

A Case of Autoimmune Pancreatitis Associated with Sclerosing Cholangitis, Retroperitoneal Fibrosis and Sjögren's Syndrome

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Key Words

Autoimmune pancreatitis · Sclerosing cholangitis ·
Retroperitoneal fibrosis · Sjögren's syndrome · IgG4 ·
Autoantibody · Antinuclear antibody · Antilactoferrin
antibody

Abstract

We report a very rare case of autoimmune pancreatitis (AIP) associated with sclerosing cholangitis, retroperitoneal fibrosis and Sjögren's syndrome. The patient had an enlarged pancreas, and autoantibodies were detected in the serum. Serum IgG and IgG4 concentrations were also elevated. Endoscopic retrograde cholangiopancreatography revealed an irregular narrowing of the main pancreatic duct from the head to the body and sclerotic change in the intrapancreatic common bile duct, which later extended to the intrahepatic bile ducts. In addition, histological examination of the liver revealed lymphocytic sclerosis around the bile ducts, similar to the histology in the pancreas of AIP. Retroperitoneal tumors were diagnosed as retroperitoneal fibrosis by histological examination. Serological and functional abnormalities suggestive of Sjögren's syndrome were detected, and histological findings of the lip were compatible with Sjögren's

syndrome. Immunohistochemistry of each lesion disclosed that most of the infiltrating lymphocytes were T cells with similar levels of both CD4+ and CD8+ cells. Moreover, some of the infiltrating plasma cells were positive for anti-IgG4 monoclonal antibody. These diseases were dramatically improved by steroid therapy. Although the pathophysiology of AIP is still unclear, the present case suggests a common pathophysiological mechanism for AIP, sclerosing cholangitis, retroperitoneal fibrosis and Sjögren's syndrome.

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Introduction

Since Sarles et al. [1] reported a case of particular pancreatitis with hypergammaglobulinemia, occasional coexistence of pancreatitis with other autoimmune diseases has been reported. These findings support the hypothesis that an autoimmune mechanism is involved in the pathogenesis and pathophysiology in some cases of pancreatitis [2–17]. Recently, similar cases without systemic autoimmune diseases have been reported, which has led to the concept of an autoimmune-related pancreatitis [10], so-called autoimmune pancreatitis (AIP) [12].

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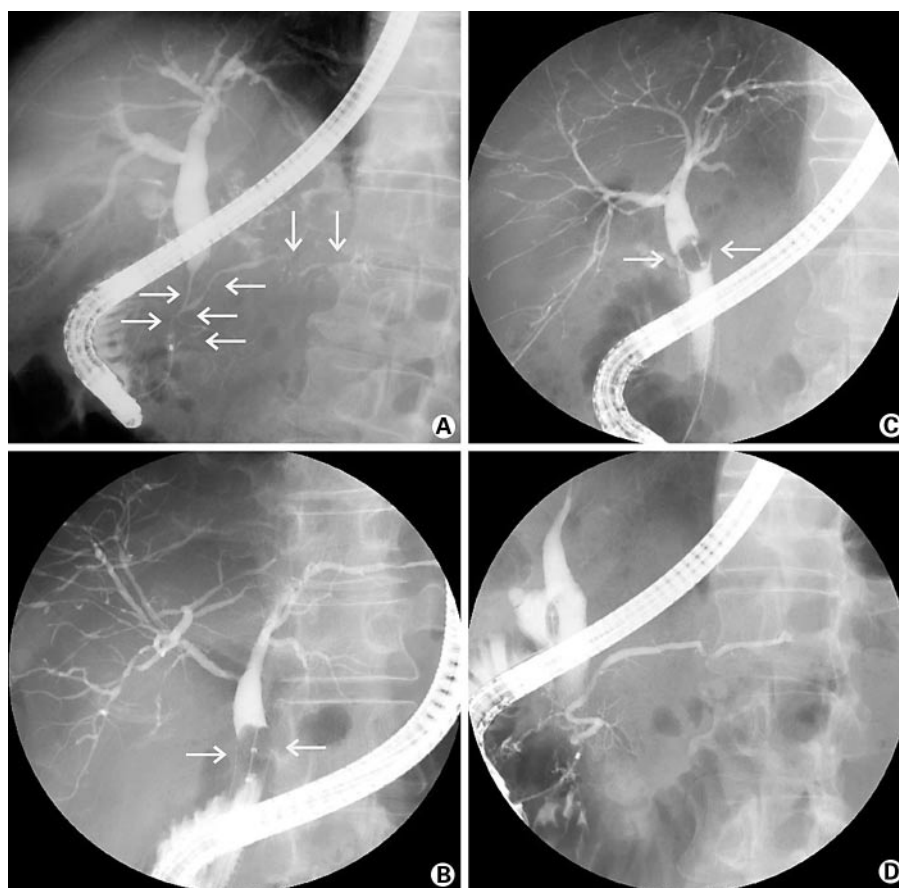


