Autoimmune Pancreatitis Rarely Progresses to Advanced Chronic Pancreatitis - Experiences from Chile

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ABSTRACT

Context Autoimmune pancreatitis is increasingly diagnosed in the everyday gastroenterology practice. It is considered as a subclass of chronic pancreatitis. Steroid treatment results in a quick recovery and long-term prognosis is good. Objective To evaluate experiences in the diagnosis, classification and late outcome of autoimmune pancreatitis in two tertiary centers in Chile. Methods Retrospective analysis of clinical files and follow-up of our patients with diagnosis of autoimmune pancreatitis between 1997 and 2017. Results Autoimmune pancreatitis was diagnosed in 83 patients in the study period. Nine of them were excluded for incomplete data (n=1) or lost to follow-up (n=8). Autoimmune pancreatitis was classified as type 1 by increased serum IgG4 level, other organ involvement and/or pancreatic histology (n=44; age: 52.95 ± 17.00, males: 33). Type 2 was assumed if IgG4 was normal and ulcerative colitis associated (n=10 age: 28.9 ± 16.83, males: 5). In 20 cases autoimmune pancreatitis was classified as not otherwise specified (age: 37.05 ± 17.40, males: 11). Steroid treatment resulted in a complete recovery in all cases. Recurrence was observed in 11 type 1 and in 3 not otherwise specified but in none of type 2 patients, with good response to a second course of steroids. Azathioprine maintenance therapy was used in 5 patients and calcineurin inhibitor in 1 patient. One patient developed chronic pancreatitis, exocrine insufficiency was detected in 2 and diabetes in 11 cases. Conclusions Autoimmune pancreatitis is increasingly recognized in Chile. The diagnosis is feasible by imaging, serology and response to steroids, classification without histology is difficult. Several cases remain undetermined. The prognosis is good, and progression to calcified chronic pancreatitis is an exception in our experience.

INTRODUCTION

An inflammatory pancreaticitis was described for the first time by Henri Sarles in 1961[1], but it was only in 1995 when the terminology of autoimmune pancreatitis (AIP) was used [2] and in 2003 when the concept of IgG4 related disease was widely accepted [3]. Later on, a second type of AIP was described, which received the name of type 2 or Idiopathic Duct-Centric Pancreatitis (IDCP) [4, 5, 6, 7, 8]. While different in several aspects, this type of disease also responds to steroid treatment. It is rare in Asia [9], somewhat more frequent in USA [4, 6].

Autoimmune factors play an important role even in the widely accepted TIGAR-O [10] classification system, where the “A” refers to “autoimmune” etiology. However, it seems to be quite different entity and unrelated to IgG4. For example, chronic pancreatitis (CP) was described in relation to systemic lupus erythematosus [11], but pancreatitis was rarely found in patients with autoimmune diseases [4]. AIP has a characteristic clinical course, radiologic findings, histology and prognosis. However, CP can be the late result of AIP and AIP continues to be accepted as a class of CP.

A lot of papers have been published on this disease from Asia, Europe and United States. However, from Latin America, major experiences were reported only from Mexico [12], and there are some case reports from Argentina [13], Peru [14, 15, 16], Brazil [17, 18] and Colombia [19]. We published our initial experience with 10 patients in 2010 [20]. In this paper we compare our experience to the observations published from other regions of the world, and evaluate difficulties in the diagnosis and classification of AIP in the daily clinical practice. The regular follow-up of our patients permits to evaluate the late outcome of this disease and its relation to the classic CP.

PATIENTS AND METHODS

We reviewed clinical files of patients treated between 1999 and 2017 with diagnosis of AIP in two tertiary hospitals with regular follow up by pancreatologists. The initial diagnosis was revised according to the International Consensus Diagnostic Criteria [21] at the moment of this analysis, and they were classified as type 1 and type 2 AIP.
If the diagnosis of AIP was established but no definitive classification was possible, they were considered as Not Otherwise Specified - NOS [22]. The patient was later on reclassified if new data made it possible (e.g. posterior appearance of inflammatory bowel disease or other IgG4 related disease). Demographic characteristics, clinical findings, laboratory tests, imaging studies and other organ involvements were registered. IgG4 serum level was not measured in 14 patients, which occurred mainly in the initial period. Later on, IgG4 was routinely checked at the moment of diagnosis and during the follow-up using an upper cut-off limit of 135 mg/dl [23].

