

## Type 1 autoimmune pancreatitis: case scenario and review of the disease

### Pancreatitis autoinmune tipo 1: caso y revisión de la enfermedad

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#### ABSTRACT

Autoimmune pancreatitis (AIP) is an uncommon disease that represents a diagnostic challenge unless it is considered as a cause of acute pancreatitis, pancreatic exocrine insufficiency and a pancreatic mass. This entity is under diagnosed and successful medical therapy is available. In this paper, we will describe a case of a 59 year-old, Hispanic woman diagnosed with autoimmune pancreatitis, a disease previously believed to affect typically older men. We will review the definition, types, clinical manifestations, radiological features, serology, histopathological findings, treatment strategies and diagnostic criteria of autoimmune pancreatitis.

**Keywords:** *Pancreatitis; Exocrine pancreatic insufficiency; Cholangitis, sclerosing (source: MeSH NLM).*

#### RESUMEN

La pancreatitis autoinmune (PAI) es una enfermedad rara que se presenta como un reto diagnóstico a menos que sea considerada como causa de pancreatitis aguda, insuficiencia pancreática exocrina y masa pancreática. Es una enfermedad sub diagnosticada y existe una terapia médica satisfactoria. En este trabajo, describiremos un caso de una mujer hispana de 59 años diagnosticada de pancreatitis autoinmune, una enfermedad que se creía previamente que afectaba típicamente a hombres de avanzada edad. Revisaremos la definición, los tipos, las manifestaciones clínicas, hallazgos radiológicos, serología, hallazgos histopatológicos, estrategias de tratamiento y criterios diagnósticos de la pancreatitis autoinmune.

**Palabras clave:** *Pancreatitis; Insuficiencia pancreática exocrina; Colangitis esclerosante (fuente: DeCS BIREME).*

#### INTRODUCTION

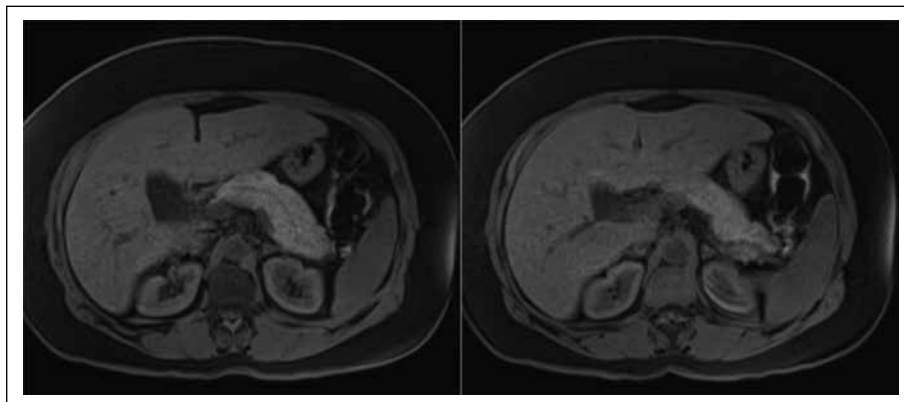
Autoimmune pancreatitis (AIP) is composed of at least two disease entities. Type 1 AIP is the pancreatic manifestation of IgG4-related autoimmune disease characterized by increased serum IgG4, lymphoplasmacytic infiltrates on histology, other organ involvement and dramatic response to steroid therapy. Type 2 AIP presents as an isolated organ disorder with granulocytic epithelial lesions on histology. Although the pathogenic mechanism remains unclear, multiple factors such as genetic background and abnormal immunity may be involved. Diagnosis of both types can be made using the International Consensus Diagnostic Criteria. There is consensus for initial steroid treatment; however, steroid maintenance and treatment for relapses are controversial. In the long term, approximately 10% of type 1 AIP may progress into chronic pancreatitis. Although controversial, autoimmune pancreatitis seems to be a risk factor for pancreatic malignancy<sup>(1-3)</sup>. Thus, these patients need to be followed in time as patients with chronic pancreatitis are.

