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Case Report

Autoimmune Pancreatitis with Primary Sclerosing Cholangitis-like Lesion

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Autoimmune pancreatitis is a recently proposed disease entity. It is sometimes associated with other inflammatory diseases such as Sjögren's disease and sclerosing cholangitis. We report here a case of autoimmune pancreatitis associated with sclerosing cholangitis. The patient was a 74-year-old Japanese male who presented with obstructive jaundice and mild epigastric pain. Computed tomography scan and magnetic resonance cholangiopancreatography showed a diffuse swollen pancreas and poor visualization of the main pancreatic duct. The distal bile ducts were stenotic with marked dilatation of the main and intrahepatic bile ducts. Consequently, a pylorus preserving pancreatoduodenectomy was performed because bile duct carcinoma could not be ruled out. Pathological findings of the removed tissues showed fibrosis with lymphoplasmacytic infiltration in both the choledochus and pancreas head, destruction of pancreatic acinar tissues and obliterative phlebitis. Postoperative laboratory studies showed elevated serum IgG and detection of antinuclear factor. Scattered IgG4-positive plasma cells detected by immunohistochemistry appeared in the pancreas and in the periductal region of the bile duct. This case was finally diagnosed as autoimmune pancreatitis associated with sclerosing cholangitis.

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Introduction

Autoimmune pancreatitis (AIP) is a unique form of pancreatitis characterized by irregular narrowing of the main pancreatic duct, lymphoplasmacytic infiltration with an increased number of IgG4-positive plasma cells, hypergammaglobulinemia with increased IgG4, and responding to glucocorticocoid treatment.[1-5] AIP has sometimes been observed in association with sclerosing cholangitis (SC).[6-8] Until its proposal as a separate disease entity, AIP with/without SC had previously been misinterpreted as ordinary acute or chronic pancreatitis, idiopathic chronic pancreatitis, primary sclerosing cholangitis (PSC), or pancreaticobiliary malignancy.[9,10] AIP with SC should be differentiated from PSC or malignacy, since AIP is sensitive for steroids.[6-8]

We report here a case of AIP associated with SC in a 74-year-old Japanese male with a description of retrospectively determined pathological findings.

Case report

A 74-year-old Japanese male was hospitalized because of epigastric pain. There was no history of prior illness or alcohol abuse. Laboratory examination showed high levels of amylase, and chronic pancreatitis was diagnosed. Symptoms subsided with the administration of a proteolytic enzyme inhibitor (camostat mesilate). A few months later, he was hospitalized again because of jaundice and loss of appetite. Vater's papilla was normal as determined by upper gastrointestinal endoscopy. Physical examination revealed jaundice and mild epigastric tenderness. Upon admission, laboratory studies showed a significant elevation of salivary gland-amylase of 178 IU/L (normal range: 40-135 IU/L), and pancreas-amylase of 135 IU/L (15-55 IU/L). Hematocrit, erythrocyte, leukocyte and thrombocyte counts were normal. Total bilirubin level was 9.3 mg/dL (0.3-1.5 mg/dL), alkaline phosphatase－568 IU/L (115-359

