 0.05% H₂O₂. Sections were then counterstained with hematoxylin, dehydrated, cleared, and mounted. Appropriate positive and negative controls were run with each batch. The number of immunohistochemically identified IgG4-positive plasma cells per high-power field (HPF) was counted in each specimen (Nikon E 600, field diameter 0.625 mm; Nikon, Tokyo, Japan). Moderate (11–30 cells/HPF) to severe (>30 cells/HPF) infiltration with IgG4-positive cells¹ was considered diagnostic of AIP.

Imaging

Available pretreatment computed tomography (CT) scans (n = 22) were reviewed by a single radiologist (N.T.) blinded to final diagnosis. Pancreatic enlargement was defined as an increase in size of the gland in the absence of a discrete mass. Mass was defined as a lesion that had different density compared with surrounding pancreatic tissue. Available endoscopic retrograde cholangiopancreatograms were reviewed.

Serum Immunoglobulin G4

The concentrations of IgG and its subclasses in serum were measured in 21 patients by automated nephelometry.²⁴ Results are expressed as mean $\pm$ standard error of the mean.

Other Organ Involvement

Presence or history of other organ involvement (PSC-like changes, Sjögren's syndrome-like salivary gland disease, mediastinal adenopathy, tubulointerstitial nephritis, and retroperitoneal fibrosis) was noted.

Response to Steroid Therapy

A total of 17 patients with histologically confirmed AIP received steroids. The indications, dosage, and duration of therapy were noted. Biliary and pancreatic duct strictures were considered steroid-responsive if follow-up imaging showed normal biliary tree and pancreatic duct, respectively. Pancreatic mass/enlargement was considered steroid-responsive if the abnormality resolved, with post-therapy imaging showing normal-appearing pancreas or pancreatic atrophy. Marked improvement was defined as measurable reduction in size but not resolution of pancreatic mass or improvement in ductal irregularity, often permitting removal of stents.

Diagnostic Groups

On the basis of review of the performance of each of the 5 criteria, we identified combinations that were diagnostic of AIP. Patients who met alternate diagnostic criteria were identified, and their profile was noted and compared with that of patients with AIP meeting histologic criteria.

Results

Histologically Confirmed Autoimmune Pancreatitis

Demographics and presentation. The mean age of the 29 patients was 63 ± 18 years (range, 14–85 years), with 23 (79%) being >50 years of age; majority (83%) were male. Presentation at the onset of symptoms was with obstructive jaundice in 23 (73%) patients, with pancreatic mass in 3, and with new-onset diabetes, steatorrhea, and pancreatitis in 1 each. Abdominal pain was present at onset in 10 of 29 (34.5%) patients but was mild in all, and none required narcotics for pain relief. At diagnosis, which was made weeks to years after onset of symptoms, 10 patients already had a resection for pancreatic mass, 7 had obstructive jaundice with distal bile duct stricture, 3 had persistent pancreatic mass, 4 had sclerosing cholangitis, 3 had nonspecific dyspeptic symptoms, and 1 each had weight loss caused by uncontrolled diabetes and steatorrhea.

Pancreatic histology and immunostaining. Pancreatic resection specimens (n = 13) showed features of LPSP in 12 of 13 patients, and 1 showed extensive fibrosis with intense lymphoplasmacytic infiltrate without obliterative phlebitis. IgG4 immunostaining was positive in 7 of 8 patients including the one who did not show full spectrum of changes of LPSP on histology; 1 patient had only a few IgG4-positive cells, despite showing LPSP on histology. Sixteen subjects underwent pancreatic core biopsy. In 7 of 16 (44%) the full spectrum of diagnostic changes of LPSP were seen. IgG4 immunostaining showed abundant IgG4-positive cells in 15 of 16 patients; 1 patient had only a few IgG4-positive cells, despite showing LPSP on histology.

