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# Autoimmune Pancreatitis: Clinical Presentation and Therapy

*Zoltán Berger Fleiszig and Carla Mancilla Asencio*

## Abstract

Autoimmune pancreatitis is a relatively recently identified entity. The dominant type 1 is the pancreatic manifestation of a systemic IgG4-related fibroinflammatory disease. The type 2 has a clearly different histology, its dominant feature is a granulocytic epithelial lesion, and it is independent of IgG4. While type 1 is rather a disease with male dominance in majors than 50-year-old people, no gender difference is observed in type 2, and the disease is more frequently seen in young people. The more frequent initial clinical manifestation is obstructive jaundice in type 1, while abdominal pain and mild acute pancreatitis in type 2. CT and magnetic resonance images are very similar, IgG4 can be normal even in type 1, and the associated involvement of other organs is frequently posterior to the pancreatic manifestation; thus, the distinction of the two types of AIP can be difficult without histology in the everyday clinical practice. Several cases can be undetermined and qualified as Not Otherwise Specified (NOS). However, all types of AIP respond quickly to steroid treatment with a complete recovery. Late prognosis is good, but up to 50% recurrence has been observed in type 1, and several authors have described progression to chronic pancreatitis.

**Keywords:** autoimmune pancreatitis, IgG4-related disease, granulocytic epithelial lesion, histology, steroid treatment, complete recovery

## 1. Introduction

Autoimmune pancreatitis (AIP) is an emerging disease, recognized with an increasing frequency in the whole world. Autoimmune factors have been known since long time to participate in the etiology of some cases of chronic pancreatitis [1]; however, their importance was somewhat marginal, no more than 3–5% of the patients of chronic pancreatitis [2, 3]. In addition, pancreatic involvement is relatively rare in the major autoimmune diseases: while described, chronic pancreatitis is only exceptionally found in lupus erythematosus [4] and Sjögren's syndrome [5, 6]. Conversely, AIP while described before [7, 8] was identified as an independent entity only in 1995 [9], and it is associated with specific IgG4-related autoimmune disease (type 1) and with inflammatory bowel disease (type 2). Their histology is characteristic and quite different when compared to pancreatic involvement in SLE or Sjögren's syndrome. This fact is very similar to the case of the liver, hepatitis associated with lupus and autoimmune hepatitis being also the two distinct diseases [10].

## 2. Definition, classification, and histology

The concept of autoimmune pancreatitis was introduced by Yoshida in 1995 [9] and accepted worldwide. The majority of cases initially described came from Asia, but later on the disease was recognized in the whole world. With the exponentially growing information, two different forms were distinguished: the type 1 or lymphoplasmacytic sclerosing pancreatitis (LPSP) and the type 2 or idiopathic duct-centric pancreatitis. Type 1 has been dominant in the whole world and represents the most frequent digestive manifestation of a systemic fibroinflammatory IgG4-related disease. Its histology is characteristic: the association of storiform fibrosis, obliterative phlebitis, and marked lymphoplasmacytic infiltration are unique, and the immunohistology can be the final proof, demonstrating the presence of more than 40% of IgG4-positive lymphocytes as compared to the whole number of IgG-positive cells. Details of the autoimmune reaction are well described, but the whole process is not known. Circulating plasmablasts are present in increased number in the active phase of the disease and decrease rapidly with the treatment [11]. Interaction of T- and B lymphocytes has been demonstrated. Th2 reaction and regulator T-cell activation are part of the process, resulting from one part in an increase of interleukins 4, 5, and 13 with a consecutive increase of eosinophils and serum IgE and from the other part increased IL-10 production, lymphoplasmacytes, and fibroblast proliferation, with an increased IgG4 level. As these diseases are recognized as IgG4-related, one could expect IgG4 lymphoplasmacytes as key factors inducing the immune reaction and organ damage. However, the characteristics of the IgG4 subclass do not permit complement activation or immune complex formation. Both IgG4 and IgG1 obtained from an active AIP patient, when injected separately, induced pancreatic damage in experimental design. However, when injected simultaneously, IgG4 was rather protective and reduced the IgG1-induced pancreatic damage [12]. Based on these experimental data, IgG1 subclass seems to be more active in producing damage, and the local increase of IgG4 cells and elevated serum IgG4 level seems to be rather a consequence. In type 2, AIP has a clearly different histology. The fibrosis is important, but not storiform, phlebitis/venulitis is rare, and if present, it is not obliterative. The essential finding is infiltration by neutrophil leucocytes, forming the typical granulocytic epithelial lesion (GEL), with duct cell damage. Similar lesions can also be observed in pancreatic lobules. While lymphoplasmacytic infiltration can exist, IgG4-positive cells are rare. A unique finding in type 2. AIP is the presence of IL-8 around the ductal cells, in particular in the damaged pancreatic ducts. IL-8 is a chemotactic factor for neutrophils, and its high expression is in line with the formation of granulocytic epithelial lesions [13]. In addition, similar accumulation of IL-8 was described in the damaged mucosa of ulcerative colitis but not in other types of colitis. This finding points out a similarity in pathomechanism of these diseases as a possible explanation of the well-known association.

