

# Autoimmune pancreatitis: the classification puzzle

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## Introduction

In 1961, Sarles et al. [1] reported the case of a non drinker patient suffering from pancreatitis associated with hypergammaglobulinemia. The authors hypothesized that the disease in this patient was an autonomous pancreatic disease of autoimmune origin. After this report, other authors around the world reported similar cases and they named the disease in several manners: chronic pancreatitis with diffuse narrowing of the pancreatic duct, primary inflammatory pancreatitis, non-alcoholic duct destructive chronic pancreatitis, lymphoplasmacytic sclerosing pancreatitis, granulomatous pancreatitis, idiopathic tumefactive chronic pancreatitis, and sclerosing pancreatocholangitis [2,3]. In 1995, Yoshida et al. [4] suggested the term "autoimmune pancreatitis" for this disease and, therefore, this term has become largely accepted for pancreatic disease of an autoimmune origin. In the last 10 years, there has been an increasing number of cases reported in Japan and Europe [5]. In this review article, we will briefly describe the main characteristics of autoimmune pancreatitis and then we will concentrate on our aim, namely, evaluating the clinical characteristics of patients having recurrence of pain from the disease.

**Key words:** autoimmune pancreatitis, classification, pathogenesis, diagnosis, therapy.

## Incidence

At present, the exact incidence of the disease is not known. The only available data are those reported in Japan and in Italy.

In these two countries, the estimated incidence of autoimmune pancreatitis is quite similar, 4.6% and 6.0% in Japan and in Italy, respectively [5] and we are awaiting data from the United States as well as from other countries in order to define the real incidence of the disease around the world. Autoimmune pancreatitis seems to have a preference for the male gender, in fact, about 80% of the cases described are males [5]. However, a geographic variation may be observed because, in Italy, the male:female ratio is 1:1. At diagnosis, the patients were more than 55 years of age [5]. Diabetes mellitus is present in about half of the patients [5].

## Pathogenesis

From a pathological point of view, the disease is characterized by diffuse or focal pancreatic swelling with a narrowing of the pancreatic duct and/or common bile duct and the histological hallmark of this type of pancreatitis is lymphoplasmacytic infiltration, especially concentrated on the pancreatic ducts [6-8]. Some authors have defined autoimmune pancreatitis [9] as the simultaneous involvement of the pancreas, the salivary glands and the liver (primary biliary cirrhosis) by means of an immune-mediated inflammatory process. Thus, the still open question is the differentiation of autoimmune pancreatitis as a primary or a secondary disease based on the absence or presence of other autoimmune diseases.

## Clinical aspects

From a clinical point of view, patients with autoimmune pancreatitis rarely complain about the typical severe abdominal pain of pancreatitis and are usually hospitalized for painless jaundice [10]; other symptoms of autoimmune pancreatitis include non-specific mild abdominal pain and weight loss. The diagnosis is sometimes quite intriguing because the disease may be mistaken for pancreatic cancer [11].

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**Table 1. Diagnostic criteria for autoimmune pancreatitis released by the Japan Pancreas Society [18]**

Criteria	Definition
I. Imaging criterion	Diffuse narrowing of the main pancreatic duct with an irregular wall (more than 1/3 length of the entire pancreas) and enlargement of the pancreas
II. Laboratory criterion	Abnormally elevated levels of serum gammaglobulin and/or IgG, or the presence of autoantibodies
III. Histopathologic criterion	Marked lymphoplasmacytic infiltration and dense fibrosis

For diagnosis, criterion I must be present, together with criterion II and/or III

**Table 2. Italian diagnostic criteria for autoimmune pancreatitis [5]**

Criteria	Definition
Criterion I.	Histology and cytology
Criterion II.	Association with other postulated autoimmune disease
Criterion III.	Response to steroid therapy

One or more criteria must be present in order to diagnose autoimmune pancreatitis

**Table 3. Korean diagnostic criteria for autoimmune pancreatitis released by the Asian Medical Center [20]**

Criteria	Definition
Criterion I.	Pancreatic imaging (essential): (1) CT – Diffuse enlargement (swelling) of pancreas and (2) ERCP – Diffuse or segmental irregular narrowing of main pancreatic duct
Criterion II.	Laboratory findings: (1) elevated levels of IgG and/or IgG4 or (2) detected autoantibodies
Criterion III.	Histopathologic findings: Fibrosis and lymphoplasmacytic infiltration
Criterion IV.	Response to steroids

Definite diagnosis: Criterion I and any of criteria II-IV

## Laboratory data

Laboratory analysis is undergoing continuous evolution. Serum amylase and lipase may often be normal or a mild elevation of the serum pancreatic enzymes may be observed, and in only a few cases is there a marked elevation of these pancreatic damage markers [12]. Hypergammaglobulinemia and IgG serum increase have been reported in percentages ranging from 37 to 76% [13,14]. Japanese authors have claimed that elevated serum levels of IgG4, a subtype of IgG, are a biochemical hallmark of autoimmune pancreatitis [15]; however, other authors have recently questioned the specificity of the IgG4 because elevated IgG4 levels are present in patients suffering from pancreatic carcinoma and other types of chronic pancreatitis [5].