Imaging. Pretreatment CT scans of 22 patients with AIP were available for re-review. Six patients had diffuse pancreatic enlargement, 10 had focal enlargement, and 3 had a distinct mass, 2 were normal, and 1 had changes of acute pancreatitis. Four patients had pancreatic calcification noted on CT at diagnosis or follow-up. A pancreatogram was performed in 7 of 29 patients, 4 with diffuse gland enlargement, 2 with focal enlargement, and 1 with a normal-appearing gland on CT. There was no correlation between CT and pancreatographic findings. Of the 4 with diffuse pancreatic

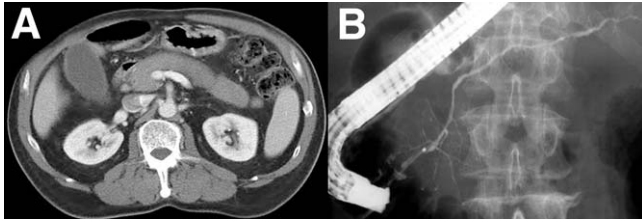


Figure 2. Diagnostic group B: typical imaging features. Characteristic diffusely enlarged “sausage-shaped” gland (A) with pancreatogram showing diffusely irregular narrow pancreatic duct (B).

enlargement on CT, 2 had focal strictures, and 2 had diffusely irregular duct on pancreatography. In the 2 with focal pancreatic enlargement on CT, 1 had diffuse irregularity and the other a focal stricture on pancreatography. The patient with a normal-appearing gland on CT had a diffusely irregular pancreatic duct. The wide spectrum of imaging findings in the pancreas is illustrated in Figure 4.

Serology. IgG4 was more frequently elevated in AIP than total IgG (15/21 [71%] vs 8/21 [38%]; $P = .03$). All patients with AIP who had elevated total IgG also had IgG4 elevation. Eleven of 12 patients with elevated serum IgG4 who had pancreatic tissue immunostaining showed abundant IgG4-positive cells. However, all 6 patients with normal serum IgG4 levels also had positive tissue immunostaining for IgG4-positive cells.

Other organ involvement. Evidence of other organ involvement was seen in 11 of 29 (38%) patients. The organs involved (other than distal common bile duct) included the common hepatic and/or intrahepatic

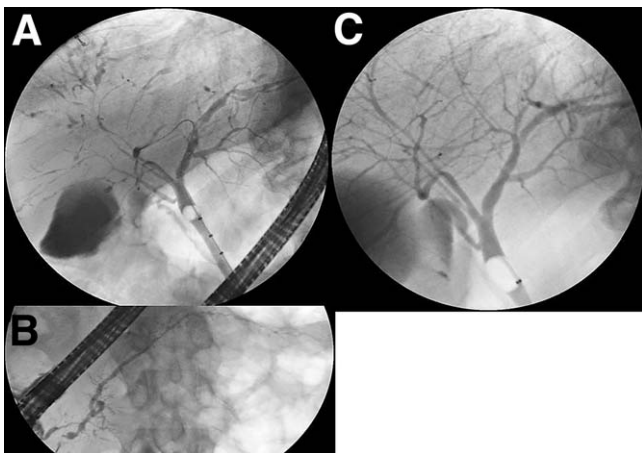


Figure 3. Diagnostic group C: response to steroid therapy. Endoscopic retrograde cholangiopancreatography shows diffuse stricturing of the intrahepatic biliary tree (A) and a diffusely irregular pancreatic duct (B). Serum IgG4 elevated at 870 mg/dL. After 12-week course of prednisone there is nearly complete resolution of intrahepatic strictures and normalization of serum IgG4 levels.