### 2.1 Autoantibodies: serology

Several autoantibodies were described in AIP, against carbonic anhydrase [14] and amylase [15], but they do not have any demonstrated role in the initiation of the autoimmune process. A cross-reaction was found against a protein of *Helicobacter*, the plasminogen-binding protein [16], but its role in the pathogenesis of AIP was not confirmed. Unspecific autoantibodies, as antinuclear and anti-DNA, can also be present. A variety of autoantibodies have been found in the sera of patients with AIP, but none of these autoantibodies appear to be disease specific. The serum IgG4 level has been found elevated in a variable proportion of confirmed type 1 AIP cases. Sensitivity above 80% was published in some papers, while others found only

<50% [17]. On the contrary, IgG4 can be elevated even in some cases of pancreatic cancer. Once increased, the serum IgG4 level is a useful marker in confirming the diagnosis of AIP type 1, but a normal value does not exclude AIP. Unfortunately, no specific test exists even for the diagnosis of AIP type 1, and type 2 is not accompanied by laboratory alterations. In our experience [18], we found IgG4 > 135 mg% in 80% of confirmed AIP type 1 cases but in none of 20 NOS undetermined cases, while several of these patients, if not the majority of them, were probably seronegative type 1. It means that the real diagnostic performance was far less than 80% in our clinical practice, even considering a lower cutoff value.

### 3. Epidemiology and clinical characteristics

AIP is increasingly recognized. For example, 900 cases were known in Japan in 2002 [19]; 2790 in 2007 [20]; and 5745 in 2011 [21]. The calculated prevalence was 4.6/100,000, while the incidence 1.4/100,000/yr. Experiences from different regions of the world have been increasingly published; the annual number of papers increased exponentially from 39 in 2000 to 935 in 2017, as found in PubMed Central. We also observed a marked increase in the diagnosis of AIP in Chile [18]. However, the worldwide increase in the frequency of this disease is probably mainly due to its better recognition rather than a so-important increase in incidence. The more frequent type 1 AIP is part of a systemic IgG4-related disease. A male dominance has been observed; about two thirds of patients are men. The average age is above 50 years. However, there are also women in considerable number. The pancreatic affection is frequently associated with manifestation of the same disease in other organs. Recurrence in the pancreas or in other organs is relatively frequent in this form. Type 2 AIP has been described later, but it is also recognized with a growing frequency. No gender difference was described, and the disease affects young people; the mean age is no more than 30 years. The only associated disease is inflammatory bowel disease (IBD), mainly ulcerative colitis, which can occur simultaneously with the pancreatitis or any other period, before or after the AIP. This form of pancreatitis seldom recurs (**Table 1**)

	Type 1 (LPSP)	Type 2 (IDCP)
Sex	Male dominance (two to three times)	No difference
Age	After fifth decade	Young people, <30
Dominant symptom	Jaundice	Pain, mild pancreatitis
Serum IgG4 level	Frequently increased (50–80%)	Normal
Associated diseases	IgG4-related organ involvement	Inflammatory bowel disease
Response to steroids	Quick, complete	Quick, complete
Relapse	>30%	Rare, <10%

*LPSP, lymphoplasmacytic sclerosing pancreatitis; IDCP, idiopathic duct-centric pancreatitis.*

**Table 1.**  
*Clinical characteristics of two types of autoimmune pancreatitis.*

### 4. Diagnosis

#### 4.1 Clinical symptoms

The clinical manifestation of AIP is variable and non-specific. The most frequent symptom is painless jaundice due to compression of intrapancreatic



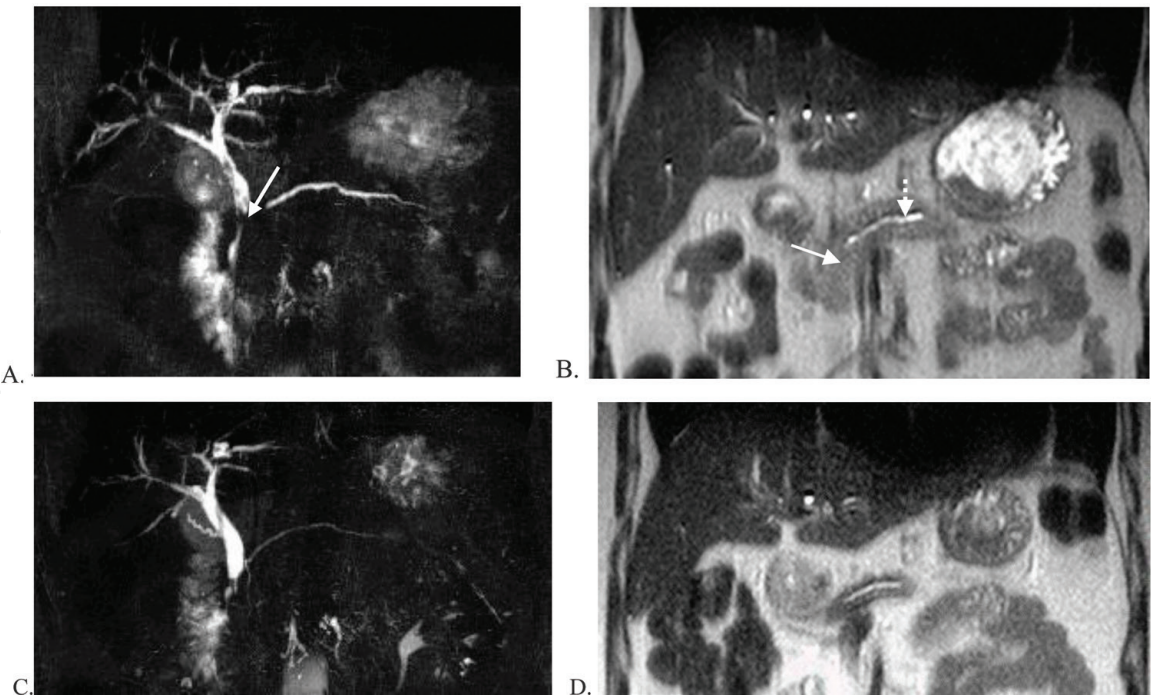
segment of choledochus by the fibroinflammatory process in the pancreatic head. Unfortunately, it shares typical symptoms of pancreatic head cancer and represents one of the most challenging difficulties in differential diagnosis. Abdominal pain and mild acute pancreatitis are also important manifestations. However, severe acute pancreatitis and major local fluid collections practically do not occur and autoimmunity is not a frequent cause of recurrent acute pancreatitis.

