

WJGP 5th Anniversary Special Issues (3): Pancreatitis**Review of the diagnosis, classification and management of autoimmune pancreatitis**

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Abstract

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis, with as yet undetermined incidence and prevalence in the general population. Our understanding of it continues to evolve. In the last few years, 2 separate subtypes have been identified: type 1 AIP has been recognised as the pancreatic manifestation of a multiorgan disease, named immunoglobulin G4 (IgG4)-related disease while type 2 AIP is a pancreas specific disorder not associated with IgG4. International criteria for the diagnosis of AIP have been defined: the HISORT criteria from the Mayo clinic, the Japan consensus criteria and, most recently, the international association of pancreatology "International Consensus Diagnostic Criteria". Despite this, in clinical practice it can still be very difficult to confirm the diagnosis and differenti-

ate AIP from a pancreatic cancer. There are no large studies into the long-term prognosis and management of relapses of AIP, and there is even less information at present regarding the Type 2 AIP subtype. Further studies are necessary to clarify the pathogenesis, treatment and long-term outcomes of this disease. Critically for clinicians, making the correct diagnosis and differentiating the disease from pancreatic cancer is of the utmost importance and the greatest challenge.

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Key words: Pancreatitis; Autoimmunity; Pancreatic cancer; Autoimmune pancreatitis; Immunoglobulin G4-related disease

Core tip: Type 1 autoimmune pancreatitis (AIP) is the pancreatic manifestation of a multiorgan disease, named immunoglobulin G4 (IgG4)-related disease while type 2 AIP is a pancreas specific disorder not associated with IgG4. Making the correct diagnosis and differentiating the disease from pancreatic cancer is of the utmost importance; an agreed diagnostic pathway should be in place and a multidisciplinary approach taken with each patient.

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INTRODUCTION

As early as 1961, Sarles *et al*^[1] described a form of idiopathic chronic pancreatitis with obstructive jaundice and hypergammaglobulinaemia, with the suspicion that there was an underlying autoimmune process. It was not until

1995, when Yoshida *et al.*^[2] coined the term “autoimmune pancreatitis” (AIP) that this concept was widely accepted and AIP differentiated from other forms of chronic pancreatitis. Since then, progress has been made in our understanding of the pathophysiology of AIP; type 1 AIP has been recognised as the pancreatic manifestation of a multiorgan disease, named IgG4-related disease, while type 2 AIP is a pancreas specific disorder not associated with IgG4^[3,4]. This review gives an overview of current thinking on the pathology of AIP, its clinical features (including serology), classification and treatment. Emphasis is placed upon the diagnostic challenge of distinguishing AIP from pancreatic cancer.

SEARCH STRATEGY

This review of the English language literature on the classification, diagnosis and management of autoimmune pancreatitis is based on papers contained within the PubMed database. Individual searches of the PubMed database were performed with the boolean operator AND, using the terms: “Autoimmune pancreatitis”, “Acute pancreatitis”, “Chronic pancreatitis”, “Pancreatic cancer”. The abstracts were screened for eligibility and all relevant publications were requested as full-text articles. References used in requested papers were then checked for any further studies of potential interest.

PATHOPHYSIOLOGY OF AIP

A definitive autoantigen for AIP has not yet been identified. Human leucocyte antigen (HLA) association studies in Japan have reported an association with HLA serotypes DRB1*0405 and DQB1*0401^[5]. This was not confirmed in a Korean study but DQB1-57 without aspartic acid was associated with disease relapse^[6]. Single nucleotide polymorphisms identified in association with either disease susceptibility or recurrence include: cytotoxic T-lymphocyte associated antigen 4, tumour necrosis factor- α and Fc receptor-like 3^[7]. However, studies of genetic risk factors in AIP remain at an early stage of investigation. A genome-wide association study in AIP would likely advance our understanding significantly.

Potential initiating mechanisms include bacterial infection and molecular mimicry^[7]. Substantial homology exists between human carbonic anhydrase II and the α -carbonic anhydrase of *Helicobacter pylori*^[8]. In theory, antibodies directed against bacterial components could behave as autoantibodies by means of molecular mimicry in genetically predisposed persons^[7]. Thus, autoimmunity is widely regarded as the initial stimulus for the Th2-cell immune response associated with AIP. Antibodies directed against potential autoantigens, such as carbonic anhydrase, lactoferrin, trypsinogen and pancreatic secretory trypsin inhibitor, may give rise to the systemic manifestations of AIP^[7-11].

Studies using animal models of experimental autoimmune pancreatitis have significant limitations, as the disease does not occur spontaneously. Current models

exhibit considerable variation in target antigens, differing methods for immune staining and differing mouse strains but have provided evidence that the disease is most likely T cell mediated, with highly beneficial effects observed with agents such as the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, which increases the number and activity of regulatory T-cells^[4].

