Pancreatic Cancer Associated with Autoimmune Pancreatitis in Remission

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Abstract

In January 2007, an 80-year-old man was admitted to our hospital for treatment of a pancreatic tumor. He had been diagnosed with autoimmune pancreatitis (AIP) in December 2003 for which steroid therapy had induced remission. In November 2006, tumor marker levels rapidly increased, and the patient was suspected of having pancreatic cancer based on imaging studies. The diagnosis was later confirmed by endoscopic ultrasound-guided fine-needle aspiration biopsy. Distinguishing AIP from pancreatic cancer is crucial; however, few previous reports have described any cases of pancreatic cancer associated with AIP. While several reports have speculated on the prognosis of AIP, natural courses of the disease remain uncertain. This report emphasizes that AIP can coexist with cancer.

Key words: pancreatic cancer, autoimmune pancreatitis, steroid therapy, tumor marker, EUS-FNA, IgG4

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Introduction

Recently, there have been many reports supporting the hypothesis that an autoimmune mechanism is involved in the pathogenesis and pathophysiology in some cases of pancreatitis; these reports have led to the disease concept of autoimmune pancreatitis (AIP) (1-5). One clinical characteristic of AIP contributory to its diagnosis is the efficacy of steroid therapy (4). It is thus crucial to distinguish AIP from pancreatic cancer, because immunosuppression by steroid therapy may accelerate the disease progression of pancreatic cancer.

There have been several cases of chronic pancreatitis in which resection was performed due to the high suspicion of pancreatic cancer (6). Because there is no gold standard for the diagnosis of AIP, the differentiation from pancreatic cancer can be difficult (7-11). On the other hand, few previous reports have described pancreatic cancer associated with AIP (12). In general, the risk of pancreatic cancer is significantly increased in patients with chronic pancreatitis (13-15). While several reports have speculated on the prognosis of AIP, natural courses of the disease remain uncertain (16, 17). Here, we report a case of pancreatic body cancer associated with AIP in remission, which was diagnosed 3 years before the detection of the pancreatic cancer.

Case Report

An 80-year-old Japanese man was admitted to our hospital for further examination and proper treatment against a suspected pancreatic body tumor in January 2007. About 3 years earlier, in December 2003, the patient had been diagnosed with AIP, which caused symptoms like obstructive jaundice. The results of blood chemistry on the previous admission were as follows: total bilirubin 7.0 mg/dl, direct bilirubin 5.4 mg/dl, aspartate aminotransferase 41 IU/l, alanine aminotransferase 48 IU/l, alkaline phosphatase 959 IU/l, γ-glutamyltransferase 289 IU/l, serum amylase 88 IU/l and C-reactive protein 0.41 mg/dl. Glucose tolerance was not impaired with an HbA1c level of 5.8%. The serum levels of CA19-9 and CEA were 64.5 U/ml (normal; 0-40 U/ml) and 3.7 ng/ml (normal; 0-5 ng/ml), respectively. An N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) excretion test indicated impaired pancreatic exocrine function with 23.7% (normal; 73.4-90.4%). Serum γ-globulin, IgG, and IgG4 concentrations were elevated: 24.4% (1.68 g/dl, normal; 10.9-20.7%), 2,190 mg/dl (normal; 1,051-1,454 mg/
Figure 1. Magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance imaging (MRI) before (a, b, c) and after (d, e, f) steroid therapy. (a, b) MRCP and ERCP showed localized severe narrowing of the distal common bile duct with dilatation of the proximal bile ducts and irregular narrowing of the main pancreatic duct from the head to the body. (c) MRI revealed a localized enlargement in the head of the pancreas (arrow). (d, e, f) After steroid therapy, those findings improved considerably.

From November 2006, serum levels of CA19-9 and DUPAN-2 rapidly increased instead of recurrence of AIP. On admission, he was well-nourished with a temperature of 36.4°C. He had neither drug nor alcohol addictions. The results of blood chemistry, including liver, biliary, and pancreatic enzyme, were within normal limits. However, the serum levels of CA19-9 and DUPAN-2 were markedly increased to 522.2 U/ml and 400 U/ml (normal; 0-150 U/ml), respectively. Abdominal CT with contrast medium revealed an irregular tumor in the body of the pancreas and dilatation of the MPD in the tail (Fig. 2a). ERCP revealed severe narrowing of the MPD around the pancreatic tumor and no abnormal findings in the CBD (Fig. 2b). 18-fluorodeoxyglucose positron emission tomography (FDG-PET) showed hot spots...
Figure 2. Concomitant pancreatic cancer 3 years after diagnosis with autoimmune pancreatitis. (a) Computed tomography (CT) revealed the irregular pancreatic body tumor, which expanded ventrally close to the stomach and was not enhanced in the enhancement study. (b) Endoscopic retrograde cholangiopancreatography (ERCP) revealed severe narrowing of the main pancreatic duct around the pancreatic tumor (arrow). (c) 18-fluorodeoxyglucose positron emission tomography (FDG-PET) showed hot spots of FDG uptake in the site of pancreatic tumor (circle). (d) Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of the pancreatic body tumor revealed adenocarcinoma. The specimen showed anisonucleosis, nuclear contour irregularity, high nuclear/cytoplasmic ratio, and presence of prominent nucleoli in the absence of inflammatory cells (Papanicolaou stain, original magnification ×400).