Histology was obtained from surgical specimens of resected pancreas (n=7), fine needle aspiration (FNA) by endosonography (n = 5), endoscopic biopsy from the papilla of Vater (n=8) and histology of other involved organs such as lymph nodes (n=2) and stomach biopsy (n=1).

Patients were treated with oral prednisone in a dose of 0.5-0.6 mg/kg body weight per day and controlled at the 3rd week to confirm the initial response to the treatment. After the 4th week, the prednisone dose was tapered by 5 mg every 2 weeks and suspended after 4-6 months. Morphological recovery of the pancreas was confirmed by magnetic resonance (MR).

The patients were regularly followed by pancreatologists in the outpatient center of both institutions and contacted by phone at the time of the conducting this study. The follow-up period was 4.1 ± 4.17 years (range 1 to 18 years, 10 of them for more than 10 years). They were monitored clinically, and with laboratory tests. MR was made on suspicion of recurrence of the disease, even if the IgG4 related disease recurred in other organ. In these cases oral steroid therapy was repeated and 1-1.5 mg/kg/day Azathioprine was added and continued for several years. Rituximab has not been used yet in our group.

**Ethics:** The retrospective analysis of the clinical files and the project was approved by Committee of Ethics in both institutions.

**Statistical Analysis**

Basic descriptive statistics were obtained including mean, median and standard deviation (SD) for continuous variables.

**RESULTS**

Data were collected from 83 patients diagnosed with AIP between 1999 and August 2017. Nine of them were excluded from this analysis for incomplete data (n=1) or lost for follow-up (n=8). Finally, 74 patients were included, of which 48 were men and 26 women, mean age 45.4 ± 17 years. All patients had characteristic imaging features, responded quickly to steroid treatment. According to the ICDC, 44 patients were categorized as type 1 AIP, 10 patients as type 2 and 20 patients as AIP- NOS (Figure 1).

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**Figure 1.** Flow-chart of the patients analyzed. For demographic and other clinical details see Table 1.
Classification as type 1 AIP was confirmed by increased IgG4 serum level (n=24), by histological findings in the resected pancreas (n=7), or involvement of other organs (n=29). All patients classified as type 2 AIP had ulcerative colitis, at the time of the AIP diagnosis or later (n=10). The remaining patients were classified as NOS (Table 1). AIP was increasingly diagnosed after 2010 (Figure 2). Type 2 and NOS patients had normal IgG4 serum levels and fulfilled the other criteria of AIP, but pancreatic biopsy was not done. Cytology of involved pancreatic tissue was obtained in some cases (n=4) by FNA.

In type 1 AIP (n=44), the main initial symptom was jaundice (n=32), followed by abdominal pain (n=16), weight loss (n=12), and mild acute pancreatitis (n=4). In type 2 (n=10) and NOS (n=20) AIP, the leading symptom was abdominal pain in (n=8 and 16, respectively) followed by jaundice, also frequent in these groups (Table 2). Other organs were involved in 29 patients with type 1 AIP. The most frequent extrapancreatic IgG4 related manifestations were bilateral nephritis (n=11), sclerosing cholangitis-like cholangiopathy (n=8) and Castleman disease (n=5). Other, non IgG4 related autoimmune diseases were also found (n=8). All 10 patients with type 2 AIP had ulcerative colitis. In NOS AIP, one patient had hypothyroidism.

