

Recent Advances in the Diagnosis and Management of Autoimmune Pancreatitis: Similarities and Differences in Japan and Korea

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Two subtypes (types 1 and 2) of autoimmune pancreatitis (AIP) are currently recognized. Type 1 AIP is related to immunoglobulin G4 (lymphoplasmacytic sclerosing pancreatitis), and type 2 AIP is characterized by neutrophilic infiltration into the epithelium of the pancreatic duct (idiopathic duct-centric pancreatitis). Although type 2 AIP is sometimes observed in the United States and Europe, most cases of AIP in Japan and Korea are type 1. The international consensus diagnostic criteria for AIP were created to be applicable worldwide and to distinguish between the two types of AIP. AIP is diagnosed based on the presence of at least one of the five cardinal features (i.e., imaging, serology, other organ involvement, histology, and response to steroid therapy). Oral steroids are the standard therapy for AIP, but immunomodulatory drugs or rituximab have been successfully used for patients with relapsed AIP in the United States and Europe. Generally, the clinical manifestations and demography of AIP are similar between Japan and Korea. However, there are differences in some aspects of the disease, including the proportion of other organ involvement, the prevalence of type 2 AIP, diagnostic criteria and maintenance therapy between the two countries. (**Gut Liver 2013;7:394-400**)

Key Words: Pancreatitis; Immunoglobulin G; Steroids

INTRODUCTION

Autoimmune pancreatitis (AIP) is a form of pancreatitis with a presumed autoimmune etiology and is currently recognized as a pancreatic lesion of immunoglobulin G4 (IgG4)-related dis-

ease.^{1,2} Since Yoshida *et al.*³ proposed AIP as a diagnostic entity in 1995, frequent reports of AIP in various countries, including Japan and Korea, have been published. A definite diagnostic serological marker for AIP remains unknown, and it is therefore diagnosed based on the presence of a combination of unique abnormalities. The diagnostic criteria for AIP established by the Japan Pancreas Society in 2002^{4,5} were revised in 2006.⁶ These criteria aimed to avoid the misdiagnosis of pancreatic cancer and to be as simple and user-friendly as possible for both general physicians and pancreatologists. The criteria consisted of the following: radiological evidence of pancreatic enlargement and irregular narrowing of the main pancreatic duct; increased serum levels of γ -globulin, IgG, and IgG4 levels, or the presence of autoantibodies; and histological evidence of both lymphoplasmacytic infiltration and fibrosis in the pancreas. Because these criteria were based on the minimum consensus for diagnosing AIP, the presence of the imaging criterion is essential. New diagnostic criteria proposed in Korea⁷ and the United States⁸ during 2006 included the additional factors of a response to steroid therapy and other organ involvement (OOI). As a first step towards the international diagnostic criteria, Japanese and Korean pancreatologists established the Asian diagnostic criteria that included response to steroid therapy as an optional criterion during 2008.⁹ Revised HISORT criteria were proposed in 2009.¹⁰

Types 1 and 2 AIP are distinct histological entities. The international consensus diagnostic criteria (ICDC) for AIP were created to be applicable worldwide and to separately diagnose both types of AIP.¹¹ This paper reviewed recent concept of AIP subtypes, the ICDC, and AIP treatment, and compared AIP between Japan and Korea.

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SUBTYPES

AIP was originally histologically characterized as dense infiltration of T lymphocytes and IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis in the pancreas; this is referred to as lymphoplasmacytic sclerosing pancreatitis (LPSP) (Fig. 1).¹² American and European pathologists described another histological appearance that is unique to AIP based on retrospective, histological assessments of resected pancreases from patients with mass-forming chronic pancreatitis. This appearance was termed idiopathic duct-centric pancreatitis (IDCP) in 2003,¹³ or AIP with granulocyte epithelial lesions in 2004.¹⁴ Neutrophilic infiltration in the epithelium of the pancreatic ducts is a characteristic feature of IDCP that is not detected in

