Autoimmune Pancreatitis, a Report of 5 cases from Tunisia: diagnostic challenge

Pancrétatite auto-immune, rapport de 5 cas de la Tunisie : Le défi Diagnostique

Gharbi Lassad, Attouki Mohamed amine, Laghmani Ezzeddine, Marsaoui Lobna, Khalfallah Med Taher

Service de chirurgie générale, hopital Mongi Slim. Sidi Daoued .La Marsa;
Faculté de Medecine El Manar Tunis

RÉSUMÉ

Prérequis : Dans cette étude, nous avons cherché à examiner rétrospectivement les dossiers des patients traités et suivis dans notre service pour pancréatite auto-immune (PAI) et de discuter la démarche diagnostique et thérapeutique.

Méthodes: Nous avons analysé les dossiers des patients admiss dans notre service pour PAI durant les sept dernières années (Janvier 2006Août 2012). Le diagnostic de l'AIP a été établi sur la base de l’imagerie, la sérologie, la cytologie et la réponse au traitement.


Conclusion: La PAI est une maladie dont l’incidence est en nette augmentation. Elle est caractérisée par une infiltration lymphoplasmocytaire associée à une fibrose. Il est nécessaire de faire le dosage des IgG4 chez qui on suspecte une PAI pour éviter un diagnostic erroné.

Mots-clés
Pancrétatite auto-immune (PAI) - diagnostique - thérapeutique.

SUMMARY

Background: In this study, we aimed to review retrospectively the records of 5 patients who were treated in our hospital and to review the current approaches in diagnosis and management of autoimmune pancreatitis (AIP).

Methods: The series of patients diagnosed with AIP pancreatitis during this 7-years period. Four of the 5 patients were males. The most common presenting symptom was abdominal pain (4/5). Two patients had preliminary diagnosis of pancreatic mass underwent surgery. Histological analysis of the surgical resection did not reveal any malignancy. During the follow-up, one of them has developed Crohn’s disease and Sjogren syndrome. One of the patients had obstructive jaundice and abdominal pain for several months. Abdominal contrast enhanced computed tomography (CECT) suggested the diagnosis of AIP, cholangitis with renal atrophy and retroperitoneal fibrosis. He was started on steroids to which he responded dramatically. One patient had been diagnosed as primary sclerosing cholangitis few months earlier on the basis of abdominal CECT features showing a dominant stricture in the common bile duct. During the follow-up, the diagnosis of AIP was suspected and finally established on the basis of repeated magnetic resonance imaging (MRI).

The last patient had history of acute pancreatitis, obstructive jaundice and abdominal pain for 3 months. An abdominal CECT suggested autoimmune pancreatitis which was confirmed by MRCP. He was started later on steroids to which he responded significantly. IgG4 was done in all cases, high in four patients.

Conclusion: AIP is a disease with increasing incidence and characterized by lymphoplasmacytic cells infiltration and fibrosis. It is necessary to evaluate patients in terms of AIP serologically to avoid wrong diagnosis and the morbidity of surgery.

Key words
Autoimmune pancreatitis (AIP). Diagnosis - management
In this study, we aimed to review the 5 patients records retrospectively who were treated and followed-up in our hospital and to review the current approaches in diagnosis and treatment of AIP.

Although several diagnostic criteria for AIP have been proposed in various countries [1–3], these criteria are not yet unified. Among them, common criteria include the presence of a diffusely enlarged pancreas, a narrowed pancreatogram, elevated IgG4 level, fibrotic changes with lymphoplasmacytic infiltration and response to steroids. However, not all AIP patients meet these criteria [4]. AIP often presents with a morphologically focal enlarged or non-enlarged pancreas [5], a normal serum IgG4 level is seen in 10–56% of patients [6], and a biopsy to confirm the diagnosis is done in only 22–44% of AIP patients [7,8]. In addition, AIP can be misdiagnosed as it can mimic pancreatic carcinoma, which can lead to unnecessary surgery [9]. In this study, we aimed to review the 5 patients records retrospectively who were treated and followed-up in our hospital and to review the current approaches in diagnosis and treatment of AIP.

