Autoimmune Pancreatitis in Hungary: A Multicenter Nationwide Study

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Key Words
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Abstract
Background: To date, most cases of autoimmune pancreatitis (AIP) have been reported from Japan. The aim of the present study was to assess the clinical features and management of AIP cases in Hungary. Methods: The demographics, clinical presentation, laboratory and imaging findings, extrapancreatic involvement, treatment response and recurrence were evaluated in the first 17 patients diagnosed with AIP in Hungary. Results: The mean age at presentation was 42.7 years (range: 16–74); 47% of the patients were women. New-onset mild abdominal pain (76%), weight loss (41%) and jaundice (41%) were the most common symptoms, with inflammatory bowel disease being the most frequent (36%) extrapancreatic manifestation. Diffuse pancreatic swelling was seen in 7 patients (41%) and a focal pancreatic mass in 8 (47%). Endoscopic retrograde cholangiopancreatography revealed pancreatic duct strictures in all study patients. The serum IgG4 level at presentation was elevated in 62% of the 8 patients in whom it was measured. All the percutaneous core biopsies (5 patients) and surgical specimens (2 patients), and 2 of the 4 biopsies of the papilla of Vater revealed the typical characteristic findings of AIP: a diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis and obliterative phlebitis. Immunostaining indicated IgG4-positive plasma cells in 62% of the 8 patients in whom it was performed. Granulocytic epithelial lesions (GEL) were present in 3 patients. The patients without GELs were older (mean age 59 years), while those with GEL were younger (mean age 34 years), and 2 of 3 were female and had ulcerative colitis. A complete response to steroid treatment was achieved in all 15 patients. Because of the suspicion of a pancreatic tumor, 2 patients with focal AIP underwent partial pancreatectomy. One patient relapsed, but responded to azathioprine. Conclusions: This first Hungarian series has confirmed several previously reported findings on AIP. AIP with GEL was relatively frequent among our patients: these patients tended to be younger than in earlier studies and displayed a female preponderance with a high coincidence of ulcerative colitis. Performance of a percutaneous biopsy is strongly recommended. The response to immunosuppressive therapy was excellent.
Introduction

Autoimmune pancreatitis (AIP) is a special type of chronic pancreatitis (CP), which displays clinical, serological, radiological and in particular histological features that are clearly distinct from other types of CP, such as alcoholic, hereditary and paraduodenal CP. The characteristics of the disease have been described in detail in excellent reviews [1–5]. Most cases of AIP have been reported from Japan. Although AIP is currently more often recognized in Europe [6–10], the number of European clinical reports to date is low and no study is available from central Eastern Europe.

AIP predominantly affects males over the age of 50 years. Recent studies demonstrated that two distinct histological patterns of AIP exist [9–11]. The histological pattern in type-1 AIP, referred to as lymphoplasmacytic sclerosing pancreatitis (LPSP), is characterized by a peri-ductal lymphoplasmacytic infiltration, storiform fibrosis, obliterator phlebitis and IgG4-positive plasma cells. LPSP corresponds to the Japanese description of AIP [12] and is thought to be the pancreatic manifestation of an IgG4-associated systemic disease [13]. IgG4-related systemic diseases may involve the biliary tree, salivary glands, retroperitoneum, stomach, lymph nodes and kidneys. An extrapancreatic manifestation is seen in about 40–50% of the cases. The histopathological pattern in type-2 AIP is known as idiopathic duct centric CP (IDCP) or granulocyte epithelial lesion (GEL)-positive pancreatitis, which resembles the European description of duct-destructive CP [9, 14].

The aim of the present prospective multicenter study was to assess the clinical features, laboratory and imaging findings, extrapancreatic involvement, treatment response and recurrence of AIP cases in Hungary.