MR of pancreas was done in all patients and in most of them also CT scan was performed as first radiologic examination. The pancreatic involvement was diffuse in 27 of 44 type 1 patients, in 2 of 10 type 2 and in 4 of 20 NOS patients. Focal tumor-like lesion was found in 17 of type 1 AIP (11 head, 6 tail) and 2 of 10 type 2 AIP patients. In 16 of the NOS group, the disease affected only partially the pancreas (7 head, 9 body and tail), but the involvement of the affected segment was diffuse, without tumor-like lesion.

ERCP was performed in 12 patients, 10 of them for obstructive jaundice with stent placement. Pancreatic resection (6 head and 1 tail) was performed in 7 type 1 AIP patients, always for diagnostic doubts, 6 of these surgeries were carried out before 2010. No surgery was performed in type 2 and NOS group. Histology of surgical

<table>
<thead>
<tr>
<th>Type 1. (n=44)</th>
<th>Type 2. (n=10)</th>
<th>NOS (n=20)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Age (mean +/- SD, yrs)</td>
<td>52.95 +/- 17.00</td>
<td>28.9 +/- 16.83</td>
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<tr>
<td>IgG4 &gt;135 mg/dl</td>
<td>24/30 (80%)</td>
<td>0/10</td>
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<tr>
<td>Symptoms</td>
<td></td>
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<tr>
<td>Jaundice</td>
<td>32</td>
<td>2</td>
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<tr>
<td>Abdominal pain</td>
<td>16</td>
<td>8</td>
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<tr>
<td>Weight loss</td>
<td>12</td>
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<tr>
<td>Acute pancreatitis</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Suspected pancreatic cancer</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Surgery</td>
<td>7</td>
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<tr>
<td>Recurrence</td>
<td>11</td>
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<tr>
<td>Exocrine insufficiency</td>
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<tr>
<td>Diabetes</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>3*</td>
<td>0</td>
</tr>
</tbody>
</table>

* The cause of death was unrelated to pancreatic disease: one patient died for acute myocardial infarction, one for complications of rheumatoid arthritis, systemic autoimmune disease and one for end stage liver disease by hepatitis C virus. Other details see in the text.

Figure 2. Diagnosis of AIP in different 5 years periods. Only some cases of type 1 disease were recognized in the first period, followed by a marked increase in time, by the appearance of type 2. and NOS patients. The proportion of NOS is the highest in the recently observed cases, several of them probably will be determined during the follow-up as type 1 or 2.
pancreatic tissue showed lymphoplasmacytic infiltrate, storiform fibrosis and venulitis, characteristic features of lymphoplasmacytic sclerosing pancreatitis (LPSP). Biopsies from the papilla of Vater showed nonspecific lymphoplasmocytic infiltrate, immunostaining for IgG4 was positive in 4 of 5 cases when it was applied. In 2 type 2 and 2 NOS patients, cytology was obtained by EUS guided FNA, showing only slight to moderate non-specific lymphoplasmocytic infiltration and no malignancy.

Treatment and Follow-Up

Four of the 40 patients with Type 1 AIP did not receive steroids, all of them had pancreatic resection. All but one surgical resection was performed only in the initial period, all patients had type 1 AIP. All the others had a complete recovery after receiving corticosteroid therapy, they responded quickly to steroids, independently of the subgroup. Post-treatment relapse observed in 11 of 44 patients with type 1 AIP which occurred after a symptom free period, and it was observed also in 3 of the 20 patients with NOS-AIP. There was no relapse in the type 2 AIP group. Of the patients who relapsed, 5 received prednisone associated with azathioprine, in the remaining 9 (6+3), a new course of prednisone alone was given. Recurrence occurred between 5 and 12 months after the suspension of first therapy. No recurrence occurred after pancreatic resection in this group. During follow-up, 11 patients developed diabetes, 6 of them requiring insulin. In 2 patients exocrine pancreatic insufficiency was demonstrated by low fecal elastase level during the follow-up, they were treated with oral pancreatic enzymes. One patient developed classical CP, with calcifications and intraductal stones 6 years after the initial episode and 3 years after a relapse. In most cases the functional and morphological recovery was complete, except for a certain degree of atrophy in the involved pancreatic segment in some patients. The functional recovery was confirmed by normal fecal elastase test, regular control of blood glucose and hemoglobin A1c level. We have not observed functional sequela or recurrence in type 2 AIP. Of the total group, there were 3 deaths, none of them related to pancreatic disease. None of our patients has developed neither pancreatic nor extrapancreatic malignancy till now.

