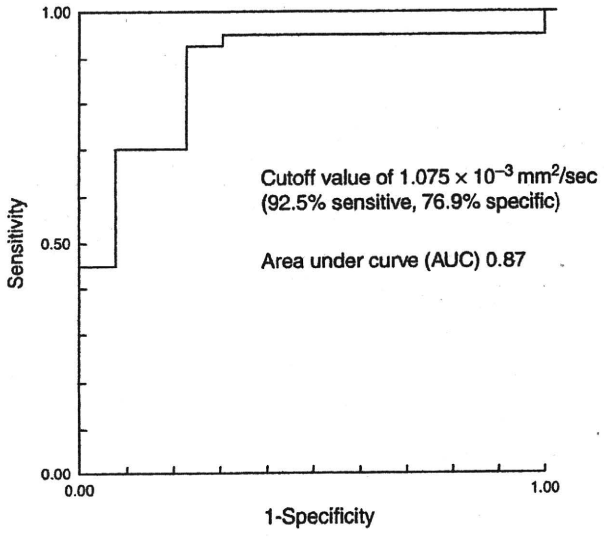

Figure 5. The receiver operating characteristic curve evaluating the optimal ADC cutoff value to distinguish AIP from pancreatic cancer. ADC, apparent diffusion coefficient; AIP, autoimmune pancreatitis.

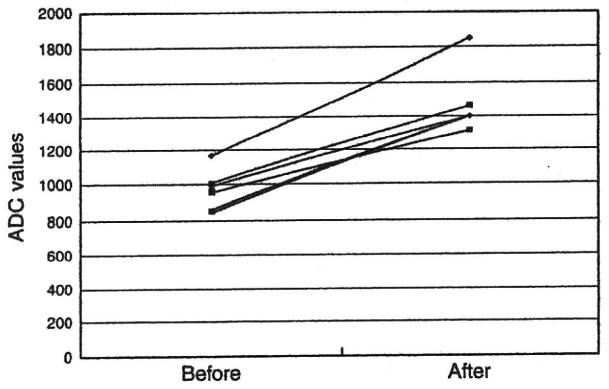

Figure 6. ADC values ($\times 10^{-6}$ mm²/s) of the pancreas with autoimmune pancreatitis before and after steroid therapy. ADC, apparent diffusion coefficient.

cancer were detected as high-signal intensity areas. However, as all pancreatic cancers showed a solitary area, diffuse or multiple high-intensity areas suggested AIP. A longitudinal high-intensity area also suggested AIP more than pancreatic cancer.

It is reported that pancreatic cancer showed lower ADC values ($1.27\pm0.52\times10^{-3}$ mm²/s (15) or $1.44\pm0.20\times10^{-3}$ mm²/s (14)) compared with normal pancreas because of increased cellularity and fibrosis (desmoplasia) of the tumor, which cause restricted diffusion. In this study, the ADC value of pancreatic cancer was $1.249\pm0.113\times10^{-3}$ mm²/s, which was also significantly lower than that of normal pancreatic tissue. On the other hand, the ADC value of AIP was $1.012\pm0.112\times10^{-3}$ mm²/s, which was significantly lower than that of pancreatic cancer. There are only two reports of ADC values in AIP. Feuerlein *et al.* (20) reported an ADC value of 0.799×10^{-3} mm²/s in one patient with diffuse AIP. Taniguchi *et al.* (19) reported that the ADC values of four AIP patients ($0.97\pm0.18\times10^{-3}$ mm²/s) were significantly lower than those of normal controls. ADC values, which are quantitative expressions of tissue diffusion characteristics, are related to the proportion of extracellular components. Guo *et al.* (21) reported a clear inverse relationship between ADC values and the cellular component of brain tumors, such as lymphoma and high-grade astrocytoma. The ADC value was significantly lower in lymphomas than in high-grade gliomas, whereas the cellular component was significantly greater in lymphomas than in high-grade gliomas. These findings suggest that increased cellularity is associated with more restricted diffusion. Thus, ADC values tend to decrease with increased tissue cellularity or cell density.

