CASE REPORT

Autoimmune Pancreatitis with Histologically Proven Lymphoplasmacytic Sclerosing Pancreatitis with Granulocytic Epithelial Lesions

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Abstract

Recent histological and clinical studies have suggested the existence of 2 distinct types of autoimmune pancreatitis (AIP): type 1 AIP related to IgG4, exhibiting lymphoplasmacytic sclerosing pancreatitis (LPSP), and type 2 AIP related to granulocyte epithelial lesions (GELs), exhibiting idiopathic duct-centric chronic pancreatitis (IDCP). We herein present a case of type 1 AIP with histologically proven LPSP with GELs. This patient had neither serum IgG4 elevation nor MPD narrowing. In this case, the clinically and histologically atypical findings for type 1 AIP are intriguing.

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


Introduction

Autoimmune pancreatitis (AIP) is a unique chronic inflammation of the pancreas, characterized by pancreatic enlargement, irregular narrowing of the main pancreatic duct (MPD), and a dramatic response to corticosteroid therapy. Numerous AIP studies have been reported, mainly by Japanese investigators, since Yoshida et al first proposed the disease concept of AIP in 1995 (1). The histological pattern of AIP commonly observed in Japan is called lymphoplasmacytic sclerosing pancreatitis (LPSP), which is characterized by abundant infiltration of IgG4-positive plasma cells and lymphocytes, storiform fibrosis, and obliterative phlebitis (2-4). The clinical characteristics of this type of AIP include significant elevations of serum IgG or IgG4 levels, the presence of various autoantibodies, and extrapancreatic organ abnormalities such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis. In contrast, another unique type of AIP, which has been called idiopathic duct-centric chronic pancreatitis (IDCP) or AIP with granulocyte epithelial lesions (GELs), has been reported in Europe and the United States. This type of AIP is histologically characterized by neutrophilic infiltration within the lumen and epithelium of interlobular ducts (5, 6). In contrast to LPSP, patients with IDCP have no serological markers of autoimmunity, and IDCP is occasionally associated with inflammatory bowel diseases such as ulcerative colitis or Crohn’s disease (7). Recently, the clinical profiles of LPSP and IDCP have begun to be referred to as “type 1” and “type 2” AIP, respectively (7-10).

We herein present a case of type 1 AIP with histologically proven LPSP with prominent neutrophilic infiltration into the acinar lobules and the epithelium of interlobular ducts, that is, LPSP with GELs. Generally, neutrophilic infiltration is rarely observed in LPSP, and even if it is observed, patients who histologically exhibit neutrophilic invasion into the duct epithelium in LPSP are rare. Moreover,
this patient showed no evidence of AIP in terms of imaging and laboratory parameters before surgery. In this case, the clinically and histologically atypical findings for type 1 AIP are intriguing.