Fig. 1. ERCP. **A** The first ERCP on admission to the first hospital. Localized severe narrowing of the distal common bile duct with mild dilatation of the proximal bile ducts was observed, and irregular narrowing of the MPD was present from the head to the body. Arrows indicate the narrowing portions. **B** The second ERCP before steroid therapy. Narrowing of the bile ducts extending to the intrahepatic bile ducts was remarkable, compared with the first ERCP in the first hospital. Arrows indicate the inflated balloon. **C, D** ERCP after steroid therapy. Neither irregularities nor obstructions were observed in the pancreaticobiliary system. Arrows indicate the inflated balloon.

Here, we report a case of AIP associated with sclerosing cholangitis, retroperitoneal fibrosis and Sjögren's syndrome. Histological findings of the liver, retroperitoneal tumors and the lip, similar to those of AIP, and good responses of all the lesions to steroid therapy suggested the presence of an autoimmune mechanism common to all the affected organs in the pathophysiology of this overlapping disease.

Case Report

A 68-year-old Japanese man had been well until August 2001, when he presented with general fatigue, loss of appetite and dry mouth. He consulted a doctor and was diagnosed as having diabetes mellitus with a high level of HbA1c (10.0%). One month later, he was admitted to the hospital because he had jaundice and pale stools. On admission, his serum total bilirubin level was 4.0 mg/dl. Endoscopic retrograde cholangiopancreatography (ERCP) revealed localized severe narrowing of the distal common bile duct with mild dilatation of the proximal bile ducts and an irregularly narrow main pancreatic duct (MPD) from the head to the body (fig. 1A). The patient was diagnosed with tumor-forming pancreatitis and obstructive jaundice.

Obstructive jaundice was improved by endoscopic biliary drainage. He was referred to our hospital for further examination because of continued general fatigue and abnormal liver function.

On admission, he was a poorly nourished man with slight jaundice and a temperature of 36.4°C. He had neither drug nor alcohol addiction. The results of blood chemistry were as follows: total bilirubin 1.8 mg/dl, direct bilirubin 0.9 mg/dl, aspartate aminotransferase 63 IU/l, alanine aminotransferase 67 IU/l, alkaline phosphatase 986 IU/l, γ -glutamyltranspeptidase 395 IU/l, leucine aminopeptidase 159 IU/l and C-reactive protein 0.5 mg/dl. The serum amylase level was 39 IU/l. Glucose tolerance was not impaired with an HbA1c level of 5.5%. The serum levels of CA19-9, DUPAN-2 and soluble interleukin-2 receptor were all increased (749, 1,600 and 577 U/ml, respectively). An N-benzoyl-L-tyrosyl-p-aminobenzoic acid excretion test indicated impaired pancreatic exocrine function at 38.1% (normal: over 70%). Serum IgG and IgG4 concentrations were elevated at 2,516.8 mg/dl (normal: 788–1,841 mg/dl) and 540 mg/dl (normal: 6–140 mg/dl), respectively. Serum antinuclear antibody and antilactoferrin antibody were positive. Shirmer and gum tests were positive for dry eye and mouth, respectively.

Abdominal ultrasonography, computed tomography and magnetic resonance imaging revealed an enlarged pancreas. Bilateral retroperitoneal tumors were also detected (fig. 2A). In contrast to the previous study, ERCP images revealed irregular narrowing of the intrahepatic bile ducts with 'withered branches' (fig. 1B), but narrowing of

