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Editorial Board of *World Journal of Gastroenterology*, Xi-Dai Long, MD, PhD, Professor, Department of Pathology, the Affiliated Hospital of Youjiang Medical University for Nationalities, BOSE 533000, Guangxi, China.  
sjtulongxd@263.net

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## Recent advances in the management of autoimmune pancreatitis in the era of artificial intelligence

Sahar Mack, Yves Flattet, Philippe Bichard, Jean Louis Frossard

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**Sahar Mack, Yves Flattet, Philippe Bichard, Jean Louis Frossard**, Division of Gastroenterology, Department of Medical Specialties, University Hospital of Geneva, Geneva 1205, Switzerland

**Corresponding author:** Jean Louis Frossard, MD, Associate Professor, Division of Gastroenterology, Department of Medical Specialties, University Hospital of Geneva, Rue Gabrielle-Perret-Gentil 4, Geneva 1205, Switzerland. [jean-louis.frossard@hcuge.ch](mailto:jean-louis.frossard@hcuge.ch)

### Abstract

Autoimmune pancreatitis (AIP) is a type of immune-mediated pancreatitis subdivided into two subtypes, type 1 and type 2 AIP. Furthermore, type 1 AIP is considered to be the pancreatic manifestation of the immunoglobulin G4 (IgG4)-related disease. Nowadays, AIP is increasingly researched and recognized, although its diagnosis represents a challenge for several reasons: False positive ultrasound-guided cytological samples for a neoplastic process, difficult to interpret levels of IgG4, the absence of biological markers to diagnose type 2 AIP, and the challenging clinical identification of atypical forms. Furthermore, 60% and 78% of type 1 and type 2 AIP, respectively, are retrospectively diagnosed on surgical specimens of resected pancreas for suspected cancer. As distinguishing AIP from pancreatic ductal adenocarcinoma can be challenging, obtaining a definitive diagnosis can therefore prove difficult, since endoscopic ultrasound fine-needle aspiration or biopsy of the pancreas are suboptimal. This paper focuses on recent innovations in the management of AIP with regard to the use of artificial intelligence, new serum markers, and new therapeutic approaches, while it also outlines the current management recommendations. A better knowledge of AIP can reduce the recourse to surgery and avoid its overuse, although such an approach requires close collaboration between gastroenterologists, surgeons and radiologists. Better knowledge on AIP and IgG4-related disease remains necessary to diagnose and manage patients.

**Key Words:** Autoimmune pancreatitis; Pancreatic ductal adenocarcinoma; Immunoglobulin G4-related disease; Prednisone; Rituximab; Artificial intelligence; Plasmablasts

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**Core Tip:** The diagnosis of autoimmune pancreatitis (AIP) is challenging. Indeed, 60% and 78% of type 1 and type 2 AIP, respectively, are retrospectively evaluated on surgical specimens of resected pancreas for suspected cancer. Obtaining a definitive diagnosis can thus prove difficult, since endoscopic ultrasound fine-needle aspiration or biopsy of the pancreas are suboptimal. This paper focuses on recent innovations in the management of AIP using artificial intelligence, new serum markers, and new therapeutic approaches and outlines the current recommendations. Improved knowledge of AIP can reduce the recourse to surgery, although this requires collaboration between gastroenterologists, surgeons and radiologists.

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## INTRODUCTION

Autoimmune pancreatitis (AIP) is a type of chronic fibro-inflammatory response in immune-mediated pancreatitis[1,2]. Histological examination reveals diffuse lymphoplasmacytic infiltration associated with extensive storiform fibrosis, acinar atrophy, and obliterative venulitis[2,3]. Radiological imaging shows ductal stenosis and an enlarged pancreas or pancreatic mass resembling pancreatic ductal adenocarcinoma (PDAC)[3]. The distinction between these two entities is sometimes difficult and has clear therapeutic implications. Indeed, AIP has a good response to steroids, which constitutes an important diagnostic criterion[4,5].