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IU/L), γ-GTP—698 U/L (10-75 U/L), AST—180 U/L (0.3-1.5 U/L), ALT—286 U/L (6-39 U/L), CA19-9—134.3 U/L (<37 U/L), CEA—2.7 ng/mL (<4.9 ng/mL), AFP—6 ng/mL (<19 ng/mL), CRP—0.4 mg/dL (<0.3 mg/dL). Abdominal ultrasound, computed tomography (CT) scan and magnetic resonance cholangiopancreatography showed a diffusely swollen pancreas without any calcification or stones (Figure 1 A). The main bile duct and the intrahepatic bile ducts were dilated, with a narrow distal bile duct (Figure 1 B). A distal bile duct stricture was also shown by endoscopic retrograde cholangiopancreatography (ERCP). There was no mass in pancreas. The main pancreatic duct of the head region was not fully visualized probably due to irregular narrowing. The pancreatic duct of the head region was also narrowed. On the basis of these radiological findings, primary sclerosing cholangitis (PSC) was suspected. An endoscopic naso-biliary drainage tube was positioned across the distal bile duct. Cytology of the bile had been negative for malignant cells in three studies, but the possibility of carcinoma of the lower common bile duct could not be ruled out because of an irregular narrowing image. Consequently, a pylorus preserving pancreatoduodenectomy was performed. There was no malignancy detected in frozen sections from the bile duct. Pathological findings of the removed pancreas showed an intense inflammatory cell infiltration around medium sized and interlobular ducts. The inflammatory infiltrates consisted mainly of lymphocytes and plasma cells. Pancreatic acini and ducts were necrotized with severe inflammation and replaced by diffuse fibrosis (Figure 2 A). Islets of Langerhans remained. Similarly, in the removed common bile duct, the lymphoplasmacytic infiltration completely encompassed the duct, where the wall changed to laminar fibrosis (Figure 2 B). Therefore, the pancreatic duct and the common bile duct were stenotic due to a diffuse lymphoplasmacytic infiltration combined with fibrosis. Scattered obliterative phlebitis was encountered in the fibrotic parenchyma of the pancreas (Figure 2 C). Additional laboratory studies showed high levels of gamma globulins of 1,839 mg/dL (870-1,700 mg/dL) and antinuclear factor (ANF) of ×40 (diffuse pattern). Cytoplasmic anti-neutrophil cytoplasmatic antibodies and rheumatoid arthritis test were negative. Serum level of IgG4 was not evaluated. For immunohistochemistry anti-IgG4 antibody was purchased from The Binding Site (Birmingham, UK), and anti-CD4 and CD8 antibodies were purchased from MBL (Nagoya, Japan). A standardized 2-step method with ENVISION+ (DAKO, Kyoto, Japan) was used for antibody detection. The reaction products were visualized using 3,3'-diaminobenzidine as a chromogen (DAKO). Scattered IgG4-positive plasma cells detected by immunohistochemistry appeared in the pancreas and in the periductal region of the bile duct (Figure 2 D). Lymphocytes were mainly composed of CD8+ T cells with some CD4+ T cells and B cells. The CD8+ T cells directly infiltrated into the epithelial cells of the bile duct. There was severe lymphocyte infiltration into the necrotic area of pancreatic acinar tissues. Most of the lymphocytes were CD8+ T cells. This case was finally diagnosed as AIP associated with SC. Lymphoplasmacytic infiltration was observed at the surgical end of the removed tissues. There has been no recurrence during the 2 years and 5 months after the operation without any treatments.

Discussion

The diagnostic criteria of AIP was published by the Japan Pancreas Society in 2002.[11] AIP is characterized by several unique clinical and diagnostic imaging features: highest incidence in elderly men (most patients being older than 50 years), diffuse enlargement of the pancreas, diffusely irregular narrowing of the main pancreatic duct on ERCP, increased serum levels of gammaglobulin (consisting of immunoglobulin G, A, M, etc.) especially of IgG4, presence of autoantibodies, and the effectiveness of steroid therapy. More than