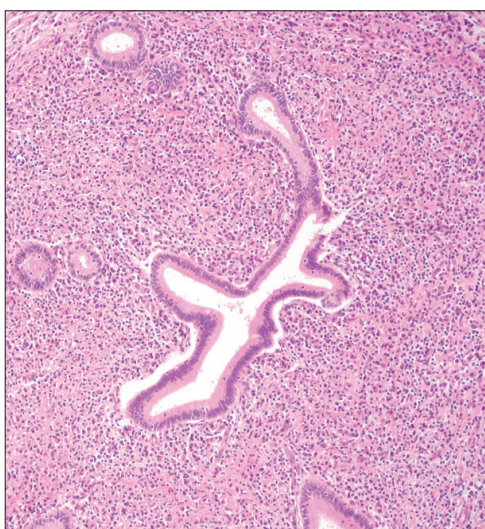


Fig. 1. Histological features of type 1 autoimmune pancreatitis showing lymphoplasmacytic sclerosing pancreatitis (H&E stain, $\times 60$).

LPSP (Fig. 2). Infiltrating IgG4-positive plasma cells and obliterative phlebitis are uncommon in IDCP. The necessity for histological assessment has rendered diagnosing IDCP difficult. Presently, LPSP and IDCP are referred to as types 1 and 2 AIP, respectively.^{15,16}

Patients with type 2 AIP are generally younger than those with type 1, might not be predominantly male, and rarely have elevated serum IgG4. Patients with type 2 AIP rarely have associated sclerosing diseases, but they are more likely to have both acute pancreatitis and ulcerative colitis than those with type 1. Both types respond well to steroid therapy, although the relapse rate is lower for type 2. The prevalence of type 2 AIP differs throughout the world.¹³⁻¹⁹ A recent international multicenter survey²⁰ has found that the proportion of patients diagnosed with type 2 AIP was lower in Asia (3.7%) than in both Europe (12.9%, $p < 0.001$) and North America (13.7%, $p < 0.001$). The two types of AIP are clinically, regionally, and ethnically different

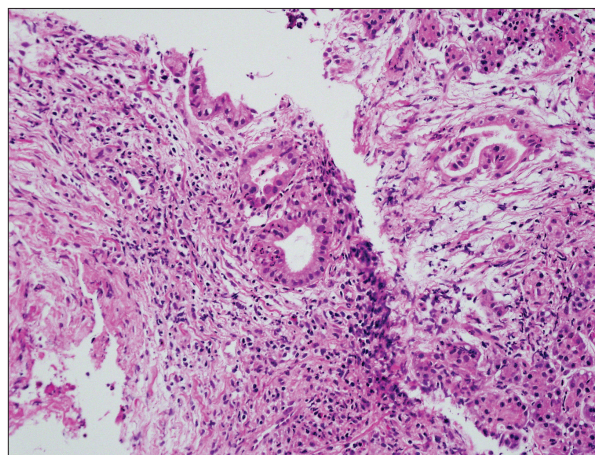


Fig. 2. Histological features of type 2 autoimmune pancreatitis showing idiopathic duct-centric pancreatitis (H&E stain, $\times 100$).

Table 1. Diagnosis and Clinicopathological Features of Types 1 and 2 Autoimmune Pancreatitis

	Type 1	Type 2
Necessity of pancreatic histology for diagnosis	Not mandatory	Mandatory
Histology	LPSP	IDCP or with GEL
Infiltration of IgG4-positive cells	Frequent	Rare
Neutrophilic infiltration	Rare	Frequent
Epidemiology	Asia>USA, Europe	Europe, USA>Asia
Age	Elderly	Young or middle-aged
Gender	Male>female	Male \geq female
Elevation of serum IgG4 levels	Frequent	Rare
Sclerosing extrapancreatic lesions	Frequent	Rare
Acute pancreatitis	Rare	Occasional
Inflammatory bowel disease	Rare	Occasional
Steroid responsiveness	Good	Good
Relapse	Occasional	Rare

IgG4, immunoglobulin G4; LPSP, lymphoplasmacytic sclerosing pancreatitis; IDCP, idiopathic duct-centric pancreatitis; GEL, granulocyte epithelial lesion.

entities, and both need to be accurately differentiated from pancreatic cancer (Table 1).