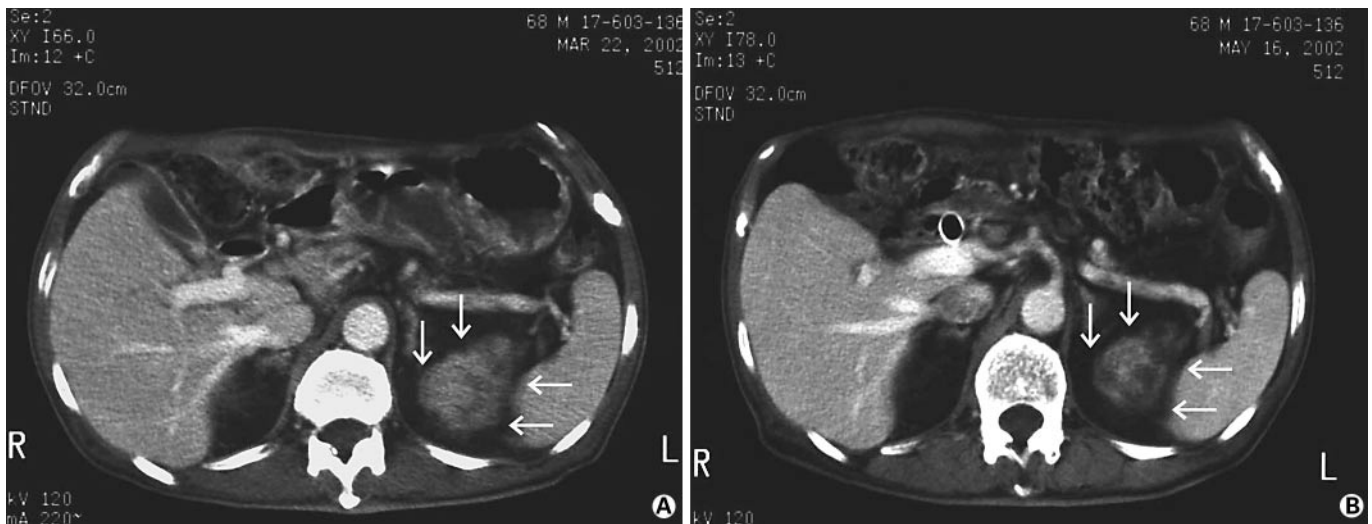


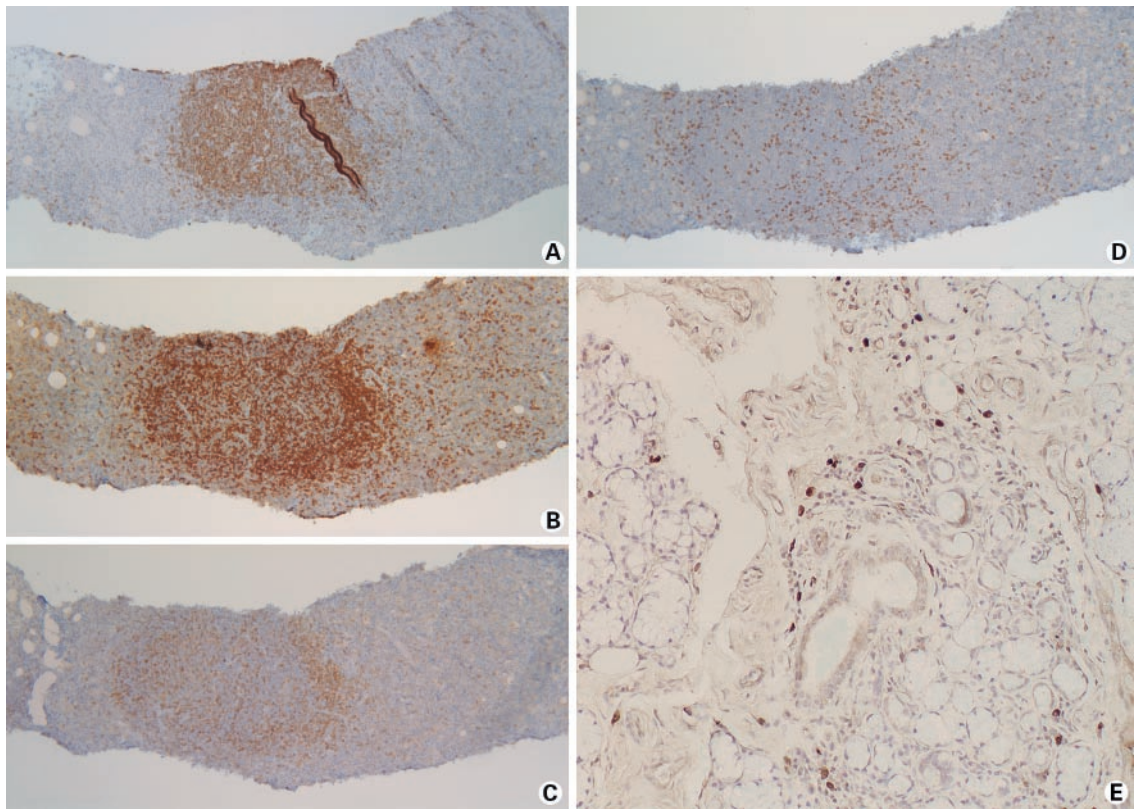
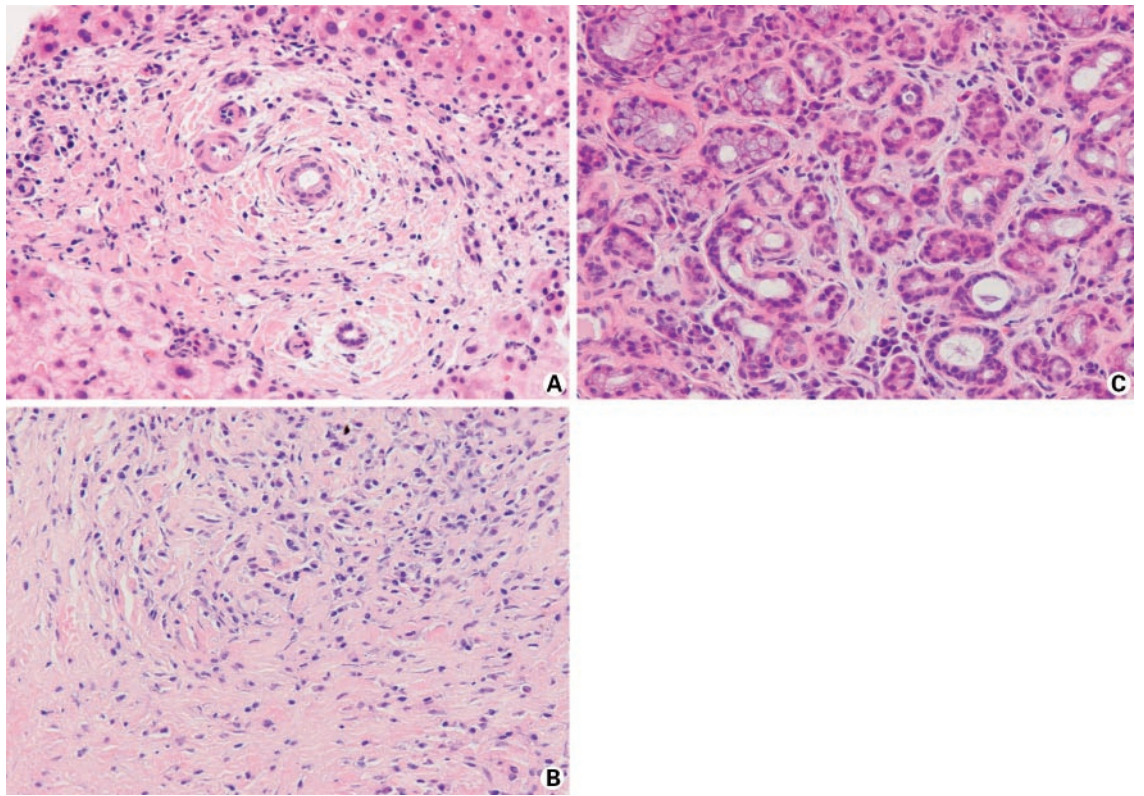
Fig. 2. Computed tomography of the retroperitoneal tumor. **A** On admission, computed tomography images revealed a retroperitoneal low-density mass, which was slightly and partially enhanced in the enhancement study. Arrows indicate the left-side tumor. **B** After steroid therapy, the retroperitoneal tumor became smaller. Arrows indicate the left-side tumor.