#### CASE REPORT

A 59 year-old Honduran woman presented with a 3-week history of nausea, vomiting, fever, productive cough and watery diarrhea. Her past medical history

was significant for acute recurrent pancreatitis of unknown etiology. She had no history of hypertriglyceridemia, hypercalcemia or gallstones. Her family history had no history of pancreatic disease or cystic fibrosis. She denied any alcohol intake, tobacco or drug use. Her physical exam showed crackles on the left pulmonary base, abdominal exam revealed mild periumbilical tenderness but was otherwise benign. Laboratory data showed leukocytosis WBC 16 400 cells/ml, normal Hb, platelet count, basic metabolic panel and liver function panel. Amylase was 163 and Lipase 644 (>3 times ULN). Ultrasound and plain CT scan of her abdomen showed a normal gallbladder without stones and an unremarkable pancreas. Nevertheless, her gastrointestinal symptoms worsened when her lipase levels rose to 1553. MRI of the abdomen revealed an enlarged homogeneous pancreatic parenchyma - sausage shaped pancreas without pancreatic duct dilation (see Figure 1) which suggested autoimmune pancreatitis. IgG4 level was 522 mg/dl (normal levels < 200 mg/dl). Endoscopic ultrasound was unavailable at the time and it was elected to give the patient a diagnostic / therapeutic trial of prednisone 40 mg PO daily. There was resolution of patient's gastrointestinal symptoms and normalization of IgG4 levels. Follow-up MRI revealed resolution of the pancreatic changes. Prednisone dosage was slowly tapered over a four-month period. Patient has not had a relapse since this episode.

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**Figure 1.** MRI of the abdomen showing an enlarged homogeneous (“sausage shaped”) pancreatic parenchyma, typical of type 1 autoimmune pancreatitis.

**DISCUSSION AND REVIEW OF THE DISEASE**

**Classification**

Two types of AIP have been described in the literature. Type 1 AIP also known as lymphoplasmacytic sclerosing pancreatitis (LPSP) is part of the IgG4 related diseases and therefore its clinical presentation can be divided in pancreatic and extra-pancreatic clinical manifestations. In the active phase, Type 1 AIP patients can present with obstructive jaundice, diffuse or segmental pancreatic enlargement with or without a pancreatic mass on imaging and steatorrhea or diabetes mellitus. In a more advanced state (burnt-out phase), the pancreas can contain calcifications and/or stones or have parenchymal atrophy. Pancreatic exocrine and endocrine insufficiency can also be seen. Involvement of extra-pancreatic organs is usual, the most common associated entities include sclerosing cholangitis, renal mass/tubulointerstitial nephritis, retroperitoneal fibrosis with or without ureteral obstruction and bilateral submandibular masses (Mikulicz disease) (1-3). Type 2 AIP also known as idiopathic duct central pancreatitis (IDCP) presents as an isolated pancreatic disorder with

granulocytic epithelial lesions on histology. Whereas type 1 AIP where relapses are common, in type 2 AIP relapses are uncommon. Table 1 shows the main differences between type 1 and type 2 AIP.

**Imaging**

Magnetic resonance imaging (MRI) allows us to evaluate pancreatic anatomy for features of AIP (4). The changes can be classified into those of the parenchyma or duct. Typical parenchymal changes include diffuse enlargement of the pancreas with featureless borders, the so-called “sausage shaped pancreas” (Figure 1). A hypoattenuating capsule-like ring is also typical. A focal mass in the pancreas is an atypical radiological presentation of AIP and therefore it must be differentiated from pancreatic adenocarcinoma (5). Duct changes include narrowing of the segment of the pancreatic duct within the affected parenchyma, which is similar to that found in pancreatic cancer; however, absent or slight upstream dilatation is usually seen in AIP. Marked upstream pancreatic duct dilation is usually found resulting from pancreatic cancer. One study showed focal enlargement of the pancreas in 67% of