In the last decade, the prevalence of AIP has increased worldwide due to the better description and recognition of the disease[6-8]. In the majority of the studies conducted in Asian countries, its prevalence more than doubled between 2011 and 2016. In Japan, for example, the prevalence was estimated at 10.1 per 100000 inhabitants in 2016 with an annual incidence of 3.1 per 100000 inhabitants [7]. The prevalence in Europe seems to be less than 1 per 100000 inhabitants (0.29/100000), or 9% of patients with non-alcoholic acute pancreatitis[8], although these numbers are most certainly underestimated due to the lack of diagnoses and the occurrence of paucisymptomatic cases that do not require treatment[8].

Two AIP subtypes, AIP-1 and AIP-2, present different clinical profiles such as mean age at disease onset, male/female ratio, geographical distribution, as well as histological and immunological features (Table 1)[9,10]. AIP-1, the most prevalent type in Asia, is a systemic disease with the possible involvement of other organs, higher immunoglobulin G4 (IgG4) in blood, IgG4 positive infiltrates, as well as increased autoantibody levels in blood. AIP-1 primarily affects men aged over 50 years and is currently considered the pancreatic manifestation of the IgG4-related disease[11]. AIP-2 corresponds to the idiopathic duct-centric pancreatitis, which can be identified by pathognomonic histological features known as granulocyte epithelial lesions[9,12]. This subgroup is more common in Europe and affects younger patients with an equivalent male/female ratio. AIP-2 often occurs with isolated cases of pancreatitis without other organ involvement, although it is associated with chronic inflammatory bowel disease in 20%-30% of cases[6,13]. The physiopathological mechanisms of AIP are poorly understood and multiple immunological pathways have been proposed. The aim of this paper is not to describe these different mechanisms.

## ESTABLISHING A DIAGNOSIS

Several diagnostic criteria have been proposed for AIP based on its clinical, biological, radiological and histological presentation in addition to treatment response: Diagnostic criteria of the Japanese (2002, 2006)[14], Korean (2007), Asian (2008) and Italian Societies of Gastroenterology (2003, 2009), as well as the Mannheim (2009) and HISORT criteria (2009)[15]. With the improved detection of AIP-2 and IgG4-related disease, a group of international experts published new reference criteria known as the International Consensus Diagnostic Criteria (ICDC) in 2011 with five main diagnostic criteria categorized according to two levels of evidence (Tables 2 and 3)[10]. New Japanese diagnostic criteria (JPS2011 followed by JPS2018) were subsequently published[16,17]. Unlike the ICDC criteria, the JPS2011 criteria provided the following clarifications: (1) Differentiation between diffuse, segmental and focal types in the classification; (2) Blood IgG4 used as the only biological marker; (3) Sclerosing cholangitis, sclerosing sialadenitis and retroperitoneal fibrosis classified as other organ involvement; (4) No level of evidence given for other organ involvement or serological criteria (IgG4); and (5) The optional use of steroids only after excluding pancreatic cancer by fine-needle aspiration (FNA)[16]. In 2018, the JPS2018 added

**Table 1 Characteristics of the two subtypes of autoimmune pancreatitis**

Characteristic	AIP-1	AIP-2
Male/female ratio	3/1	1/1
Mean age	65 yr	40 yr
Geographical distribution	Asia > Europe and United States	Europe and United States > Asia
Clinical presentation	Jaundice 60%-80%. Acute pancreatitis 15%. Weight loss 65%	Acute pancreatitis 80%. Jaundice < 30%
Biological presentation	IgG4 > 1.35 g/L (sensitivity 70%, specificity 93%). IgG4 > 2.7 g/L (sensitivity 53%, specificity 99%). Lipase < 3xN. Cholestasis: > 80% of cases. Diabetes: 65% of cases. Insulin-dependent diabetes: 20% of cases. Exocrine pancreatic insufficiency: 40% of cases	Unspecific. Lipase > 3xN. Rare endocrine and exocrine pancreatic insufficiency
Histological criteria	Lymphoplasmacytic infiltration without neutrophils. Storiform fibrosis. Obliterative venulitis. IgG4 plasma cells > 10 in a high-power field	Destruction of inter- and intralobular ducts by neutrophils (granulocytic epithelial lesions). Few or no IgG4 plasma cells
Relapse rate after corticosteroid therapy	> 30%	< 15%

AIP: Autoimmune pancreatitis; IgG: Immunoglobulin G.