The histopathology of the pancreas in AIP is very characteristic: dense infiltration of lymphocytes and plasma cells with dense fibrosis or edema in the involved pancreatic lesion (1–4). Although cancer cell infiltration with desmoplastic stroma is the typical histopathological feature of pancreatic cancer, the cellularity of dense lymphoplasmacytic infiltration in AIP is obviously greater than that of pancreatic cancer. Increased cellularity and edematous change in AIP may induce lower ADC values in AIP than in pancreatic cancer. Using an ADC cutoff value (1.075×10^{-3} mm²/s) seems to be useful for distinguishing AIP from pancreatic cancer.

After steroid therapy, high-intensity areas on DWI disappeared or were markedly decreased with improvement in pancreatic enlargement. The ADC values of reduced pancreatic lesions increased to nearly that of normal pancreas after steroid therapy. DWI may also be useful for evaluating the effect of steroid therapy and for monitoring relapse during follow-up.

This study had some limitations. The first limitation was the lack of histopathology of the pancreas in 10 AIP patients, so that the degree of lymphoplasmacytic infiltration could not be assessed. The second limitation was the small number of AIP patients examined. Moreover, as AIP is a relatively rare disease, there were only 13 AIP patients. A further study of more cases is necessary. However, this is the first report about the utility of DWI to distinguish AIP from pancreatic cancer; therefore, a prospective, differential diagnostic study on using this cutoff value will further elucidate the utility of DWI.

In conclusion, DWI is useful for detecting AIP and for evaluating the effect of steroid therapy. ADC values were significantly lower in AIP than in pancreatic cancer. An ADC cutoff value may be useful for distinguishing AIP from pancreatic cancer.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

Guarantor of the article: Terumi Kamisawa, MD.

Specific author contributions: None.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ It is sometimes difficult to differentiate autoimmune pancreatitis (AIP) from pancreatic cancer.

WHAT IS NEW HERE

✓ On diffusion-weighted magnetic resonance imaging (DWI), diffuse or multiple high-signal intensity areas suggest autoimmune pancreatitis (AIP) rather than pancreatic cancer.

✓ The apparent diffusion coefficient (ADC) values for AIP were significantly lower than those for pancreatic cancer.

✓ An ADC cutoff value of 1.075×10^{-3} mm²/s may be useful for distinguishing AIP from pancreatic cancer.

✓ After steroid therapy, the ADC values of the reduced pancreatic lesion increased almost to the values of normal pancreas.

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Positive Response to Steroid Therapy for Autoimmune Pancreatitis Evaluated With Fluorodeoxyglucose Positron Emission Tomography