**Table 1.** Comparison between type 1 and type 2 autoimmune pancreatitis (2).

	TYPE 1 (LPSP)	TYPE 2 (IDCP)
Region	Asia>USA>Europe	Europe>USA>Asia
Age	Old - 7 <sup>th</sup> decade	Young - 5 <sup>th</sup> decade
Gender	75% men	equal
Clinical presentación	Obstructive jaundice (painless)	Obstructive jaundice (painless) Acute pancreatitis / abd pain
Other organ involvement	50% (proximal bile duct, salivary glands, kidney, retroperitoneum)	Not seen
Association w UC	Occasionally	Common (10-20%)
IgG4 levels	70%	25%
Histology	Lymphoplasmacytic infiltration. Storiform fibrosis. Obliterative phlebitis. Abundant IgG4 staining (>10 cells/HPF)	Gel-granulocytic-epithelial lesion Sacnt IgG4 staining
Steroid responsiveness	Excellent ~ 10%	Excellent ~100%
Recurrence	Common (20-60%)	Rare (<10%)

**Table 2.** A practical approach for using the International Consensus Diagnostic Criteria<sup>13</sup>

Parenchymal imaging	Strength of collateral evidence (IgG4, other organ involvement and pancreatic ductal imaging)	FNA	Steroid trial	Pancreas histology needed
Diffuse enlargement	Any	No	No	No
Focal enlargement/atypical	Strong	No	No	No
Focal enlargement/atypical	Modest	Yes	Yes	No
Diffuse or focal enlargement	None	Yes	Yes	Yes

the patients with AIP, diffuse enlargement in 33% and a hypo attenuating parenchyma in 90% of patients. The main pancreatic duct was stenotic or not visible within the parenchyma affected in all the patients. Of note, all these changes seen on CT normalized after treatment with immunosuppressors<sup>(4)</sup>.

### Serology

The most useful serological marker for the diagnosis of type 1 AIP is IgG4, as it is elevated in 75% of patients. IgG4 can also be elevated in other conditions that simulate AIP including pancreatic cancer, chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis and Sjogren disease.

IgG4 levels can be elevated in up to 10% of patient with pancreatic adenocarcinoma, although levels are usually less than two fold the upper limit of normal. IgG4 levels above 135 mg/dl have a sensitivity of 50 to 92% and specificity higher than 90% for the diagnosis of AIP. IgG4 levels might correlate with disease activity, higher presence of extra-pancreatic manifestations and higher relapse rate<sup>(6)</sup>. Combining the tumor marker CA 19.9 (<74 U/ml) and IgG4 levels (>100 mg/dl) measurement has proven to be useful to distinguish AIP from pancreatic cancer with sensitivity of 94% and specificity of 100%<sup>(7)</sup>.

### Histopathology

Endoscopic ultrasound (EUS) with tissue acquisition has an important diagnostic role for those patients with indeterminate findings on CT, or typical radiological findings but lack of collateral evidence (serology, extra-pancreatic involvement). EUS allows tissue acquisition via FNA or trucut biopsy. Fine needle aspiration (FNA) can be performed to obtain a sample for cytology, most useful to distinguish from pancreatic cancer. FNA has the disadvantage of not preserving the pancreatic architecture and cytology can be falsely negative in up to 40% of patients with pancreatic cancer. On the other hand, a trucut biopsy obtained via EUS preserves the histological architecture and allows immunohistochemistry studies<sup>(8)</sup>. Pathology remains the gold-standard test for the diagnosis of type 1 and type 2 AIP. Lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis and abundant IgG4 staining are

typical of type 1 AIP. The presence of granulocytic epithelial lesions is characteristic of type 2 AIP<sup>(9)</sup>.

### Diagnosis

Different diagnostic criteria for AIP have been elaborated. The JapanPancreas Society criteria in 2002<sup>(10)</sup>, the Mayo clinic criteria in 2006<sup>(11)</sup> and more recently the International Consensus Diagnostic Criteria (ICDC) in 2011<sup>(12)</sup>. The ICDC considers imaging, serology, other organ involvement, and response to steroids in order to provide a definitive or probable diagnosis<sup>(12)</sup>. Table 2 shows a practical approach for using the ICDC<sup>(13)</sup>.

