LONG-TERM OUTCOME OF AUTOIMMUNE PANCREATITIS AFTER ORAL PREDNISOLONE THERAPY

Takayoshi Nishino 1, Fumitake Toki 2, Hiroyasu Oyama 3, Kyoko Shimizu 1 and Keiko Shiratori 1

Abstract

Objective We investigated the long-term outcome of autoimmune pancreatitis (AIP) including morphological changes in the pancreas, pancreatic duct, biliary tract, pancreatic function, and changes in the clinical manifestations after oral prednisolone (PSL) therapy.

Patients and Methods We prospectively followed 12 patients for a period of over 12 months (median follow-up period: 41 months; range: from 13 to 133 months). All twelve patients were treated with PSL. The morphological findings consisted of pancreatic enlargement (n=12), an irregularly narrowed main pancreatic duct (n=12), and bile duct stricture (n=10), and salivary gland swelling was observed in six patients. The initial dose of PSL was 30-40 mg/day, and it was subsequently tapered.

Results All 12 patients responded to PSL therapy. The enlargement of the pancreas and the irregularly narrowed main pancreatic duct improved to almost normal. Pancreatic atrophy developed in four of them (4/12, 33%), but no pancreatic calcification was observed in any of the patients. The bile duct stricture improved to various degrees in all 10 patients, but it persisted in the lower part of the bile duct in four of them (4/10, 40%). The salivary gland swelling also improved after PSL therapy. There was no recurrence of enlargement of the pancreas or irregularly narrowed main pancreatic duct after PSL therapy, but the bile duct stricture recurred in one case, and in three cases there was a relapse of salivary gland swelling that required a temporary increase in PSL dose during tapering. No deterioration of pancreatic exocrine function was detected in any of the patients. A malignant tumor was diagnosed in two patients during PSL therapy: early gastric cancer in one and rectal cancer in the other. All patients are alive.

Conclusions AIP treated with PSL has a favorable long-term outcome based on the morphological findings and assessments of pancreatic function. However, since two of the twelve patients developed a malignancy during PSL therapy, strict follow up should be part of the management of AIP.

Key words: autoimmune pancreatitis, prednisolone, long-term outcome, associated malignancy

(DOI: 10.2169/internalmedicine.45.1565)

Introduction

Autoimmune pancreatitis (AIP) has recently been proposed as a disease entity characterized by the following unique clinical, diagnostic imaging, and pathological features: highest incidence in elderly men, pancreatic enlargement, irregularly narrowed pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP), increased serum IgG and IgG4 levels, presence of serum autoantibodies, and lymphoplasmacytic infiltration with fibrosis in the pancreas (1-3). Since corticosteroids have been found to occasionally be effective against AIP both morphologically and symptomatically, they have been used to treat many AIP patients (4-9), but little has been known about the long-term outcome of patients after the induction of a clinical remission by steroid therapy. We therefore investigated the long-term outcome of AIP, including in terms of morphological

1 Institute of Gastroenterology, Department of Medicine, Tokyo Women’s Medical University, School of Medicine, Tokyo
2 Toki Clinic, Gunma
3 Department of Clinical Laboratory, Tokyo Women’s Medical University, School of Medicine, Tokyo
Received for publication September 8, 2005; Accepted for publication February 3, 2006
Correspondence to Takayoshi Nishino, Institute of Gastroenterology, Department of Medicine, Tokyo Women’s Medical University, School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666

497
changes in the pancreas, pancreatic duct, biliary tract, changes in pancreatic function, and changes in clinical manifestations.

**Patients and Methods**

Between January 1992 and March 2005, we prospectively monitored the course of 12 patients, 6 men and 6 women aged 56-77 years old (median age: 65 years old), every month for a period of over 12 months after the start of PSL therapy (median follow-up period: 41 months; range: 13-133 months). The diagnostic criteria for AIP were based on those established by the Japan Pancreas Society (10) and the number of patients in this study who met each of the criteria is shown in parentheses: 1) an irregularly narrowed main pancreatic duct for more than 1/3 of the length of the entire pancreas on ERCP images (n=12) and enlargement of the pancreas on ultrasonography (US) or computed tomography (CT) images (n=12); 2) elevated serum gamma-globulin level (above 2.0 g/dl, n=5) and/or IgG level (above 1,800 mg/dl, n=6) and/or IgG4 level (above 135 mg/dl, n=8), or presence of serum autoantibodies (n=5); 3) fibrotic change and lymphocyte and plasma cell infiltration in the pancreas (n=7). Fulfillment of at least criterion 1 plus criterion 2 and/or 3 was required to make the diagnosis of AIP. Percutaneous aspiration biopsy of the pancreas was performed with a 21-gauge fine needle under US guidance in 7 patients, and the characteristic histological findings of lymphoplasmacytic infiltration and fibrosis were confirmed. The bile duct stricture was observed in 10 patients, and resultant obstructive jaundice was a major symptom in 7 patients. Six patients underwent percutaneous transhepatic or endoscopic biliary drainage before steroid therapy. All 12 patients were treated with oral prednisolone (PSL) therapy. The initial dose of PSL was 30-40 mg/day, and it was tapered by 5 mg every 2 weeks until the dose reached 15 mg/day, after which it was tapered by 2.5 mg every 4-8 weeks. The maintenance dose was 2.5-5 mg/day. PSL therapy was withdrawn in three patients (cases 1, 2, and 7). It was been possible to follow the clinical course of all 12 patients for more than one year, and their clinical manifestations were evaluated monthly during that period. Before PSL therapy, all patients were examined by upper gastrointestinal endoscopy and colonoscopy, and they were confirmed to be free of gastrointestinal malignancy.