#### 4.2 Serology

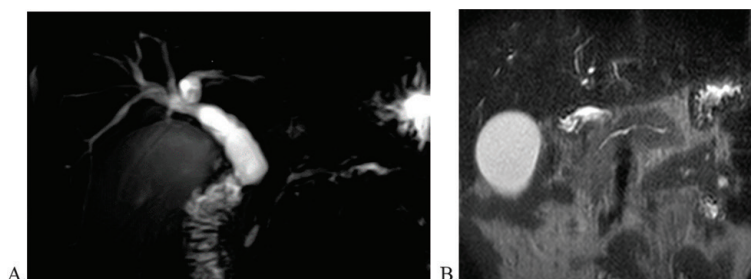
As described above, the only valuable serological marker is the serum IgG4 level [17]. However, its performance in the diagnosis is variable: it can be increased only in type 1, not in type 2. Other unspecific autoantibodies have low sensibility in AIP and are not used routinely. Sometimes, IgE and peripheral eosinophils can be increased. If altered, they help in the diagnosis; if not, they have no value in excluding it.

#### 4.3 Images

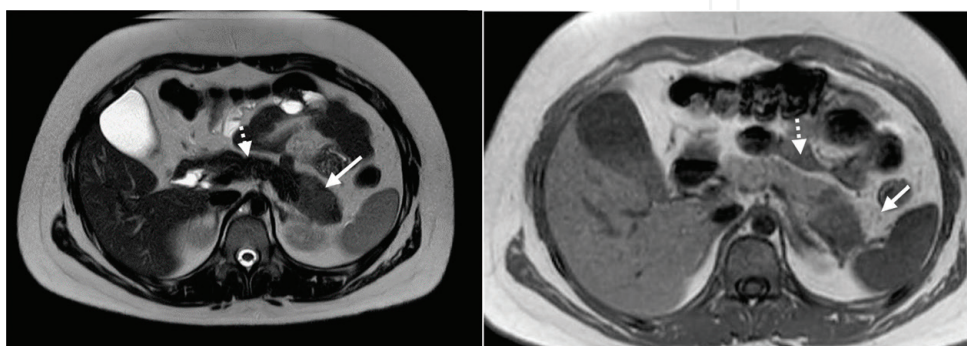
Radiologic exams, CT scan, and MR are the bases of the diagnosis in the everyday clinical practice [22]. Typical sausage-like increase in pancreatic size with a peripheral halo is seen in several cases when the pancreas is diffusely affected. Frequently, only segments of pancreas are involved. In these cases the differences in density or signal intensity as compared to the normal segments (**Figures 1b, 2b and 3a,b**), the late enhancement with contrast, and the irregular stricture of the main pancreatic duct can be helpful. In the difficult situation when there is a clinical suspicion of pancreatic cancer, even without a clear-cut mass, the absence of significant upstream duct dilation is an important element which



**Figure 1.** (a) Magnetic resonance cholangiography showing pancreatic duct stricture in the head and stenosis of intrapancreatic segment of choledochus with proximal dilatation. Pancreatic duct is only slightly dilated in the body and tail. (b) Pancreatic head is enlarged with slightly hyperintense signal in T2. The pancreatic duct is only seen in the body and tail. (c and d) The same patient and same images after 2 months of treatment. Almost complete recovery, with slight pancreatic atrophy. The images of this chapter come from the Radiology Department of Clinical Hospital of University of Chile and are the authors' property.



**Figure 2.**  
 (a) Markedly dilated choledochus, proximal to the stenotic intrapancreatic segment of the bile duct. Irregular multiple stenosis of the main pancreatic duct. (b) Again, the structured pancreatic duct is practically not seen in the augmented pancreatic head, but the upstream dilatation is only mild.