SUBTYPES OF AUTOIMMUNE PANCREATITIS

Type 1

This is the more classically described and recognised form of the disease. It is now recognised as a pancreatic manifestation of an immunoglobulin G4 (IgG4) related systemic disease^[4,7,12-14]. It is associated with histological findings of a lymphoplasmacytic sclerosing pancreatitis (LPSP). This consists of a dense lymphoplasmacytic infiltration and fibrosis involving the pancreatic lobules, ducts and peripancreatic adipose tissue. Storiform or “swirling” fibrosis and obliterative phlebitis are also characteristic features^[15-17]. The lymphoplasmacytic infiltrate is also rich in IgG4 positive cells^[18]. It is frequently associated with sclerosing extrapancreatic lesions such as sclerosing cholangitis, retroperitoneal fibrosis and sclerosing sialadenitis^[13,19-21]. Type 1 AIP tends to affect older males, with 80% of patients being over 50 years of age at the time of presentation. It is also associated with elevation in serum levels of IgG4 in up to 75% of patients^[19,20].

The HISORt criteria from the Mayo clinic^[22] and the Japanese consensus criteria^[23] were mainly produced to facilitate the diagnosis of Type I AIP.

Type 2

This is a relatively recently described form of AIP^[3,4]. It has a unique histological pattern, consisting of an idiopathic duct-centric pancreatitis or AIP with a granulocytic epithelial lesion. The inflammation is centred on the exocrine pancreatic system, with neutrophilic infiltration within the lumen and epithelium of the interlobular ducts being a characteristic feature. The neutrophils are sometimes so numerous that microabscesses can be seen in the lobules and ducts. The entire wall of the duct may be infiltrated by neutrophils and plasma cells. The infiltrate frequently involves the duct epithelium and can obliterate it. It differs from LPSP in that there is little obliterative phlebitis and the inflammatory infiltrates have few IgG4 positive cells^[24,25].

Much less is known regarding the clinical features of Type 2 AIP. However it appears to be associated with a younger subset of patients and there is no gender preponderance. There also appears to be an association with ulcerative colitis. Type 2 AIP patients usually have a dramatic response to steroid therapy, associated with a low frequency of relapse^[25]. Until recently, existing criteria have not been that helpful in the diagnosis of type 2 AIP, but with recent publication of the International Association of Pancreatology (IAP) diagnostic guide-

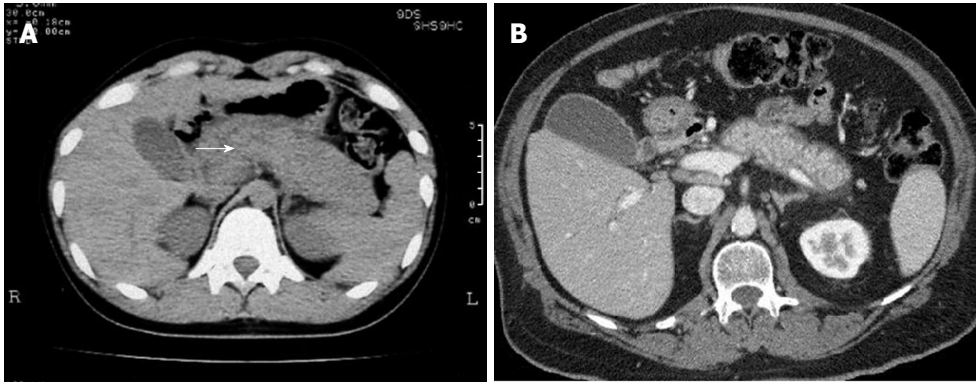


Figure 1 Computed tomography. A: Computed tomography (CT) findings in autoimmune pancreatitis: Showing diffuse enlargement and a “sausage like” appearance of the pancreas (arrow); B: Axial contrast enhanced CT image demonstrating a characteristic low signal rim or halo surrounding the body and tail of the pancreas in another patient with autoimmune pancreatitis.

lines^[26], it is anticipated that more data will confirm and further characterise this subtype.

Variation in the geographic distribution of the two subtypes may help to explain the heterogeneity of disease morphology observed worldwide.

CLINICAL PRESENTATION

The presentation of AIP is varied, but a classical picture is obstructive jaundice, often painless or with mild epigastric pain. Less commonly, new onset diabetes or symptoms of pancreatic insufficiency and weight loss may occur. A rarer presentation is acute pancreatitis and its sequelae. A characteristic feature of type 1 AIP is extrapancreatic other organ involvement. In Type 1 AIP the majority are male and over the age of 50. Some patients are only diagnosed post-operatively, having had a resection for a presumed pancreatic cancer.

The clinical picture in Type 2 autoimmune pancreatitis appears to affect a younger cohort of patients, more likely in their 4th decade of life and there is no gender preponderance. There are more reports of this group presenting with acute pancreatitis, and a higher frequency of association with ulcerative colitis^[25]. However, the numbers of patients reported in the worldwide literature are still very small and further clarity is expected to emerge with time, to further define this subgroup.