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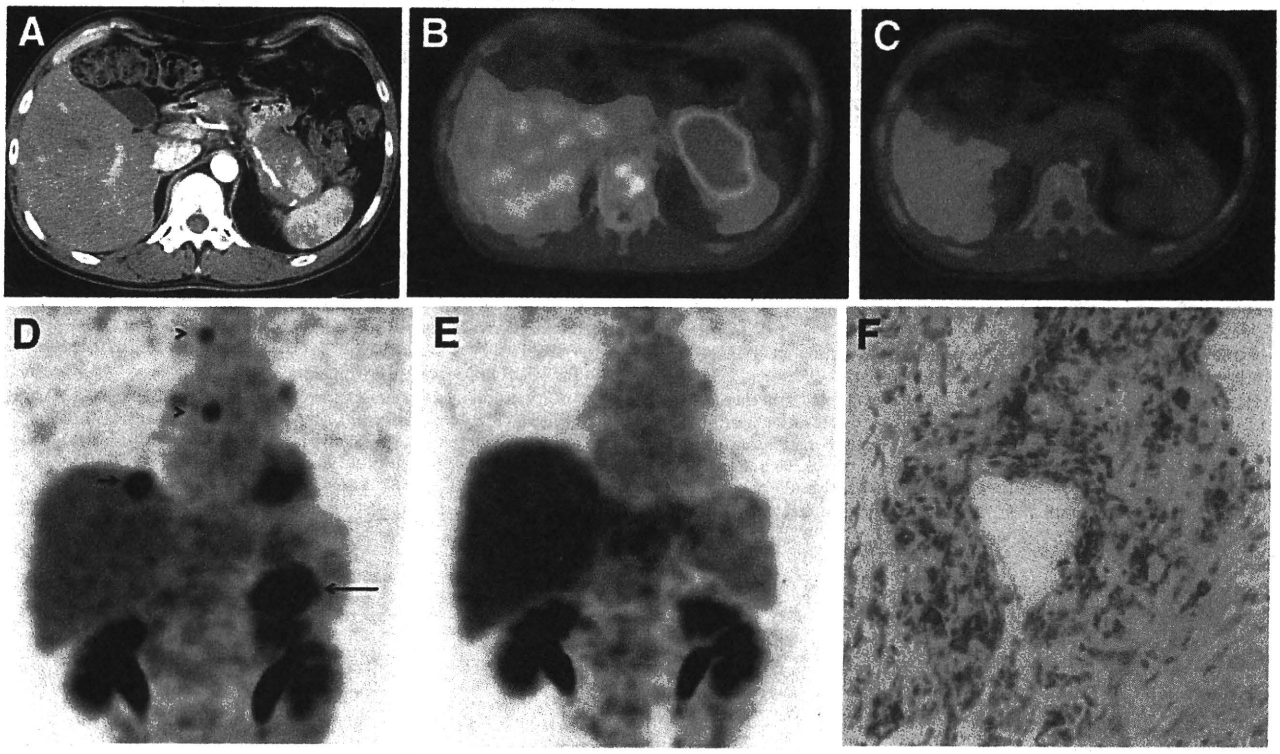

A 45-year-old man with a history of excessive alcohol consumption visited a general practitioner due to sudden severe abdominal and back pain. Moderately elevated serum amylase indicated acute pancreatitis. Although the symptoms were relieved by conservative medical management within a few days, he was referred to our hospital because a computerized tomography (CT) scan revealed a mass in the pancreatic tail. A detailed CT scan showed an enlarged pancreas with encasement of the splenic artery, obstruction of the splenic vein, a growth that had invaded the retroperitoneum (Figure *A*), a hepatic mass of 2 cm, and parabronchial lymphadenopathy. The main pancreatic duct was not detected in the pancreatic tail on magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP) failed. The pancreatic and hepatic lesions appeared as high-intensity areas on diffusion-weighted magnetic resonance imaging (MRI). Positron emission tomography (PET) scans also revealed intense fluorodeoxyglucose (FDG) uptake in the pancreatic (Figure *B* and Figure *D*, *long arrow*) and hepatic lesions (Figure *D*, *short arrow*), as well as in the parabronchial and mediastinal lymph nodes (Figure *D*, *arrowheads*). The imaging findings indicated advanced pancreatic cancer with hepatic and extensive lymph node metastases, but laboratory findings, including tumor markers such as CA19.9 and CEA, and serum IgG4 levels were normal. However, because the enhancement was delayed in the enlarged pancreas, we performed endoscopic ultrasonography (EUS)-guided fine needle aspiration before administrating chemotherapy. Histological examination of the obtained pancreatic tissue revealed dense fibrosis with abundant infiltration of lymphocytes and IgG4-positive cells, but no cancer cells (Figure *F*). Steroid therapy with oral

Conflicts of interest

The authors disclose no conflicts.

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prednisolone (30 mg/day) was started considering a diagnosis of autoimmune pancreatitis with extensive extrapancreatic lesions. Two months later, FDG uptake had vanished on FDG-PET scan (Figure *C* and Figure *E*).