## Patients and Methods

**Autoimmune pancreatitis (AIP) presents a unique subset of chronic inflammatory pancreatic disorder with distinct clinical, morphologic, and histopathological features that typically responds dramatically to steroid therapy [1-2]. AIP affects various organs, including the bile duct, retroperitoneum, kidney, parotid and lacrimal glands. It represents a recently described subset of chronic pancreatitis that is immune mediated.**

**Although several diagnostic criteria for AIP have been proposed in various countries [1–3], these criteria are not yet unified. Among them, common criteria include the presence of a diffusely enlarged pancreas, a narrowed pancreatogram, elevated IgG4 level, fibrotic changes with lymphoplasmacytic infiltration and response to steroids. However, not all AIP patients meet these criteria [4]. AIP often presents with a morphologically focal enlarged or non-enlarged pancreas [5], a normal serum IgG4 level is seen in 10–56% of patients [6], and a biopsy to confirm the diagnosis is done in only 22–44% of AIP patients [7,8]. In addition, AIP can be misdiagnosed as it can mimic pancreatic carcinoma, which can lead to unnecessary surgery [9]. In this study, we aimed to review the 5 patients records retrospectively who were treated and followed-up in our hospital and to review the current approaches in diagnosis and treatment of AIP.**

### Introduction

Autoimmune pancreatitis (AIP) presents a unique subset of chronic inflammatory pancreatic disorder with distinct clinical, morphologic, and histopathological features that typically responds dramatically to steroid therapy [1-2]. AIP affects various organs, including the bile duct, retroperitoneum, kidney, parotid and lacrimal glands. It represents a recently described subset of chronic pancreatitis that is immune mediated.

Although several diagnostic criteria for AIP have been proposed in various countries [1–3], these criteria are not yet unified. Among them, common criteria include the presence of a diffusely enlarged pancreas, a narrowed pancreatogram, elevated IgG4 level, fibrotic changes with lymphoplasmacytic infiltration and response to steroids. However, not all AIP patients meet these criteria [4]. AIP often presents with a morphologically focal enlarged or non-enlarged pancreas [5], a normal serum IgG4 level is seen in 10–56% of patients [6], and a biopsy to confirm the diagnosis is done in only 22–44% of AIP patients [7,8]. In addition, AIP can be misdiagnosed as it can mimic pancreatic carcinoma, which can lead to unnecessary surgery [9]. In this study, we aimed to review the 5 patients records retrospectively who were treated and followed-up in our hospital and to review the current approaches in diagnosis and treatment of AIP.

### Patients and Methods

**A retrospective analysis of all cases of AIP seen in the last seven years (January 2006 – August 2012) was performed. Records of all patients with the diagnosis of AIP were retrieved and analyzed. The diagnosis of AIP was established on the basis of imaging studies, serology, cytology and response to treatment. Details about clinical presentation were retrieved, and the time gap between the initial presenting symptom and final diagnosis was recorded. All patients had undergone a work-up for pancreatitis which included abdominal contrast-enhanced computed tomography (CECT). As the diagnosis of AIP was not suspected clinically in all the patients in the first evaluation, they were treated as per the clinical indication until the correct diagnosis of AIP was established. For the same reason, serology was done after a gap in clinical presentation in three patients in whom follow-up radiology initially suggested AIP, and subsequent serology confirmed the diagnosis. Prednisolone was started at a dose of 40 mg/day for 4 weeks followed by a tapering off of 5 mg per week over the next 7 weeks. Periodic follow up was carried out in all patients at four-week intervals. Follow-up visits included clinical evaluation, liver function test and imaging studies.**

### Results

Five patients were diagnosed as having AIP during this 7-years period. Clinical presentation and proof of diagnosis for all 5 patients are reported in Tables 1 and 2. Four of the 5 patients were males. The most common presenting symptom was abdominal pain (4/5) followed by obstructive jaundice (3/5) and weight loss of 6 kg (1/5). One patient (case #1) had obstructive jaundice and abdominal pain for several months. CECT suggested the diagnosis of autoimmune pancreatitis by showing diffuse enlargement of the pancreas with a capsule like low-density rim surrounding the pancreas (Fig 1), cholangitis with renal atrophy and retroperitoneal fibrosis (Fig 2). Magnetic resonance cholangiopancreatography (MRCP) confirmed the diagnosis by showing dilated intrahepatic biliary stricture upstream extent of regular and common hepatic duct (Fig 3). There was no stenosis neither at the level of intrahepatic bile duct nor the pancreatic duct. He was started on steroids to which he responded dramatically (Fig 4).

