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CASE REPORT

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Autoimmune pancreatitis as an initial manifestation of systemic lupus erythematosus

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Abstract We report a case of systemic lupus erythematosus that concomitantly occurred with autoimmune pancreatitis. The clinical manifestations of pancreatitis improved in response to steroid therapy. Although the pathogenesis of autoimmune pancreatitis is still controversial, as is that of systemic lupus erythematosus, the observations in the present case suggest the presence of an autoimmune mechanism underlying autoimmune pancreatitis.

Key words Autoimmune pancreatitis (AIP) · Sjögren's syn-drome (SjS) · Steroid pulse therapy · Systemic lupus erythematosus (SLE)

Introduction

A novel disease concept of "autoimmune pancreatitis (AIP)" has been proposed,[1,2] and diagnostic criteria for AIP were proposed by the Japan Pancreas Society in 2002.[3] According to these criteria, AIP can be diagnosed by findings on pancreatic imaging studies and at least one of the following serological and histological findings. In imaging studies, a diffuse narrowing of the main pancreatic duct with an irregular wall (for more than one-third of the length of the entire pancreas) and enlargement of the pancreas were observed. As regards the serological findings, abnormally elevated levels of serum gammaglobulin and/or IgG, or the presence of autoantibodies, were observed. Histological findings showed fibrotic changes with lymphocyte and plasma cell infiltration. Among a group of autoimmune diseases, Sjögren's syndrome (SjS) has been well documented as a complication of AIP.[1,3] However, no AIP case accompanied by systemic lupus erythematosus (SLE) has been described in previous literature. We report the case of a Japanese woman with SLE and SjS, who showed the clinical manifestations of AIP at the onset of SLE.

Case report

A 57-year-old woman was admitted to hospital with a high fever (38°C), general fatigue, and a skin rash on her face. She had noticed swelling of the right inguinal lymph nodes for 1 month prior to the first visit to the hospital. A histochemical study of a biopsy specimen obtained from the lymph node showed reactive lymphoid hyperplasia. Laboratory examination revealed 6.9 mg/dl of total protein, 3400/μl white blood cell count, and negative C-reactive protein. The patient was treated with several types of antibiotic for 3 weeks, but showed no notable response. Subsequently, she was transferred to our hospital for further examination. No drug ingestion was reported before the disease onset.

On admission to our hospital, the patient's body temperature was 37.3°C, pulse rate 88 beats/min, and blood pressure 130/70 mmHg. Several oral aphthae were observed. There was no particular finding in a physical examination of her neck and chest. She did not complain of any abdominal symptoms and her abdomen was flat and soft. Swollen right inguinal lymph nodes were palpable without tenderness. A neurological examination showed no abnormal findings. The patient had habitually drunk 1.5 l beer every day for the past 10 years, and had been suffering from recurrent pyelonephritis for 20 years. There was no notable family history of autoimmune or pancreatic diseases.

Peripheral blood cell counts revealed mild anemia, leukocytopenia, and lymphocytopenia (Table 1). Blood chemistry showed normal levels of creatinine and blood urea nitrogen, and slightly increased levels of hepatobiliary and pancreatic enzymes. However, for 2 weeks after admission, her hepatobiliary and pancreatic enzymes had in-

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Table 1. Laboratory findings on admission

	On admission	2 weeks later
RBC ($\times 10^4$/μl)	363	283
Hemoglobin (g/dl)	10.6	8.1
Platelets ($\times 10^4$/μl)	12.6	5.6
WBC (/μl)	2200	1700
Lymphocytes (/μl)	726	493
ALP (IU/l; 70–220)	179	477
γ-GTP (IU/l; 5–50)	60	526
Total bilirubin (mg/dl)	0.5	1.3
ALT (IU/l)	48	224
AST (IU/l)	121	663
LDH (IU/L)	1159	1965
Crn (mg/dl)	0.4	0.4
BUN (mg/dl)	4	8
CRP (mg/dl)	0.2	0.1
Total protein (g/dl)	6.3	5.4
γ-globulin (g/dl)	1.63	nd
lgG (mg/dl)	1560	nd
lgA (mg/dl)	348	nd
lgM (mg/dl)	68	nd
Coombs test (direct)	(+)	nd
Coombs test (indirect)	(−)	nd
Anti-dsDNA IgG (U/ml)	nd	<5.0
Anti-dsDNA IgM (U/ml)	nd	<5.0
RA test	(−)	nd
Anti-Sm antibody (<−5)	7.4 (±)	(−)
ANA	3160 (speckled)	nd
LE cells	(+)	nd
C3 (mg/dl; 80–151)	34.9	38.4
C4 (mg/dl; 17–40)	4.3	3.1
CH_{50} (UML; 30–45)	8.9	9.2
P-amylase (IU/l; 30–110)	487	1351
S-amylase (IU/l; 30–150)	60	41
Lipase (IU/l; 7–60)	nd	1349
PLA2 (ng/dl; 130–400)	nd	5480
Trypsin (ng/ml: 110–460)	nd	12000
Elastase 1 (ng/ml; 100–400)	nd	>5000
S-IL2 R (U/ml; 220–530)	1300	nd
HTLV-I	(+)	nd

