CASE REPORT

IgG4-Negative Autoimmune Pancreatitis with Sclerosing Cholangitis and Colitis: Possible Association with Primary Sclerosing Cholangitis?

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Abstract

We report a case of autoimmune pancreatitis (AIP) with cholangiography and histopathology showing features characteristic of primary sclerosing cholangitis (PSC) and colitis. A 55-year-old previously-healthy man was diagnosed with anti-nuclear antibody (ANA)-positive AIP according to the finding of serum biochemistry, abdominal US (ultrasonography), CT (computed tomography) and ERCP (endoscopic retrograde cholangiopancreatography). However, bead-like strictures of intrahepatic bile ducts were also found and liver tissue showed onion skin-like periductal fibrosis but no anti-IgG4-positive cells. In addition, colon fiberscopy showed a pancolitis similar to ulcerative colitis indicating that, in this case, there may be an association with PSC. Here, we report a rare case of IgG4-negative AIP with sclerosing cholangitis and colitis with many clinical features that support an association with PSC.

Key words: autoimmune pancreatitis, cholangitis, primary sclerosing cholangitis, colitis

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Introduction

Autoimmune pancreatitis (AIP) is suggested as one phenotype of autoimmune-related systemic disease (1) and is often associated with sclerosing cholangitis. In some cases, sclerosing cholangitis associated with AIP has radiological features similar to those of primary sclerosing cholangitis (PSC) although the two diseases are thought to be separate clinical entities. The two diseases are usually distinguished using precise observations from cholangiography in conjunction with serum IgG4 levels and histopathological findings of periductal fibrosis with abundant lymphocytes and IgG4-positive plasma cell infiltration (2-4). Here, we describe a rare case of AIP in which cholangiography and histopathology show features characteristic of PSC and colitis.

Case Report

A 55-year-old previously-healthy man presented with a 6-month history of watery diarrhea and epigastralgia from September 2004. He visited his primary care hospital and was diagnosed with liver dysfunction of unknown origin. Two months later he developed sudden back pain and severe epigastralgia and was urgently admitted to hospital and diagnosed with acute pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) showed severe strictures of the lower common bile duct. The patient was referred to our hospital for further examination.

On admission, serum biochemistry showed a cholestatic pattern of liver dysfunction and impaired glucose tolerance with decreased secretion of endogenous insulin (Table 1). Anti-nuclear antibodies (ANA) were detected at a titer of 40-fold, but no other autoantibodies were detected. Levels of serum immunoglobulins, including IgG4, were within the

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Figure 1. Abdominal ultrasound shows a diffusely swollen, hypoechoic pancreas.

normal range. Serum tumor markers were slightly elevated.

Abdominal ultrasound showed a diffusely swollen pancreas (Fig. 1). An abdominal CT scan also suggested pancreatic swelling (Fig. 2). ERCP revealed irregular strictures over one-third of the main pancreatic duct (Fig. 3). Aspiration cytology of pancreatic juice was class II. According to the diagnostic criteria of the Japan Pancreas Society (2006), the patient was diagnosed with ANA-positive AIP.

Cholangiography showed a stricture of the lower common bile duct then dilatation, which may be compatible with findings of AIP. However, bead-like strictures of intrahepatic bile ducts, a characteristic finding in PSC, were also found (Fig. 4). To confirm the presence of sclerosing cholangitis, laparoscopy-assisted liver-wedge biopsy was performed. Hematoxylin Eosin (HE) staining showed onion skin-like periductal fibrosis with mild infiltration of lymphocytes and obliteratorive phlebitis (Fig. 5). An immunohistochemical study using anti-IgG4 antibody showed no IgG4-positive cells in the liver tissues (data not shown).

Colon fiberoscopy showed a pancolitis similar to that seen in ulcerative colitis (UC), except for sparing of or mild inflammation in the rectum (Fig. 6). Microscopic study showed abundant lymphocytes infiltration in the lamina propria, but neither crypt abscess nor IgG4-positive lymphocyte was found. Oral steroid therapy (PSL 30 mg/day) was started. During dose tapering, watery diarrhea appeared at a dose of 5 mg/day, so the dose of PSL was increased to 10 mg/day. At a dose of 7.5 mg/day, the patient appeared clinically to obtain remission with improvement in serum biochemistry (Table 2). ERCP and colonoscopy were performed 8 months after PSL therapy for its evaluation. ERCP showed that the stricture of the MPD was improved, but bead-like strictures of intrahepatic bile ducts remained (Fig. 7). Colon fiberscope did not show any remarkable changes of colonic mucosa showing residual granular change of colon mucosa and redness (data not shown).

Discussion

In the case presented, abdominal ultrasound and abdominal CT scan showed inflammatory swelling of the whole pancreas and ERCP showed strictures characteristic of AIP (5) over one-third of the MPD. Based on the diagnostic criteria of the Japan Pancreas Society (2006), we diagnosed this pancreatic lesion as ANA-positive AIP.

Cholangiography showed strictures of the lower common bile duct and dilatation after confluent stricture. After steroid therapy, strictures of the MPD were improved on ERCP images. Liver dysfunction and diabetes with decreased secre-
Figure 2. Arterial phase (left) and venous phase (right) of an abdominal CT scan shows inflammatory swelling from the body to the tail of the pancreas. Pancreatic swelling disappeared after PSL therapy.

Figure 3. ERCP shows stenosis of the main pancreatic duct (MPD) and irregularity of the duct wall over one-third of its length (arrow).

Figure 4. ERCP shows a stricture of the lower common bile duct and dilatation after confluent strictures, while the beaded appearance of intrahepatic bile ducts can be seen (arrow).

