Inflammatory Pseudotumors of the Pancreas and Liver with Infiltration of IgG4-Positive Plasma Cells

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Abstract

Recently, it has been reported that autoimmune pancreatitis (AIP) can be complicated with various extra-pancreatic lesions. Here, we report a very rare case of pancreatic and hepatic inflammatory pseudotumor (IPT) with the infiltration of IgG4-positive plasmacytes. The patient showed pancreatic and hepatic masses with elevated levels of serum IgG4. Endoscopic retrograde cholangiopancreatography revealed narrowing of the intrapancreatic bile duct. Fluorine-18fluorodeoxyglucose positron emission tomography suggested pancreatic cancer with hepatic metastasis. Histopathologic findings showed fibrosis and infiltration of IgG4-positive plasmacytes, suggesting IPT. The present case suggests a possible common mechanism in the development of AIP and IPT of the liver.

Key words: autoimmune pancreatitis, inflammatory pseudotumor, pancreatic cancer

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Introduction

Several investigators have reported that autoimmune mechanisms may be involved in the etiology of chronic pancreatitis. Yoshida et al first proposed the concept of “autoimmune pancreatitis” (AIP) (1). We previously reported the characteristic clinical features of AIP (2, 3) as follows: (i) irregular narrowing of the main pancreatic duct (MPD); (ii) massive lymphoplasmacytic inflammation. Kamisawa et al proposed IgG4 related sclerosing disease (4), in which IgG4-positive plasmacytes infiltrate extensively not only the pancreas but also other organs such as the bile duct, gall bladder, liver, salivary gland, lymph nodes or retroperitoneum.

Hepatic inflammatory pseudotumor (IPT) is a rare benign lesion characterized by polyclonal lymphoplasmacytic infiltration with varying degrees of dense fibrosis and is often misdiagnosed as primary hepatic malignant tumor. Zen et al have recently shown that the bile duct lesions associated with hepatic IPT accompanied sclerosing cholangitis (SC) were identical to those associated with AIP accompanied SC, suggesting that these conditions may be included in a common disease entity (5). AIP frequently accompanies SC, which may be related to hepatic IPT, but little is known about a direct association of AIP and hepatic IPT. Here, we report a case of spontaneously vanishing pancreatic and hepatic IPT.

Case Report

A 54-year-old man with jaundice, and no history of drug or alcohol abuse was suspected of having pancreas head cancer, as indicated by the presence of a pancreatic head mass shown by computed tomography (CT) and stenosis of the intrapancreatic bile duct (Fig. 1). Endoscopic retrograde cholangio-pancreatogram (ERCP) did not show a diffuse narrowing of main pancreatic duct (MPD), as in a typical case of AIP. A cystic lesion was also found behind the pancreatic head mass. He was treated with endoscopic biliary...
drainage (EBD). EBD was removed after seven days, and the jaundice did not recur. The patient was subsequently suspected of having mass forming pancreatitis, and was referred to our hospital for further examination.

On admission, a physical examination showed no significant findings. Relevant laboratory data showed 0.9 mg/dl of total serum bilirubin (normal, <1.2); 503 IU/l of alkaline phosphatase, (107-323); 333 IU/l of gamma-glutamyl transpeptidase (gamma-GTP), (11-64), 146 IU/l (12-31) of aspartate amino transaminase (AST) (12-31), 76 IU/l of alanine amino transferase (ALT) (7-35), 69 IU/l of amylase (36-129), 46.0 IU/l of lipase (8-40), and 504 ng/dl of elastase I, (<400). Hepatitis B surface antigen and Hepatitis C virus antibody were negative. Pancreatic secreting function of BT-PABA (N-benzoyl-L-tyrosyl-p-aminobenzoic acid) was decreased by an estimated 44.9% as measured by urine excretion test (73.4-90.4%). IgG, IgG4, IgA, and IgM were 2105.9 mg/dl (788-1841), 213 mg/dl (6-140), 313.3 mg/dl (89-503), and 181.7 mg/dl (60-271), respectively. Rheumatoid factor 27 IU/ml (<18) was positive. Antinuclear antibody was negative. Among tumor markers, CEA was 1.6 ng/dl (<5.0); DUPAN-2, 190 U/ml (<150); and CA19-9, 31.5 U/ml (<37).

Abdominal CT showed lesions of the pancreatic head mass and of the hepatic mass in the left lobe (Fig. 2). This hepatic mass was not detected at the previous hospital. Abdominal ultrasound study (US) revealed a hepatic mass in the area of S4. Fluorine-18fluorodeoxyglucose positron emission tomography (FDG-PET) showed abnormal uptake in both the masses, consistent with a diagnosis of pancreatic cancer with hepatic metastasis (Fig. 3). To confirm the diagnosis, we performed biopsy of the hepatic mass, and found extensive infiltration and fibrosis of lymphocytes, suggesting IPT. In addition, immunohistochemical findings showed that infiltrated plasma cells were positive for anti-IgG4 monoclonal antibody (Fig. 4). There were no signs of primary SC, ulcerative colitis or any other autoimmune disorders. The pancreatic and hepatic masses disappeared naturally after 3 months and 12 months, respectively. The above observations led to diagnose him with pancreatic and hepatic IPT with

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**Figure 1.** Endoscopic retrograde cholangiopancreatography (ERCP). ERCP image is not typical of AIP (A) shows and (B) localized narrowing of intrapancreatic bile duct.