Autoimmune pancreatitis is a recently recognized type of pancreatic disease that has received considerable focus worldwide. Because pancreatic masses can form in autoimmune pancreatitis, it is sometimes difficult to differentiate it from pancreatic cancer.[1] FDG-PET is a valuable tool for diagnosing several types of malignancies. The uptake of FDG occurs in autoimmune pancreatitis as well as in pancreatic cancer because it results from increased glucose utilization caused by both tumor cells and inflammation.[2] However, because autoimmune pancreatitis is frequently associated with various extrapancreatic lesions that also accumulate FDG, FDG-PET can be a useful tool to discriminate autoimmune pancreatitis from pancreatic cancer.[3] Furthermore, the disappearance of abnormal FDG uptake after steroid therapy can confirm a diagnosis and potentially assess the disease activity of autoimmune pancreatitis.

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Original Paper

FDG–PET/CT Findings of Autoimmune Pancreatitis

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ABSTRACT

Background/Aims: This study aimed to evaluate the clinical utility in Fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) in the management of patients with autoimmune pancreatitis (AIP), with special emphasis on differentiating AIP from pancreatic cancer (PC).

Methodology: FDG-PET/CT findings of 10 AIP patients were compared with those of 14 PC patients.

Results: There were no significant differences between AIP and PC in early and delayed maximum standardized uptake value (SUVmax), and in the ratio of delayed to early SUVmax. Abnormal extrapancreatic FDG uptake was observed in 5 AIP patients, in the hilar lymph nodes (n=4), mediastinal lymph nodes (n=2), abdominal lymph nodes (n=2), and bilateral salivary glands (n=2). After steroid therapy, the abnormal FDG uptake in the pancreas disappeared almost completely in two patients, and the FDG uptake in the hilar, mediastinal and abdominal lymph nodes decreased in one patient.

Conclusions: FDG-PET/CT may be helpful to differentiate AIP from PC by assessing FDG-uptake patterns in the pancreas and extrapancreatic lesions, it may have the potential to assess the disease activity of AIP and its extrapancreatic lesions, and it may be useful as a monitoring marker for tapering or stopping steroid therapy.

KEY WORDS: Autoimmune pancreatitis; FDG–PET; Pancreatic cancer; CT; Steroid

ABBREVIATIONS: Fluorodeoxyglucose (FDG); Positron Emission Tomography (PET); Computed Tomography (CT); Autoimmune Pancreatitis (AIP); Pancreatic Cancer (PC); Region Of Interest (ROI); Endoscopic Ultrasonography; Guided– Fine Needle Aspiration (EUS–FNA); Maximum Standardized Uptake Value (SUVmax); Maximum Intensity Projection (MIP)

INTRODUCTION

Autoimmune pancreatitis (AIP) is a recently described clinical entity in which the pathogenesis may involve autoimmune mechanisms. AIP is characterized radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct, and it is sometimes associated with various extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, and lymphadenopathy. Steroid therapy is dramatically effective for treating both the pancreas and the extrapancreatic lesions; therefore, to avoid unnecessary surgery, an accurate diagnosis of AIP is required. The most important disease that should be differentiated from AIP is pancreatic cancer (PC) (1,2).

Positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose (FDG) is a valuable tool for diagnosis and staging of several types of malignancies. However, since FDG uptake is caused by increased glucose utilization of tumor cells and is also observed at sites of inflammation or infection, the phenomenon is not specific to tumors (3,4). FDG-PET/CT allows fusion of structural and attenuation information provided by computed tomography (CT) with functional imaging derived from FDG-PET, improving the radiologic assessment of normal anatomic structures and pathologic lesions. FDG-PET/CT allows accurate location of hypermetabolic foci identified at FDG-PET with its morphologic structure on CT (5). Since it has been reported that FDG-PET revealed abnormal diffuse accumulation of radioactivity in the pancreas of AIP, the FDG-PET findings of several AIP cases have been reported (6-10). However, there are few systematic studies of AIP patients (9,10). The clinical utility of FDG-PET/CT for differentiating AIP from PC was investigated.

