Autoimmune pancreatitis (AIP) sometimes forms a pancreatic mass lesion, which is often difficult to distinguish from pancreaticobiliary malignancy, however it generally responds to steroid therapy. A 70-year-old man was referred to our institute with the suspected diagnosis of pancreatic cancer due to a mass lesion detected at the pancreatic head. Various images demonstrated an ill-defined mass at the enlarged pancreatic head with focal narrowing of the main pancreatic duct. Serum antinuclear antibody (ANA) was negative (x40 dilution) on the onset. Forceps biopsy from the narrowed pancreaticobiliary duct and fine-needle aspiration biopsy under endoscopic ultrasonography (EUS-FNAB) ruled out pancreaticobiliary malignancy. Steroid therapy was started at 40 mg per day but was not effective according to subsequent image analyses. Repeated EUS-FNA from the pancreatic mass was performed but was again negative for carcinoma. Seven months later, under steroid-off condition, still no response was recognized in the clinical image but the titer of serum ANA was increased to be positive (x80), satisfying the criteria of AIP in Japan (2006). Although very rare, this is a case meeting Japanese criteria of AIP after withdrawal of steroid without response to steroid in the clinical images, suggesting the necessity of careful follow-up.

Key words: autoimmune pancreatitis, criteria, diagnosis, steroid, response

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Introduction

It is sometimes difficult to accurately diagnose autoimmune pancreatitis (AIP), as AIP occasionally demonstrates similar findings to pancreaticobiliary malignancy (1, 2) and is rarely accompanied with pancreaticobiliary carcinomas (3, 4). Steroid is used as standard therapy for AIP, when it is accompanied by symptoms such as obstructive jaundice and abdominal pain (5), and it is effective to almost all patients (5). Although not included in the Japanese diagnostic criteria of AIP (6), to avoid facile use for therapeutic diagnosis, response to steroid is commonly evaluated as one of the criteria of AIP in U.S.A. (7), Korea (8) and Asia (9). In Asan Medical Center, for diagnostic purpose, two weeks of steroid trial (dose: 0.5 mg/kg of oral prednisolone per day) with subsequent assessment of its response was analyzed prospectively for clinical outcome. Response to the steroid trial was confirmed in all 15 cases with AIP, in contrast to no response in 7 cases with pancreatic cancer (10).

We herein report a case of AIP meeting criteria after the withdrawal of steroid, without response in images for over seven months from the start of steroid therapy.

Case Report

A 70-year-old man was referred to our institute under the alternative diagnosis of pancreatic cancer or mass-forming pancreatitis on the mass lesion in his pancreatic head. He...
was pointed out to have a high blood sugar level two months before the detection of the pancreatic lesion, otherwise there was nothing particular in his medical history. His family history was not remarkable. He had a smoking history of 1 pack of tobacco for 55 years until current admission, but he denied any daily alcohol intake. In the serum examination, only antinuclear antibody (ANA) was borderline with x40 dilution positivity, but no other specific findings [total-bilirubin 0.6 mg/dL, AST 23 U/L, ALT 31 U/L, LDH 165 U/L, ALP 332 U/L, γGTP 25 U/L, total protein 7.0 g/dL, albumin 4.5 g/dL, BUN 16.0 mg/dL, Cre 0.7 mg/dL, CRP 0.01 mg/dL, TPHA(-), HBs-antigen (-), HCV-antibody (-), CEA 3.1 ng/mL, CA19-9 8 U/mL, γ-globulin 13.4%, IgG 840 mg/mL, IgG4 58.9 mg/dL, RAPA (-), AMA (-), anti-DNA antibody (-), anti-SSA (-) and anti-SSB (-)].

Ultrasonography (US) (Fig. 1A, B) demonstrated a low-echoic, enlarged pancreatic head with scattered high echoic spot and duct penetrating sign. Multi-detector computed tomography (MDCT) (Fig. 2A) showed ill-defined, pancreatic head mass, 3.5 cm in size. Mass lesion was faintly less enhanced compared to the background pancreas during the early to delayed phase. Endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 3A) showed incomplete stenosis at the lower bile duct and a 2 cm of narrowing of the main pancreatic duct (MPD) at the pancreatic head with mild dilatation (4 mm) in the upstream. Intraductal ultrasonography (IDUS) of the choledochus showed a low-echoic, pancreatic lesion around the lower bile duct (Fig. 3C) and focal wall thickening of the adjacent upstream (Fig. 3B), otherwise no skip lesion was found. Histology of tissues from the pancreaticobiliary duct and ampulla (11) obtained by forceps biopsy (2.2 mm, FB-46Q, Olympus, Tokyo) and that from the pancreatic mass by fine needle aspiration biopsy under endoscopic ultrasonography (EUS-FNA) (12) (EchoTip, 22-gauge, Wilson-Cook, NC) (Fig. 1C) were both negative for cancer and not specific to AIP. T1- and T2-weighted magnetic resonance image (MRI) both demonstrated the focally enlarged, pancreatic head as a homogeneous, low-intensity lesion. MRCP did not show lesions other than the pancreatic head (Fig. 4). Positron emission tomography using 18F-fluorodeoxygluucose (FDG-PET) (Fig. 5) showed accumulation of FDG at the pancreatic head (SUVmax: 3.9) as well as at a mediastinal lymph node, like other cases of AIP (13). The clinical image showing a focally enlarged pancreatic head with narrowing of the MPD met one criterion but the serum marker was negative as the level of ANA was x40 dilution of positivity, therefore criteria of AIP were not fulfilled even after a full set of examinations. Steroid therapy was started with 40 mg/body/day and decreased 5 mg each week. However, no response was recognized by both US

Figure 1. (A) Horizontal view of abdominal ultrasonogram (US) showing a 3.5 cm low echoic lesion with an irregular margin at the pancreatic head. (B) Duct penetration recognized at the central site of the massive lesion (arrows). (C) Fine-needle at the center of the mass for aspiration biopsy under endoscopic ultrasonogram (EUS). Biliary stent shown as double high-echoic streaks within the mass (arrows). (D) Numerous vascular flow signals depicted within the low-echoic mass lesion seven months after the start of steroid therapy.
Figure 2. (A, B, C) Computed tomography (CT) of the pancreatic head mass, not showing the obvious difference in size of the lesion between before (A), three weeks after (B) and seven months after the start of steroid therapy (C).