#### Table 1: Clinical profile of the five patients before final diagnosis.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Presentation</th>
<th>Duration of symptoms at final diagnosis (months)</th>
<th>Initial diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Male</td>
<td>Mid abdominal pain, obstructive jaundice</td>
<td>2</td>
<td>Autoimmune pancreatitis</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>Female</td>
<td>Mid abdominal pain</td>
<td>5</td>
<td>Pancreatic mass</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>Male</td>
<td>Painless obstructive jaundice</td>
<td>8</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>Male</td>
<td>Mid abdominal pain, weight loss</td>
<td>3</td>
<td>Pancreatic mass</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>Male</td>
<td>Abdominal pain, jaundice, acute pancreatitis</td>
<td>3</td>
<td>Autoimmune pancreatitis</td>
</tr>
</tbody>
</table>

#### Table 2: Proof of diagnosis in the five patients.

<table>
<thead>
<tr>
<th>Cases</th>
<th>CECT</th>
<th>MRI</th>
<th>Initial treatment</th>
<th>CA 19-9</th>
<th>ACE</th>
<th>IgG4</th>
<th>Other organ involved</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bulky pancreas with loss of lobulations with a dilated CBD and tapered lower end</td>
<td>Stricture lower CBD and confluence</td>
<td>None</td>
<td>Normal</td>
<td>NA</td>
<td>elevated</td>
<td>Renal atrophy, Retroperitoneal fibrosis</td>
<td>Prednisolone</td>
<td>Improved</td>
</tr>
<tr>
<td>2</td>
<td>Pancreatic head mass</td>
<td></td>
<td>Whipple procedure</td>
<td>Normal</td>
<td></td>
<td></td>
<td>Crohn disease, Gougerot-Sjogren disease</td>
<td>Prednisolone</td>
<td>Improved</td>
</tr>
<tr>
<td>3</td>
<td>Sausage-shaped pancreas with a dilated CBD having a tapered lower end</td>
<td>Stricture lower CBD and confluence</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>elevated</td>
<td>Cholangitis</td>
<td>Prednisolone</td>
<td>Improved</td>
</tr>
<tr>
<td>4</td>
<td>Pancreatic Tail mass</td>
<td>Lesion of pancreatic tail Angiomas</td>
<td>Distal splenopancreatectomy</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
<td>No</td>
<td>Prednisolone</td>
<td>Improved</td>
</tr>
<tr>
<td>5</td>
<td>Sausage-shaped pancreas with a dilated CBD having a tapered lower end</td>
<td>Stricture lower CBD and confluence</td>
<td>None</td>
<td>Normal</td>
<td>Noraml</td>
<td></td>
<td>No</td>
<td>Prednisolone</td>
<td>Improved</td>
</tr>
</tbody>
</table>
Two patients (Cases #2 and #4), with an initial diagnosis of pancreatic mass underwent surgery. In the first case, the patient underwent Whipple procedure for a mass lesion in the head of the pancreas. The patient recovered from surgery uneventfully. In the second case, the patient underwent open distal spleno-pancreatectomy for a tail lesion (Fig 5). In postoperative, she developed a fluid collection treated with percutaneous drainage and intravenous antibiotics. Histological analysis of the surgical resection specimen did not reveal signs of malignancy, but dense fibrosis with lymphoplasmacytic infiltration and acinar atrophy. The follow up of these two cases was respectively 7 and 2 years. During the follow-up, one patient (case #2) has developed Crohn’s disease and Sjogren syndrome.

One patient (Case #3) have been diagnosed with primary sclerosing cholangitis several months earlier based on the abdominal CECT features that showed a dominant stricture in the common bile duct. During the follow-up, the diagnosis of autoimmune pancreatitis was suspected and finally established on the basis of repeated magnetic resonance imaging (MRI) and IgG4 serology.
The last patient (Case #5) had a history of acute pancreatitis, obstructive jaundice (serum bilirubin greater than 10 mg/dl; reference range: 0.3-1.0 mg/dl) and abdominal pain for 3 months. An abdominal CECT suggested autoimmune pancreatitis which was confirmed by MRCP (Fig 6). He was started on steroids to which he responded significantly. IgG4 level was normal in his case.

The mean of follow up of all cases was 3 years.