SEROLOGY

Type 1 AIP is associated with a number of serological abnormalities, in particular an elevated IgG4^[18,19]. Hamano *et al*^[19] reported that a cut-off value of 135 mg/dL for serum IgG4 concentration differentiates AIP from pancreatic cancer with an accuracy of 97%, a sensitivity of 95% and specificity of 97%. An elevated IgG4 is however not diagnostic of Type 1 AIP, but is a characteristic along with other identified criteria. The Mayo clinic reported a sensitivity, specificity and positive predictive value of 76%, 93% and 36% respectively, using a cut-off value for IgG4 of 140 mg/dL^[27]. Elevated IgG4 levels also may be found in PSC, acute and chronic pancreatitis

and up to 10% of patients with pancreatic cancer^[19]. Serum IgG4 of more than 2 times the upper limit of normal greatly increases the specificity for AIP.

Other elevated markers may include: rheumatoid factor, carbonic anhydrase, antilactoferrin and antinuclear antibodies^[9,10]. A study from Frulloni *et al*^[28] in Italy identified an anti plasminogen-binding peptide antibody which was elevated in 94% of their AIP patients. In this cohort of AIP patients, they had a relatively low prevalence of elevated IgG4 (at only 54%). This was a single centre study of 20 patients and clearly more studies are needed to assess this and other autoantibodies as potential markers for AIP and as aids to distinguish AIP from pancreatic malignancy.

IMAGING

Imaging is essential in establishing a diagnosis of AIP. Three different forms of the disease process can be seen, including diffuse, focal or multifocal disease, with the diffuse form being the most common. A contrast enhanced computed tomography (CT) scan is the gold standard for investigation as it is essential to look for a pancreatic malignancy and evidence of metastatic disease. Figure 1A shows the contrast enhanced CT findings characteristic of Type 1 AIP: a diffusely enlarged or “sausage shaped” pancreas with loss of the normal pancreatic clefts and delayed and peripheral rim enhancement^[29]. Figure 1B shows a characteristic surrounding hypoattenuating/low signal rim or halo on CT. Generally there is minimal associated peripancreatic soft tissue stranding and rarely inflammation of the mesentery. Local peripancreatic lymphadenopathy can be observed. Pancreatic calcification and pseudocyst formation is not a recognised typical finding in autoimmune pancreatitis. CT may also find extra pancreatic lesions such as retroperitoneal fibrosis.

The focal form of the disease is less common and is characterized by a focal mass lesion within the pancreas and can be mistaken for pancreatic malignancy (Figure 2). Normally dilatation of the pancreatic duct is less marked in autoimmune pancreatitis than that associated with pancreatic malignancy. Typically the main pancre-

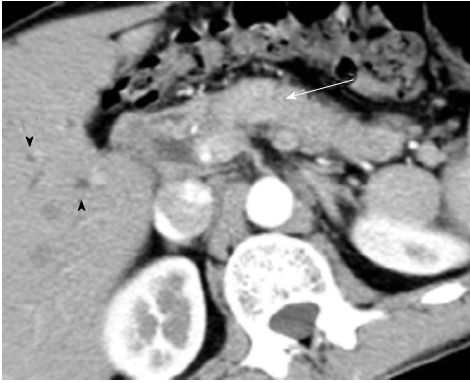


Figure 2 Focal enlargement of the pancreatic parenchyma in the head of the pancreas (arrow), and dilatation of the intrahepatic bile ducts visible (arrowheads).

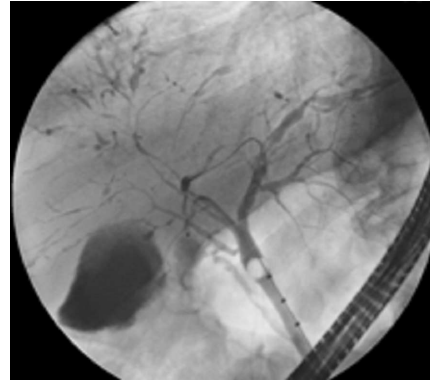


Figure 3 Endoscopic retrograde cholangiopancreatography findings of multiple and focal strictures and dilatation in the intrahepatic bile ducts in autoimmune pancreatitis.

atic duct is irregularly narrowed in affected segments of the pancreas. In the multifocal form of the disease, the pancreatic duct is of normal calibre in non affected segments. Magnetic resonance imaging (MRI) shows diffuse or localised enlargement of the pancreas with lower density in T1 weighted images and higher density in T2 weighted images compared with each of the liver images.

Sclerosing cholangitis is observed in a proportion of patients with autoimmune pancreatitis and can be seen in isolation. The intrapancreatic portion of the common bile duct is the most affected segment of the biliary tree. Affected segments of the biliary tree demonstrate irregular stricturing and associated contrast enhancement. Generally strictures associated with autoimmune disease are long and continuous whereas multifocal short strictures are more typical of primary sclerosing cholangitis (PSC), although differentiation between the two can be difficult in some cases (Figure 3).