Late outcome was worse in type 1 AIP: More frequent recurrence and permanent functional damage, and the only advanced chronic pancreatitis with calcifications was observed in this subgroup. In contrast, we have not observed functional sequela or recurrence in type 2 AIP and only three relapses in NOS AIP patients, with a complete recovery after repeated steroid treatment.

DISCUSSION

After several case reports, our descriptive, retrospective study is the first analysis of major experiences on AIP from South America. The prevalence of AIP is not known: it was estimated about 4.6/100,000 in Japan [9], with predominance of type 1, while the incidence was estimated in about 0.29/100,000/yr in a study published from Germany [24], being considered as a relatively rare disease also in Spain [25]. Type 2 was also rare in Korea [26], UK [27] and Hungary [28]. In a study of Schneider et al, no cases of AIP were found in patients with chronic alcoholic pancreatitis but autoimmune etiology was considered probable in 9% of non-alcoholic CP [24]. In our group, AIP has been diagnosed in the last years with a frequency similar to that of CP, which is considered a relatively rare disease in Chile [29]: 69 of our patients with AIP were seen after 2006 vs. 87 CP cases seen in the same period. Following our AIP patients with regular clinical, laboratory controls and even images if necessary, we found the progression to chronic pancreatitis in one exceptional case. On the other hand, only in 3 of our 121 CP cases we could detect some autoimmune factors [29], including also the present patient. These facts also support our opinion: AIP cannot be considered simply as a subclass of CP [30]. In the worldwide accepted TIGAR-O classification [10], clinical characteristics, progressive evolution of pancreatic damage and even histology are very similar in toxic (T), idiopathic (I), genetic (G) etiologies and even in the recurrent (R) form, demonstrating that it is the same disease. However, obstructive (O) pancreatitis is considered as a separate entity in this classification, for its differences in the histology and the capacity to recover even completely, once the obstruction resolved. We think, that AIP is quite different if we compare to classic CP: on the basis of clinical characteristics, complete recovery in response to steroids, lack of exocrine and endocrine insufficiency and even its histology, we suggest that it should be considered as a distinct entity. While AIP patients do require regular control with gastroenterologist including pancreatic exocrine and endocrine function, this control must be focused on the eventual recurrence of the disease and search for involvement of other organs.

Type 1 AIP has been found dominant in Asia and type 2 almost exceptional [9, 26]. Almost exclusively type 1 was published in UK [27] and 3 type 2 were observed in 17 Hungarian cases [28]. Also in Spain, 45 of 52 patients were type 1 and only 5 of them type 2 [25]. Our experiences are similar to well-known literature data in several aspects: type 1 AIP was markedly more frequent, with similar demographic characteristics and excellent rapid response to steroid treatment, with a tendency to recurrence in about 25-30%. While the diagnosis of type 1 AIP has been
established in the majority of cases without histology of pancreas, this classification was definitely confirmed by other criteria, as increased IgG4 serum level and/or other organ involvement by the IgG4 related disease. On the contrary, the only proof for type 2 AIP in our experience was the association with inflammatory bowel disease (IBD), in particular with ulcerative colitis (UC). We did not obtain histology of pancreas, because the cytology obtained by FNA via endosonography has a limited value in the diagnosis of AIP [31] and it is not without risk. Thus, the diagnosis of type-2 AIP in our material could be questionable in some cases, as it was shown in the recent national study from Japan [32]. In the future, improvement in the EUS biopsy needles [33, 34] can increase the diagnostic performance and histology hopefully will be available without elevated risk for the diagnosis of AIP, in particular for type 2. However, clinical characteristics of our patients considered as probable type 2-AIP were similar to those described elsewhere in the world: no gender difference, markedly younger age, no recurrence, normal serum IgG4 and rapid and complete response to steroids.