Discussion

When diagnosing AIP, it is important to differentiate it from neoplastic lesions and to avoid facile therapeutic diagnosis by steroid administration, because immunosuppression by steroid therapy may accelerate disease progression of neoplastic lesions. However, no gold standard currently exists for the diagnosis of AIP, and it is sometimes difficult to differentiate AIP from pancreatic cancer (7-11).

There have been several cases of chronic pancreatitis in which resections were performed because of high suspicion of pancreatic cancer (6). However, from histological examination of the resected tissue in these cases, it was found that some cases of chronic pancreatitis that morphologically only resembled pancreatic cancer actually represented cases of atypical pancreatitis with fibrotic change and lymphoplasmacytic infiltration (lymphoplasmacytic sclerosing pancreatitis). There is growing evidence that patients with AIP also exhibit histopathological symptoms of lymphoplasmacytic sclerosing pancreatitis (4, 18-21). From this point of view, AIP has been gradually accepted as a new clinical entity; its recognition has reduced the number of unnecessary laparotomies and pancreatic resections, as most patients with AIP respond to steroid therapy.

Increased levels of serum γ-globulin, IgG, or IgG4 and the presence of autoantibodies are often detected in patients with AIP, but are seldom observed in patients with pancreatic cancer. Hamano et al analyzed serum samples from pa-
tients with AIP and with pancreatic cancer and reported levels of IgG4 to be significantly and specifically higher in those with AIP (22). On the other hand, Ghazale et al reported that increased serum IgG4 levels are only characteristic of AIP and are not sufficient to diagnose AIP (23). Moreover, they suggested that a slight elevation in serum IgG4 alone is not sufficient to differentiate AIP from pancreatic cancer. Thus, increased levels of serum IgG4 should only be considered as a useful diagnostic tool for AIP, especially since the significance of this condition in the pathogenesis and the pathophysiology of AIP is still unclear. Some patients with AIP, particularly with obstructive jaundice, demonstrated elevated serum tumor markers which normalized after steroid therapy. In the present case, the serum level of CA19-9 had once normalized after inducing remission of AIP and stayed within the normal range for 3 subsequent years, but recently it rapidly re-ascended in association with pancreatic cancer. Thus, if tumor markers develop beyond control of steroid therapy in AIP, we must suspect concomitant pancreatic cancer.

The characteristic US finding in AIP is a swelling hypoechoic pancreas with echogenic spots. On CT with contrast medium, delayed enhancement of the swelling pancreatic parenchyma similar to a normal pancreas becomes evident in most cases. Additionally, a capsule-like low-density rim surrounding the pancreas is observed in some cases, the formation of which might be induced by inflammatory and fibrous changes involving the peripancreatic adipose tissue (24). ERCP reveals diffuse or localized irregular narrowing of the MPD and occasional stenosis of the distal CBD. As AIP gains acceptance as a distinct clinical entity, diagnosis by imaging studies is relatively easy when these typical diffuse changes are evident. However, it is still difficult to differentiate the localized irregular narrowing of the MPD sometimes seen in AIP from similar changes caused by pancreatic cancer. In these cases of localized narrowing, the absence of notable dilatation of the upper part of the MPD and delayed enhancement of the enlarged portion, similar to a normal pancreas, help to avoid a misdiagnosis with pancreatic cancer. Nevertheless, it is advisable to obtain specimens from the MPD or CBD strictures for cytopathological evaluation. When the diagnosis remains in doubt, EUS-FNA may also be helpful as in the present case.

In general, the risk of pancreatic cancer is significantly increased in patients with chronic pancreatitis (13-15). While several reports have speculated on the prognosis of AIP, the natural course of the disease remains uncertain. Inoue et al reported a case of pancreatic cancer synchronously existing with AIP (12). Unlike their case, in the present case pancreatic cancer developed 3 years after diagnosis with AIP. According to both laboratory results and imaging studies, it is unlikely that the pancreatic cancer was present 3 years earlier at the time of diagnosis of AIP. It is still unclear whether AIP has malignant potential or has a cancer inhibitory effect due to exaggerated immune response. Further study of long-term prognosis of AIP is required.

In conclusion, in patients with obstructive jaundice or pancreatic tumor suggestive of pancreatic cancer, AIP should be considered in the differential diagnosis by means of serologic, imaging, or cytopathological studies, in order to avoid unnecessary laparotomy or pancreatic resection. However, this report emphasizes that AIP can coexist with pancreatic cancer, synchronously or metachronously.

References


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