Endoscopic ultrasound (EUS) is being used more frequently for pancreatic core biopsies, which acts as an aide to histological diagnosis and is likely superior to fine needle aspiration (FNA)^[30]. Typical EUS findings in AIP include: diffuse hypoechoic spots, absence of a discrete mass and chronic inflammatory cells on aspiration cytology. Mizuno *et al.*^[30] and Levy *et al.*^[31] have demonstrated the benefits of the use of EUS-guided biopsies to aid in the diagnosis of AIP^[32]. Future refinement of diagnosis may be obtained with the use of contrast-enhanced EUS and elastography^[4]. The use of positron emission tomography (PET) and its potential role for diagnosis of AIP is yet to be validated^[33].

OTHER ORGAN INVOLVEMENT

In Type 1 AIP, which may be considered part of an IgG4 systemic disease process, there are a significant number of associated extrapancreatic lesions. The most common are: hilar lymphadenopathy, sclerosing cholangitis, retroperitoneal fibrosis, salivary and lacrimal gland involvement and tubulointerstitial nephritis^[21,22,34,37]. There are other conditions that have been less frequently reported, such as hypophysitis and chronic thyroiditis. It is this link

to other organ involvement that led clinicians to consider AIP as part of a systemic IgG4 related disease, analogous to sarcoidosis, another systemic disease in which diverse organ manifestations are linked by the same histopathological characteristics^[7].

Biliary disease is one of the most common extrapancreatic manifestations of AIP. Although the main cause of jaundice in AIP is obstruction at the level of the intrapancreatic portion of the common bile duct, associated with an inflammatory pancreatic head mass, stricturing in the rest of the biliary tree is increasingly recognised. This condition has been termed IgG4-associated cholangitis (IAC) and has been reported to occur in 20%-88% of cases of AIP^[38]. A possible overlap between IAC and PSC is also suggested by the finding that 9%-36% of patients with PSC have increased serum IgG4 levels, compared with less than 1% in other liver diseases^[39,40]. Of note, PSC patients with raised serum IgG4 levels have a more rapid progression to liver transplantation compared to those with normal levels^[38].

Extrapancreatic disease can be a useful factor in the diagnosis of autoimmune pancreatitis, distinguishing it from pancreatic cancer, and forms part of the HISORT criteria. It also provides collateral evidence for AIP, according to the IAP diagnostic guidelines. The evidence to support the association between these conditions and AIP include: multiple reports indicating frequent or intimate concurrence, extrapancreatic pathological findings of severe lymphoplasmic infiltration and storiform fibrosis with numerous IgG4 positive plasma cell infiltrations and a combined favourable response to steroid therapy^[23,26,41].

DIAGNOSIS OF AIP

There is no single diagnostic test for AIP and there is significant variation in clinical practice worldwide, particularly between Asia and North America/Europe. The biggest challenge associated with the diagnosis of AIP is that it can closely resemble pancreatic cancer. Most commonly AIP presents with obstructive jaundice and pancreatic enlargement; other worrying symptoms such as

Table 1 The Mayo clinic HISORt criteria for the diagnosis of autoimmune pancreatitis

Category	Criteria
Histology	One of the following: Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis (LPSP) Lymphoplasmacytic infiltrate with storiform fibrosis showing abundant IgG4 positive cells (> 10 cells/HPF)
Imaging (CT)/(MRI)	Typical; diffusely enlarged gland with diffuse rim enhancement, diffusely irregular attenuated pancreatic duct Other; focal pancreatic mass or enlargement; focal pancreatic duct stricture; pancreatic duct stricture, pancreatic atrophy; pancreatic calcification or pancreatitis
Serology	Elevated serum IgG4 level
Other organ involvement	Hilar/intrahepatic biliary strictures, persistent distal biliary strictures, parotid or lacrimal gland involvement, mediastinal lymphadenopathy or retroperitoneal fibrosis
Response to steroid therapy	Resolution/Marked improvement of pancreatic or extrapancreatic manifestation with steroid therapy

LPSP: Lymphoplasmacytic sclerosing pancreatitis; CT: Computed tomography; MRI: Magnetic resonance imaging; IgG4: Immunoglobulin G4; HPF: High powered field.

weight loss and new onset diabetes may also be present. Less commonly AIP can present with features of acute pancreatitis or unexplained pancreatic insufficiency. Misdiagnosis at this stage has the potential to be catastrophic, as an undiagnosed cancer may cause delay or loss of the opportunity for potential curative cancer surgery. The opposite scenario of a pancreatoduodenectomy being undertaken for benign disease (with its high risk of morbidity and mortality) is also unsatisfactory.

In 2002 the Japan Pancreas Society published guidelines for diagnosis of AIP. These were updated in 2006 and again in 2009. The HISORt criteria from the Mayo^[22] clinic require histology, imaging, serology, other organ involvement and response to therapy for diagnosis. The inclusion of response to steroids as part of the diagnosis is one of the criteria that differentiates the Mayo recommendations from the Japanese. In Japan, endoscopic retrograde pancreatography (ERP) is routinely performed to aid in the diagnosis of AIP. More recently, the IAP has published their International consensus diagnostic criteria (ICDC)^[26], in an attempt to bridge the divide in clinical practise around the globe and offers criteria for the diagnosis of both subtypes of AIP.