INTERNATIONAL CONSENSUS DIAGNOSTIC CRITERIA

The ICDC for AIP¹¹ were developed for use to diagnose AIP safely, to avoid misdiagnosing pancreatic cancer as AIP, and to diagnose AIP at acute presentation. Criteria for the two types of AIP were independently developed, and AIP is diagnosed based on one or more of the following cardinal features: imaging characteristics of the pancreatic parenchyma and pancreatic duct, serology, OOI, pancreatic histology, and the optional criterion of response to steroid therapy. Depending on diagnostic reliability, each feature has been categorized as either level 1 or 2. Types 1 and 2 AIP can be diagnosed as definitive or probable, but they are sometimes indistinguishable (AIP-not otherwise specified).

Cross-sectional pancreatic computed tomography or magnetic resonance imaging is considered the first essential clue, and findings have been classified as typical diffuse enlargement and indeterminate images of segmental or focal enlargement of the pancreas. Endoscopic retrograde pancreatography findings of the pancreatic duct are long or multiple (level 1), or segmental

or focal (level 2) narrowing without marked upstream dilatation. Levels 1 and 2 serological criteria for type 1 AIP are marked (>270 mg/dL) and mildly (>135 mg/dL) elevated serum IgG4 values. The OOI criteria for type 1 AIP include either histological findings of any three of the four features in extrapancreatic organs or typical radiological evidence of proximal bile duct stricture or retroperitoneal fibrosis (level 1), as well as histological, physical, or radiological evidence of symmetrically enlarged salivary/lacrimal glands or renal involvement (level 2). The level 1 histological criteria for type 1 AIP consist of LPSP with more than three features on core biopsy or resected specimens; and level 2 consist of any two features on core biopsy specimens.

A diagnostic steroid trial is an optional criterion. Response to steroid therapy is defined as rapid (within 2 weeks), radiologically demonstrable resolution, or obvious improvement in pancreatic or extrapancreatic manifestations. However, a steroid trial should be applied only after a negative work-up for cancer, including endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) (Table 2). In the criteria for type 2 AIP, there are no serological criterion; the criterion of OOI are only level 2 (clinically diagnosed inflammatory bowel disease); and the histological criteria are granulocytic infiltration and absent or scant IgG4-positive cells.

Table 2. Level 1 and 2 Criteria for Type 1 Autoimmune Pancreatitis

Criterion	Level 1	Level 2
Parenchymal imaging	Typical: diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical): segmental/focal enlargement with delayed enhancement
Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
Serology	IgG4, >2×_ upper limit of normal value	IgG4, 1-2×_ upper limit of normal value
Other organ involvement	(1) or (2) (1) Histology of extrapancreatic organs Any three of the following: a) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration b) Storiform fibrosis granulocytic infiltration c) Obliterative phlebitis d) Abundant (>10 cells/HPF) IgG4-positive cells (2) Typical radiological evidence At least one of the following: a) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture b) Retroperitoneal fibrosis	(1) or (2) (1) Histology of extrapancreatic organs including endoscopic biopsy of bile duct Both of the following: a) Marked lymphoplasmacytic infiltration with fibrosis without granulocytic infiltration b) Abundant (>10 cells/HPF) IgG4-positive cells (2) Physical or radiological evidence At least one of the following: a) Symmetrically enlarged salivary/lacrimal glands b) Radiological evidence of renal involvement described in association with AIP
Histology of the pancreas	LPSP (core biopsy/resection) At least three of the following: (1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration (2) Obliterative phlebitis (3) Storiform fibrosis (4) Abundant (>10 cells/HPF) IgG4-positive cells	LPSP (core biopsy) Any two of the following: (1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration (2) Obliterative phlebitis (3) Storiform fibrosis (4) Abundant (>10 cells/HPF) IgG4-positive cells

