Idiopathic Duct-Centric Pancreatitis (IDCP) with Immunological Studies

Takeo Kusuda¹, Kazushige Uchida¹, Sohei Satoi², Masanori Koyabu¹, Norimasa Fukata¹, Hideaki Miyoshi¹, Tsukasa Ikeura¹, Yutaku Sakaguchi¹, Katsunori Yoshida¹, Toshio Fukui¹, Masaaki Shimatani¹, Mitsunobu Matsushita¹, Makoto Takaoka¹, Akiyoshi Nishio¹, Yoshiko Uemura³, A-Hon Kwon² and Kazuichi Okazaki¹

Abstract

A 65-year-old woman with elevated serum levels of pancreatic enzymes was referred to our hospital for further examinations. Abdominal US and contrast-enhanced CT demonstrated swelling of the pancreas body and tail. MRCP and ERCP revealed abrupt ending of the MPD in the pancreas body. Under the suspicion of malignancy, distal pancreatectomy and splenectomy were performed. The histopathological findings showed idiopathic duct-centric pancreatitis (IDCP) with granulocytic epithelial lesions (GEL). As most cases of Japanese autoimmune pancreatitis (AIP) are lymphoplasmacytic sclerosing pancreatitis (LPSP), the present case seems to be helpful to clarify the clinical findings of IDCP in Japan.

Key words: autoimmune pancreatitis (AIP), Idiopathic duct-centric pancreatitis (IDCP), lymphoplasmacytic sclerosing pancreatitis (LPSP), granulocytic epithelial lesion (GEL), IgG4

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Introduction

Since Sarles et al reported a case of idiopathic pancreatitis with hypergammaglobulinemia in 1961 (1), several investigators have reported that autoimmune mechanisms may be involved in the etiology of chronic pancreatitis. Yoshida et al first proposed the concept of “autoimmune pancreatitis” (AIP) in 1995 (2). Thereafter, many cases of AIP have been reported mainly from Japan until the disease concept was accepted worldwide. As previously reported, the characteristic features (3, 4) of the Japanese patients with AIP show (i) diffuse enlargement of the pancreas on US, CT and MRI, (ii) irregular narrowing of the pancreatic duct (sclerosing pancreatitis) on endoscopic retrograde cholangiopancreatographic (ERCP) images, (iii) histologically termed lymphoplasmacytic sclerosing pancreatitis (LPSP) with fibrosis, abundant infiltration of lymphocyte and IgG4-positive plasmacytes and obliterative phlebitis, and (iv) it is often associated with extrapancreatic lesions, such as sclerosing cholangitis similar to primary sclerosing cholangitis (PSC), sclerosing cholangitis, sclerosing sialoadenitis, retroperitoneal fibrosis, interstitial renal tubular disorders, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and pseudotumor of the liver (5-7). On the other hand, in Western countries, another type of AIP different from the AIP commonly observed in Japan has been reported. In a study performed by a group at the Mayo Clinic, it was demonstrated that there may be two histological types of AIP, LPSP and idiopathic duct-centric pancreatitis (IDCP) (6, 8). IDCP was characterized by lobular fibrosis and pancreatic duct damage mainly caused by infiltration of neutrophils without obliterative phlebitis (8). Zamboni et al also recognized a subtype of AIP occurring in a subset of patients who are younger and more commonly have ulcerative colitis and Crohn’s disease, which is characterized by the presence of granulocytic epithelial lesions (GEL) (9). There are a number of similarities in the clinical and histopathological findings between AIP

¹The Third Department of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Moriguchi, ²Department of Surgery, Kansai Medical University, Moriguchi and ³Department of Pathology, Kansai Medical University, Moriguchi

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Correspondence to Dr. Kazuichi Okazaki, okazaki@hirakata.kmu.ac.jp
with GEL and IDCP, but not between AIP with LPSP and AIP with GEL or IDCP. Although Japanese AIP cases are almost all LPSP (4, 7), those concerning IDCP have been rarely reported from Japan (10). Therefore, it still remains unclear whether the clinical manifestations of the Japanese patients with IDCP are similar to those of Western countries or not. Herein, we report the first case of IDCP in Japan with full radiological and histopathological findings.