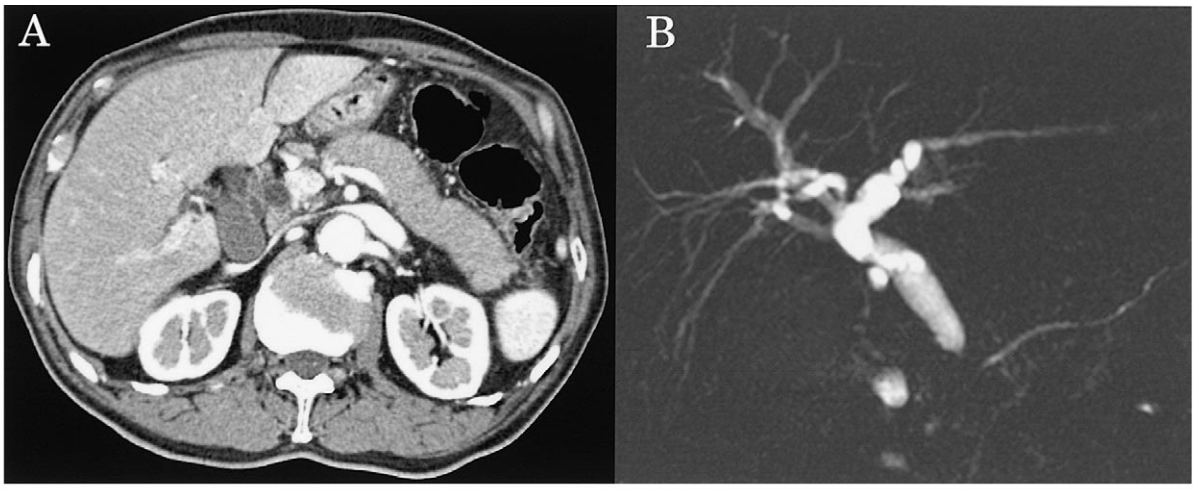

Figure 1. A. Computed tomography (CT) scan shows diffuse enlargement of the pancreas with sharp borders, poorly enhancing on arterial phase with its so called "sausage-like appearance". **B.** Magnetic resonance cholangiopancreatography (MRCP) shows narrowing of the distal main bile duct with upstream dilatation of the bile duct. The main pancreatic duct is in normal range.