METHODOLOGY

Between April 2006 and January 2009, 10 AIP patients (8 males and 2 females, average age 64.5 years) underwent FDG-PET/CT. The diagnosis of AIP was based on the revised clinical diagnostic criteria of AIP 2006 (11). All patients showed pancreatic enlargement and irregular narrowing of the main pancreatic duct. Pancreatic changes were diffuse (n=2) or segmental in the pancreatic head (n=3), pancreatic body and tail (n=4) and pancreatic tail (n=1). Stenosis of the lower bile duct was detected in 5 patients. Serum IgG4 levels were elevated in 8 patients. The histological findings of the specimens obtained from the pancreas of 4 patients by endoscopic ultrasonography guided- fine needle aspiration (EUS-FNA) were compatible with lymphoplasmacytic sclerosing pancreatitis. Five pa-

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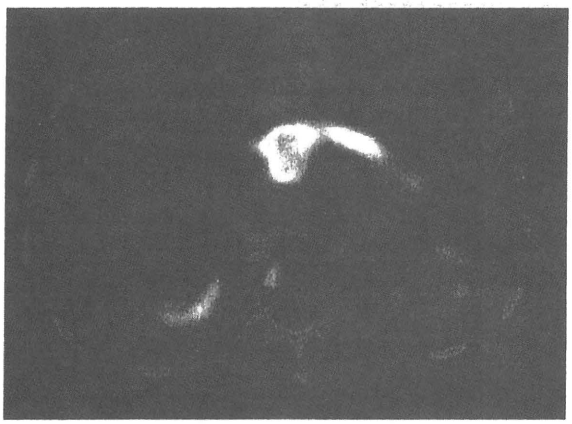

FIGURE 1
FDG–PET/CT image of an AIP patient (Case 1) showing wide pathologic uptake of FDG in the pancreas.

tients were given steroid therapy, and all of them responded well clinically and radiologically. Two AIP patients also underwent follow-up FDG-PET/CT 5 months and 11 months after starting steroid therapy, respectively. During the same period, 14 patients (9 males and 5 females, average age 59.6 years) with histologically confirmed PC underwent FDG-PET/CT.

The FDG-PET/CT scan was performed with an Aquiduo machine (Toshiba, Tokyo, Japan). CT scans for attenuation correction and anatomic co-registration were obtained under expiratory breath-holding. No oral contrast media were used. After CT scanning, PET emission data were obtained in 3D mode for 2 min in each bed position, for a total of 14-18 minutes.

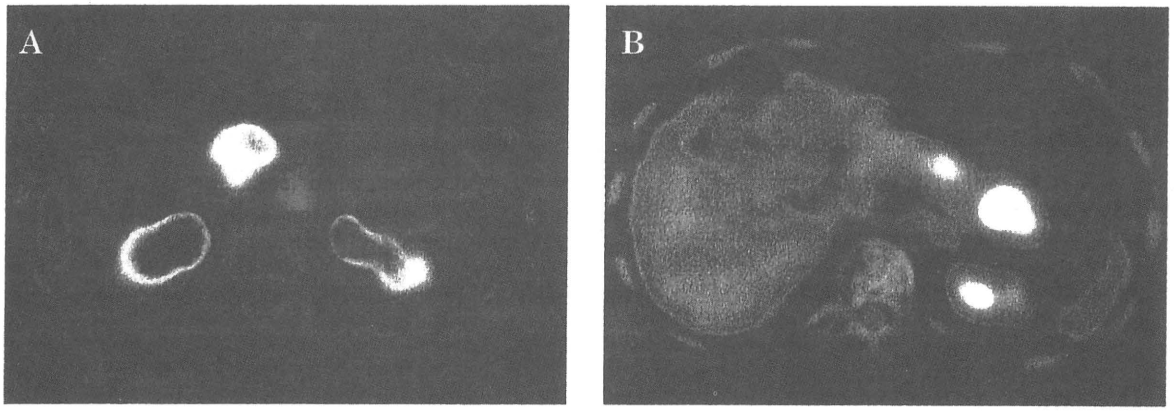

FIGURE 2
FDG–PET/CT image of an AIP patient (Case 2) showing skipped pathologic uptake of FDG in the head (**A**) and tail (**B**) of the pancreas.