Figure 5. Hematoxylin and Eosin-stained liver tissue (×100) shows onion skin-like periductal fibrosis with mild lymphocytic infiltration (left), and obliterative phlebitis (right).

tion of endogenous insulin were also improved by steroid therapy. This clinical course supported the diagnosis of AIP (4, 6, 7).

However, a number of findings were atypical for AIP. First, despite the presence of multiple organ involvement, serum IgG4 was within normal limits and IgG4-immunostaining was negative (2). IgG4-related systemic disease tends to be confined to the pancreas in patients with low serum IgG4 (8). Secondly, the present case was associated with a pancolitis similar to that in UC. To our knowledge there are no epidemiological studies on the clinical features of colitis with AIP. Among the twenty cases of AIP we have treated (not published) only this case manifested gastrointestinal symptoms. Abundant IgG4-positive plasma cell infiltration in colonic mucosa has been reported (1) and foci of slightly pale, thickened mucosa with loss of a visible vascular pattern has been observed in some cases (9). However, the case presented here was IgG4-negative pancolitis.
Figure 6. (a) Colon fiberscopy shows diffuse mucosal opacification and granular change, scattered redness, and vascular hypo-permeability. (b) HE-stained tissue showed abundant lymphocytes infiltration in the mucosa, but no IgG4-positive lymphocyte was found (data not shown).

Table 2. Time-series Data for Serum Biochemistry after Steroid Therapy Shows Normalization of Biliary Enzymes and Recovery of Endogenous Insulin Secretion

<table>
<thead>
<tr>
<th></th>
<th>Time after oral PSL therapy and dose of oral PSL (mg/day)</th>
<th>1 month</th>
<th>3 months</th>
<th>4 months</th>
<th>6 months</th>
<th>8 months</th>
</tr>
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<tr>
<td></td>
<td>PSL 20mg</td>
<td>PSL 10mg</td>
<td>PSL 5mg--10mg</td>
<td>PSL 10mg</td>
<td>PSL 7.5mg</td>
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<tr>
<td>TB (mg/dl)</td>
<td>0.7</td>
<td>0.5</td>
<td>0.7</td>
<td>0.6</td>
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<tr>
<td>AST (IU/l)</td>
<td>12</td>
<td>19</td>
<td>32</td>
<td>28</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>32</td>
<td>18</td>
<td>47</td>
<td>34</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>232</td>
<td>292</td>
<td>843</td>
<td>414</td>
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<tr>
<td>γ-GTP (IU/l)</td>
<td>27</td>
<td>50</td>
<td>178</td>
<td>125</td>
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<tr>
<td>LDH (IU/l)</td>
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<td>217</td>
<td>218</td>
<td>240</td>
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<tr>
<td>CRP (mg/dl)</td>
<td>0.06</td>
<td>0.08</td>
<td>0.74</td>
<td>0.10</td>
<td>0.12</td>
<td></td>
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<tr>
<td>Amylase (IU/l)</td>
<td>95</td>
<td>90</td>
<td>82</td>
<td>95</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>122</td>
<td>120</td>
<td>108</td>
<td>125</td>
<td>N.E.</td>
<td></td>
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<tr>
<td>hba1c (%)</td>
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<td>N.E.</td>
<td>N.E.</td>
<td>5.9</td>
<td>6.1</td>
<td></td>
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<tr>
<td>C-peptide (ng/ml)</td>
<td>3.8</td>
<td></td>
<td></td>
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</tbody>
</table>

WBC, white blood cells; TP, total protein; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; MPO-ANCA, myeloperoxidase antibody:antineutrophil cytoplasmic antibody; CEA, carcinoembryonic antigen; hba1c, hemoglobin Alc; N.E., not examined.

with AIP. Finally, clinical characteristics of PSC such as onion skin-like periductal fibrosis in liver tissue and a beaded appearance on cholangiography were found in this case of AIP. Nishino et al (10) have recently reported differences between sclerosing cholangitis with AIP and PSC. According to their report, such a case of sclerosing cholangitis should be diagnosed as PSC but not AIP-associated cho-

langitis. Unfortunately, there is currently no international consensus on the diagnostic criteria for PSC. The diagnostic criteria from the Mayo Clinic in 2003 includes: 1) typical characteristic abnormalities involving the biliary tree, 2) compatible clinical and biochemical findings, and 3) exclusion of secondary sclerosing cholangitis. However, Takikawa et al have reported that the criteria of compatible clinical
and biochemical findings should not be strictly applied for the diagnosis of Japanese PSC patients and has proposed radiographic findings as the gold standard (11). Our case can be diagnosed as PSC using either criterion (7, 12, 13). In addition, the sclerosing cholangitis seen in the present case, is morphologically different from that usually seen in AIP (4). Kawa et al (14) suggested that sclerosing cholangitis associated AIP is possibly included in the older patient group of Japanese PSC and proposed that sclerosing cholangitis with AIP should be included in the exclusion criteria for the Mayo Clinic’s diagnostic criteria for PSC. However, the present case shows that AIP and PSC would coexist in accordance with both criteria of PSC and AIP. We found only one report showing IgG4 negative sclerosing cholangitis associated with AIP (15). Unfortunately their diagnosis is still controversial because it was based on only mild dilation of the main pancreatic duct on ERCP and periductal sclerosis with lymphocytic infiltration on pancreas biopsy. To the best of our knowledge, this is the first report of AIP associated with PSC. There may be cases diagnosed as PSC associated with UC which may involve pancreatic duct strictures like this case. Of interest, this case of PSC had a good response to PSL therapy just like sclerosing cholangitis with AIP. The study of a case of PSC with pancreatic duct stricture might provide a novel therapeutic algorithm using PSL.

In conclusion, we reported a rare case of IgG4-negative autoimmune pancreatitis with sclerosing cholangitis and colitis similar to UC; many clinical features support an association with PSC.

References