Diagnostic steroid trial

Response to steroid (Rt) rapid (e2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations

ERP, endoscopic retrograde pancreatography; IgG4, immunoglobulin G4; HPF, high power field; AIP, autoimmune pancreatitis; LPSP, lymphoplasmacytic sclerosing pancreatitis.

Definitive type 1 can be diagnosed only from a histological assessment of resected pancreas or core biopsy specimens showing LPSP. Any single additional nonductal cardinal criterion is necessary to definitively diagnose definitive type 1 AIP when imaging findings are diffuse. When patients have segmental or focal imaging findings, two or more of any level 1 and ductal level 2 cardinal criteria are necessary. To confirm the diagnosis in association with the response to steroid therapy, one nonductal level 1 or ductal level 1 with any nonductal level 2 cardinal criterion is necessary. Response to steroid with one nonductal level 2 cardinal criterion is diagnosed as probable type 1 AIP (Table 3).

Either histologically confirmed IDCP or clinical inflammatory bowel disease with level 2 histology and a response to steroid therapy is needed for a definitive diagnosis of type 2 AIP.

TREATMENT AND PROGNOSIS

Oral steroids have become the standard therapy because the fibroinflammatory process in AIP responds well to these drugs.²¹ However, pancreatic cancer must be differentiated from AIP before starting steroid treatment. According to an international study of AIP,²⁰ steroids are administered to 681 of 684 (74%) patients with type 1 AIP, and remission was achieved in 99.6% of them.

The indications for steroid therapy in AIP published in the Japanese consensus guidelines for the management of AIP²² include symptoms such as obstructive jaundice due to associated sclerosing cholangitis, and symptomatic extrapancreatic lesions such as hydronephrosis due to retroperitoneal fibrosis. Endoscopic or percutaneous transhepatic biliary drainage must proceed first for patients with obstructive jaundice, and glucose levels must be controlled in those with diabetes mellitus (DM) before starting steroid therapy. Oral prednisolone is usually started at 0.6 mg/kg/day and tapered by 5 mg every 1 to 2 weeks; these patients are periodically monitored by serological and imaging tests from the start of therapy. Magnetic resonance cholangiopancreatography is useful for noninvasive judging responses to steroids in the pancreaticobiliary ducts. The pan-

creas usually returns to the normal size within a few weeks, and biliary drainage becomes unnecessary. A rapid response to steroids is reassuring and confirms the diagnosis of AIP. If steroid effectiveness is reduced, the patient should be re-evaluated for suspected pancreatic cancer. The initial dose of steroids should be administered for 2 to 4 weeks, and then gradually tapered to a maintenance dose of 2.5 to 5 mg/day over 2 to 3 months. Maintenance therapy usually continues for 1 to 2 years to prevent relapse. However, the optimal duration of maintenance therapy is an issue requiring further investigation, as continued steroid therapy might increase the risk of steroid-induced adverse events. Elderly persons who are already at higher risk for osteoporosis and complications of glucose intolerance often develop AIP.

The international study²⁰ found that the enlarged pancreas returned to near-normal size in 65.7%, became atrophic in 28.4%, and remained enlarged in 5.9% of patients treated with steroids. Elevated serum IgG4 levels decreased in 95.7% of the treated patients and returned to within normal limits for 45.7%. Among patients treated with steroids for type 1 AIP, 35.8% relapsed and relapse usually occurred after discontinuation of the therapy. The proportion of patients with relapse was significantly higher among those with (56.1%) than without (25.7%) sclerosing cholangitis in the intrahepatic or hilar bile duct.