SUMMARY OF DIAGNOSTIC CRITERIA

Guidelines regarding diagnostic criteria vary worldwide. Although criteria have been developed by other groups, the most influential come from the United States^[22], Japan^[23] and the International Association of Pancreatology^[26]. Below are the definitions from these three different groups.

Japan/Asian

In 2002 the Japan Pancreas society published their data for the diagnosis of AIP; this was further revised in 2006. In 2009 Okazaki *et al*^[23] published the Japanese consensus guidelines for management of autoimmune pancreatitis. There are 3 main criteria. For the diagnosis to be confirmed, criterion 1 must be present along with criterion 2 and/or criterion 3.

Imaging: Diffuse or segmental narrowing of the main

pancreatic duct with irregular wall and diffuse or segmental enlargement of the pancreas with imaging studies such as: Ultrasound, CT, MRI or ERP.

Serology: High serum gammaglobulin IgG or IgG4, or the presence of autoantibodies, such as antinuclear antibodies or rheumatoid factor.

Histology: Marked inter-lobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.

There is an optional criterion for patients fulfilling criterion 1 alone: a response to steroid therapy, with the caveat that malignancy of the pancreas or biliary tract must be excluded. In 2006, a mandatory ERP became part of these guidelines.

United States

The Mayo clinic HISORt criteria are based on 5 main diagnostic criteria: histological findings, imaging, serology, other organ involvement and response to steroid therapy^[22,42]. The detailed features are listed in Table 1. Essentially, use of these criteria enable patients to be categorised into three diagnostic groups [diagnostic pancreatic histology, typical imaging and serology, steroid responders (after careful work-up to exclude cancer)]. Patients in one or more of these categories are deemed to have AIP.

International association of pancreatology

The goals of the IAP were to develop international consensus on the diagnostic criteria that can be applied worldwide, to safely diagnose AIP and to avoid a misdiagnosis of pancreatic cancer^[26]. They reviewed all existing criteria, including the Japanese and HISORt. The consensus opinion was that the terms type 1 and type 2 should be used to describe the clinical profiles associated with LPSP and idiopathic duct-centric pancreatitis, respectively. Tables 2-4 shows the diagnostic criteria for definitive and probable AIP type 1 and 2. This uses a combination of 1 or more of 5 cardinal features of AIP: (1) imaging features of the following: pancreatic parenchyma (on

Table 2 International consensus diagnostic criteria for type 1 autoimmune pancreatitis

Diagnosis of type 1 AIP			
Diagnosis	Cardinal feature	Imaging evidence	Collateral evidence
Definitive type 1	Histology	Typical/indeterminate	Confirmed LPSP
	Imaging	Typical Indeterminate	Any level 1/2 ≥ 2 level 1
	Steroid response	Indeterminate	Level 1 S/OOI and Rt OR Level 1 D and level 2 S/OOI/H and Rt
Probable type 1		Indeterminate	Level 2 S/OOI/H and Rt

LPSP: Lymphoplasmacytic sclerosing pancreatitis; AIP: Autoimmune pancreatitis; S: Serology; OOI: Other organ involvement; Rt: Response to steroid therapy; H: Histology

CT/MRI) and pancreatic duct [ERCP or magnetic resonance cholangiopancreatography (MRCP)]; (2) serology (IgG, IgG4 and antinuclear antibody); (3) other organ involvement (OOI); (4) histopathology of the pancreas; and (5) response to steroid therapy.

Level 1 and level 2 criteria are then specified, according to the strength that specific findings add to the likelihood of diagnosis. For example, a greater than 2-fold elevation of IgG4 is considered a level 1 criteria; a lesser elevation level 2. Further specification is given for pancreatic ductal and parenchymal appearances, histology and response to steroids. Thus, definite and probable type 1 and type 2 AIP can be diagnosed.

In all cases the criteria are geared towards excluding a diagnosis of pancreatic cancer rather than screening for AIP, *i.e.*, they emphasise specificity rather than sensitivity. Only the IAP guidelines include the diagnostic features of Type 2 autoimmune pancreatitis.

DISTINGUISHING AIP FROM PANCREATIC CANCER

In view of its presentation with obstructive jaundice and pancreatic enlargement, AIP often needs to be distinguished from pancreatic cancer. As ERCP features have been reported to have limited sensitivity to diagnose AIP in Western centres, Figure 4 shows a strategy to aid in differentiation, diagnosis and management of AIP versus pancreatic cancer, based upon the experience and algorithm of the Mayo Clinic^[22]. When features highly suggestive of either AIP or pancreatic cancer are present (a low-density mass, pancreatic ductal dilatation, pancreatic duct cut off, upstream pancreatic atrophy or liver lesions suggestive of metastases), the diagnostic and management pathway is usually clear. However, in indeterminate cases, further cancer work-up is required in the first instance. In the event of a negative cancer work-up, a pancreatic core biopsy is helpful in categorising patients if a positive diagnosis can be made. Equivocal or inadequate results are more problematic and a trial of steroids or surgery should be considered.