**DISCUSSION**

AIP has been defined as “the pancreatic manifestation of a systemic fibro-inflammatory disease which affects not only the pancreas but also other various organs including bile duct, salivary glands, the retroperitoneum and lymph nodes. Organs affected by AIP have a lymphoplasmacytic infiltrate rich in IgG4 positive cells and the inflammatory process responds to steroid therapy” [1]. The systemic disease of which AIP is a manifestation has been called IgG4-related systemic disease (ISD) in recognition that all organs affected show a dense lymphoplasmacytic infiltrate rich in IgG4-positive cells [10-11].

Although the frequency of occurrence has increased due to the technological advances in ultrasonography, computed tomography and magnetic resonance imaging, AIP is still a rare disease currently and is difficult to distinguish it from pancreatitis and pancreatic cancer in the early period. The first diagnostic criteria were proposed by the Japan Pancreas Society in 2002 which were later modified in 2006 [3, 12, 13]. These diagnostic criteria are important for differentiating autoimmune pancreatitis from its mimickers, such as pancreatic adenocarcinoma and primary sclerosing cholangitis. Recently, HISORt criteria have been proposed by the Mayo Clinic and include pancreatic histology (H), typical imaging (I), serology (S), other organ involvement (O) and response to steroid therapy (Rt) [1]. Accordingly, patients can be grouped into 3 groups: Group A includes diagnostic pancreatic histology, Group B includes typical imaging and positive serology and Group C includes patients with unexplained pancreatic disease with positive serology and/or other organ involvement (OOI) with resolution/mark improvement in pancreatic/extrapancreatic manifestations with steroid therapy. AIP predominantly affects males of middle age [14–15]. The common presenting symptoms of AIP are abdominal pain, jaundice and weight loss. The pain intensity is typically mild, frequently described by patients as only ‘abdominal discomfort’. Typical periods of acute pancreatitis are very rare. The major differential diagnosis in this situation is pancreatic or biliary cancer, often leading to surgical resection.

In our cases, the mild pain and jaundice were the most symptoms. One patient has a history of acute pancreatitis and two patients underwent surgical resection for suspected pancreatic mass.

AIP is characterized by irregular narrowing of the main pancreatic duct (MPD), and narrowing of the MPD is an essential criterion for the diagnosis of focal/segmental AIP according to the Japanese diagnostic criteria 2011.

Typical cases of AIP show a diffuse enlargement of the pancreas the so-called ‘sausage-like’ appearance on computed tomography (CT), ultrasound (US) and magnetic resonance imaging (MRI). On dynamic CT and MRI, there is delayed enhancement of the swollen pancreatic parenchyma. Since inflammatory and fibrotic changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, which appears as a low-density region on CT and as a hypodense area on T2-weighted MRI, is detected in some cases. US show an enlarged hypoechoic pancreas with hyperechoic spots. Pancreatic calcification or pseudocysts are seldom observed. Some cases show a focal enlargement of the pancreas, similar to that seen with pancreatic cancer.
Magnetic resonance cholangiopancreatography (MRCP) is often helpful in characterizing the pancreatic and bile ducts, although the narrowed segment of the pancreatic duct is not well visualized. The MRCP findings of skipped, nonvisualized main pancreatic duct lesions, in conjunction with other imaging studies, are useful in supporting the diagnosis of AIP.

Increasingly, endoscopic ultrasound (EUS) has been used to evaluate patients for AIP [16,17]. Not only can the parenchyma and biliary and pancreatic ducts be visualized, EUS also provides an opportunity to obtain Trucut biopsy samples. Intraduct ultrasound can also be used to evaluate indeterminate biliary strictures.

EUS was not available in our cases and the diagnosis was based on CT scan images, MRI images and serology.

Classically, the predominant histological feature of AIP has been dense infiltration of the periportal space with plasma cells and T lymphocytes. Associated with this infiltrate is acinar destruction, obliterator phlebitis involving the major and minor veins, and storiform or “whirling” fibrosis of the pancreatic parenchyma, which can extend to contiguous peripancreatic soft tissue.

Immunological abnormalities include hypergammaglobulinaemia, elevated serum IgG4 levels and the presence of autoantibodies including antinuclear antibody, anti smooth muscle antibody, rheumatoid factor, antilactoferrin antibody and antipancreatic amylase antibody II [18-19].

Elevated IgG4 (>135 mg/dL) is the hallmark of AIP, being elevated in more than 90% of patients [20]. The elevation of IgG4 has been confirmed in several studies [21–22].