the MPD improved to a certain extent. To obtain a diagnosis, needle biopsies of the liver, retroperitoneal tumors and lip were performed. Histological findings of the liver revealed a mild infiltration of lymphocytes, neutrophils and plasma cells around the portal areas and fibrosis around the bile ducts with little destruction of the lobules, which is consistent with primary sclerosing cholangitis (PSC) (fig. 3A). Specimens of the retroperitoneal tumors revealed fibrotic changes with an infiltration of plasma cells and lymphocytes, suggesting retroperitoneal fibrosis (fig. 3B). Lip biopsy revealed a mild infiltration of lymphocytes and plasma cells scattered in the lobules of the minor salivary glands, suggestive of Sjögren's syndrome (fig. 3C). Immunohistochemistry of the liver, retroperitoneal tumors and lip revealed that T cells infiltrated predominantly over B cells in all the tissues, with similar levels of both CD4+ and CD8+ T cells. Only the retroperitoneal tumors showed lymphoid follicles without monoclonality, which consisted mainly of B cells (fig. 4A–D). IgG4-positive plasma cells stained by anti-IgG4 monoclonal antibody were also observed in these tissues (fig. 4E). According to the Japanese diagnostic criteria for AIP (table 1), we diagnosed this patient as having AIP combined with PSC, retroperitoneal fibrosis and Sjögren's syndrome.

Oral administration of prednisolone was initiated at a dose of 30 mg/day and was tapered by 5 mg/week to 10 mg/day. The patient's symptoms and abnormal blood chemistries, including tumor markers, serum gamma globulin concentration and autoantibodies, dramatically improved 14 days later. After 4 weeks, abnormal ERCP images such as irregular narrowing of the intrahepatic bile ducts and MPD improved almost completely (fig. 1C, D). Subsequent follow-up examinations by computed tomography and magnetic resonance imaging revealed that the retroperitoneal tumors were smaller (fig. 2B). At the outpatient clinic, he has been in a good condition without recurrence on 10 mg/day prednisolone for 16 months.

Fig. 3. Histological examination of the liver (**A**), the retroperitoneal tumor (**B**) and the lip (**C**). **A** Mild infiltration of lymphocytes, neutrophils and plasma cells with fibrosis around the biliary duct in the portal area with little destruction of the lobules was observed. Expansion of the portal area with an infiltration of inflammatory cells was noted. These findings are compatible with PSC. Hematoxylin and eosin stain. Original magnification $\times 200$. **B** Fibrosis with an infiltration of mononuclear cells including plasma cells and lymphocytes was present, and is compatible with retroperitoneal fibrosis. Hematoxylin and eosin stain. Original magnification $\times 200$. **C** Histological findings of the minor salivary gland indicated a mild infiltration of lymphocytes and plasma cells scattered in the lobules, which is compatible with Sjögren's syndrome. Hematoxylin and eosin stain. Original magnification $\times 200$.

Fig. 4. Immunohistochemistry of specimens of the retroperitoneal tumor (**A–D**) and of the lip (**E**). **A** Immunohistochemistry using L26 mouse monoclonal antibody (Dako Corp., Carpinteria, Calif., USA) indicated that CD20+ B cells were scarcely observed in the retroperitoneal tumor except in the lymphoid follicle. Original magnification $\times 100$. **B–D** Immunohistochemistry using anti-CD3 (Dako Corp.; **B**), anti-CD4 (Novocastra Laboratories, Newcastle, UK; **C**) and anti-CD8 (Dako Corp.; **D**) mouse monoclonal antibodies demonstrated that most of the infiltrating lymphocytes were CD3+ T cells, and levels of both CD4+ and CD8+ T cells were similar. Original magnification $\times 100$. **E** Immunohistochemistry using anti-IgG4 mouse monoclonal antibody (Caltag Laboratories, Burlingame, Calif., USA) indicated that some plasma cells in the minor salivary gland were IgG4 positive. Original magnification $\times 200$. These representative findings (**A–E**) were also observed in the other lesions.



Discussion

Although the pathogenesis and pathophysiology of this condition are still unclear, the concept of AIP is becoming accepted [2–17]. The characteristic findings in most cases of AIP can be summarized as follows: (1) no symptoms or only mild symptoms, usually without acute attacks of pancreatitis; (2) diffusely irregular narrowing of the MPD and occasional stenosis of the intrapancreatic bile duct on ERCP images; (3) diffuse enlargement of the pancreas; (4) increased levels of serum gamma globulin or IgG; (5) presence of autoantibodies; (6) fibrotic changes with lymphocyte infiltration in the pancreas; (7) occasional association with other autoimmune diseases; (8) rare pancreatic calcification or cysts, and (9) effectively treated with steroids [10, 13]. Diagnostic criteria for AIP based on these characteristics have been proposed by The Japan Pancreas Society (table 1) [18].