Table 3 International consensus diagnostic criteria for type 2 autoimmune pancreatitis

Diagnosis of type 2 AIP		
Diagnosis	Imaging evidence	Collateral evidence
Definitive type 2	Typical/indeterminate	Histologically confirmed or clinical inflammatory bowel disease and level 2H and Rt
Probable type 2	Typical/indeterminate	Level 2 H/clinical inflammatory bowel disease and Rt

AIP: Autoimmune pancreatitis; Rt: Response to steroid therapy; H: Histology.

Using the Mayo Clinic strategy, AIP was successfully distinguished from pancreatic cancer in most patients but 27% required a pancreatic core biopsy, steroid trial or surgery to clarify the diagnosis^[43]. Kamisawa *et al*^[44] have reported their Japanese strategy when investigating patients presenting with mass lesions. Strategies based upon the Japanese criteria can be simpler but rely on ERP. Despite this, surgery was still required to make a diagnosis in 6 of 37 (16%) patients. Further evaluation and comparison is required to determine the optimal and least invasive diagnostic pathway.

In our view, when distinguishing AIP from pancreatic cancer, the most important tips or principals of diagnosis include the following: (1) clinical presentations not suggestive of AIP include marked cachexia, anorexia and severe pain requiring opiates; (2) a thorough negative work up for other aetiologies should be undertaken, in particular for pancreatic or biliary cancer; (3) histological diagnosis of AIP requires preservation of tissue architecture (showing lymphoplasmacytic infiltrate with >10 IgG4 positive cells/high power field), which renders FNA less helpful for diagnosis; (4) steroid therapy should only be commenced when other aetiologies for pancreatic disease have been excluded, and only in those patients whose response may be adequately assessed. It should not be used as a substitute for a thorough search for the aetiology; (5) objective improvement in the appearance of the pancreas on cross-sectional imaging should be evident within 2 wk of steroid use. Subjective improvement in symptoms or even a decline in serum IgG4 levels can occur in pancreatic cancer or lymphoma and should not be used as response criteria; (6) in AIP, CA 19-9 levels drop with treatment; a rising CA 19-9 suggests this diagnosis is incorrect; and (7) the diagnosis of AIP is difficult. An agreed diagnostic pathway should be in place and a multidisciplinary approach taken with each patient, to ensure that pancreatic cancer patients are not treated with steroids and, conversely, AIP patients not treated with cancer surgery.

INITIAL TREATMENT, MAINTENANCE AND RELAPSE

Although it is well established that spontaneous resolution can occur in up to 30% of cases of AIP^[45], symptomatic patients are best treated with corticosteroids (*i.e.*,

Table 4 International consensus diagnostic criteria level 1 and 2 criteria for type 1 and 2 autoimmune pancreatitis

Criterion	Type 1 AIP	
	Level 1	Level 2
Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement	Indeterminate: Focal enlargement with delayed enhancement
Ductal imaging (ERP)	Long or multiple strictures (> 1/3 duct length) without upstream dilatation	Focal narrowing without upstream dilatation (< 5 mm)
Serology	IgG4 > 2x upper limit	IgG4 1-2x upper limit
Other organ involvement	Extrapancreatic organ histology. Any 3 of : 1 Lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration 2 Storiform fibrosis 3 Obliterative phlebitis 4 > 10 cells/HPF IgG4-positive cells Typical radiology. Any one of: 1 Segmental/multiple proximal or distal biliary stricture 2 Retroperitoneal fibrosis	Extrapancreatic organ histology including bile duct biopsies. Both of: 1 Marked lymphoplasmacytic infiltration without granulocytic infiltration 2 10 cells/HPF IgG4-positive cells Physical or radiological evidence of at least one of: 1 Enlarged salivary/lachrymal glands 2 Renal involvement
Histology of pancreas	LPSP and 3 of: 1 Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2 Obliterative phlebitis 3 Storiform fibrosis 4 > 10 cells/HPF IgG4-positive cells	LPSP and 2 of: 1 Periductal lymphoplasmacytic infiltrate without granulocytic infiltration 2 Obliterative phlebitis 3 Storiform fibrosis 4 > 10 cells/HPF IgG4-positive cells
Response to steroid (Rt)	Rapid (< 2 wk) radiological demonstration of marked improvement in pancreatic/extrapancreatic manifestations	Marked improvement in pancreatic/extrapancreatic manifestations
Type 2 AIP		
Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement	Indeterminate: Focal enlargement with delayed enhancement
Ductal Imaging (ERCP)	Long (> 1/3 duct length) or multiple strictures without upstream dilatation	Focal narrowing without marked upstream dilatation (< 5 mm)
Other organ involvement		Clinically diagnosed inflammatory bowel disease
Histology of pancreas	IDCP. Both of: 1 Granulocytic infiltration of duct wall with or without acinar inflammation 2 0-10 cells/HPF IgG4-positive cells	Both of : 1 Granulocytic and lymphoplasmacytic acinar infiltrate 2 0-10 cells/HPF IgG4-positive cells
Response to steroid (Rt)	Rapid (< 2 wk) radiological demonstration of marked improvement in manifestations	

LPSP: Lymphoplasmacytic sclerosing pancreatitis; IDCP: Idiopathic duct-centric pancreatitis; AIP: Autoimmune pancreatitis; IgG4: immunoglobulin G4; ERP: Endoscopic retrograde pancreatography; Rt: Response to steroid therapy; HPF: High powered field.