**Figure 3.**  
 Focal AIP in the pancreatic tail. (a) T2, hyperintensity of the signal; (b) T1, hypointense signal. Arrow: the swollen pancreatic segment. Pointed arrow: normal pancreas. Note the clear limitation between the normal and involved segments.

helps to distinguish the two pathologies with diametrically different prognoses (**Figures 1a,b, 2a,b** and **5a**). It is noteworthy that neither necrosis nor major peri-pancreatic fluid collection are seen in AIP. Sometimes, pseudocysts can complicate the disease [23]; they also respond to steroids and can disappear even completely. It is important to emphasize that there is no difference in the radiologic alterations in types 1 and 2 of AIP.

#### 4.3.1 When to perform diagnostic ERCP and biliary drainage?

The necessity of ERCP in order to establish the diagnosis of AIP nowadays is an exception. Magnetic resonance images have a similar sensibility in the diagnosis. If performed, irregular and usually multifocal narrowing of the main pancreatic duct is seen in the affected pancreatic segment, without an important upstream dilatation (**Figure 5a**). Stenosis of intrapancreatic segment of choledochus is frequent, and, sometimes, irregular strictures of extra- and intrahepatic bile ducts can show the associated IgG4-related cholangitis, very similar to the primary sclerosing cholangitis (PSC) (**Figures 5b** and **6a**). The clinical need of ERCP is determined in the majority of the cases by the severe obstructive jaundice and the intention to drain the obstructed dilated bile duct with a biliary endoprosthesis (**Figures 5b** and **6b**). However, it is at least a matter of discussion: the decrease in bilirubin level in response to steroid treatment is strikingly rapid, and it seems better to avoid unnecessary instrumentalization of biliary tract with the risk of bacterial contamination. Once ERCP is performed without the previous suspicion of AIP and contrast material injected in the obstructed bile duct, stent placement is mandatory as in any other causes of bile duct obstruction. In our practice, we performed ERCP only in our first



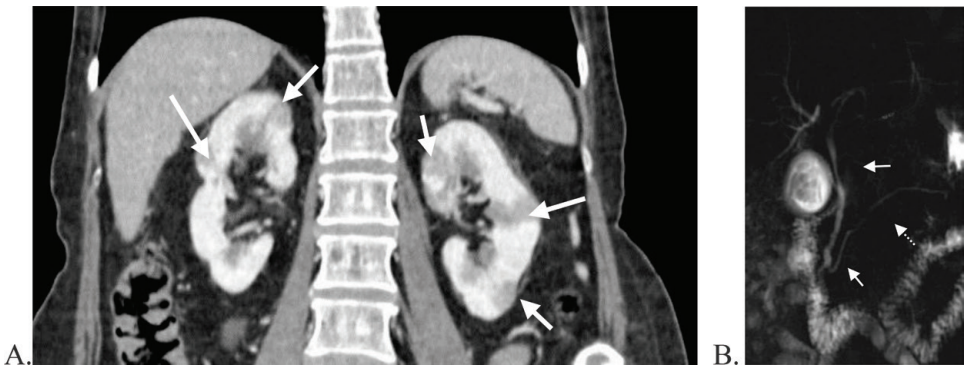
patients, later on only in some exceptional cases when even concomitant sclerosing cholangitis was not excluded, and it was impossible to avoid biliary stent placement. In fact, Chari's group published the same tendency from Mayo Clinic [24].

4.4 Other organ involvement

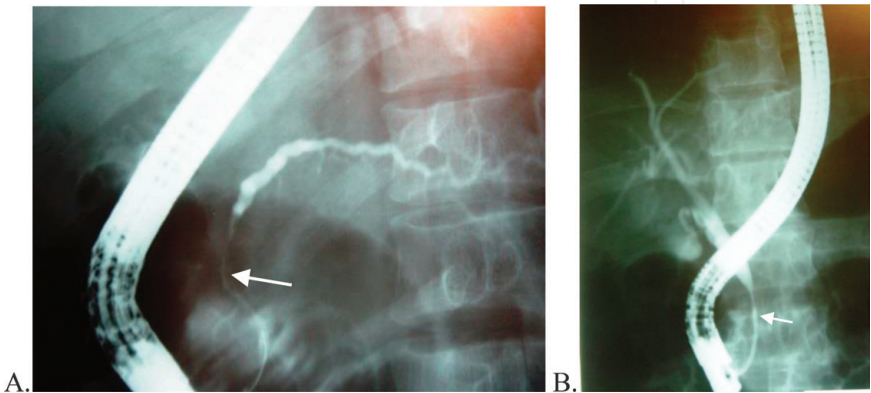
A type 1 AIP is a systemic disease; we can see frequently signs of the disease in other organs. Fibroinflammatory tumor-like pathology of lacrimal and salivary glands is clearly visible, palpable, and easy to access for a biopsy. However, other manifestations, as frequent bilateral nephritis, can be asymptomatic but easily detectable on the MR image (**Figure 4a**), frequently synchronous with the pancreatic disease. Peritoneal fibrosis and aortitis can occur in different times, before or later, as compared to AIP. In our experience PSC like cholangitis and bilateral multifocal nephritis were the most frequent extrapancreatic manifestations, found in 8 and 11 of our 44 type 1 patients, respectively [18]. Any of these manifestations, in particular when their histology confirms IgG4-related disease, can be considered as a definitive proof for type 1 AIP. For type 2, the association of IBD makes probable the diagnosis, but cannot be considered as a definitive proof.