**Figure 2.** Computed tomography (CT). (A) Initial abdominal CT (at the previous hospital) shows a pancreatic mass and cystic lesion. After one month, abdominal CT shows (B) pancreatic mass and (C) hepatic mass. Pancreatic cyst disappeared naturally.
Figure 3. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET showed strong uptake in the liver and pancreatic head. These results are consistent with pancreatic cancer with hepatic metastasis, although this patient did not have either.

Discussion

Since Sarles et al reported a case of idiopathic pancreatitis with hypergammaglobulinemia (6), many investigators have suggested that an autoimmune mechanism is involved in some instances of idiopathic pancreatitis. We previously reported that patients with AIP frequently have autoantibodies (2, 3). Hammano et al reported that patients with AIP show high serum IgG4 concentration, and that the values are closely associated with the disease activity (7). The common characteristics in a typical case of AIP can be summarized as follows: (i) increased levels of serum gamma globulin, IgG or IgG4, (ii) presence of autoantibodies, (iii) enlargement of the pancreas, (iv) irregular narrowing of the MPD, (v) rare pancreatic cysts and calcification, (vi) fibrotic change with lymphocyte infiltration, (vii) no symptoms or only mild symptoms, (viii) occasional association with other autoimmune disease, (ix) responsiveness to steroid therapy (1-3). In this report, the pancreatic images suggested an unusual phenotype of AIP because of MPD images and of pancreatic cyst found by ERP. The relationship between the pancreatic mass and the cyst is unclear. This cystic lesion disappeared naturally. It may be concerned with pancreatitis, however, we tentatively diagnosed the patient with pancreatitis involving an autoimmune phenomenon.

Figure 4. Histological examination of the liver. (A) Mild infiltration of lymphocytes and plasma cells with fibrosis was observed. (B) Immunohistochemistry using anti-human IgG4 mouse monoclonal antibody (Caltag Laboratories, Burlingame, CA, USA) indicated that plasmacytes in the liver were IgG4 positive. Original magnification is 100x.
AIP is associated with various extra pancreatic diseases, such as SC, sialoadenitis, retroperitoneal fibrosis, or thyroiditis. SC is one of the common complications with AIP. SC with AIP may seem similar to primary SC, but these two types of SC are quite different in responsiveness to steroid therapy (8). Although the present case can be diagnosed as AIP by serological and histological examination, it is an unusual case of AIP compared with previously reported cases, because of a rare complication with hepatic IPT. IPT occurs in various major organs, and shows irregular proliferation of myofibroblasts intermixed with an infiltration of inflammatory cells, mainly lymphocytes and plasma cells. It is currently reported that AIP patients show high levels of serum IgG4 (7), although the role of IgG4 is unclear. Kamisawa et al reported that IgG4-positive plasma cells are abundantly seen not only in the pancreas but also in other involved organs (4, 9). Two case reports of hepatic IPT with AIP appear on MedLine before January 2007 (10, 11). Kannno et al reported IgG4-related hepatic IPT (10). Sasahira et al also reported that the plasmacytes are infiltrated in the hepatic IPT (11). In addition, several cases of IgG4-related IPTs with AIP have been reported (5, 10, 12, 13), suggesting that IgG4-positive plasmacytes may be involved in the development of IPT as well as AIP. We too report here that a patient diagnosed with pancreatic and hepatic IPTs and whose clinical history was suggestive of AIP, showed high levels of serum IgG4 and infiltration of IgG4-positive plasma cells in the hepatic IPT, supporting the idea that IgG4-positive plasmacytes may be involved in the development of both pancreatic and hepatic IPTs as well as AIP. The mass lesions in the liver and pancreas seem different in their vascularity on the enhanced CT images. This finding may reflect disease activity.

Interestingly, FDG-PET in the present report revealed an unusual case of pancreatic and hepatic masses with high accumulation. FDG-PET is usually useful to differentiate between malignant and benign tumors, although it is reported that active AIP sometimes show a high FDG accumulation (14). Thus, FDG-PET cannot necessarily distinguish AIP from pancreatic cancer with hepatic metastasis.

In conclusion, the present case in which the patient was diagnosed with AIP and hepatic IPT suggests that IgG4-related immunological mechanisms may be involved in the development of IPTs as extrapancreatic lesions associated with AIP.

References