RBC, red blood cells; ALP, alkaline phosphatase; GTP, glutamyltranspeptidase; ALT, alanine aminotransferase; AST, asparate aminotransferase; LDH, lactate dehydrogenase; Crn, creatinine; BUN, blood urea nitrogen; CRP, c-reactive protein; RA, rheumatoid arthritis; ANA, antinuclear antibodies; LE, lupus erythematosus; PLA2, pancreatic phospholipase A2; S-IL2 R, soluble IL2 receptor; HTLV, human T-cell lymphotropi virus; nd, not done

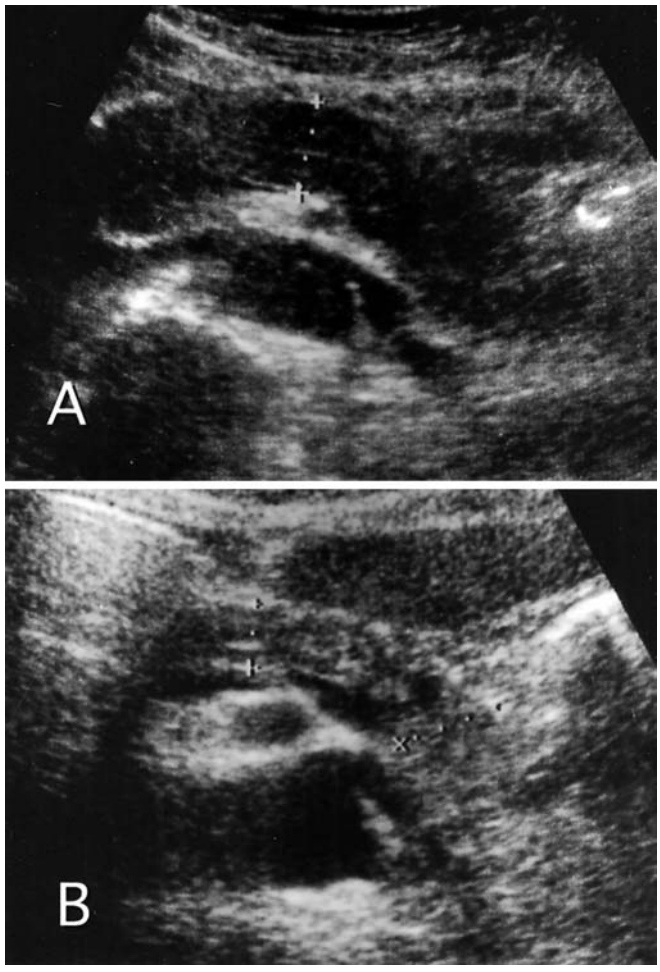

Fig. 1. Abdominal ultrasonography. Before steroid therapy, the pancreas is diffusely swollen with low echogenecity of the parenchyma (**A**). Three months after steroid therapy, the pancreas swelling has disappeared (**B**)

creased rapidly (Table 1). Pancytopenia also appeared. Her serum calcium concentration was low (6.8 mg/dl). C-reactive protein was within the normal ranges. Urinalysis showed proteinuria (1.4 g/day), but no evidence of any type of cast.

An antinuclear antibody test was positive, with a titer of 1:160 and a speckled staining pattern. In a tissue specimen obtained by skin biopsy from her face, LE cells were identified. Serum autoantibodies to double-stranded DNA, La (SS-B), and cardiolipin (β2-GPI dependent) were all negative. Anti-Ro (SS-A) and anti-carbonic anhydrase (CA) II antibodies (see ref. 4 and discussion below) were positive. Anti-Sm antibody was marginally positive, γ-globulin level was slightly increased, but immunoglobulin subclasses were in the normal ranges. Serum complement levels were low. Along with the skin eruption on the face and oral aphthae, these findings indicated that the patient suffered from SLE and possibly also acute pancreatitis. In addition, she complained of thirst, and a pathological study of a lip biopsy specimen showed the marked infiltration of mononuclear cells. Although she had no symptoms of xerophthalmia, these findings indicated that she had secondary SjS complications.