### Therapy

During an initial episode, induction of remission with high-dose steroids is typically used. i.e. prednisone 40 mg PO daily for four weeks. This is followed by a slow taper of the steroid over several months i.e. decreasing 5 mg per week. The Mayo clinic proposes complete withdrawal of the steroids while the Japanese society recommends to maintain patients with low-dose steroids in an attempt to prevent relapses. In case of relapse after finishing the course of steroid, the initial dose of prednisone be increased and/or the duration of the induction therapy can be prolonged, and the taper can be done more gradually as well. Both the complete withdrawal of the steroid or maintenance with low dose steroid are reasonable options. Another therapeutic option in cases of relapse would be to start maintenance therapy with an immunomodulator such as azathioprine (2 mg/kg/day), mercaptopurine (1 mg/kg/day) or mycophenolate mofetil (750 mg bid) along with prednisone. The steroid can be tapered off while maintaining the immunomodulatory<sup>(2,3)</sup>. Hart et al did find a difference in relapse free survival between patients with relapsing AIP treated with prednisone alone vs. prednisone plus immunomodulatory<sup>(14)</sup>. In refractory cases, rituximab, which is a monoclonal antibody directed against the CD 20 antigen on B-lymphocytes, can be used. In the same study, above performed at the Mayo clinic, found that 83% of the patients with relapsing AIP achieved remission with rituximab<sup>(10)</sup>. See Figure 2 for a simplified therapeutic algorithm<sup>(3)</sup>.

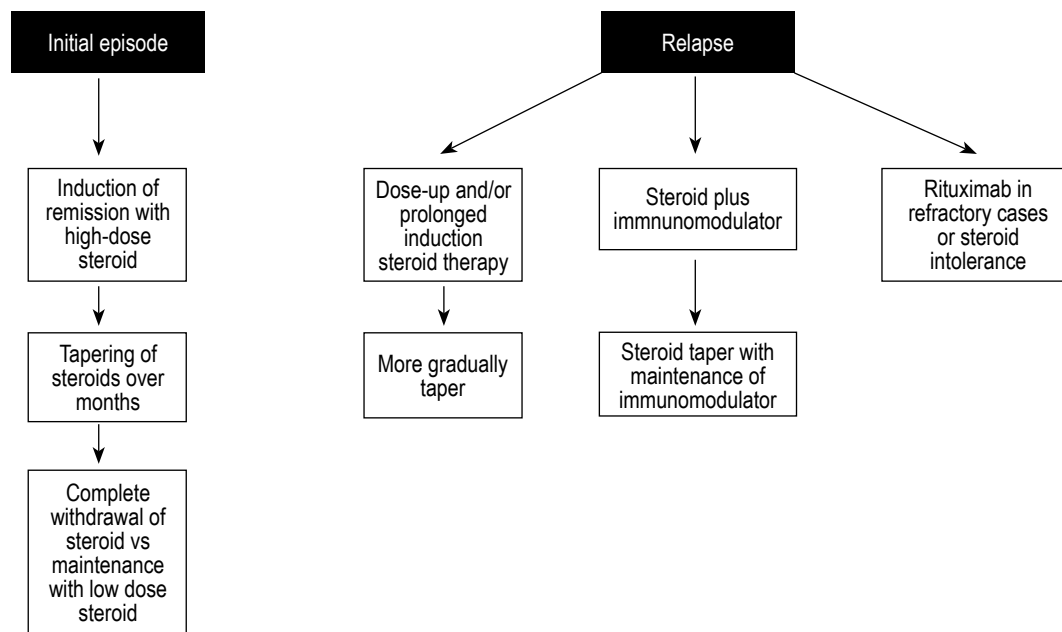


Figure 2. Simplified treatment algorithm for AIP <sup>(3)</sup>.

## CONCLUSIONS

- AIP is uncommon but it should be in the differential diagnosis of any case of pancreatitis.
- Physicians should be aware of the typical and atypical radiological features of AIP.
- Not every focal pancreatic mass on imaging is cancer. AIP can also present as a focal pancreatic mass.
- High IgG4 levels are suggestive but not diagnostic of type 1. High IgG4 levels can be seen in many other conditions.
- In not clear-cut cases, endoscopic ultrasound with FNA and/or trucut biopsy is recommended for an accurate diagnosis.
- AIP has an excellent response to steroids; nevertheless, relapses are common, and may need long term maintenance therapy.

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