**Table 2 Summary table of the International Consensus Diagnostic Criteria for autoimmune pancreatitis-1[10]**

ICDC	Level 1	Level 2
P: Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (rim-like enhancement)	Indeterminate: Segmental or focal enlargement with delayed enhancement
D: Ductal imaging	Single long stricture (> 1/3 length of MPD) or multiple stricture without marked upstream dilatation	Segmental or focal narrowing without marked upstream dilatation (< 5 mm)
S: Serology	IgG4 > 2x upper limit of normal value (> 2.70 g/L)	IgG4 rate: 1-2x upper limit of normal value
OOI: Other organ involvement	Histology of extra-pancreatic organ (3/4)  Typical radiological evidence: (1) Stenosis of intrahepatic bile duct or proximal and distal common bile duct; and (2) Retroperitoneal fibrosis	Histology of extra-pancreatic organ must show both: (1) Periductal lympho-plasmacytic infiltration without granulocyte epithelial lesions; and (2) > 10 cells/HPF of IgG4 positive cells  Physical or radiological evidence (1/2): (1) Symmetrically enlarged salivary/lachrymal glands; and (2) Radiological renal involvement
H: Pancreatic histology	3/4 criteria	2/4 criteria
Periductal lymphoplasmacytic infiltration without granulocyte epithelial lesions		
Obliterative phlebitis		
Storiform fibrosis		
> 10 cells/HPF of IgG4 positive cells		
Rt: Corticosteroid response	Rapid (≤ 2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapaneatic manifestation	

HPF: High power field; ICDC: International Consensus Diagnostic Criteria; IgG: Immunoglobulin G; MPD: Main pancreatic duct.

two new factors to its diagnostic criteria: The use of magnetic resonance imaging (MRI) for radiological diagnosis, primarily using magnetic resonance cholangiopancreatography, and the use of endoscopic ultrasound (EUS)-FNA in order to exclude a neoplastic process by histology[17].

The main limitation of this diagnostic algorithm concerns AIP-2 patients with normal IgG4 levels and disease limited to the pancreas[18]. Indeed, 50% of AIP-1 patients present with other organ involvement [19], which facilitates the diagnosis. If specific clinical, morphological, or biological evidence confirms the AIP diagnosis, no further investigation is necessary. Nevertheless, in the presence of a focal mass or



**Table 3 Summary table of the International Consensus Diagnostic Criteria for autoimmune pancreatitis-2[10]**

ICDC	Level 1	Level 2
P: Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (rim-like enhancement)	Indeterminate: Segmental or focal enlargement with delayed enhancement
D: Ductal imaging	Single long stricture (> 1/3 length of MPD) or multiple stricture without marked upstream dilatation	Segmental or focal narrowing without marked upstream dilatation (< 5 mm)
OOI: Other organ involvement		Clinically diagnosed inflammatory bowel disease
H: Pancreatic histology	Both of the following: (1) Granulocytic infiltration of duct wall with or without granulocytic acinar inflammation; and (2) Absent or scant (0-10 cells/HPF) IgG4-positive cells	Both of the following: (1) Granulocytic and lymphoplasmacytic acinar infiltration; and (2) Absent or scant (0-10 cells/HPF) IgG4-positive cells
Rt: Corticosteroid response	Rapid ( $\leq 2$ wk) radiologically demonstrable resolution or marked improvement in manifestations	