Case Report

A 65-year-old woman with elevated serum levels of pancreatic enzymes, as discovered by an annual health check, was referred to our hospital for further examination in the beginning of December 2004. She had no history of other illness or alcohol abuse. Furthermore, the symptom of inflammatory bowel disease including diarrhea was absent. Physical examination at the time of admission revealed no significant findings. Laboratory examinations showed the following values (normal range): peripheral white cell count, 4,600/μL; peripheral eosinocyte count, 690/μL; C-reactive protein, 0.04 mg/dL (<0.3 mg/dL); total bilirubin, 0.7 mg/dL; alkaline phosphatase, 313 IU/L (107-323 IU/L); γ-glutamyl transpeptidase, 13 IU/L (8-45 IU/L); aspartate aminotransferase, 23 IU/L (12-31 IU/L); alanine aminotransferase, 18 IU/L (6-24 IU/L). Pancreatic enzymes were elevated: amylase 292 IU/L (32-112 IU/L), lipase 473 IU/L (16-60 IU/L), and elastase-1 950 ng/dL (100-400 ng/dL). Hepatitis B surface antigen and antibody to hepatitis C virus were negative. Serum γ-globulin, IgG levels were 1.43 g/dL (0.7-1.6 g/dL), 1,523 mg/dL (870-1,700 mg/dL), respectively. Serum autoantibodies were all negative, including antinuclear antibody, rheumatoid factor, anti-Ro antibody (SS-A), anti-La antibody (SS-B), and anti-mitochondrial antibody. Among tumor markers, CEA was 1.1 ng/dL (<5.0); DUPAN-2, 25 U/mL (<150); and CA19-9, 25.3 U/mL (<37). Abdominal US showed the partially enlarged pancreas body and tail with homogenous hypoechoic pattern (Fig. 1). Contrast-enhanced CT demonstrated moderate swelling in the body and tail of the pancreas with homogenous enhancement, but not capsular-like low density rim or swelling of peripancreatic lymph nodes (Fig. 2). MRI demonstrated the enlarged pancreas body and tail with no obvious intensity of change (Fig. 3A, B). MRCP revealed obstruction of the main pancreatic duct (MPD) in the body concordant with pancreas cancer tumors (Fig. 3C). ERCP demonstrated abrupt ending of the MPD in the pancreas body and irregular strictures of the pancreatic ducts in the pancreas head (Fig. 4). Transpapillary biopsy of the obstructive pancreatic duct and cytology of the pancreatic duct did not show malignancy. We were not able to identify a mass in the pancreas in the image, but also were not able to deny the possibility of the pancreatic cancer because we showed the disruption of the pancreatic duct. Therefore, we performed distal pancreatectomy and splenectomy. The postoperative course was uneventful and the patient was discharged after eight days. After hospital discharge, the patient had no recurrence to date.

The cut surface of the resected specimen showed swelling

Figure 1. Abdominal ultrasonography (US) of the pancreas. US showed the partially enlarged pancreas body and tail with homogenous hypoechoic pattern (arrow).

Figure 2. Contrast-enhanced computed tomography (CT) of the pancreas. Contrast-enhanced CT demonstrated moderate swelling in the body and tail of the pancreas with homogenous enhancement, but not capsular-like low density rim or swelling of peripancreatic nodes. (A) early phase (B) delayed phase.
Figure 3. Magnetic resonance imaging (MRI) of the pancreas. MRI demonstrated swelling in the body and tail of the pancreas with no obvious intensity of change (A; T1 intensive image, B; T2 intensive image). Magnetic resonance cholangiopancreatography (MRCP) revealed obstruction of the main pancreatic duct in the body (C).