**Diagnostic imaging of the pancreas and biliary tract**

Imaging studies, including US, CT, and ERCP, were performed in all 12 patients. Images of the pancreatic duct and biliary tract were obtained by ERCP. Pancreatic swelling was evaluated by CT. The width of the pancreas along its longitudinal axis was measured on CT images and compared with the transverse diameter of the vertebral body according to Haaga et al (11). The pancreas was considered enlarged when the width of the pancreatic body or tail was more than 2/3 the transverse diameter of the vertebral body, or if the width of the pancreatic head was more than the full transverse diameter of the vertebral body. The maximum diameter of the pancreatic body of the AIP patients was also measured by CT. The anatomical locations of the bile duct stricture were classified into three groups: the upper, the middle, and lower part of the bile duct, based on the ERCP findings.

**Diagnostic imaging after PSL therapy**

PSL therapy was concluded to have been effective when an irregularly narrowed main pancreatic duct recovered to approximately its normal diameter, and/or a narrowed bile duct recovered to approximately more than 80% of its normal diameter. Follow-up imaging of the pancreatic duct and bile duct was performed at least once by ERCP, and then by ERCP and/or magnetic resonance cholangiopancreatography (MRCP).

The maximum diameter of the pancreatic body was measured more than 12 months after the start of PSL therapy. The pancreas was also examined for calcification by CT.

**Pancreatic exocrine function and HbA1c values**

Pancreatic exocrine function was evaluated by the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion test. The glycosylated hemoglobin value (HbA1c) was also measured.

**Evaluation of salivary gland swelling**

Salivary gland swelling was diagnosed on the basis of gallium-67 citrate (Ga-67) accumulation in the salivary glands during Ga-67 scintigraphy, and/or diagnosed clinically by palpitation.

**Results**

**Morphological changes after PSL therapy**

All 12 patients responded to the PSL therapy (Table 1). The enlargement of the pancreas improved to almost normal within one month. Pancreatic atrophy developed in four cases, but no pancreatic calcification was observed in any of the patients (Fig. 1). The irregular narrowing of the main pancreatic duct had improved to almost normal size in all 12 patients, but the irregularity of the main pancreatic duct or side branches in several segments had persisted in five patients. There was no recurrence of pancreatic swelling or narrowed main pancreatic duct. The bile duct stricture in all 10 patients improved to various degrees after PSL therapy, and in 6 of them it improved to almost its normal diameter. Recovery was only slight to moderate in the other 4 patients, however, and the stricture became approximately 30-40% of the normal diameter. It was possible to withdraw the biliary drainage tube within one month after the start of PSL therapy. Recurrence of the bile duct stricture after tapering of the PSL dose was observed in one case and required a
Figure 1. Abdominal CT scan of an autoimmune pancreatitis patient before (A) and after (B) oral prednisolone (PSL) therapy. Pancreatic atrophy was observed after 12 months of PSL therapy.

Temporary increase in the PSL dose.

**Changes in serum IgG4 concentration**

The serum IgG4 concentration was elevated in 8 of 9 patients tested (Table 1). The concentration decreased in all patients after PSL therapy, but failed to decrease as far as the normal range in two patients who experienced a relapse of the salivary gland swelling. The IgG4 level in case 9 increased again (from 135 mg/dl to 195 mg/dl) when the salivary gland swelling relapsed.

**Changes in pancreatic exocrine function and endocrine function**

Pancreatic exocrine function

The BT-PABA test revealed reduced pancreatic exocrine function in 6 (67%) of the 9 patients in whom it was performed before PSL therapy. PSL therapy had improved pancreatic exocrine function in 3 of the 8 patients tested after PSL therapy, and it did not adversely affect pancreatic exocrine function in any of the patients examined after PSL therapy.

Ten of the 12 AIP patients were diagnosed with diabetes mellitus (DM), and the HbA1c level improved in 3 of the 12 patients after PSL therapy. Two patients (cases 2 and 9) experienced a transient loss of glycemic control after PSL therapy, but their HbA1c values returned to their level before treatment (Table 2).

**Complications of AIP**

**Sjögren syndrome and salivary gland swelling**

Three patients were diagnosed with Sjögren syndrome based on salivary gland swelling, decreased salivation, lacrimal gland swelling, and decreased lacrimation. Another three patients were found to have bilateral salivary gland swelling based on Ga-67 accumulation and/or palpation when diagnosed with AIP, but they did not exhibit any clini-
Figure 2. Gallium-67 citrate (Ga-67) scintigram of a patient with autoimmune pancreatitis before (A) and after (B) oral prednisolone (PSL) therapy. There was abnormal Ga-67 accumulation in the salivary glands and lacrimal glands bilaterally. The salivary gland swelling and lacrimal gland swelling improved after PSL therapy.