Patients and Methods

Between May 1, 2008, and October 30, 2010, patients diagnosed with AIP in Hungarian Gastroenterological Centers were enrolled in our study. The diagnosis of type-1 AIP was established according to the HISORt criteria [15], while type-2 AIP was distinguished on the basis of the presence of the histological criterion GEL [9, 11]. Patient data were retrieved from medical documentation and follow-up data and were collected prospectively. All the patients participated in the continuous clinical follow-up. Treatment was carried out in the course of everyday clinical practice. All the patients underwent abdominal CT. In the event of obstructive jaundice, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) was performed, and a polyethylene stent was inserted into the bile duct if optimization of bile flow was necessary. Depending on the local possibilities, magnetic resonance cholangiopancreatography and/or diagnostic ERCP were performed to visualize abnormalities in the biliopancreatic region. When focal enlargement of the pancreas was detected, ultrasound-guided fine-needle aspiration or core biopsy was carried out. If the papilla of Vater was swollen, the biopsy was taken by means of duodenoscopy. The diagnosis of type-1 AIP was supported by the presence of duct centric lymphoplasmacytic infiltration, storiform fibrosis, obliterator phlebitis and >10 IgG4-positive plasma cells per high power field. IgG4 immunohistochemical staining was performed with monoclonal anti-human IgG4 antibody (Invitrogen, Carlsbad, Calif., USA). IgG4 seronegativity and the presence of GEL were diagnostic of type-2 AIP. The level of serum IgG4 was measured in the available samples (Binding Site Ltd., Birmingham, UK).

After the diagnosis of AIP had been established, the patients were treated with 30–40 mg prednisolone per day for 1–2 months. After 4 weeks, response was assessed. Response to therapy was defined as complete when a symptomatic improvement and complete resolution of the imaging abnormalities were seen. In the event of an adequate therapeutic response, the steroid dose was tapered to 5 mg/week. If a relapse occurred during the decrease in the steroid dose, the level of prednisolone was increased during the acute flare-up, and azathioprine at a dose of 1–2 mg/kg body weight per day was added for long-term immunosuppression. In patients who had undergone stent implantation in the bile duct, ERCP examination was repeated after steroid therapy; in case of improvement of the stenosis, the stent was removed.

Data were statistically evaluated using the \( \chi^2 \) test. Values of \( p < 0.05 \) were accepted as statistically significant.

Results

AIP was diagnosed in 17 patients during the study period. At the time of establishment of the diagnosis, the median age of the patients was 42.7 years (range: 16–74); 47% of them were women (Table 1). The most frequent symptoms were mild abdominal pain, a moderate weight loss and obstructive jaundice. In 5 patients (29%), inflammatory bowel disease had been diagnosed earlier, 2 patients had type-1 diabetes mellitus and another patient had sialadenitis. The serum levels of pancreatic enzymes

Table 1. Clinical presentation of the AIP patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42.7 (16–74)</td>
</tr>
<tr>
<td>Female, n</td>
<td>8 (47%)</td>
</tr>
<tr>
<td>Abdominal pain, n</td>
<td>13 (76%)</td>
</tr>
<tr>
<td>Weight loss, n</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Obstructive jaundice, n</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Autoimmune disorder, n</td>
<td>8 (47%)</td>
</tr>
</tbody>
</table>
and Ca 19-9 were mildly elevated in 40% of the 15 and 17% of the 6 patients, respectively, in whom it was evaluated. The serum IgG4 level at presentation was elevated in 62% of the 8 patients in whom it was assessed. Serum levels of antinuclear antibody were increased in 50% of the patients in whom it was measured. Imaging examinations revealed a diffuse, sausage-like widening of the pancreas in 7 patients (41%) and focal enlargement of the pancreas in 8 patients (47%; fig. 1a, c), while in 2 patients (12%) the pancreas did not exhibit any enlargement. In 66% of the patients with type-2 AIP, there was a focal mass in the pancreas. ERCP revealed stenosis of Wirsung’s duct with a wall irregularity in all study patients; in 4 patients (33%), the stenosis was diffuse, and in 8 patients (67%) it was segmental (fig. 2a, b). Seven patients (41%) had obstructive jaundice; ERCP revealed stenosis of the intrapancreatic portion of the common bile duct (fig. 2b) in all of them; a stent was implanted in 3 patients to ensure bile flow. These stents were removed after resolution of the strictures following steroid therapy. For histological examination, sampling was performed with different means. In 1 case the sample obtained by ultrasound-guided fine-needle aspiration was not appropriate for establishment of the diagnosis of AIP; however, cytological examination did not reveal tumor cells either. All 5 cases receiving percutaneous ultrasound-guided core biopsy demonstrated a periductal lymphoplasmacytic infiltration with whirling fibrosis and phlebitis (fig. 3).