HPF: High power field; ICDC: International Consensus Diagnostic Criteria; IgG: Immunoglobulin G; MPD: Main pancreatic duct.

diffuse pancreatic enlargement without associated autoimmune disease or specific biological and morphological features, a biopsy is necessary for histological analysis. The effectiveness and feasibility of obtaining pancreatic samples by EUS-FNA or biopsy (EUS-FNB) are still the subject of debate. Indeed, the primary aim of EUS-FNA and EUS-FNB is to collect pancreatic tissue so as to exclude a malignant process and thus contribute to the AIP diagnosis. The ICDC therefore recommends the use of biopsy tissue (trucut biopsy). However, given that this procedure is not feasible in all healthcare establishments, it is not compulsory in the diagnostic algorithm, although it is an important diagnostic criteria of the JPS2018 classification[17]. In the last decade, the proportion of pancreatic samples obtained by EUS has significantly increased from 48% in 2007 to 86% in 2016 in Japan[7]. Several studies nevertheless report the difficulty in diagnosing AIP with EUS-FNA (sensitivity of 43%-60%) and obtaining a sufficient amount of fibrotic tissue[11-16], which explains the shift toward EUS-FNB[20,21]. A Japanese study on 44 AIP patients obtained an adequate histological sample in 93% of cases, leading to a confirmed diagnosis of AIP in 43% of cases, a diagnosis of idiopathic chronic pancreatitis (CP) in 50% of cases, and no false positives for pancreatic cancer[22].

### Laboratory tests

The serological diagnostic criteria corresponds to IgG4 levels at the upper limit of normal between 135 and 140 mg/dL[23]. It is generally accepted that IgG4 levels twice the normal limit are a valid criteria for AIP, although this can also occur in 10% of PDAC. Moreover, elevated IgG4 levels that are more than twice the normal value are associated with recurrence and exocrine pancreatic insufficiency in IgG4-related disease[24]. Nonetheless, some AIP-1 cases do not present elevated blood IgG4 or IgG4-positive cells on histology[25].

The efficacy of monoclonal anti-CD20 antibodies in AIP highlights the possible involvement of B cells in the pathogenesis of this disease[26,27]. Two types of B cells have been investigated in IgG4-related disease: Regulatory B cells and plasmablasts. Derived from the B cell lineage, plasmablasts are characterized as CD27<sup>+</sup>CD38<sup>+</sup>, which situates them between B cells and plasmocytes. Diagnostic tools such as the quantification of circulating plasmablasts in serum have already been shown to contribute to the diagnosis of AIP in patients with autoimmune disease[10]. In a retrospective study on 37 patients with IgG4-related disease, all patients showed high levels of plasmablasts, while only 64% had high IgG4 serum[28].

### Imaging

When investigating pancreatic lesions, several types of imaging are necessary, as no single imaging technique can provide a definitive diagnosis of AIP. The most typical feature is a global enlargement of the pancreatic gland associated with the loss of lobulations, giving it a sausage-like appearance[29]. The capsule-like rim sign, which can also be seen with other procedures, is a relatively distinctive feature of AIP in computed tomography (CT). This sign is defined by a band-like structure around all or part of the pancreas. It is characterized by a lower absorption than the pancreatic parenchyma of the lesion during the pancreatic parenchymal phase and shows a delayed enhancement pattern with dynamic CT. Other elements have been described such as decreased peripheral enhancement causing a peripheral halo or ring, involution of the pancreatic tail, enhancement of the thickened bile duct wall resembling a cocoon, stenosis of the Wirsung duct without upstream dilation, and focal hyperdense pseudotumors. MRI shows a loss of T1 signal intensity and the T2 hyperintensity of the parenchyma correlated with an inflammation of the gland. In terms of ducts, stenosis of the Wirsung duct without upstream dilation can be observed, even in the focal pseudotumors[29]. A capsule-like rim reflecting the strong fibrosis of the peripancreatic lesions can be observed on T2-weighted images as a low signal and is highly specific



to AIP. EUS findings in AIP can be hypoechoic with scattered high-echo spots in the enlarged area in some cases show a diffuse or localized lesion of the parenchyma and irregularities in the main pancreatic duct such as bile duct wall thickening, or produce a duct-penetrating sign[30]. Further use of Positron-Emission-Tomography-Fluorodeoxyglucose can be useful in detecting other organs involved in AIP.