In the present case, the enlargement of the pancreas with narrowing of the MPD, which was observed in the first ERCP, improved completely after steroid therapy. Although histological examination of the pancreas was not performed, those abnormal pancreatic images, together with an increased level of serum IgG and the presence of autoantibodies, are consistent with the criteria for AIP [18]. Histological findings of the liver and the retroperitoneal tumors indicating fibrosis and predominant infiltration of T cells, which are similar to the histological characteristics of the pancreas in AIP [9], also support the diagnosis of AIP.

In addition, there was an elevated serum IgG4 level. Although the clinical significance of the serum IgG4 elevation is still unclear, it often accompanies AIP [13, 14, 17, 19]. After administration of an oral steroid, levels of IgG, IgG4 and autoantibodies returned to normal, similar to the pancreatic images.

AIP is often associated with other autoimmune diseases, including PSC [20] and Sjögren's syndrome [21]. In the present case, ERCP findings of the intrahepatic bile ducts and histological findings of the liver indicated the presence of PSC. In addition, sicca symptoms and histological findings from the lip biopsy revealed the coexistence of Sjögren's syndrome. Coexistence of AIP with PSC and Sjögren's syndrome suggests that there are common target antigens in the pancreas and other exocrine organs, such as the bile ducts and salivary glands. Autoantibodies such as antinuclear antibody, antilactoferrin antibody, anticarbonic anhydrase II antibody and rheumatoid factor are frequently detected in patients with AIP [9, 10, 17]. Among them, carbonic anhydrase II and lactoferrin are present in

Table 1. Diagnostic criteria for AIP proposed by the Japan Pancreas Society in 2002 [18]

- 1 Pancreatic imaging studies show diffuse narrowing of the main pancreatic duct with irregular wall (more than 1/3 of the length of the entire pancreas) and enlargement of the pancreas
 - 2 Laboratory data demonstrate abnormally elevated levels of serum gamma globulin and/or IgG, or the presence of autoantibodies
 - 3 Histopathological examination of the pancreas shows fibrotic changes with lymphocyte and plasma cell infiltration
- For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3.

exocrine cells of various organs, including the pancreas, biliary ducts, salivary glands and distal renal tubules [9]. The high prevalence of these antibodies in AIP suggests that carbonic anhydrase II and lactoferrin are candidates for the target antigens in exocrine cells. Confirming this hypothesis, we reported previously that exogenous administration of carbonic anhydrase II and lactoferrin induced AIP in neonatally thymectomized mice [22].

Patients with AIP often have narrowing of the distal common bile duct due to compression by the enlarged pancreatic head. Indeed, the present case initially presented with severe narrowing of the distal common bile duct that caused obstructive jaundice. On the other hand, some cases of AIP are associated with PSC or biliary lesions similar to PSC [1, 4, 23]. Such PSC-like biliary lesions in AIP are reported as 'lymphoplasmacytic sclerosing pancreatitis with cholangitis' [23], 'sclerosing pancreatocholangitis' [4] or an 'inflammatory pseudotumor from sclerosing cholangitis' [1]. It is still unclear, however, whether sclerotic lesions of the biliary tracts observed in AIP are the same as those in PSC. In this regard, in contrast to typical PSC, administration of steroids is usually effective on biliary lesions in AIP [4, 9, 11]. Indeed, in the present case, steroid treatment improved the intrahepatic biliary lesions dramatically. Such a good response to steroid administration suggests that the sclerotic lesions of the bile ducts observed in AIP are an entity distinct from typical PSC [4].

The etiology of retroperitoneal fibrosis remains unclear in most cases. Some investigators previously reported pseudotumors of the pancreas associated with retroperitoneal fibrosis [24–28], but in the present case, radiologic and ultrasonographic findings revealed no pseudotumor of the pancreas. Steroid therapy is effective [24, 29] and antinuclear antibodies are detected [15, 30–32] in some patients with retroperitoneal fibrosis, suggesting that an autoimmune mechanism is involved in some

cases of retroperitoneal fibrosis. Supporting this idea, steroid administration significantly decreased the size of the retroperitoneal mass of our patient.

In conclusion, we report a case with a disease complex of AIP, sclerosing cholangitis, retroperitoneal fibrosis and Sjögren's syndrome, all of which are responsive to steroid therapy. Whether the pathophysiology of the present case is distinct from that of typical AIP, or AIP is a part of the manifestation of the disease complex remains to be elucidated.

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