Ultrasonography and computed tomography showed diffuse enlargement of the pancreas, but no peripancreatic involvement (Figs. 1A and 2A). Neither calcification nor cyst formation were detected in the pancreas. There was no biliary stone, and no other notable findings in the biliary system. Abdominal magnetic resonance imaging (MRI) showed diffuse enlargement of the pancreas. T1-weighted images showed the pancreas with a higher signal intensity than that of the liver. T2-weighted images showed a lower signal intensity than that of the liver. It is interesting that the signal intensity of the pancreas was almost equal to that of the spleen. Endoscopic retrograde pancreatography (ERP) carried out 1 month after the steroid pulse therapy, as described below, showed diffuse narrowing and irregularity of the main pancreatic duct (Fig. 3A), which appeared as the thumb-prints as previously reported in AIP cases.[1,2]

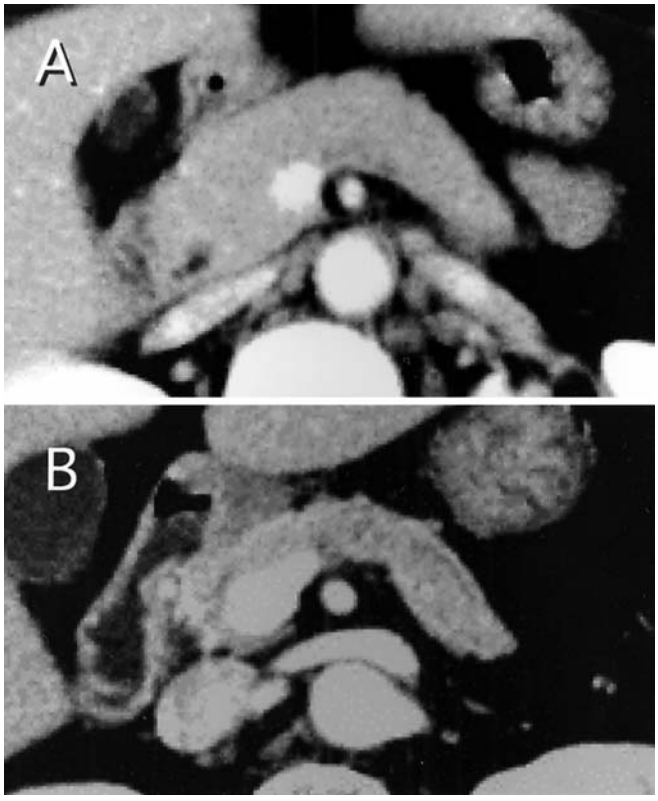

Fig. 2. Abdominal computed tomography shows diffuse enlargement of the pancreas but no peripancreatic involvement prior to steroid therapy (**A**). Three months after steroid therapy, the pancreas has decreased in size and seems atrophic rather than normal (**B**)