4.5 Histology

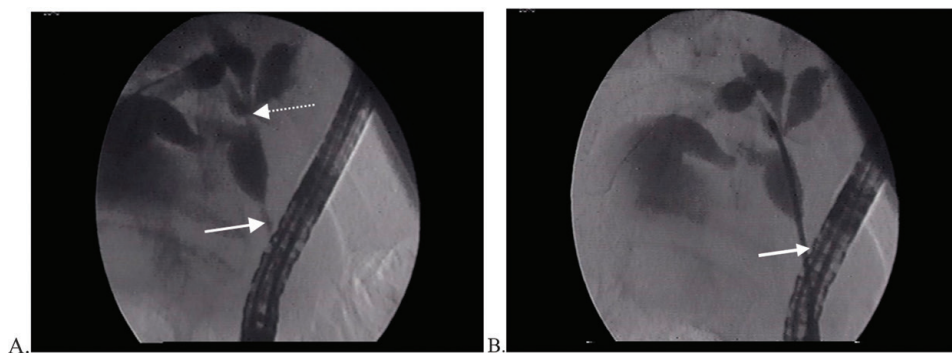
Histology is a definitive diagnosis. Unfortunately, in the everyday clinical practice, the access to an adequately evaluable biopsy sample is not easy. Characteristic



**Figure 4.**  
(a) Nephritis in IgG4-related, type 1. AIP, concurrent with pancreatitis. Arrow: involved renal areas.  
(b) Primary sclerosing cholangitis like simultaneous extra- and intrahepatic biliary tract lesions. Arrows: bile duct strictures. Pointed arrow: pancreatic duct stricture.



**Figure 5.**  
ERCP of a patient. (a) Long stricture of pancreatic duct in the head (arrow), with a moderate upstream dilatation in the body and tail. (b) Bile duct stricture in the same patient (arrow).



**Figure 6.** ERCP of another patient. (a) Multiple stenotic segments in the bile duct: a long stricture is observed in the distal half of choledochus (arrow) and a shorter stenosis in the hepatic hilum (pointed arrow). (b) Stent (arrow) placement in the bile duct.

histology is easily seen in a surgically resected pancreas [25]. However, this is too late for the patient, who could have been treated safely with steroids instead of a major surgery. Percutaneous pancreatic biopsy made by interventional radiologists has some risks and not a currently used method. Endosonography (EUS)-guided biopsy would be the recommended way to obtain pancreatic tissue. EUS image itself is even somewhat superior to MR and gives valuable information in the differential diagnosis. In addition, fine-needle aspiration by EUS is the safest way to obtain pancreatic cytology. However, cytology has a good performance in the diagnosis of pancreatic cancer but not in the diagnosis of AIP, this latter requiring a real tissue sample biopsy [26–28].

#### *4.5.1 When to perform EUS and FNA? Value of cytology and biopsy in differential diagnoses.*

Diagnosis of type 1 AIP can be made with high certainty in many patients: clinical symptoms, characteristic images supported by elevated serum IgG4 level, and other organ involvement can assure the diagnosis without pancreatic histology. However, in the absence of these latter conditions, establishing the definitive diagnosis of even type 1 AIP can be difficult. In type 2 AIP, IgG4 is practically never increased, and IBD is the only associated pathology, but only probable diagnosis can be done without histology. With the availability of new biopsy needles (shark, core biopsy), which permit to obtain a small tissue cylinder, diagnostic performance of pancreatic biopsy has dramatically increased, without major risk of complications: clinically significant hemorrhage and pancreatitis are rare, below 1%. Thus, biopsy should be considered in every patient with a suspicion of seronegative type 1 and in type 2 AIP, preferably before initiating a relatively long steroid treatment.

#### **4.6 Response to glucocorticosteroid treatment**

The improvement in the pancreatic morphology in response to steroid treatment is very quick, easily detectable already after 2 weeks. This fact can be used even in the differential diagnosis: while AIP improves rapidly, pancreatic cancer evidently does not respond to steroids, and no change in the pancreatic morphology can be observed after 2 weeks. In addition, it was demonstrated by Moon et al. [29] that the “lost” 2 weeks did not change the resectability of the malignant lesion. This short treatment trial is only acceptable if a good biopsy is not available or the histologic finding is uncertain in a patient of high surgical risk. It means that steroid treatment trial has to be restricted to the cases, when:



- EUS and pancreatic biopsy is not available or its result is uncertain.
- Conditions of very strict and early control are assured.
- The patient is known and followed by a multidisciplinary group.
- If there is no clear improvement after 2 weeks of treatment, steroids are withdrawn and the patient goes to surgery.