Figure 3. (A) Endoscopic retrograde cholangiopancreatography (ERCP) showing the irregular, focal, narrowing of the main pancreatic duct (MPD) and lower bile duct (BD). (B) Intraductal ultrasonogram (IDUS) just at the upper-side of the stenosis of BD showing mild wall thickening (arrowheads) and faintly dilated MPD (thin arrow). (C) IDUS at lower BD showing massive low echoic lesion surrounding BD.

and MDCT (Fig. 2B) examinations at two to three weeks after the start of steroid. EUS-FNA was re-performed to thoroughly rule out cancer one month after starting steroid when the steroid amount was minimized to 10 mg/body/day, and we re-confirmed no malignant pancreatic tissue. In three months, just before withdrawal of steroid intake, the serum ANA level increased to x80 dilution and ranged within x40-x80 of dilution afterward (Fig. 6), finally meeting the criteria of AIP. Seven months after the start of steroid, contrast-enhanced US demonstrated a moderate to high level of enhancement throughout the mass lesion (14), compared with the surrounding pancreas from 15 seconds to after 3 minutes after intravenous injection of contrast medium (Sonazoid<sup>TM</sup>, Amersham Health, Oslo, Norway)(Fig. 1D) and MDCT also showed no response to steroid (Fig. 2C).

Discussion

Diagnosis of AIP is sometimes difficult, when lacking some of the criteria and showing atypical images (1, 2), negative serum markers and/or histology do not fulfill the conditions of lymph-plasmacytic sclerosing pancreatitis (LPSP) (6). The Japanese criteria of AIP (6) are established based on the minimum consensus not only for the specialist of pancreaticobiliary field but also for general clinicians initially to avoid misdiagnosis of pancreateobiliary malignancy, so that they emphasize the importance of negative work-up, not including the response to steroid therapy.

The current case was problematic in diagnosis, although finally fulfilled the criteria of Japan (6), Korea (8) and Asia (9), but not HISORt criteria of Mayo Clinic (7). HISORt includes steroid response as criterion but not
autoantibody as a serum marker. Concerning the current case, the diagnosis of AIP was defined after steroid withdrawal not only by two conditions meeting Japanese criteria; i.e., focal pancreatic enlargement with narrowing of MPD and positive serum ANA, but also by image characteristics such as enhancement in the pancreatic mass from early to late phase by contrast-enhanced US (14) and FDG accumulation in typical extrapancreatic lesion or mediastinal lymph node (13). Although the lowest limit of positivity, repeated results of increased level of serum ANA (positive with x80 of dilution) after withdrawal of steroid were also suggestive of the association of the autoimmune system. These findings were in contrast to findings not typical as AIP, such as low level of serum IgG and IgG4, negative histology of LPSP in the obtained tissues, dilatation of main pancreatic duct (4 mm) at the upstream of narrowing and no capsule-like rim formation in T2-weighted MRI image. Moreover, negative work-up for pancreatobiliary malignancy was confirmed by normal serum CA19-9, duct penetration within the mass detected by US, and negative cancer tissue by forceps biopsy and repeated EUS-FNA (12). In our previous study, definitive FDG accumulation at a mediastinal lymph node was recognized in 53.8% (7/13) of cases with AIP (13). The Japanese National Pancreatic Cancer Registry (15) reported that elevation of serum CA19-9 is detected in 71.7% of pancreatic cancer, of which the size ranges between 2.1 cm-4.0 cm. Mizuno et al (12) reported 100% (14/14) sensitivity of EUS-FNA using a 22-gauge needle for pancreatic cancer forming a focal mass not diffuse lesion.

Figure 4. (A) T1-weighted and (B) T2-weighted magnetic resonance image (MRI) both show the low-intensity mass at the pancreatic head.

Figure 5. Positron emission tomography (PET) scan showing faint accumulation of FDG at the pancreatic head (SUV max: 3.9) and obvious intake at the mediastinal lymph node.
The level of serum antinuclear antibody was increased up to ×80 of dilution after withdrawal of steroid therapy.

The group of Asan Medical Center emphasized the usefulness of two weeks of steroid trial after negative work-up for malignancy, with 100% sensitivity and specificity (10). Steroid trial is nowadays used widely outside of Japan for cases with indefinite diagnosis of AIP. Importantly, this diagnostic option was applied after the negative work-up for known disease (7). However, according to a study of 17 large centers in Japan, although rare, 2% (8 of 459 cases) of steroid treated AIP did not show remission by standard steroid therapy (5). We encountered a case, meeting Japanese criteria of AIP after withdrawal of steroid, without response to steroid therapy in the clinical images. Clinician must bear in mind that a steroid trial may not be an ace of spade in the diagnosis of a case suspected of AIP.

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References