Relapsed AIP can be effectively treated by readministering steroids or increasing the dose. Patients with relapse after steroid withdrawal in the United States^{23,24} and United Kingdom²⁵ have been treated with immunomodulatory drugs such as azathioprine to maintain remission. Patients with AIP that were refractory to steroids were recently treated with rituximab, a monoclonal antibody directed toward the CD20 antigen on B lymphocytes, with an excellent outcome.²⁴

An international standard regimen of therapy for AIP that includes the necessity for treatment with which type of drugs and the duration of maintenance therapy needs to be established.

The long-term prognosis of AIP is not well known. Recurrent attacks of AIP can result in pancreatic stone formation,^{20,26,27} and recent reports have described several patients with pancreatic cancer complicated with AIP.²² Although the relationship

Table 3. Diagnosis of Definitive and Probable Type 1 Autoimmune Pancreatitis Using the International Consensus Diagnostic Criteria

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI+Rt or level 1 D+level 2 S/OOI/H+Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H+Rt

AIP, autoimmune pancreatitis; LPSP, lymphoplasmacytic sclerosing pancreatitis; H, histological criterion; D, ductal criterion; S, serological criterion; OOI, other organ involvement criterion; Rt, response to steroid.

*Level 2 D is counted as level 1 in this setting.

between the two diseases remains unclear, not only AIP, but also pancreatic cancer, needs to be carefully considered during follow-up.

SIMILARITY AND DIFFERENCE OF AIP IN JAPAN AND KOREA

The first Korean case of AIP was reported in 2002.²⁸ Generally, the clinical manifestation and demography are similar between Japan and Korea. However, there are some differences in some aspect including the proportion of OOI, type 2 AIP, diagnostic criteria, and maintenance therapy between two countries.

1. Demography and initial symptoms

According to the Korean multicenter study before 2007,²⁹ the mean age of the patients was 56 years, and 73% were men. Obstructive jaundice (52%) was the most common initial symptom. Another Korean single center study also showed the following characteristic features:³⁰ clinical findings similar to those of pancreatic cancer including weight loss (60%), obstructive jaundice (54.5%), and recent-onset diabetes (29.1%) as the major symptoms; a preponderance in elderly men (57.7 years old; male, 81.8%). Asian multicenter study also showed similar results (Table 4).³¹ Among 138 Korean patients with AIP, the mean age of the patients was 57 years, and 72% were men. Obstructive jaundice (54%) was the most common symptom, and weight loss was also associated in 35%. Exacerbation of pre-existed DM was also a common symptom (18%). Among 137 Japanese patients with AIP, the mean age of the patients was 62 years, and 80% were men. Obstructive jaundice (46%) was the most common symptom, but weight loss was associated only in 4%. Interestingly, asymptomatic detection was very common (26%). Obstructive jaundice was the most common symptom in both countries. However, weight loss and exacerbation of preexisted DM were more common in Korea than Japan. It may be explained that the patients were usually detected earlier in Japan than Korea.

Table 4. Comparison of the Demography and Initial Symptoms of Patients with Autoimmune Pancreatitis³¹

	Japan	Korea
No. of patients	137	138
Mean age, yr	62.2	57.2
Male:Female	3.9:1	2.6:1
Obstructive jaundice, %	46	54
Weight loss, %	4	35
Exacerbation of DM, %	5	18
No symptom, %	26	6

DM, diabetes mellitus.

2. OOI

Among 138 Korean patients with AIP, sclerosing cholangitis was the most common extrapancreatic lesion (81%) (Table 5).³¹ DM was frequently associated with AIP (47%) and retroperitoneal fibrosis (13%) and renal involvement (9%) were relatively common. In Japan, sclerosing cholangitis was also the most common extrapancreatic lesion (60%) and DM was frequently associated with AIP (36%). However, sclerosing sialoadenitis (22%) and sclerosing cholecystitis (10%) were relatively common OOI. Sclerosing cholangitis was the most common extrapancreatic lesion in both countries. However, sclerosing sialoadenitis and sclerosing cholecystitis were more common in Japan than Korea.