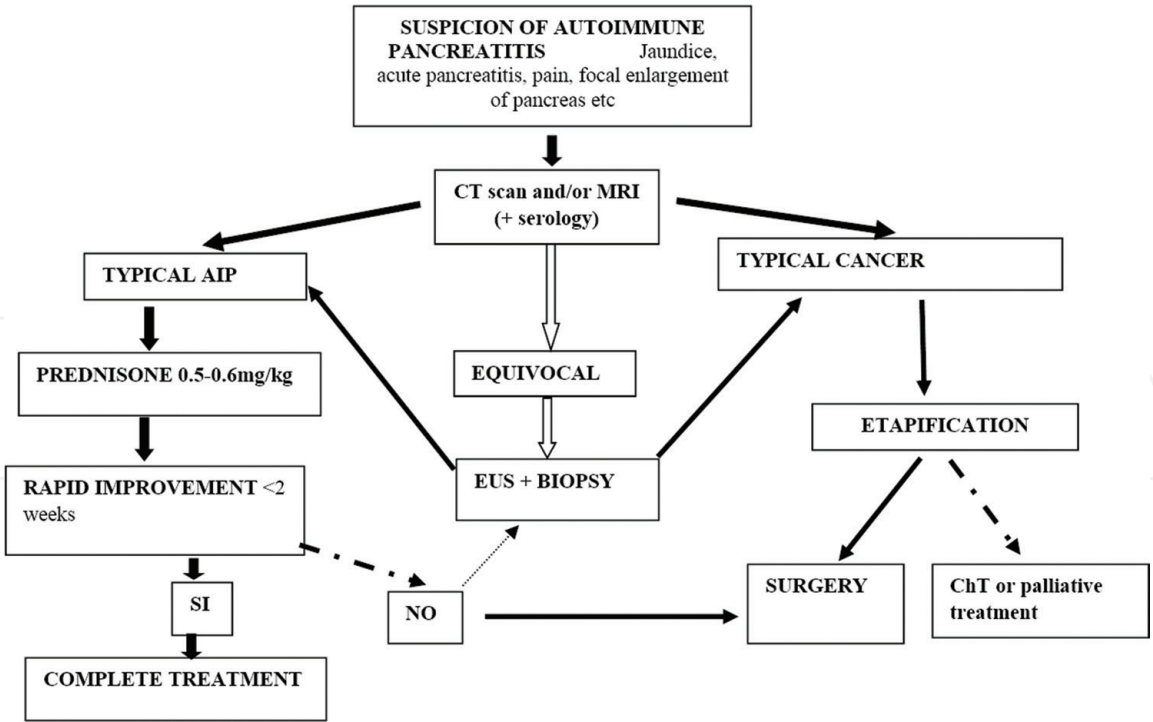
In conclusion, in the everyday clinical practice, the basis of the diagnosis is radiology, showing typical characteristic images of the pancreas (**Table 2**). However, differential diagnosis is not always easy and other parameters could be of utility. Unfortunately, no specific autoantibodies have been discovered till now. Increased, >270 mg/dl serum IgG4 level seems to be quite specific but not enough sensitive in the diagnosis of type 1 AIP, and IgG4 has no value in type 2. Other organ involvement can be useful again in the diagnosis of type 1 AIP. In addition, imaging alterations do not distinguish between type 1 and type 2. Thus, type 2 AIP almost always requires biopsy and histology; in its absence the diagnosis can be only highly probable but not definitive [30]. Type 1 AIP can be definitely demonstrated without biopsy in the majority of cases. However, several patients have an undetermined AIP, which is named NOS [31], a mixture of seronegative type 1 and possible type 2 cases. A useful simple algorithm in the differential diagnosis is proposed in **Figure 7**.

After the diagnosis of AIP, the classification has practical and prognostic significance. As described above, characteristic image on MRI associated with serum IgG4 level more than double of upper limit of normal (>270 mg%) and/ or simultaneous or sometimes previous presence of IgG4-related disease in other organs are sufficient to establish definitive diagnosis of type 1 AIP, even without histology. If IgG4 is normal and the only associated disease is ulcerative colitis or Crohn's disease, the classification in type 2 AIP is probable, but not definitive. If the patient does not have any associated disease, only NOS AIP is the clinically