Malignancy could not be excluded in 2 AIP cases because of the presence of a pancreatic mass (both involved type-2 AIP), and pancreatic head resection was performed. Histological examination of the resected specimen supported the diagnosis of AIP. In 4 cases, biopsy samples were taken from the swollen papilla of Vater during duodenoscopy; 2 of them were diagnostic of AIP; in both cases, only the pancreatic head was affected. IgG4 immunohistochemical examinations could be performed in 8 patients, of whom 5 (63%) were positive (fig. 4a). However, in the serologically negative cases granulocytic

**Fig. 1.** CT scan demonstrates diffuse enlargement of the pancreas in a 62-year-old female patient (a). Following a 4-week steroid treatment (32 mg), she is symptom free, and the pancreas volume becomes normal (b). CT reveals focal enlargement (arrow) of the pancreas in a 72-year-old male (c).
infiltration of the ductal epithelial cells (GEL) was revealed besides the classical lymphoplasmacytic infiltration, i.e. IDCP was identified (fig. 4b).

Concerning the demographics of the patients with the two histological types of AIP, a majority of the LPSP patients were older, while the IDCP patients were significantly younger. There was no male predominance in our IDCP patients, and an association with ulcerative colitis was common (table 2).

A complete response was achieved in all 15 patients during steroid therapy. The patients became asymptomatic within a short time, the elevated liver function decreased, and the enlargement of the pancreas and the narrowing of the bile duct had reversed by 4 weeks after starting the steroid therapy (fig. 1b). A relapse occurred in 1 patient (7%) during the dose reduction in prednisolone, but remission was again achieved following a dose increase in steroid treatment and the administration of azathioprine as long-term immunosuppression.

**Discussion**

To date, a majority of the AIP cases have been reported from Japan, and even the existence of the disease was debated in the West until comparatively recently [16, 17]. Our study tends to confirm recent data [6–10] indicating that AIP is not restricted to some specific region of the world, but also occurs in central Eastern Europe. The epidemiology of our AIP series differs from those previously reported. A nationwide study indicated that the peak age at onset was 61–65 years, and those older than 46 years accounted for 96% of the overall number of patients [18]. AIP predominantly affects men in Japan, with a male:female ratio of 2.85:1 [17]. In contrast to the Japanese data, the patients in our series were appreciably younger, with a median age at presentation of 42.7 years, and the male:female ratio was 1.13:1. Our patients were...
even younger than the AIP patients reported in recent UK, European and US series, where the median age at presentation was 53, 56 and 62.5 years, respectively [7, 9, 19]. Moreover, there was a male preponderance (100, 66 and 65% were male in the UK, European and US studies, respectively), in agreement with the reports from East Asia. In support of our study, a lower median age (43.4 years) at presentation was also reported in an Italian study [6], although they noted a male predominance (62%).