Non-specific autoantibodies, such as antinuclear antibodies, antimitochondrial antibodies and so on have a low sensitivity in diagnosing autoimmune pancreatitis; the detection rate of specific antibodies such as antilactoferrin and anticarbonic anhydrase II antibodies have not been widely assessed in clinical setting because they require a special laboratory for their measurement which is available to only a low number of clinicians. A number of groups have tried to find other laboratory indicators of autoimmune pancreatitis and evaluation of the alleles of major histocompatibility complex genes seems to be a promising tool for identifying patients susceptible to autoim-

mune pancreatitis. One report mentioned that DRB1\*0405 and DQB1\*0401 are significantly more frequent in patients with autoimmune pancreatitis when compared to chronic calcifying pancreatitis [16]. At the present time, however, further studies are required to evaluate the value of each laboratory indicator and to find a more reliable one.

## Imaging evaluation

Imaging evaluation is essential in the diagnosis of autoimmune pancreatitis [17]. Ultrasound is often the first imaging technique to be utilized in a patient with obstructive jaundice or with upper abdominal pain and a hypoechoic diffuse swelling in the pancreas (sausage-like appearance), or a focal swelling of the pancreas simulating a neoplastic lesion can be observed as well as a dilation of the extrapancreatic bile duct, secondary to an involvement of its intrapancreatic portion. Contrast-enhanced ultrasonography can successfully visualize fine vessels in pancreatic lesions and may play a pivotal role in the depiction and differential diagnosis of pancreatic tumors. In particular, some Authors have analyzed the enhancement of focal pancreatic lesions and it has been shown that, while most of the inflammatory pancreatic masses

**Table 4. A proposal of revised Korean diagnostic criteria for autoimmune pancreatitis [20]**

Criteria	Definition
Criterion I.	Pancreatic imaging (essential): (1) CT – Diffuse enlargement (swelling) of pancreas and (2) ERCP – Diffuse or segmental irregular narrowing of main pancreatic duct
Criterion II.	Laboratory findings: (1) elevated levels of IgG and/or IgG4 or (2) detected autoantibodies
Criterion III.	Histopathologic findings: fibrosis and lymphoplasmacytic infiltration
Criterion IV.	Association with other postulated autoimmune disease

Definite diagnosis: I+II+III+IV or I+II+III or I+II or I+III; Probable diagnosis: I+IV (Rediagnosed as “definite” if “response to steroids” is present); Possible diagnosis: I (Rediagnosed as “definite” if “response to steroids” is present)

**Table 5. A proposal of revised Japanese diagnostic criteria for autoimmune pancreatitis (modified) [21]**

Criteria	Definition
<b>I. Clinical criteria</b>	
Criterion 1	Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).
Criterion 2	High serum $\gamma$ -globulin, IgG, or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor.
Criterion 3	Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.
<b>II. Relationship to extrapancreatic lesions and other associated disorders</b>	AIP may be associated with sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Most AIP patients with sclerosing sialadenitis show negativity for both anti-SSA and anti-SSB antibodies, which may suggest that AIP differs from Sjögren's syndrome. Sclerosing cholangitis-like lesions accompanying AIP and primary sclerosing cholangitis respond differently to steroid therapy and have different prognoses, suggesting that they are not the same disorder.
Diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 and/or 3, are fulfilled. However, it is necessary to exclude malignant diseases such as pancreatic or biliary cancers	
<b>Description notes</b>	
<b>A. Imaging studies</b>	
<b>1. Diffuse or localized swelling of the pancreas</b>	
a.	On US, pancreatic swelling is usually hypoechoic, sometimes with scattered echogenic spots
b.	Contrast-enhanced CT generally shows delayed enhancement similar to a normal pancreas with sausage-like enlargement, and/or a capsular-like low-density rim.
c.	MRI shows diffuse or localized enlargement of the pancreas with lower density in the T1-weighted image and higher density in the T2-weighted image compared with the corresponding liver image.
<b>2. Diffuse or localized narrowing of the pancreatic duct</b>	
a.	Unlike obstruction or stricture, narrowing of the pancreatic duct extends over a larger range, where the duct is narrowed with irregular walls. In typical cases, more than one-third of the entire length of the pancreatic duct is narrowed. Even in cases where the narrowing is segmental and extends to less than one-third of the total length, the upper part of the main pancreatic duct rarely shows notable dilatation.
b.	When the pancreatic images show typical findings but laboratory data do not, AIP is possible. However, without histopathological examination, it is difficult to distinguish AIP from pancreatic cancer.
c.	To obtain images of the pancreatic duct, it is necessary to use endoscopic retrograde cholangiopancreatography in addition to direct images taken during an operation or of specimens. Currently, it is difficult to depend for the diagnosis on magnetic resonance cholangiopancreatography.
<b>3. The pancreatic image findings described above may be observed retrospectively from the time of diagnosis</b>	
<b>B. Laboratory data</b>	
1.	In many cases, patients with AIP show increased levels of serum $\gamma$ -globulin, IgG, or IgG4. High serum IgG4, however, is not specific to AIP, since it is also observed in other disorders such as atopic dermatitis, pemphigus, or asthma. Currently, the significance of high serum IgG4 in the pathogenesis and the pathophysiology of AIP is unclear.
2.	Although increased levels of serum $\gamma$ -globulin ( $\geq 2.0$ g/dl), IgG ( $\geq 1800$ mg/dl), and IgG4 ( $\geq 135$ mg/dl) may be used as a criterion for the diagnosis of AIP, further studies are necessary.
3.	Autoantibodies such as antinuclear, anti-lactoferrin, anti-carbonic anhydrase antibody and rheumatoid factor are often detected in patients with AIP.
<b>C. Histopathological findings of the pancreas</b>	
1.	Fibrotic changes associated with prominent infiltration of lymphocytes and plasma cells, occasionally with lymphoid follicles, are observed. In many cases, infiltration of IgG4-positive plasma cells is observed.
2.	Lymphocytic infiltration is prominent in the periductal area, together with interlobular fibrosis, occasionally including intralobular fibrosis.
3.	Inflammatory cell infiltration involves the ducts and results in diffuse narrowing of the pancreatic duct with atrophy of acini.
4.	Obliterative phlebitis is often observed.
5.	Although fine-needle biopsy under ultrasonic endoscopy is useful for differentiating AIP from malignant tumors, diagnosis may be difficult if the specimen is too small.
<b>D. Endocrine and exocrine function of the pancreas</b>	
Some patients with AIP show a decline of exocrine pancreatic function and develop diabetes mellitus. In some cases, steroid therapy improves endocrine and exocrine pancreatic dysfunction.	