3. Types 1 and 2 AIP

An international multicenter survey showed that the proportion of type 2 AIP was different between Asian and Western countries.¹⁹ In USA, patients with IDCP were 19 (15%) among total 129 AIP patients. However, patients with IDCP were only two (1.2%) among 165 Japanese AIP patients and seven (5.6%) among 124 Korean patients. Those with LPSP were approximately 16 years older than those with IDCP.¹⁹ However, recent Korean single center study showed that type 2 AIP in all histologically confirmed AIP cases in Korea may not be as rare as originally thought.³² Among 120 patients with AIP, type 2 AIP patients were 15 (12.5%).

4. Differential diagnosis of pancreatic cancer

There are some clinical situations in which the image features are not typical for diagnosis of AIP. If the clinical and radiologic findings are not typical for pancreatic cancer, tissue acquisition is recommended through EUS. EUS guided Trucut biopsy was proven to be a safe and accurate procedure for obtaining a histological diagnosis in patients with suspected AIP.³³ Indeed, the EUS guided trucut biopsy is not always technically successful such as in pancreatic head lesions. However, EUS-FNA is always technically possible and it can exclude pancreatic cancer. In addition, newly developed biopsy needle (Procore; Cook, Bloom-

Table 5. Differences in the Involvement of Other Organ Involvement³¹

	Japan	Korea
No. of patients	137	138
Sclerosing cholangitis	82 (60)	95 (81)
Sclerosing sialoadenitis	30 (22)	8 (7)
Sclerosing cholecystitis	14 (10)	2 (2)
Retroperitoneal fibrosis	9 (7)	15 (13)
Renal involvement	4 (3)	11 (9)
Diabetes mellitus	49 (36)	56 (47)

Data are presented as number (%).

Table 6. Treatment of Autoimmune Pancreatitis^{19,31}

	Japan	Korea
Initial Pd dose	0.6 mg/kg	0.6 mg/kg or 30–40 mg
Tapering	5 mg/1–2 wk	5 mg/1–2 wk
Cessation, yr*	1–2	1
Maintenance, %	98	57
Response rate, %	100	100
Relapse rate, %	15	26

Pd, prednisolone.

*The longer cessation period may be related to the higher maintenance rate in Japan.

ington, IN, USA) can make it possible to obtain core specimen in head and uncinate portion³⁴ and is available in many Korean tertiary hospital. In Korea, tissue acquisition is strongly recommended in atypical case. If pancreatic cancer can be ruled out in atypical cases, a short term steroid trial is a useful method for the diagnosis of AIP. The Korean prospective study already have proved that 2-week steroid trial after initial negative investigation for malignancy is safe and useful in differentiating AIP from pancreatic cancer.³⁵

5. Treatment and prognosis of AIP

Steroids are a standard therapy for AIP and the indications for steroid therapy in AIP include symptoms such as obstructive jaundice and the presence of symptomatic extra-pancreatic lesions. The initial recommended dose of oral prednisolone for induction of remission is 0.6 mg/kg/day, administered for 4 weeks in Japan and Korea. Tapering schedules are similar between two countries (5 mg/1 to 2 wk). Maintenance therapy with a small dose of prednisolone was performed in almost all cases in Japan (98%), but the frequency of maintenance therapy was lower in Korea (57%) (Table 6).^{19,31} The average duration of maintenance therapy was 24 months in Japan and 13 months in Korea.³¹ In Korea, the relapse rate of cases receiving steroid therapy was 26% which was higher than 15% in Japan. The higher relapse rate in Korea may be due to the lower frequency of routine maintenance therapy and shorter duration of maintenance therapy in Korea.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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