### Artificial intelligence

The use of artificial intelligence in the medical domain has expanded rapidly in recent years. Artificial intelligence is a mathematical technique that automates the learning and recognition of data patterns. Diagnostic techniques such as digestive EUC (DEUS) can interact with this interface. A database was developed in Rochester using DEUS images of normal pancreas (NP) and pancreas of patients with AIP, PDAC, and CP with the aim to develop a convolutional neural network, a type of network with artificial neurons that recognize and classify images [convolutional neural network (CNN)] able to distinguish between these entities. For every patient in each cohort, all available still images and recorded video assets were identified and extracted. Images and videos obtained from both the radial and curvilinear echoendoscopes were included. Potentially confounding image features and patient identifying information were removed during image processing. Liver images, images with marks or annotations, and images in which calcification was visible were excluded. Using data from the training and validation subsets, various candidate CNN architectures, optimizers, and configurations were implemented, trained, and evaluated to determine an effective design for the EUS-CNN. Occlusion heatmaps were then generated and used to assess the features identified by the CNN model to differentiate all conditions (AIP, PDAC, CP, and NP). In a cohort of 585 patients (146 AIP, 292 PDAC, 72 CP, and 73 NP) with 1174461 extracted images, the CNN was 99% sensitive and 98% specific to differentiate AIP from NP, 95% sensitive and 71% specific to differentiate AIP from CP, 90% sensitive and 93% specific to differentiate AIP from PDAC, and 90% sensitive and 85% specific to differentiate AIP from all other pancreatic diseases[31]. Other groups have used this technology to discriminate portal venous CT images with the aim to differentiate between AIP and PDAC[32].

## PANCREATIC CANCER AS A DIFFERENTIAL DIAGNOSIS

As the main important differential diagnosis of AIP is pancreatic cancer, it is important to recognize any differences in the clinical, radiological, and histological features[3,6]. Clinically, AIP patients present with mild abdominal pain such as discomfort, rarely with weight loss, and fluctuant jaundice that tends to respond positively to steroid therapy. On the other hand, PDAC patients present severe, persistent, and progressive abdominal pain with weight loss and progressive jaundice. Extrapancreatic manifestations are more frequent in AIP, whereas PDAC is more localized in the pancreatic gland and induces lower bile duct stenosis, presenting metastatic lesions and direct invasion in some cases. Biologically, IgG4 is elevated in AIP patients, although elevated levels have also been reported in a few cases of PDAC[33]. By contrast, elevated carbohydrate antigen 19-9 is rarely seen in AIP. Radiologically, smooth margins and capsule-like rims in the body and tail region that represent severe fibrotic changes are seen in the CT and MRI of patients with AIP. Amelioration of swelling after steroid treatment is a characteristic of AIP, whereas PDAC patients do not or rarely present an improvement. Duct dilatation should raise the suspicion of PDAC. Using contrast-enhanced CT, AIP is characterized by homogenous delayed enhancement of the gland that indicates the diffuse loss of parenchymal volume and severe fibrosis, whereas heterogenous enhancement that represents necrosis or bleeding in the tumor can be seen in PDAC. Using EUS, AIP is characterized by a duct penetrating sign as well as a diffuse homogenous hypoechoic pattern and linear or reticular hyperechoic inclusions that reflect interlobular fibrosis. In PDAC, EUS findings show a localized hypoechoic mass and a double duct sign, often accompanied by lymph node swelling or vascular invasion. Histological patterns of AIP are characterized by periductal lymphoplasmacytic infiltration, storiform fibrosis, and obstructive phlebitis. Immunohistological identification of carcinoma cells is observed in PDAC, and inflammatory reactions can be commonly observed.