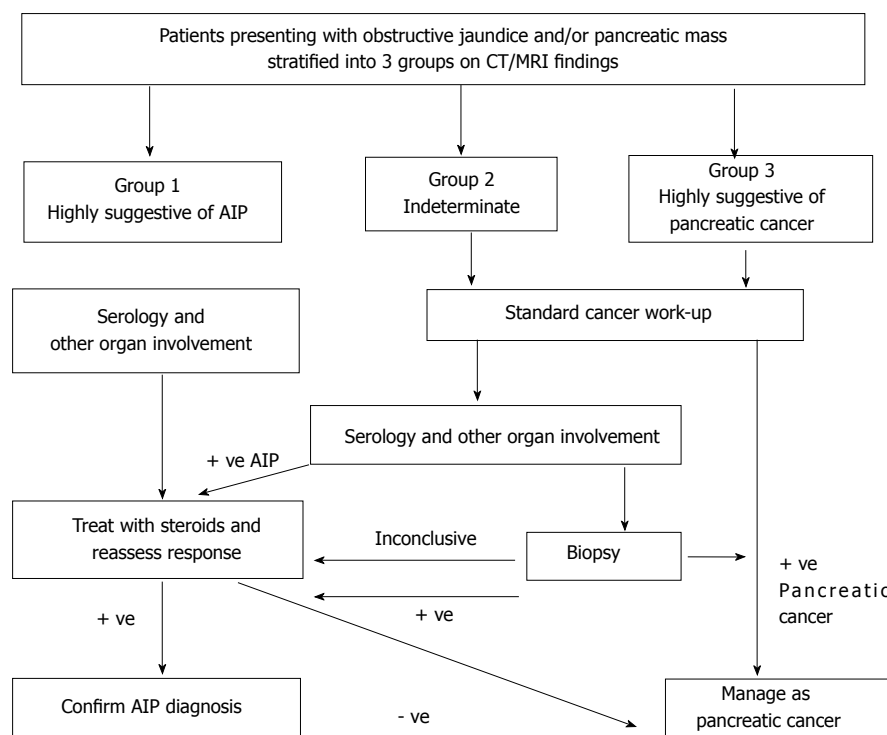


Figure 4 A strategy for distinguishing autoimmune pancreatitis from pancreatic cancer (based upon the Mayo clinic strategy^[23]). CT: Computed tomography; MRI: Magnetic resonance imaging; AIP: Autoimmune pancreatitis.

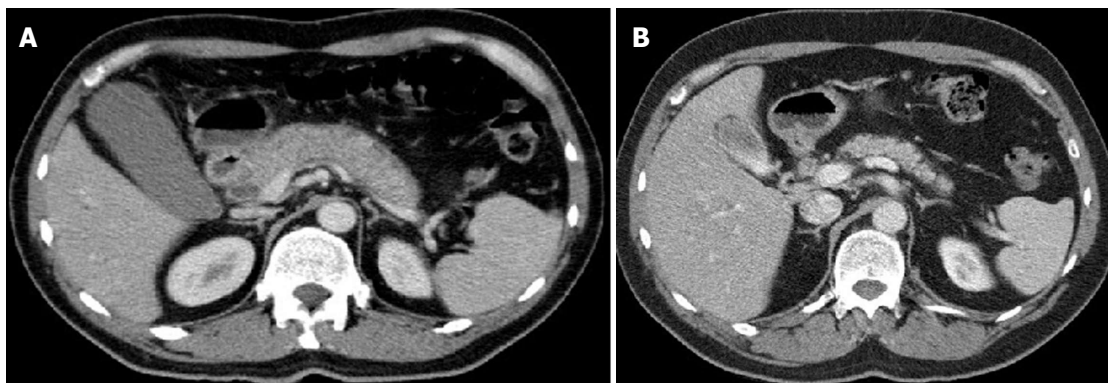


Figure 5 Axial computed tomography image. A: Demonstrating a characteristic sausage shaped enlarged pancreas with surrounding halo in keeping with autoimmune pancreatitis; B: From the same patient 8 mo later following corticosteroid therapy demonstrating response to treatment.

prednisolone). A large multicentre retrospective trial from Kamisawa *et al*^[46] in 2009 identified 563 patients with AIP and found that 98% responded to steroid therapy versus 74% that improved without. The response can be dramatic. An improvement of imaging findings, with resolution of pancreatic enlargement and biliary stricturing can be seen following corticosteroid treatment in Figure 5.