Figure 4. Endoscopic retrograde cholangiopancreatography (ERCP). ERCP image demonstrated abrupt ending of the main pancreatic duct in the body compatible with pancreatic cancer.

Figure 5. Macroscopic findings of the pancreas. The cut surface of the resected specimen showed swelling of parenchyma with the whitish indurated tissue (Fig. 5A). The picture of loupé of the greatest surface of cut specimen (Fig. 5B).

Histologically, prominent lobular inflammation consisted of edema and infiltrating neutrophils, lymphocytes, and plasma cells. Although fibroblastic proliferation and fibrosis were seen, inflammatory infiltrate cells were scarce between the lobules. Neutrophils were sometimes prominent in and around the intralobular duct. Numerous microabscesses were found in the intralobular duct. Neutrophils involved the duct epithelium and lumen, and the epithelial cells were destroyed. Obliterative phlebitis was not observed (Fig. 6). From these findings, the histopathological diagnosis made of parenchyma with the whitish indurated tissue (Fig. 5)).

was IDCP. On immunohistochemical staining, IgG1-positive plasma cells were abundant (Fig. 7B), but IgG4-positive plasma cells were not (Fig. 7A). Abundant infiltration of
Figure 6. Histological findings of the pancreas (Hematoxylin and Eosin staining). Although fibroblastic proliferation and fibrosis are seen, inflammatory infiltrates are scarce between the lobules (A, ×20; D, ×20). Periductal inflammation with destruction of pancreatic epithelia by abundant neutrophils suggested a granulocyte epithelial lesion (GEL) (B, ×40; C, ×400). Inflammatory cells were few in fibrosis. Microabscess was seen in the intralobular duct (E, ×100; F, ×400).

Foxp3-positive T lymphocytes was observed around the intralobular ducts (Fig. 7C). Predominant infiltration of CD3-positive, CD4-positive and CD8-positive T lymphocytes was seen around the interlobular ducts (Fig. 7D-F). In addition, the infiltrated cells contained CD79a-positive plasma cells (Fig. 7G).

We examined 9 patients with LPSP (6 women and 3 men; mean age 54 years; range, 56-73 years), 9 patients with alcoholic pancreatitis (9 men; mean age, 53 years; range, 39-75 years), and only one patient with IDCP (woman, age: 65). The numbers of IgG4-positive plasma cells (IgG4/HPF) were significantly higher in LPSP (20.0 ± 6.0 cells/HPF) than in alcoholic chronic pancreatitis (2.1 ± 0.9 cells/HPF; p<0.05). The numbers of IgG1-positive plasma cells (IgG1/HPF) were significantly lower in LPSP (7.6 ± 2.4 cells/HPF) than in alcoholic chronic pancreatitis (12.1 ± 1.8 cells/HPF; p<0.05). The ratio of IgG4/HPF to IgG1/HPF (IgG4/G1 ratio) was significantly higher in AIP (2.72 ± 0.76) than in alcoholic chronic pancreatitis (0.18 ± 0.09; p<0.05). The numbers of Foxp3-positive cells (Foxp3/HPF) in patients with LPSP (15.3 ± 3.0 cells/HPF) were significantly increased compared with alcoholic chronic pancreatitis (1.7 ± 0.5 cells/HPF; p<0.05). However, the IDCP case showed Foxp3-positive cells; 9.7 cells/HPF, IgG4-positive plasma cells; 8.0 cells/HPF, IgG4/G1 ratio; 0.39, IgG1-positive plasma cells; 20.7 cells/HPF, respectively (Table 1).

Discussion

Since Sarles et al reported a case of idiopathic pancreatitis
with hypergammaglobulinemia (1), many investigators have suggested that an autoimmune mechanism is involved in some instances of idiopathic pancreatitis. We previously reported that patients with AIP frequently have autoantibodies (3, 4). Hamano et al reported that patients with AIP show a high serum IgG4 concentration, and that the values are closely associated with the disease activity (11). Japanese AIP cases are almost exclusively LPSP (4, 7).