## TREATMENT

Approximately 10%-25% of patients spontaneously improve and do not require specific treatment or intervention. Since no triggers for AIP have been identified to date, no lifestyle modifications have been proposed. Nevertheless, according to the 2017 recommendations, untreated patients with active AIP should receive treatment with the exception of those with a steroid contraindication[34]. The treatment of choice and the standard treatment at present is corticosteroid therapy. There are currently no standard therapeutic protocols regarding the indications for corticosteroid therapy, its duration, posology, monitoring measures, and maintenance therapy. In Asia, the initial dose of prescribed oral

prednisone is 0.6 mg/kg/d for 2 to 4 wk, followed by a single maintenance dose of 7.5 mg/d for 6 mo to 3 years. In the United States and Europe, the dose is 40 mg/d for 4 wk followed by a recommended reduction of 5 mg per week following symptom improvement; a single maintenance dose of 5-7.5 mg/d is recommended for 12 wk to 6 mo. A smaller dose of 30 mg/d can be given to diabetic patients[35]. An alternative administration with two courses of methylprednisolone 500 mg for 3 d with a 4-d interval can be useful to induce remission in refractory cases[34].

The aim of treatment is to improve symptoms, prevent fibrosis development within the affected organs, and improve endocrine and exocrine pancreatic insufficiency. Corticosteroid therapy has an effectiveness of around 90%, with a recurrence rate of 30%-50% after reducing treatment. The rate of recurrence is higher in AIP-1 (31%-37.5%) than in AIP-2 (9%-15.9%)[36,37]. Treatment evaluation by imaging and biological analysis is recommended within 1-2 wk of induction.

Three treatment options exist in the case of recurrence. The first approach is to maintain long-term low-dose corticosteroids (7.5 mg/d for 1-3 years), while the second is to use immunomodulator therapy such as azathioprine (2 mg/kg/d for 1-3 years)[38], methotrexate, or mycophenolate mofetil. A new therapeutic approach was proposed with rituximab, a monoclonal anti-CD20 antibody, and it seems to be a promising treatment, notably in IgG4-related disease[34,39].

Diverse studies comparing immunomodulators with corticosteroids alone did not show its superiority in terms of efficacy[34,40]. For patients who are resistant or intolerant of steroids and immunomodulators, rituximab is the only possible therapeutic alternative to induce remission. Rituximab can be used as first-line treatment for patients with a high risk of recurrence. Proximal duct involvement, young age, and higher alkaline phosphatase at initial presentation are high risk factors of recurrence after first-line treatment[41]. Moreover, for these patients with a significantly higher chance of recurrence, an induction and maintenance phase (375 mg/m<sup>2</sup> 1x/wk every 2-3 mo for 2 years) would be significantly more effective than an induction phase alone (375 mg/m<sup>2</sup> per week for 4 wk or two injections of 1000 mg at 15 d interval)[41].

## CONCLUSION

To conclude, the diagnosis of AIP remains challenging for clinicians as it must rapidly be distinguished from PDAC. The available diagnostic tools such as EUC are currently evolving, and the use of artificial intelligence could lead to the development of new approaches, allowing for a more precise diagnosis of AIP and a better differentiation of the disease from pancreatic cancer. The use of rituximab in the treatment algorithm in case of recurrence has already been proven, and it should be proposed as first-line treatment for patients with risk factors for recurrence. The optimal dose and treatment duration are yet to be defined.

## FOOTNOTES

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**Country/Territory of origin:** Switzerland

**ORCID number:** Sahar Mack 0000-0002-6971-2992; Jean Louis Frossard 0000-0002-6309-1603.

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