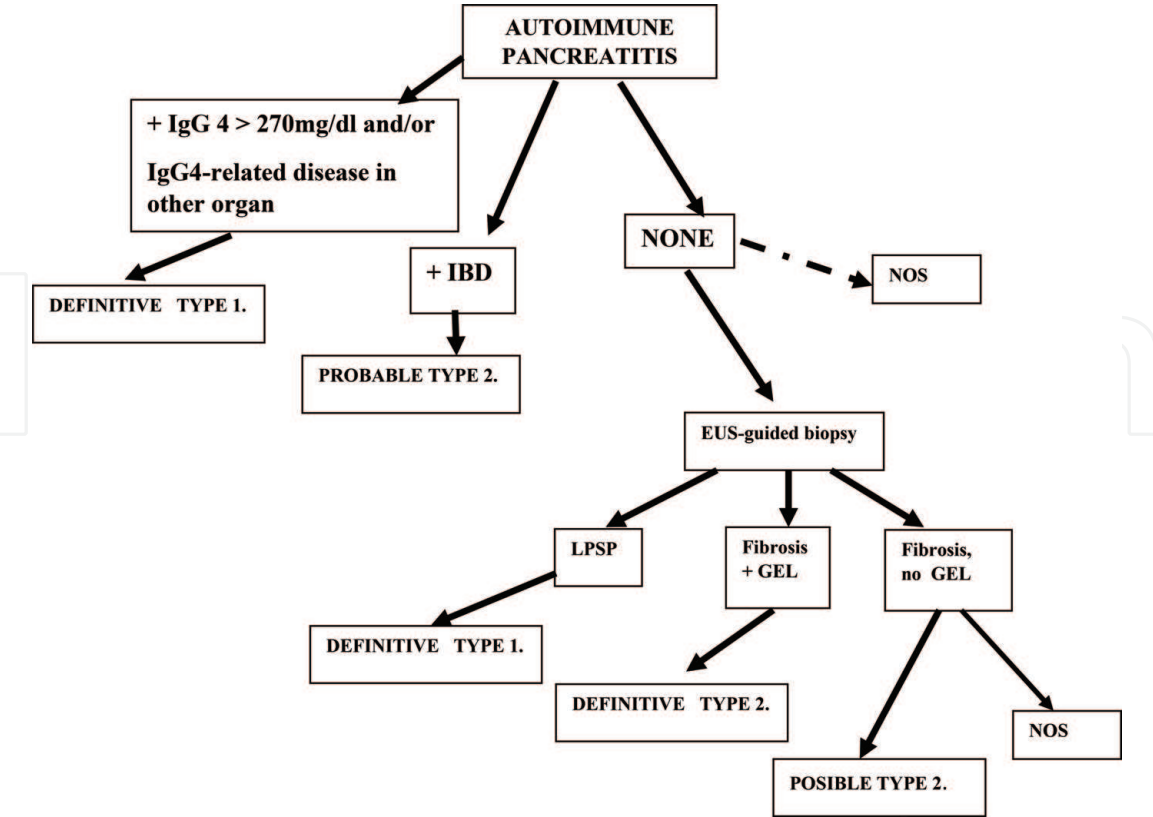
	Increase in size	Dilatation of ducts	Parenchyma	Neighborhood
Acute pancreatitis	Diffuse	No	Edema +/- necrosis	Fluid collections
Chronic pancreatitis	Focal	Diffuse, irregular	Atrophy +/- calcifications	—
Groove pancreatitis	Head, groove	Upstream, regular	Normal	—
Autoimmune pancreatitis	Focal or diffuse	Stricture +/- slight upstream dilatation	Altered signal, contrast enhancement and diffusion	—
Pancreatic cancer	Focal (hypovascular mass)	Marked upstream	Upstream atrophy	Metastasis in lymph nodes

*Note the unique combination of findings in autoimmune pancreatitis. The absence of more significant upstream dilatation of pancreatic duct and altered signal in the parenchyma, both useful as compared to pancreatic cancer. On the other hand, the absence of necrosis and peripancreatic fluid collections helps to distinguish it as compared to acute pancreatitis.*

**Table 2.**  
Characteristic alterations in pancreatic and peripancreatic morphology, useful in the differential diagnosis.



**Figure 7.**  
A simplified algorithm for the differential diagnosis and treatment of autoimmune pancreatitis. Briefly: Once AIP is suspected on the basis of medical history or abdominal US findings, CT scan or MRI is performed, of course completed with determination of the IgG4 level in the serum. These data can be sufficient to establish definitive diagnosis of AIP or pancreatic cancer and initiate proper treatment. The effect of steroid treatment must be confirmed after a short time, about 2 weeks: if no improvement is detectable, the diagnosis of AIP is improbable, and the patients must be reevaluated for surgery or at least biopsy. If the initial workup gives an equivocal result, EUS and biopsy (not cytology!) is necessary to define the diagnosis and treatment. CT, computed tomography; MRI, magnetic resonance imaging; EUS, endosonography; ChT, chemotherapy.



**Figure 8.**  
Classification of AIP in different subclasses. Type 1 can be frequently demonstrated without histology, while definitive diagnosis of type 2 requires biopsy in the majority of cases. NOS is clinically a useful category, in particular, when no biopsy is available. For details, see text. LPSP, lymphoplasmacytic sclerosing pancreatitis; GEL, granulocytic epithelial lesion; NOS, Not Otherwise Specified; IBD, inflammatory bowel disease.

possible diagnosis. In these latter cases, pancreatic biopsy is advisable, guided by EUS and taking core biopsy, not cytology. Several cases will show typical histology of type 1 AIP. In others, the absence of significant IgG4-positive lymphoplasmacytic infiltration and the presence of granulocytic epithelial lesions with or without neutrophil infiltration of the pancreatic lobules prove definitively type 2 AIP. However, typical histological features of type 2 can be also absent in the core biopsy: in these cases the diagnosis continues to be NOS or sometimes probable type 2 (**Figure 8**).