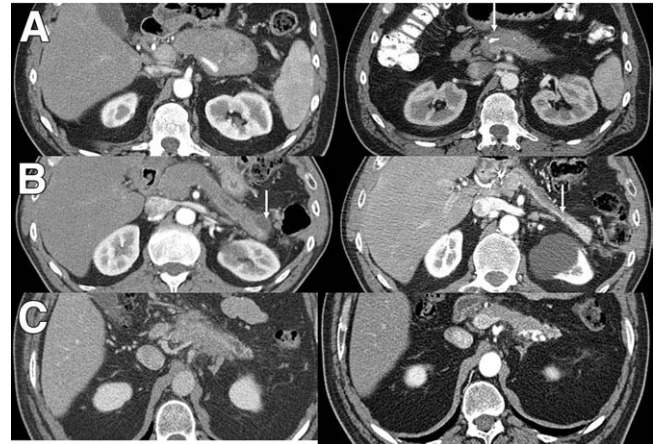


Figure 4. Spectrum of CT appearances of the pancreas in AIP. (A) *Left panel:* diffuse swelling of pancreas, body/tail > head with elevated serum IgG4 (351 mg/dL). *Right panel:* 6 months after completion of steroid course, multiple intraductal calculi (arrow) seen in the absence of pain or clinical pancreatitis. (B) *Left panel:* peripancreatic fluid collection (arrow) with elevated serum IgG4 (1710 mg/dL). *Right panel:* 10 months after steroid therapy there is marked pancreatic atrophy. (C) *Left panel:* unresectable pancreatic body mass with dilatation of duct in the tail with normal serum IgG4. Core biopsy of mass showed abundant IgG4-positive cells. *Right panel:* 6 weeks after steroid course, there is marked reduction in size of mass.

bile duct ($n = 5$), retroperitoneum ($n = 3$), salivary gland ($n = 2$), and mediastinal lymph nodes ($n = 1$). The intrapancreatic portion of the bile duct was frequently involved, and the stricture was indistinguishable from malignant biliary obstruction. Involvement of proximal extrahepatic ducts and intrahepatic biliary tree raised suspicion of primary sclerosing cholangitis and/or cholangiocarcinoma.

Response to steroids. A total of 17 patients received steroids. Indications for starting therapy included persistent pancreatic enlargement/mass ($n = 6$), intrahepatic biliary strictures ($n = 3$), obstructive jaundice with distal biliary stricture ($n = 5$), and 1 each with retroperitoneal fibrosis, pancreatitis with pancreatic duct stricture, and uncontrolled diabetes and weight loss. All patients were treated with oral prednisone. The most common regimen involved an induction dose of 40 mg for 4 weeks followed by a taper (5 mg/week) during a period of 8 weeks. The patients have been followed for a median of 6.5 months (range, 2–56 months) after initiation of steroid treatment. All patients have shown complete resolution or marked improvement in the manifestations for which steroids were started.

Diagnostic categories. On the basis of this experience we propose new criteria for diagnosis of AIP (Table 3). AIP can be diagnosed in subjects with characteristic histology (LPSP) and/or pancreatic IgG4 immunostaining (group A, Figure 1), in subjects who meet

Table 3. Diagnostic Groups: Patients Meeting Criteria for ≥1 of the Groups Have AIP

Group A: diagnostic pancreatic histology (Figure 2)	Presence of one or both of the following criteria Resection specimen or core biopsy showing the full spectrum of changes of LPSP, ie, periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis. Presence of a lymphoplasmacytic infiltrate without other features of LPSP is not diagnostic of AIP. ≥10 IgG4-positive cells/HPF IgG4 on immunostain of pancreatic lymphoplasmacytic infiltrate.
Group B: typical imaging + serology (Figure 1)	Presence of all the following criteria CT or magnetic resonance imaging scan showing diffusely enlarged pancreas with delayed and “rim” enhancement Pancreatogram showing diffusely irregular pancreatic duct Elevated serum IgG4 levels
Group C: response to steroids (Figure 3)	Presence of all the following criteria Unexplained pancreatic disease after negative work-up for known etiologies including cancer Elevated serum IgG4 levels and/or other organ involvement confirmed by presence of abundant IgG4-positive cells Resolution/marked improvement in pancreatic and/or extrapancreatic manifestations with steroid therapy