show a pattern of enhancement similar to the normal pancreatic gland ("isovascular"), a focal pancreatic tumor is hypovascular to the surrounding normal parenchyma. A focal or diffuse swell-

ing of the pancreatic gland can be observed at both computed tomography and magnetic resonance imaging. Dynamic imaging at computed tomography or magnetic resonance imaging shows

a delayed enhancement of the segments of the gland which are involved. In some cases, minimal peripancreatic stranding suggesting inflammation can be seen. Moreover, a capsule-like smooth rim can be observed which is hypodense on computed tomography and hypointense on T2 weighted images, showing delayed enhancement on dynamic imaging. This is thought to correspond to an inflammatory process involving peripancreatic tissues and appears to be a characteristic finding of autoimmune pancreatitis. Pancreatic calcifications are rarely seen in autoimmune pancreatitis. Involvement of the main pancreatic duct and the biliary duct is well-described in the literature. Endoscopic retrograde cholangiopancreatographic criteria for the diagnosis of autoimmune pancreatitis include diffuse irregular narrowing of the main pancreatic duct and abnormalities which normalized after steroid therapy. The same alterations can be observed at MR cholangiopancreatography. The invasion of vessels, vascular encasement, mass effect and fluid collections are absent in autoimmune pancreatitis.

## Diagnostic criteria

There are no internationally accepted diagnostic criteria for the diagnosis of autoimmune pancreatitis. The diagnostic criteria widely used for autoimmune pancreatitis are those proposed by the Japan Pancreas Society [18] and are reported in *Tab. 1*; interestingly, the criteria do not include symptoms or common laboratory findings as they are not specific to autoimmune pancreatitis [12,19]. Italian criteria include some differences with respect to the Japanese diagnostic criteria (*Tab. 2*) [5] such as the association with other autoimmune diseases and the response of the disease to steroid treatment. Korean researchers utilize a third classification which takes into account the Japanese and the Italian diagnostic criteria (*Tab. 3*) [20]. Furthermore, new classification systems have been proposed from Korean researchers (*Tab. 4*) [20], and, very recently, by Japanese Research Committee of Intractable Diseases of the Pancreas (*Tab. 5*) [21].

## Therapeutic options

Autoimmune pancreatitis usually responds to steroid therapy. There are numerous reports of dramatic response of this disease to above mentioned therapy. However, spontaneous resolution without treatment has also been noted. Autoimmune pancreatitis is a fibro-inflammatory disease and intense inflammation is often accompanied by intense fibrosis; thus, even if the inflammatory component responds to steroid therapy; the fibrosis often permanently disfigures, damages and sometimes destroys the organ [22].

## Open questions

There is a need for a classification system for such a rare disease; therefore, an international consensus statement releasing widely accepted guidelines for autoimmune pancreatitis would

be welcome in order to help in evaluating the possible presence of autoimmune pancreatitis in patients with an undefined etiology; in fact, a recent study has reported that clinical or biochemical autoimmune stigmata are present in 40% of patients with idiopathic chronic pancreatitis and, therefore, autoimmune mechanisms may be frequent in idiopathic pancreatitis [23].

We also need to know the duration of steroid treatment and the possible cause of failure of steroid therapy in some patients; finally, we need to evaluate the reason why some patients experience more attacks of pain in a disease characterized by a painless course.

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