### Case Report

A 55-year-old man was admitted to our hospital for further investigation of a pancreatic mass that had been detected incidentally by abdominal ultrasonography (US) in a medical checkup. The patient was asymptomatic; he did not experience any abdominal pain, fever, diarrhea, or melena. His physical examination findings were unremarkable. He had a personal history of diabetes mellitus for 2 years, which was controlled by an α-glucosidase inhibitor and metformin. There was no history of diagnosis of pancreatitis, autoimmune disease or inflammatory bowel disease. In the serum examination, tumor markers (carcinoembryonic antigen, CA19-9, DUPAN-2) and serum IgG4 levels were within normal limits. Antinuclear antibody was not detected. Dynamic abdominal CT scans during the early phase revealed ill-defined, hypoattenuating masses in both the body and tail of the pancreas, but showed neither capsule-like rim around the pancreas nor swelling of peripancreatic lymph nodes (Fig. 1). On magnetic resonance cholangiopancreatography (MRCP), the MPD lumen was not visible at the pancreatic body, and the upstream pancreatic duct was slightly dilated (Fig. 2A). ERP revealed disruption of the MPD at the pancreatic tail. No irregular narrowing was observed in the visualized MPD (Fig. 2B). Cholangiography revealed a normal biliary duct. Endoscopic ultrasonography (EUS) revealed a hypoechogenic and homogeneous mass in the pancreatic tail measuring 24 mm, but the mass in the pancreatic body detected by CT was not visible. Cytology of pancreatic juice obtained by ERP and that of fine needle aspiration under EUS from the pancreatic tail mass were negative for malignant cells. Additional diagnostic imaging with fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed a pathologic uptake pattern with standard uptake values of 3.1 and 3.9 in the pancreatic body and tail, respectively (Fig. 3). No accumulation of FDG was found in extrapancreatic organs or tissues, such as the lachrymal gland, salivary gland, biliary duct, retroperitoneal space, and lymph node. Distal pancreatectomy was performed because disruption of the MPD and PET positivity suggested pancreatic cancer. Gross examination of the resected specimen revealed 2 firm mass lesions of whitish tissue with clear margins that measured 18×24 mm and 32×32 mm in the pancreatic body and tail, respectively (Fig. 4A). Histological examination of these lesions revealed dense lymphoplasmacytic periductal and interacinar infiltration, storiform fibrosis, and obliterative phlebitis (Fig. 4B, C, D). Scattered lymphoid follicles were also present. These findings were consistent with LPSP. In addition, neutrophilic infiltration into the acinar epithelium, that is, GEL, although the degree of these findings varied according to the location in the affected pancreas (Fig. 4E, F). Calcifications and protein plugs were not found in the pancreatic ducts. Immunohistochemically, abundant IgG4-positive plasma cells (>20 cells/HPF) were detected (Fig. 4G). No malignant cells were found. Based on these findings, we diagnosed him with AIP with histologically proven LPSP with GEL. The patient’s postoperative course was uneventful, and he is currently doing well.

### Discussion

Recent histological and clinical studies have suggested the existence of 2 subtypes of AIP: type 1 AIP related to IgG4 exhibiting LPSP, and type 2 AIP related to GELs exhibiting IDCP (10, 11). Both types share some representative pathology, such as pancreatic enlargement, narrowing of the MPD, lymphoplasmacytic infiltration with fibrosis in the pancreas, and dramatic response to steroids. However, in contrast to LPSP, patients with IDCP have neither elevated serum IgG4 nor abundant infiltration of IgG4-positive cells in the pancreas. Therefore, it is still controversial as to whether IDCP should be considered an entity of AIP.

In 2002, the diagnostic criteria for AIP were published for the first time by the Japan Pancreas Society, and were revised in 2006 (3). In addition to the Japanese criteria, various diagnostic criteria have been proposed, including those of Korea (12), the Mayo Clinic (13), Asia (14), and Italy (15), but there have been no internationally accepted criteria to diagnose AIP. Recently, experts from around the world proposed an international consensus diagnostic criteria (ICDC) for AIP (9). The ICDC comprises 5 cardinal features, involving findings regarding imaging of the pancreatic parenchyma and duct, serology, other organ involvement, histology of the pancreas, and response to steroid therapy.