Japanese imaging criteria and have elevated serum IgG4 levels (group B, Figure 2), and in subjects in whom their pancreatic/extrapancreatic disease responds to steroid therapy (group C, Figure 3). We reviewed our database and identified an additional 20 patients who met the expanded diagnostic criteria for AIP (Table 4). There was no difference in age distribution, gender, proportion with diffuse pancreatic enlargement, proportion with elevated serum IgG4, or response to steroids among the 3 groups. However, the proportion with other organ involvement was significantly greater in patients in group C, reflecting the fact that these patients were referred predominantly for extrapancreatic manifestations of AIP and often did not have a pancreatic lesion amenable to biopsy.

Discussion

Unlike usual chronic pancreatitis, AIP is a relatively painless disease, despite histology showing chronic pancreatic inflammation and evidence of pancreatic edema, peripancreatic inflammation, and in some cases

pancreatic calculi. Although the most common acute presentation of AIP is with obstructive jaundice, it has protean other manifestations, both pancreatic and extrapancreatic.^{1,13,25–29} Many patients present during the postacute phase, months to years after initial presentation, and some might seek medical attention for extrapancreatic disease. In such patients the pancreas might show persistent mass; however, it is more likely that the gland might be atrophic, show calcification,³⁰ or even be radiographically normal. The wide spectrum of changes on pancreatic imaging in AIP is shown in Figure 4.

AIP should be suspected in patients with unexplained pancreatic disease presenting with or having history of obstructive jaundice, pancreatic mass/enlargement, pancreatitis, pancreatic atrophy, or exocrine insufficiency. However, our data suggest that search for AIP in patients with abdominal pain as the predominant symptom is likely to be low yield. In patients presenting with an extrapancreatic manifestation, presence or history of unexplained pancreatic disease or painless “chronic pancreatitis” might be an important diagnostic clue.

In patients suspected to have AIP, the diagnosis can be made in 1 of 3 ways. Regardless of pancreatic imaging features, the diagnosis of AIP can be made if histology shows all features of LPSP (periductal lymphoplasmacytic infiltrate with storiform fibrosis and obliterative phlebitis) or by immunostaining, if the characteristic lymphoplasmacytic infiltrate has >10 IgG4-positive/HPF (group A, Table 3). Thus, histologic criteria could be considered the gold standard for diagnosis of AIP. A combination of characteristic pancreatic imaging and elevation in serum IgG4 is also diagnostic (group B, Table 3); however, in our study these criteria lacked sensitivity because only 3 patients met these criteria (group C, Table 4). Finally, in patients with a strong suspicion of AIP (idiopathic pancreatic disease associated with elevated serum IgG4 level and/or other organ involvement), the diagnosis can be confirmed if the manifestations, pancreatic and/or extrapancreatic, resolve or markedly improve with steroid therapy (group C, Table 3).

Crucial to preoperative identification of AIP is the question of whether the diagnosis of AIP can be made on pancreatic core biopsy specimens. We confirm findings of a recent study by Zamboni et al⁵ that pancreatic core biopsies are often nondiagnostic by routine histology alone because they do not show the complete spectrum of diagnostic changes of LPSP due to small sample size and lack of a duct or vein in the biopsy specimen. We show that the diagnostic yield of core biopsies can be significantly enhanced by tissue immunostaining for