The results of recent European and American studies have led to AIP being subclassified into types 1 and 2 [9–11]. Type 1, LPSP, the disease classically described in Japan, primarily affects elderly males [3, 5, 18]. Type 2, AIP, which frequently occurs in Europe, is seen in younger patients and does not display a gender predilection [9, 10]. There have been only 2 studies where the incidence of type-2 AIP was reported: 37.5% in a European study [10] and 27.5% in a US study [20]. In our series, 37.5% of the AIP cases with available results of pancreas histology proved to be type-2 AIP and a further 3 patients had ‘probable’ type-2 AIP based on the imaging data, the normal serum IgG4 level and the response to steroids. The somewhat higher incidence of type-2 AIP in our series may explain the younger age and the female predominance among our AIP patients. Nevertheless, a male pre-

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**Fig. 3.** Histological examination demonstrates storiform fibrosis around the atrophic lobules with a dense mononuclear cell infiltration (HE; a), fibrosis rich in collagen fibers (trichrome dye; b), periductal lymphoplasmacytic infiltration (HE; c) and venulitis (HE; d).
ponderance was not observed among our type-1 AIP patients either.

An association of AIP with other autoimmune diseases was reported in 35–56% of the Japanese cases [3, 5, 18], which is in accord with our Hungarian series (47%). However, in our series, the nature of the autoimmune diseases differed from that reported in previous studies [2, 5, 7, 19]. Inflammatory bowel disease was the most frequent (5 of 8) associated autoimmune disease, confirming the Italian study [6]. This can be explained by the pronounced occurrence of type-2 AIP in our series.

It was earlier demonstrated that the serum IgG4 level is a highly sensitive (95%) and specific (97%) indicator in the diagnosis of AIP [21]. We observed elevated serum IgG4 levels in only 62% of our patients, a finding in agreement with a report from the US, where the serum IgG4 level was elevated in 71% of the patients [15]. This emphasizes that the detection of a normal IgG4 level does not exclude the presence of AIP. About 20% of AIP patients do not have elevated serum IgG4 levels. These cases may include IDCP, LPSP with low activity, or sclerosing pancreatitis other than LPSP or IDCP [22].

Certain histological features in the pancreas are diagnostic of AIP [1, 15]. Eight of our patients exhibited a discrete mass in the pancreas. Ultrasound-guided pancreatic core needle biopsies in 5 of these patients were all diagnostic, demonstrating a lymphoplasmacytic infiltration of the pancreas. One ultrasound-guided pancreatic fine-needle aspiration was not diagnostic. Four patients had biopsies of the swollen papilla and in 2 of them a lymphoplasmacytic infiltration was noted histologically. The major duodenal papilla is a conduit between the duodenum and the pancreatobiliary system, and its pathological examination may reflect underlying pancreatobiliary disorders. Previous studies have demonstrated a 55–80% sensitivity of positive IgG4 immunostaining of the major papilla [23]. Our finding was similar to this result. AIP was manifested as a focal enlargement of the pancreatic head in the 2 patients with positive IgG4 immunostaining of the major papilla. Furthermore, the postoperative histological examination of the resected pancreatic head mass in another focal AIP patient revealed the typical lymphoplasmacytic infiltration of the papilla of Vater, although IgG4 immunostaining was negative. The other 2 patients with negative IgG4 immunostaining of the major papilla had the diffuse form of AIP, and 1 of them had probable IDCP.

The response to steroid therapy is a HISORT criterion in the diagnosis of AIP. In agreement with previous reports [1, 3, 6, 7, 19], rapid symptomatic response and improvements in liver biochemistry and morphology were observed 4 weeks after the start of steroid therapy. However, in contrast to the earlier reports, recurrence was rarely encountered. In our series, only 1 patient had a recurrence. The long-term follow-up will disclose the final number of patients who relapse.

In conclusion, AIP is present in the Hungarian population. Various previously reported findings on the clinical presentation and management of AIP were confirmed in our series. AIP with GEL was relatively frequent among

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Fig. 4. Histological findings in AIP. a Type 1: periductal accumulation of IgG4-positive plasma cells (HE). b Type 2: duct with GEL (HE).
our patients; these patients were younger, and presented a female preponderance and a high coincidence of ulcerative colitis. Performance of a percutaneous biopsy is strongly recommended. The response to steroid therapy was excellent. Further work is required to determine the distribution and characteristics of type-2 AIP more accurately.

References


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