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Figure 1. Abdominal CT scans during early phase show low-density masses in the body (arrow) and tail (arrowhead) of the pancreas.
The principal features of ICDC are as follows: 1) definitive or probable diagnostic criteria for both type 1 and type 2 AIP are established; 2) each feature is categorized as level 1 or 2 findings depending on the diagnostic reliability; and 3) AIP cases clinically indistinguishable between type 1 and type 2 AIP are classified as AIP-not otherwise specified. Furthermore, unlike the Japanese and Korean criteria, the ICDC allow a diagnosis of AIP to be made on the basis of histological findings alone. In the ICDC, the definitive diagnosis of type 1 AIP (LPSP) is made when at least 3 of the following histological findings are present on resection or biopsy specimens: 1) periductal lymphoplasmacytic infiltrate without granulocytic infiltration; 2) obliterative phlebitis; 3) storiform fibrosis; and 4) abundant (>10 cells/HPF) IgG4-positive cells. Conversely, a definitive diagnosis of type 2 AIP (IDCP or AIP with GELs) is made when both of the following findings are fulfilled: 1) granulocytic infiltration of the duct wall with or without granulocytic acinar inflammation and 2) absent or scant (0-10 cells/HPF) IgG4-positive cells. In the case described here, we made a definitive diagnosis of type 2 AIP (IDCP or AIP with GELs) is made when both of the following findings are fulfilled: 1) granulocytic infiltration of the duct wall with or without granulocytic acinar inflammation and 2) absent or scant (0-10 cells/HPF) IgG4-positive cells. In the case described here, we made a definitive diagnosis of type 1 AIP (LPSP), but not type 2 AIP (IDCP or AIP with GELs), according to the ICDC, as obliterative phlebitis, storiform fibrosis, and abundant IgG4-positive cells were detected upon histological examination of the resected specimen. However, in addition to the above histological finding, we also observed neutrophilic infiltration into the acinar lobules and, occasionally, into the duct epithelium. These findings are characteristic of IDCP or AIP with GELs, but are almost never observed in LPSP. This peculiar condition of concomitant LPSP and GELs may suggest that yet another category exists with an overlap between type 1 and type 2 AIP, or it may simply result from secondary acute inflammation developing on the background of LPSP. In the present case, the degree of neutrophilic infiltration into the duct epithelium and destruction of the duct lumen appeared to be less severe compared to the previous reports regarding IDCP and AIP with GELs (5, 6). However, it is already known that the number of GELs and their severity differ greatly from patient to patient (6), and it is unclear why these differences of the degree arise. Further studies are necessary to clarify the precise pathogenesis of the synchronous presence of LPSP and GELs.

The present patient had no evidence of AIP in terms of imaging and laboratory parameters before surgery. ERP demonstrated the obstructed MPD but not the narrowed MPD, which were evocative of pancreatic cancer. In the Japanese criteria, ERP findings are essential to making the diagnosis of AIP (3). ERP features of AIP include an irregular narrow stricture of MPD without upstream dilatation, multifocal strictures, and side branches arising from the stricture site. According to the retrospective studies on ERP findings in AIP patients, the frequency of MPD obstruction in AIP is reported to be up to 5.9% (16). We previously reported a Japanese patient with IDCP with an obstructed MPD on ERP (17). In that case and the present case, MPD obstruction may have resulted from destruction and obliteration.

Figure 2. (A) MRCP shows an unvisualization of the main pancreatic duct at the pancreatic tail (arrow). (B) ERP reveals disruption of the MPD at the pancreatic tail (arrowhead).

Figure 3. FDG-PET shows hot spots of FDG uptake in the pancreatic body and tail.
Figure 4. (A) Surgical specimen shows 2 whitish mass lesions in the pancreatic body (arrow) and tail (arrowhead). (B)(C) Dense lymphoplasmacytic periductal and interacinar infiltration and storiform fibrosis are observed. (D) Obliterative phlebitis is detected (Elastica-Masson staining). (E) Neutrophilic infiltration into the acinar lobules is observed (arrow). (F) There is occasional neutrophilic invasion into the duct epithelium (arrow). (G) Immunohistochemical labeling with an antibody to IgG4 reveals numerous IgG4-expressing plasma cells in the inflammatory infiltrate.

Although ERP is very useful in the differential diagnosis between AIP and pancreatic cancer (16), it is difficult to differentiate cases of AIP with MPD obstruction from pancreatic cancer. In addition, the serum IgG4 level is considered a highly sensitive and specific marker of AIP (18). However,
approximately 20% of AIP patients exhibit no elevated serum IgG4 levels (19). As observed in the present case, even patients with a histologically confirmed LPSP with abundant infiltration of IgG4-positive cells can exhibit IgG4 seronegativity. Thus, elevated IgG4 is not entirely specific for AIP.

In conclusion, we here report a case of LPSP with GEL without serum IgG4 elevation and MPD narrowing. We should expect that some patients will exhibit imaging and/or histological features atypical for AIP.

The authors state that they have no Conflict of Interest (COI).

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