Table 4. Demographic and Clinical Profiles of the 3 Diagnostic Groups

Diagnostic groups	Median age (y) (range)	Gender (% male)	Histology	Imaging (CT): diffuse pancreatic enlargement	Serology: elevated serum IgG4	Other organ involvement	Response to steroids
Group A: diagnostic histology (n = 29)	72 ^a (14–85)	24/29 ^a (83%)	Diagnostic 29/29 (100%)	6/22 (27%) ^a	15/21 ^a (71%)	11/29 ^b (38%)	17/17 ^a (100%)
Group B: characteristic imaging with elevated serum IgG4 (n = 3)	59 (38–75)	3/3 (100%)	Not done	3/3 (100%)	3/3 (100%)	1/3 (33%)	1/1 (100%)
Group C: response to steroids (n = 17)	60.5 (33–77)	14/17 (82%)	Supportive (lymphoplasmacytic infiltrate + fibrosis) (n = 7), nondiagnostic (n = 1)	9/17 (53%)	13/16 (81%)	12/17 (71%)	17/17 (100%)

^aP = not significant vs group B or C.

^bP = .03 vs group C.

IgG4-positive cells. In our study, although only 7 of 16 (44%) core biopsies showed the full spectrum of diagnostic changes of LPSP, IgG4 immunostaining showed abundant IgG4-positive cells in 15 of 16 patients, and either histology or immunostain was diagnostic in all 16.

Apart from histology and imaging, we used serum IgG4 levels and other organ involvement as clinical clues to suspect AIP. We confirm the observation by Hamano et al¹⁸ that serum IgG4 is more sensitive than total serum IgG for diagnosis of AIP. However, we found a lower sensitivity for serum IgG4 compared with that reported by Hamano et al (78% vs 95%). Interestingly, tissue infiltration with IgG4-positive cells was seen even in the absence of elevation in serum levels of IgG4.

We found other organ involvement in 24 of 49 (49%) patients with AIP. In patients presenting with jaundice, the presence of unusual extrapancreatic findings such as retroperitoneal fibrosis, intrahepatic biliary strictures, or salivary gland enlargement are important clues to the diagnosis of AIP. In patients with predominantly extrapancreatic disease, immunostaining the tissue from an involved organ to look for infiltration with IgG4-positive cells can provide supportive evidence.¹ We used this approach in the patient with renal failure in whom the kidney biopsy showed IgG4-positive interstitial nephritis.³¹ Recent studies suggest that many other organs might be affected by this disease including breast,³² kidney,³¹ and stomach.³³ Future studies are likely to expand the spectrum of this disease considerably, which has appropriately been called systemic IgG4 disease.¹³

Although pancreatic histology is the most definitive way to diagnose AIP, in some patients it might not be

feasible to obtain pancreatic biopsy. In such patients, response to steroids is helpful in confirming the diagnosis of AIP because no other pancreaticobiliary disease, especially pancreatic cancer, is known to respond to steroids. All 35 patients treated with steroids in our study exhibited significant improvement or resolution of manifestations of AIP. AIP is a fibroinflammatory disorder. The inflammatory component consisting of a lymphoplasmacytic infiltrate resolves with steroid therapy. However, this is accompanied by intense fibrosis that is unaffected by therapy and might cause permanent damage to the affected organ. Therefore, restoration of normal structure and function does not occur in all patients with AIP despite steroid therapy.

A note of caution needs to be sounded regarding use of steroid trial for diagnosis of AIP. Steroid trial should not be used as a substitute for a thorough search for etiology and should be given only to patients with negative work-up for known etiologies for pancreatic/biliary disease, especially cancer. Moreover, steroids should only be given to those in whom the response can be objectively assessed. In patients without pancreatic mass/enlargement or manifest extrapancreatic disease, it might be difficult to assess steroid response.

In summary, in the absence of a diagnostic serologic test for AIP, its diagnosis rests on identifying unique patterns of abnormalities. The Japanese criteria for AIP focus heavily on characteristic pancreatic imaging and therefore lack sensitivity to diagnose the wide spectrum of manifestations of AIP. The proposed criteria reflect the current understanding of AIP as a systemic steroid-responsive disorder characterized by tissue infiltration with IgG4-positive cells and clearly identify a wider

spectrum of manifestations of the disease than do the Japanese criteria. Improved understanding of the pathogenesis of AIP will help the development of better diagnostic biomarkers for AIP.

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