Our experience is consistent with the existence of significant differences between type 1 and type 2 AIP, both in clinical characteristics and outcome, but not in radiological findings and in steroid responsiveness, which are similar in both groups. We found some differences in the distribution but not in the character of morphological alterations detected by MRI: diffuse involvement of the pancreas and mass-forming lesions were considerably more frequent in type 1, but the parenchymal alterations and duct stricture were common in the three subgroups. In absence of increased IgG4 level or other diagnostic criteria, distinguish LPSP and IDCP at the moment of initial presentation is very difficult, almost impossible. In addition, there are several cases, when the clinical classification in type 1 or 2 is not possible, for this eventuality appeared a third, undetermined class, denominated as No Otherwise Specified (NOS) [22]. This subclass of AIP is probably a mixture of type 1 and 2 patients, without sufficient information to achieve a definitive classification. We found the NOS-AIP category useful for the clinical practice for the patients when the diagnosis of AIP was established with strong probability by other criteria – radiology and response to steroid - but without elevated IgG4 nor other organ involvement, as a consequence, the classification remained undetermined. Some of our patients were reclassified during follow-up.

While some spontaneous improvement does exist in this disease, complete recovery is far more frequent and even the late prognosis is better if the patient receive an adequate treatment [35]. The question is, which is the adequate treatment? [21, 36]. In our practice, steroid treatment was used in all patients as described. After recurrence or after association of other IgG4 related disease, we added Azathioprine and maintained its use for several years. Some groups argue in favor of maintenance steroid therapy: less relapse was seen if a low dose of 5 mg/day was maintained for two years [37]. However, about 70% of our type 1 patients, all patients with the type 2 AIP and 17 out of 20 NOS class had no relapse without maintenance treatment and we agree that the treatment must be individually tailored [38]. We did not observe recurrence after surgical resection of pancreas, even in the four cases without steroid treatment. However, the small number of the operated patients does not permit any conclusion and the surgery is certainly not the recommended treatment for AIP.

On the other hand, there are several doubts regarding the prognosis and late outcome of this disease. The likelihood of progressing to CP has been widely discussed. Biliary stenting by ERCP [39] and significant focal stenosis of main pancreatic duct [40] were found as risk factors for formation of pancreatic stones. In fact, we saw one exceptional patient with chronic calcifying pancreatitis and pancreatic ductal stones, who has previously undergone an ERCP when a suprapapillary stenosis of pancreatic duct was found, which disappeared after posterior steroid treatment. After the recovery, we observed diabetes somewhat more frequently (n=11) while overt exocrine insufficiency was detected only in 2 patients. Increased risk of pancreatic and even extrapancreatic cancer was published after AIP [41] but it was not confirmed by others [42]. No malignant tumors have been observed in our group.

Our study has several limitations. First of all, it is a retrospective study. We did not search for a histologic diagnosis in AIP. Obviously, the risks to obtain histology specimen of the pancreas is relatively elevated and the cytology has limited value. Thus, in contrast to our 44 type 1 patients, the classification of type 2 and NOS remains always a somewhat uncertain in our patients. The strength of our experience is in the relatively large number of patients who fulfilled all the other diagnostic criteria and in the long and regular follow-up.

CONCLUSION

AIP is a relatively new disease, we recognize it with a rapidly increasing frequency. Our experiences, until now the biggest in South America, show similar observations than in the rest of the world. The excellent and rapid response to steroid treatment permits to avoid unnecessary endoscopic and surgical interventions. Late prognosis is good, progression to advanced chronic pancreatitis is exceptional, significant endocrine and exocrine insufficiency is rare and no associated malignant disease was observed. When compared to CP, the morphology, clinical characteristics and late outcome of AIP are clearly different. In our experience, progression to CP can be avoided by treatment, regular follow-up and repeated treatment of recurrences.

Conflict of Interest

The authors do not have conflict of interest.
References