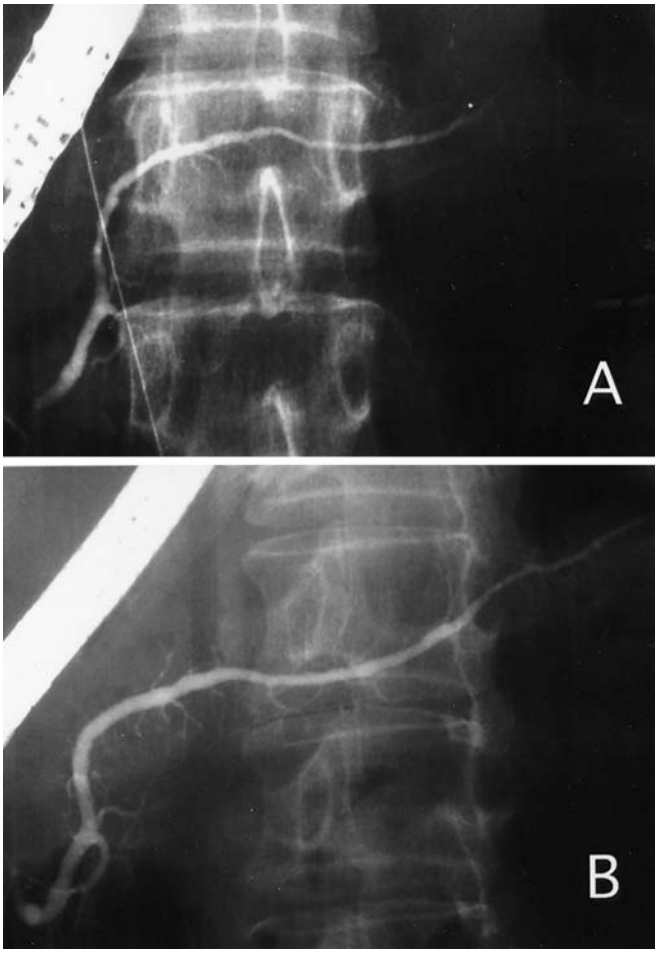

Fig. 3. Endoscopic retrograde pancreatography performed 1 month after steroid pulse therapy shows diffuse narrowing and irregularity of the main pancreatic duct, which appears as thumb-prints, as previously reported in cases with autoimmune pancreatitis (**A**). Three months after steroid therapy, the pancreatic ductal configuration appears almost normal (**B**)

The patient was initially treated with intravenous administration of 1000 mg/day gabexate mesillate and 40 mg/day prednisolone (PSL) per os. However, her clinical symptoms and signs did not subside. On the 9th day after admission, she started to experience seizures and hallucinations. Cerebral MRI revealed a spotty lesion with isointensity on T1-weighted images and high intensity on T2-weighted images in the left parietal lobe of the cerebrum. An examination of the cerebrospinal fluid showed an increased IgG index (1.01, normal range <0.76) and identified oligoclonal IgG bands. These findings suggested an additional complication from central nervous system (CNS) lupus. Subsequently, the patient was treated with an intravenous injection of 1 g methylprednisolone for 3 days, followed by oral administration of 80 mg/day PSL and 100 mg/day azathioprine (Fig. 4). After 1 month of the steroid therapy, her hepatobiliary and pancreatic enzymes gradually decreased and serum complement increased to within the normal ranges. Ultrasonography and computed tomography examination carried out 3 months after the treatment showed a marked decrease in the size of the pancreas (Figs. 1B and 2B). ERP also showed an obvious improvement in the narrowing of the main pancreatic duct (Fig. 3B). The improvement in clinical manifestations in response to the steroid therapy indicated a diagnosis of autoimmune pancreatitis. The patient continued to be treated in an outpatient clinic, and has been in remission on 10 mg/day PSL and 50 mg/day azathioprine, without exacerbation, for 2 years.

Discussion

Since Sarles et al.[5] first reported several cases of idiopathic pancreatitis with hypergammaglobulinemia, many investigators have suggested an autoimmune mechanism as one of the causative factors implicated in the pathogenesis of idiopathic pancreatitis. Recently, Yoshida et al.[2] reported an unusual type of pancreatitis, in which ERP revealed diffuse narrowing of the entire main pancreatic duct, and histological studies showed fibrosis and lymphocytic infiltration in the periductal parenchyma of the pancreas, and they proposed a novel disease entity, AIP. The characteristic clinical manifestations of AIP include no or mild abdominal symptoms, no history of alcohol abuse, a high incidence of obstructive jaundice and diabetes mellitus, the