In contrast, AIP with neutrophilic infiltration in the epithelium of the pancreatic duct (idiopathic duct-centric pan-
creatitis: IDCP, or granulocyte epithelial lesion: GEL) has been reported by American and European pathologists (6, 8, 9). In a recent study, Zhang et al reported that while LPSP consistently shows moderate to severe infiltration with IgG4-positive cells, IDCP rarely shows excess IgG4-positive cells (12). In the present case IgG4-positive cells were not abundant. Prior to the concept of IDCP or GEL, in 1997 Ectors et al (13) reported the concept of non-alcoholic duct destructive chronic pancreatitis (NDCP) characterized by histological findings distinguishable from LPSP: a neutrophil predominant lobular inflammation and a duct destructive infiltrate without obliterative phlebitis (8, 13). The features seen in patients with NDCP are similar to those of IDCP although it still remains unclear whether these two entities represent different manifestations of the same disease or not. The clinical features of AIP in Western countries have been reported to be elderly males, frequent association with inflammatory bowel disease, and a weaker association with other sclerosing diseases, which seems to be different from Japanese AIP (LPSP). Frulloni et al recently reported that the focal type of AIP (63%) is more common than the diffuse type (37%) of the 87 Italian patients with AIP patients (54 males and 33 females, mean age 43.4 ± 15.3 years). Of total patients, 30% had ulcerative colitis, and 66% of focal AIP and 27% of diffuse AIP showed increased serum levels of IgG4. Although the histopathological findings were not evaluated in their series, IDCP may be predominant in the diffuse type of AIP (14). In Japan, the above Western type of AIP cases has not been confirmed yet owing to the limited number of studies.

Therefore, AIP might be a heterogeneous disease with different clinical aspects, and these patients with young onset might be another subtype distinguishable from the usual AIP as defined in Japan (15). Although a single study of young Japanese patients with AIP reported more frequent abdominal pain and increased serum amylase elevations compared with aged patients (16), it was unclear whether these young patients had IDCP or not.

The present patient had no abdominal pain, but did have an elevated level of serum amylase. Serum IgG4 was not measured. She had no other organ involvement. Radiological findings did not demonstrate the typical findings of AIP as shown in the Japanese diagnostic criteria (17, 18). In the US, CT, and MRI images of the present case, the pancreas was slightly swollen, but it lacked a capsular-like low density rim on the enhanced CT images. Pancreatogram on ERCP showed the abrupt ending of the MPD without irregular narrowing of MPD. Immunohistochemically, in this IDCP case, the density of IgG1-positive cells was higher than the density of IgG4- and Foxp3-positive cells. The ratio of IgG4/HPF to IgG1/HPF was calculated in each case. Values are the mean ± SD. * p<0.05

### Table 1. Immunohistochemical Findings of 19 Cases of Tumor-forming Type of Pancreatitis

<table>
<thead>
<tr>
<th>Infiltrated cells</th>
<th>Non-alcoholic (n=10)</th>
<th>Alcoholic (n=9)</th>
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<tbody>
<tr>
<td></td>
<td>IDCP (n=1)</td>
<td>LPSP (n=9)</td>
</tr>
<tr>
<td>IgG1</td>
<td>20.7</td>
<td>7.6±2.4*</td>
</tr>
<tr>
<td>IgG4</td>
<td>8.0</td>
<td>20.0±6.0*</td>
</tr>
<tr>
<td>IgG4/IgG1</td>
<td>0.39</td>
<td>2.72±0.76*</td>
</tr>
<tr>
<td>Foxp3</td>
<td>9.7</td>
<td>15.3±3.0*</td>
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IgG1-, IgG4-, and Foxp3-positive cells contained within the portal tracts selected in each specimen were counted under five different high power fields (HPF). IgG4/IgG1; the ratio of IgG4/HPF to IgG1/HPF was calculated in each case. Values are the mean ± SD. * p<0.05

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References


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