Initial steroid dose varies slightly according to guideline. In the Mayo clinic a standard initial dose is 40 mg per day of oral prednisolone, for 4 wk. If there is obvious clinical and radiological improvement, the dose is decreased by 5 mg/wk until it is stopped at 11 wk^[47]. The Japanese consensus statement on treatment and prognosis of AIP specifies that an initial oral prednisolone dose for induction of remission of 0.6 mg/kg per day is recommended. The initial dose is administered for 2-4 wk and then gradually tapered. The IAP guidelines specify dose of prednisolone of 0.6-1.0 mg/kg per day with reassessment at 2 wk^[26]. The study that formed the basis of the IAP consensus guideline regarding the two week reassessment after a trial of steroid treatment was the prospective study of Moon *et al*^[40]. After a 2-wk steroid trial, response to steroids was assessed on the basis of a marked improvement in pancreatic duct narrowing, and a reduction in size of the pancreatic mass. All patients who responded to steroids (15/22) were diagnosed as AIP after a median follow-up of 27 mo, whereas all patients who did not respond to steroids (7/22) were diagnosed with pancreatic cancer, with a complete resection being possible in 6/6 patients who accepted surgery. Induction of remission with rituximab, a monoclonal antibody directed against the CD20 antigen on B lymphocytes, is currently under investigation^[4, 48].

Differing rates of tapering are also recommended. Chiefly, the distinction is between the 5 mg/wk reduction of prednisolone, after initial treatment versus a more gradual approach recommended by the Japanese. The Japanese consensus document advocates that the dose be tapered by 5 mg every 1-2 wk, after 2-4 wk at the initial dose, based on changes in the clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP). The dose is tapered to a main-

tenance dose over a period of 2-3 mo.

A maintenance dose of 2.5-5.0 mg/d is recommended by the Japanese, to prevent relapse. This is not recommended by the Mayo clinic group, who take the view that the universal use of maintenance therapy is not warranted because the risks of long term steroid use outweighs the benefits^[47]. A wide range of relapse rates are reported, from 22%-100%^[38]. In the Mayo clinic experience of 78 type 1 AIP patients with a median follow-up of 42 mo, symptomatic disease relapse was seen in 47% patients with a 3-year cumulative relapse rate of 59% in type 1 AIP patients who were medically managed^[49]. This wide variation in relapse rates may be due to lack of a uniform definition of disease relapse, short follow-up times, small patient populations, differences in steroid treatment regimens, lack of identification of subtypes and ethnic variation.

Treatment of relapse is effectively achieved with corticosteroids. The Japanese consensus guideline states that remission can be obtained with the same prednisolone dose as the initial dose in most relapsed AIP cases, but that it may be necessary to taper more gradually^[50]. In Europe and the United States, azathioprine has often been introduced for the treatment of relapsing disease, despite pancreatitis being a known side-effect of azathioprine. Acute pancreatitis occurs in approximately 2% of cases of azathioprine use, but there is no evidence as yet that this risk is increased in AIP. Some advocate that, as in autoimmune hepatitis (AIH), AIP should be managed by azathioprine, with or without low dose steroids for at least three years. This analogy is not completely convincing; in AIH disease relapse is almost universal in those who cease immunosuppression early whereas the relapse rate is much more variable in AIP. Moreover, in a recent study from the Mayo group, in patients with relapsing AIP, azathioprine was not shown to be superior to another course of steroids alone^[51].

Related areas of management include: biliary stenting, treatment of endocrine and exocrine failure and consideration of pancreatic cancer risk in AIP. Patients presenting with obstructive jaundice should certainly be considered for biliary stenting at ERCP. This is the Japanese practice^[50] as it fits in with their strategy, which

includes endoscopic pancreatography in an intrinsic role among their diagnostic tests. However, resolution of jaundice occurs in AIP with steroid treatment without stenting, and obviously, this avoids the risks of ERCP. Avoiding the morbidity and mortality associated with ERCP and biliary stenting is also increasingly attempted in suspected pancreatic cancer, as routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of overall complications^[52]. Diabetes mellitus is common in AIP and although improvement has been reported upon commencing steroids, often requires treatment with oral hypoglycemic agents or insulin^[47]. Similar considerations apply to exocrine pancreatic failure. Patients should receive pancreatic enzyme supplementation if pancreatic exocrine insufficiency is suspected, based on the presence of clinical features such as: diarrhoea, steatorrhoea, weight loss, metabolic bone disease or vitamin or mineral deficiency. There is no established association between AIP and pancreatic cancer, just case reports of both conditions. It is not unreasonable to suppose the AIP shares a similar association with pancreatic cancer as with other forms of chronic pancreatitis, given the florid inflammatory response that may persist and relapse over years. Careful follow up of these patients will provide the definitive answer to this question but in the interim this seems the prudent approach to take.

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