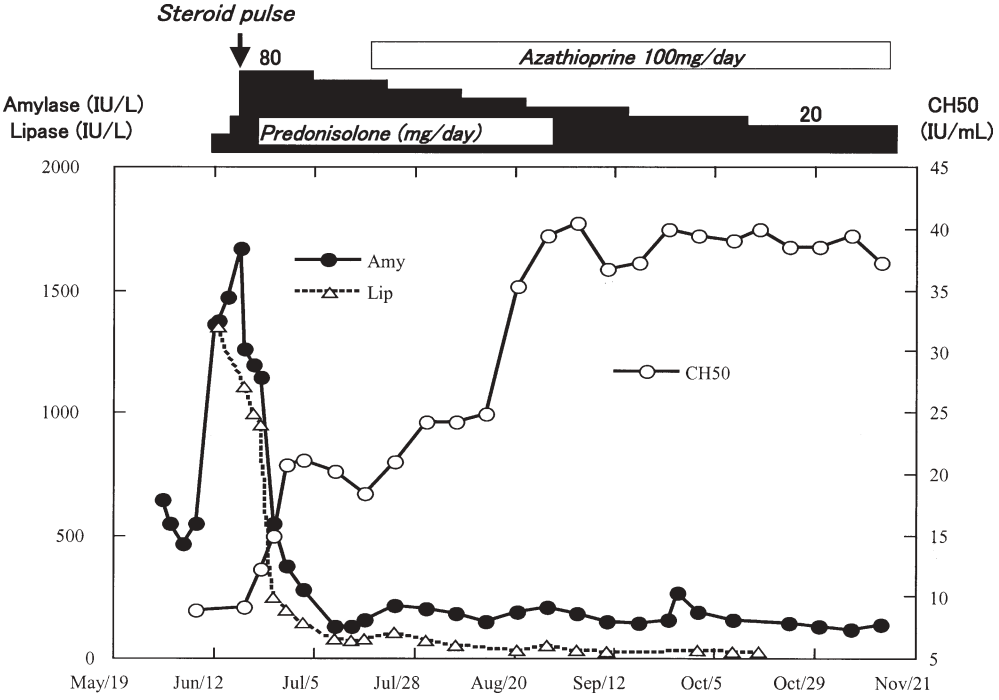

Fig. 4. The clinical course

occasional coexistence of other autoimmune disease such as SjS, increased levels of serum gammaglobulin and/or IgG, and the effectiveness of steroid therapy.[1,2]

The present case fulfilled the American Rheumatology Association criteria for SLE.[6] Increased levels of serum pancreatic enzymes and diffuse swelling of the pancreas shown by ultrasonography and computed tomography suggested a complication of acute pancreatitis in the context of a lupoid episode. It was unusual for acute pancreatitis, however, that the patient never complained of abdominal symptoms. Because she started to show active symptoms due to CNS lupus in the course of the disease, steroid pulse therapy followed by oral administration of a large amount of PSL and an immunosuppressive drug had to be given. Accordingly, we had no chance to obtain tissue specimens from the pancreas and kidney in this case. It is of great interest that, as a result of the steroid therapy, the patient's laboratory data and pancreas swelling improved dramatically. It is also notable in this case that ERP showed diffuse narrowing of the main pancreatic duct, which disappeared in response to the steroid therapy. Furthermore, the patient was diagnosed as having SjS as an additional complication. Based on these findings, we concluded that she suffered from AIP along with SLE.

Acute pancreatitis has sometimes been documented as a complication of SLE.[7] As mechanisms implicated in the pathoetiology of acute pancreatitis in patients with SLE, vasculitis with ischemia, autoimmune phenomena, and the toxic effects of steroids or other drugs have been suggested.[7] One of these, the toxic effects of steroid, is unlikely in the present case, since serum levels of pancreatic enzymes were already increased at admission and dramatically decreased to within the normal range following the steroid therapy. Recently, antiphospholipid antibody has been proposed as a causative factor of acute pancreatitis in patients with SLE.[8] In the present case, however, β2-GPI-dependent anticardiolipin antibody was negative, and no clinical symptoms or signs suggesting thrombosis were observed.

We previously reported that patients with idiopathic pancreatitis and SjS have serum antibody to CA II, and suggested that CA II plays a role as a target antigen in the autoimmune process involved in AIP.[4] We also reported that immunization with CA II induced periductal lymphocytic infiltration in the salivary glands in mice having particular H-2 haplotypes.[9] Recently, Uchida et al.[10] successfully induced mononuclear cell infiltration around the ducts in the salivary glands and also in the pancreas by immunization with CA II in neonatally thymectomized mice. Similar results were induced in nude mice by transplantation with $CD4^+$ cells from the neonatally thymectomized and CA II-immunized mice.[10] Serum antibody to CA II was positive in the present case, which was shown by an enzyme-linked immunosorbent assay, as previously reported.[4] Although the exact mechanism governing the pathogenesis of AIP is still undefined, an autoimmune reaction toward certain molecules in the pancreas possibly causes a massive infiltration of mononuclear cells that results in the swelling of the pancreas and narrowing of the main pancreatic duct. Interestingly, serum antibody to CA II was also shown to be present in 25.4%–31.6% of SLE patients.[11,12] These findings suggest that CA II plays some role in the pathogenesis of AIP, SjS, and SLE that were concomitantly seen in the present case.

To our knowledge, this is the first report of AIP complicated by SLE. In the present case, AIP first appeared prominently with the onset of SLE. Along with positive serum antibody to CA II, the clinical evidence observed in the present case suggests the presence of an autoimmune

mechanism underlying AIP. In cases with AIP, SLE should be considered as a possible complication along with SjS.

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