AIP has recently been further classified into type 1 and type 2 AIP [23,24]. Type 1 AIP is a classical AIP that shows lymphoplasmacytic sclerosing pancreatitis and is considered the pancreatic manifestation of IgG4-related systemic disease. It is commonly complicated with OOI [25,26]. Type 2 AIP shows a histology of idiopathic duct centric chronic pancreatitis and is not related to IgG4 [23, 24] although it is reported that type 2 AIP responds well to steroid therapy, similar to type 1 AIP [23].

In our series, only one patient had normal IgG4 level and can be classified as type 2 AIP.

The others are classified type 1 AIP.

AIP can be complicated by a variety of extrapancreatic lesions, which appear synchronously or metachronously with the pancreatic lesion, share the same pathological conditions, and show a favorable response to glucocorticosteroid therapy, characteristics indicative of a common pathophysiological background. Among the variety of extrapancreatic diseases, lacrimal and salivary gland lesions are some of the most frequent, found in 23%-39% of patients with AIP [27].

Extrapancreatic lesions may mimic or be misdiagnosed as primary lesions of the corresponding organs, e.g., lachrymal and salivary gland lesions for Sjogren syndrome. It is therefore necessary to differentiate between IgG4-related diseases and inherited diseases of the corresponding organ.

Two patients have extrapancreatic manifestations. It was synchronous in one case with renal atrophy, retroperitoneal fibrosis, and metachronous in one case with the appearance of Crohn disease and Sjogren syndrome.

AIP can mimic pancreatic cancer in its clinical presentation, imaging features and laboratory workup. Differentiating between these two entities requires implementation of clinical judgment and experience along with objective parameters that may suggest either condition. No strategy has been proposed for the surgeon to implement when facing borderline cases.

Two of our patient undertaken surgical resection for suspected pancreatic mass. The diagnosis was made on pancreatic specimen.

The treatment of choice for AIP is the use of corticosteroids with multiple authors reporting dramatic response rates with prolonged therapy [1, 20]. Although improvement in clinical findings with steroid therapy may be useful in the differential diagnosis of AIP from pancreatic cancer, facile diagnostic steroid trial should be avoided to not misdiagnose pancreatic cancer as AIP serological and imaging tests should be done 2 weeks after initiating steroid therapy. Rapid response to steroids is reassuring and confirms the diagnosis of AIP. If steroid effectiveness is reduced, the patient should be reevaluated on suspicion of pancreatic cancer.

In the Japanese guidelines [28], before starting steroid therapy, biliary drainage is usually done in cases with obstructive jaundice. However, as there are some patients whose jaundice is relieved by steroid therapy alone, it is unclear if biliary obstruction can be treated with steroid therapy alone without biliary drainage [29].

Magnetic resonance cholangiopancreatography is useful to observe the response to steroids in the pancreaticobiliary ducts noninvasively [30]. Pancreatic size usually normalizes within a few weeks. Rapid response to steroids is reassuring and confirms the diagnosis of AIP.

Remission is defined as the disappearance of clinical symptoms and resolution of the pancreatic and/or extrapancreatic manifestations on imaging studies [31]. None for our patients had biliary drainage before starting steroids. Clinical remission was observed after the two first week of treatment. Radiological remission was observed after one month. The exact steroid treatment protocol for patients who have AIP is not standardized; however, most practitioners initiate therapy with between 30 and 40 mg of prednisone daily. These doses are usually effective to induce remission; it is unclear if starting at lower doses would be equally effective. Resolution of symptoms is generally rapidly achieved within 2 to 3 weeks of corticosteroid initiation. Laboratory parameters of AIP also improve.

Imaging studies have demonstrated that improvement can be observed within 1-2 months [29]. Long-term maintenance of patients on a low dose of prednisone (2.5–10 mg daily) has been suggested for preventing a possible relapse of AIP [32]. Other clinicians adopt non steroid immunomodulatory medications for the maintenance of remission in patients who relapse after steroid with drawal by using either azathiprine or mycophenolate mofetil, which appear to be equally effective [11].

**CONCLUSION**

AIP is a unique subtype of recently identified chronic pancreatitis that is immune mediated and represents one manifestation of a systemic IgG4-related disease process. Although a rare condition, it is important to recognize because it responds often dramatically to immune system-modulating treatment. The diagnosing of AIP can sometimes be challenging, however, and it is imperative that clinicians be cautious when considering this diagnosis in patients suspected of having a pancreatic malignancy.
Références