## **5. Treatment**

Once the diagnosis of AIP is established, treatment with steroids should be started. While some tendency to spontaneous improvement can exist in several cases, steroid treatment is far superior, and the recovery of pancreatic involvement is almost always complete after a relatively short, some month of treatment [32, 33]. The widely accepted dose of prednisone is relatively low, about 0.5–0.6 mg/kg/day. Others initiate the treatment with 40 mg prednisone/day. After 3–4 weeks with this treatment, the steroid dose is tapered, reducing it 5 mg/day every 2 weeks. Finally, the treatment can be stopped after the complete morphological recovery demonstrated by CT scan or magnetic resonance. However, some authors argue in favor of a maintenance treatment with prednisone in a dose as low as 5 mg/day for 2 years, and they found less recurrence with this conduct, but it is impossible to avoid completely the recurrence of the disease in the pancreas or in some other organ. The recurrent disease also responds to steroid treatment. However, in case of recurrence, it is advisable to initiate a longer treatment with some steroid-sparing agent, azathioprine (1.0–1.5 mg/kg/day) or mycophenolate (2 to 3 g/day) for several years. If these treatments fail, rituximab has been shown effective in the treatment of the first episode of the disease and also in its recurrence. In our experience, steroid treatment with or without steroid-sparing agents was effective in all but one cases; we recently used rituximab 1000 mg repeated in 15 days, i.e., 2000 mg as total dose, in one exceptional patient, with a good initial result. The Mayo Clinic experience [34] is in favor to repeat rituximab 1000 mg every 2–6 months and use it as maintenance treatment. Diabetes becomes frequently clinically overt during the acute phase, as a consequence of the disease itself and the effect of corticosteroids. Insulin treatment can be necessary, but it is transitory in the majority of the patients. Close control is mandatory in order to adjust the insulin dose, which changes rapidly during the treatment: insulin requirement initially increases and later on decreases rapidly. Clinically evident pancreatic exocrine insufficiency during the acute phase is not observed; enzyme supplementation is not necessary.

The effect of steroids is uniformly excellent. It means that if steroids fail to induce remission, one must have serious doubts in the diagnosis, whatever was the basis to establish it. In these cases histological diagnosis is mandatory and surgery is probably inevitable. In spite of the growing knowledge about AIP, the differential diagnosis can be difficult, and AIP continues to be a histological finding of some patients operated on with the suspicion of pancreatic cancer. However, surgery is not a good treatment for AIP; the recurrence without prednisone treatment continues to be a real possibility. In addition, pancreatic resection has surgical morbidity and late metabolic consequences, which are hardly justifiable in a benign medically treatable disease.



## 6. Late prognosis: progression to chronic pancreatitis

AIP has been considered as a subclass of chronic pancreatitis (CP). There is no doubt that autoimmune factors can have some importance of the pathogenesis of CP and also in some cases of recurrent acute pancreatitis (RAP). There is also a possibility that the idiopathic advanced CP in several cases can be the late consequence of unrecognized and untreated AIP. However, clinical and epidemiological characteristics; morphological alterations in CT, MR, and EUS; images and histology are all quite different when compared to CP [35]. In addition, CP is a progressive damage to the pancreas, while AIP is a reversible disease after an adequate treatment. There are contradictory observations in the literature about the long-term outcome of AIP [36–38]. When we evaluate the published observations, we must be cautious, and we have to remember that AIP was definitively described only in 1995; it means that follow-up of patients for a period longer than 20 years is lacking. Biliary stenting by ERCP [39] and significant focal stenosis of the main pancreatic duct [40] were found as risk factors for formation of pancreatic stones and progression to CP. Exocrine and endocrine insufficiencies were described in a significant number of patients [41], even without detectable changes of advanced pancreatic disease. However, pancreatic enzyme replacement therapy has not been routinely used even in these cases. Our limited experiences are different: while 11 of our 74 patients had diabetes, clinically overt exocrine insufficiency was observed only in 2 of them [18], requiring oral pancreatic enzyme replacement therapy. We can find similar doubts in the literature about the risk of malignancy: higher incidence of pancreatic and extrapancreatic cancer was described by some authors [42] but not confirmed by others [43]. We did not observe malignant disease in our cohort of patients.

The possibility of AIP to PC requires longer observations. However, we insist that AIP in our opinion is not a simple subclass of CP. The differences are as strong as or even stronger than in the case of obstructive pancreatitis. Both of these entities can be reversible with an adequate timely treatment, and probably both of them can progress to CP if their cause persists unresolved [44]. If it is true, it underlines even more the importance of the early diagnosis and proper treatment.

## 7. Conclusions

Autoimmune pancreatitis is an increasingly recognized, relatively new disease, identified definitively only in 1995. Two types of the AIP are described, type 1 or lymphoplasmacytic sclerosing pancreatitis (LPSP) and type 2 or idiopathic duct-centric pancreatitis. While type 1 is part of an IgG4-related systemic disease, type 2 is limited to the pancreas and can be associated only with inflammatory bowel disease. The diagnosis is not easy; detection of morphological alterations is the clue in recognizing AIP and distinguishing it from other pancreatic diseases. Once the diagnosis is made, the clinical classification of types 1 and 2 also can be difficult. For this reason, an indeterminate category Not Otherwise Specified (NOS) is useful in the everyday clinical practice. All types of AIP respond rapidly and completely to steroid treatment. The late prognosis is good, but residual morphological and functional pancreatic changes can be present. Progression to advanced CP probably can be prevented with adequate treatment. These characteristics make AIP a unique pancreatic disease: its correct diagnosis avoids unnecessary surgery, and it is the only pancreatic disease when we have the possibility to achieve a complete recovery with noninvasive medical treatment. It is particular also among the autoimmune diseases: an excellent

response to low-dose steroids and in relatively short time, with a real possibility to stop the treatment and a relatively low risk of recurrence or progression.

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## **Conflict of interest**

The authors declare no conflict of interest.

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