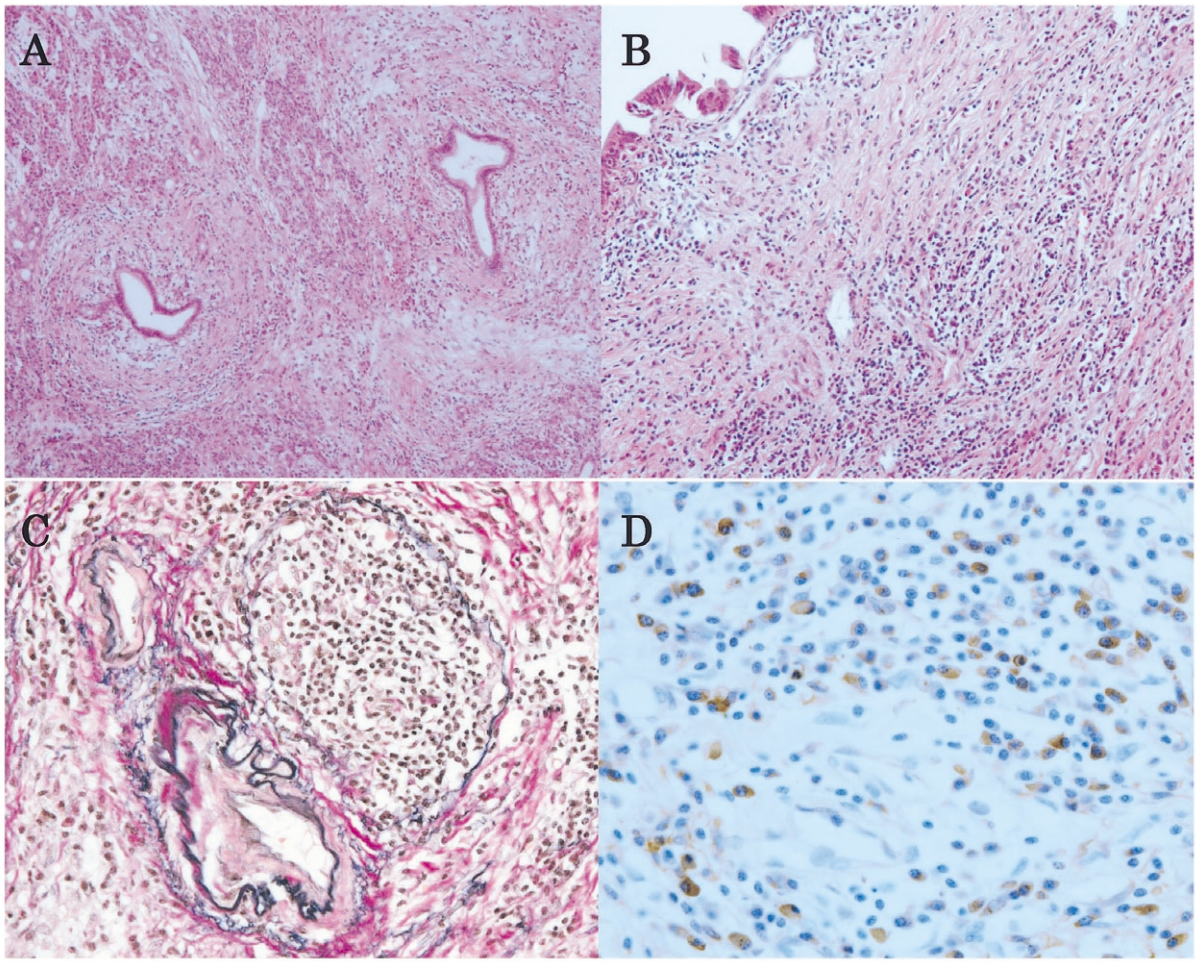

Figure 2. Pathological findings of pancreas and choledochus. **A.** Pancreas. The fibroblastic periductal proliferation and lymphoplasmacytic infiltration. Lymphoplasmacytic infiltration was observed around the pancreatic duct, while the acini were relatively well preserved. HE staining. **B.** Choledochus. In the removed common bile duct, the lymphoplasmacytic infiltration completely encompassed the duct, resulting in laminar fibrosis in the wall. HE staining. **C.** Obliterative phlebitis. Obliterative phlebitis scattered in the fibrotic lesion of pancreas. Elastica van Gieson staining. **D.** Immunostaining of IgG4. Infiltration of IgG4 positive plasma cells was detected around the pancreatic duct.

150 cases of AIP or pancreatitis with narrow pancreatic duct have been reported in the Japanese literature.

AIP has been diagnosed as an ordinary acute or chronic pancreatitis, idiopathic chronic pancreatitis, or pancreaticobiliary malignancy.[9,10] It is important to be aware of the existence of this rare variant of chronic pancreatitis. For instance, in Korea the first reported case of AIP was in 2002, and approximately 30 more cases of AIP have been described in the following two years. This sudden increment in Korea was thought to be an increasing awareness of the entity rather than a rise in the true incidence.[9] The incidence of AIP in chronic pancreatitis is comparable to reports from Japan and Italy that were 4.6%, and 6.0%, respectively.[9] The compilation of accumulated cases should contribute accurate epidemiological data in the future. Also, the awareness of AIP with SC might help to avoid unnecessary surgery for sometimes suspected but unproven pancreaticobiliary malignancy.

The serum IgG4 levels have reportedly been able to distinguish AIP from pancreaticobiliary malignancy with a high sensitivity (90.2%) and specificity (97.5%).[12] A multicenter study on the sensitivity and specificity of serum IgG4 level in the diagnosis of AIP is warranted.[13] In pathological analysis, scattered IgG4-positive plasma cells appeared in the pancreas and in other organs of coexisting autoimmune disorders, e.g., salivary gland of Sjögren's syndrome and bile duct of sclerosing cholangitis.[14] It seems that AIP is a systemic disorder related to IgG4, and thus AIP can be thought of as an "IgG4-related autoimmune disease" or "IgG4-associated multifocal fibrosis".[15,16] Immunohistochemically, CD8+ T cells appeared in the necrotic area of the pancreatic acini and the epithelial cells of bile duct. In the experimental rat model of AIP, the role of the activated CD4+ T cell was reported.[17] At present the interrelation between IgG4 and cellular immunity has not been clearly established.

Many cases of bile duct stricture associated with chronic pancreatitis have been reported, and most of these patients were diagnosed as having PSC associated with chronic pancreatitis.[6-8] A recent consensus holds that steroids are ineffective against PSC.[6-8]

The presence of an increased number of IgG4-positive plasma cells in the bile ducts is a characteristic of AIP-SC. The IgG4-positive plasma cell/mononuclear cell ratio in tissue specimens is a useful index to help distinguish AIP with SC from PSC.[18] The term "sclerosing pancreatocholangitis" has been proposed for AIP and related lesions as a new disease entity for bile duct change and pancreatitis.[19]

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