Table 2. Long-term Changes in BT-PABA and HbA1c Values before and after Oral Prednisolone Therapy.

<table>
<thead>
<tr>
<th>Case</th>
<th>BT-PABA (%)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>54</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>NE</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>79</td>
<td>NE</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

Table 3. Diseases Complicating Autoimmune Pancreatitis.

<table>
<thead>
<tr>
<th>Case</th>
<th>DM</th>
<th>Sjögren syndrome</th>
<th>Salivary gland swelling</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(x)</td>
<td>(x)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>2</td>
<td>(x)</td>
<td>(x)</td>
<td>(+)</td>
<td>RA</td>
</tr>
<tr>
<td>3</td>
<td>(x)</td>
<td>(x)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>4</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>6</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>8</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>9</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>10</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>Rectal cancer</td>
</tr>
<tr>
<td>11</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>12</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis, (-)*: salivary gland swelling relapsed during PSL tapering and required a temporary increase in the PSL dose. No additional relapses occurred after increasing the PSL dose and then tapering it more slowly.

Malignancy as a complication during the course of PSL

Two AIP patients were diagnosed with a malignancy while being treated with PSL (Table 3). One patient (case 7) was diagnosed with early gastric cancer after 29 months of PSL therapy and was treated by endoscopic mucosal resection. The other patient (case 10) was diagnosed with advanced rectal cancer (stage 3a) after 13 months of PSL therapy, and partial rectal resection was performed. All patients are alive.

Other complications

Patient 2 had been diagnosed with rheumatoid arthritis before the diagnosis of AIP.

Discussion

Diffuse infiltration by numerous lymphocytes and plasma cells and marked fibrosis around the pancreatic duct and bile duct are very characteristic histological findings of AIP (10-14), and it has been suggested that CD8- and CD4-positive lymphocytes and IgG4-positive plasma cells may play an important role in the pathogenesis of AIP (13, 14). Recently many AIP patients have come to be treated with PSL, but little is known about the long-term outcome of PSL therapy, for example, in terms of morphological changes, pancreatic function, or complications.

The irregularly narrowed main pancreatic and bile duct stricture improved to various degrees in all patients in the present study. However, irregularity of the main pancreatic duct and side branches in several segments, or bile duct stricture in the lower portion of the bile duct persisted in several cases. These findings are the same as in previous reports (5, 6). Takayama et al (9) reported pancreatic stone formation in eight of 42 AIP patients. Six of the 8 experienced a relapse, and the other 2 patients, one who had received PSL therapy and one who had not, were in the non-relapse group. Although four of the 12 patients in our own series developed pancreatic atrophy, no pancreatic stones were detected. One possible reason for the difference in pancreatic stone formation is that there were no cases of relapsing pancreatitis in our series. Moreover, pancreatic stone formation sometimes occurs during long-term observation of AIP patients without PSL therapy, and additional cases need to be accumulated.

The pancreatic exocrine function and endocrine function of many AIP patients are impaired by extensive destruction of the pancreatic islets and acini involved by the inflammatory process (15). Pancreatic exocrine function did not deteriorate in any of the patients treated with PSL in our study, and it improved in about half of them. In addition, pancre-
atic endocrine function assessed on the basis on HbA1c values improved in three patients, and PSL therapy did not cause any deterioration of diabetes mellitus in any patients. We concluded that PSL therapy should be recommended for AIP patients whose pancreatic exocrine or endocrine function is impaired.

Recent studies (5, 9) have revealed persistently high serum IgG4 level or recurrence of elevated levels in patients in a clinically active state, including relapse, and one patient in the present study experienced a recurrence of the elevation in IgG4 level when salivary gland swelling relapsed. Regular measurement of IgG4 may help to predict and control the relapse of AIP during maintenance therapy.

Based on the discovery of IgG4-positive plasma cell infiltration in multiple organs, AIP is now considered a systemic disease (13). Three patients in the present study experienced a recurrence of salivary gland swelling, and one patient was found to have a recurrence of bile duct stricture during PSL therapy without recurrence of the pancreatitis. These three patients required a temporary increase in the PSL dose of about 10 mg/ day and slower tapering (1 mg / 2 week) to prevent further recurrence. AIP patients should be followed up not only for possible recurrence of pancreatitis but also for recurrence of extra-pancreatic involvement.

Two patients developed a malignancy during PSL therapy. The mechanism of carcinogenesis in AIP is still unclear, but one possible contributing cause is the immunosuppressed state of the patients produced by longstanding PSL therapy. Moreover, because a high mortality rate related to malignancy has been reported in chronic pancreatitis (16), we concluded that AIP patients should be followed up for possible complication by malignancy the same as chronic pancreatitis patients.

In conclusion, AIP treated with PSL has a good long-term outcome based on the morphological findings, pancreatic function, and clinical manifestations in this study. However, two of the 12 patients developed a malignancy during PSL therapy. The management of AIP requires strict follow-up.

References