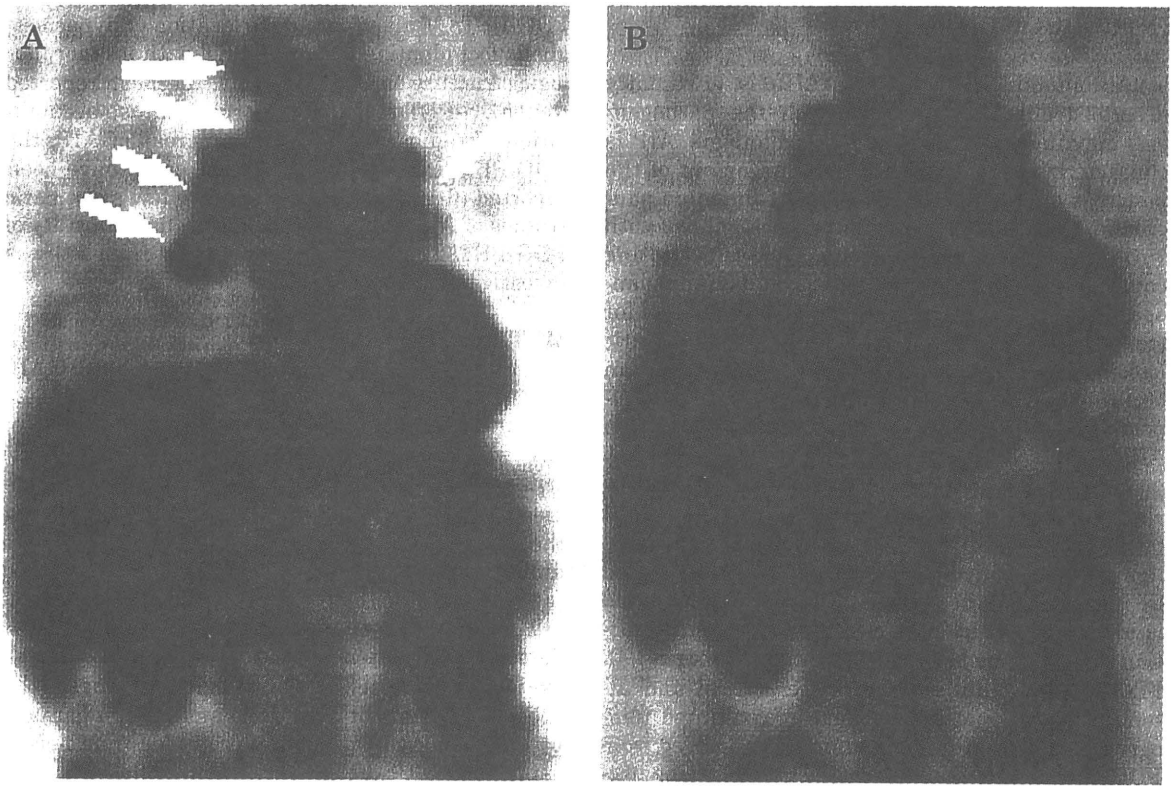

FIGURE 3
Whole–body FDG PET coronal maximum in–tensity projection (MIP) image of an AIP patient (Case 1) showing pathologic FDG uptake in the hilar, mediastinal, and abdominal lymph nodes (arrows) as well as in the pancreas (**A**). After steroid therapy, the pathologic uptake decreased (**B**).

After at least 4 h of fasting, the patient was injected with 3.7 MBq/kg of F-18 FDG intravenously. Oral hydration and bladder emptying were done before collecting the PET/CT data. An early whole-body scan was performed in all patients 60 min after FDG injection, with additional delayed scan of the upper abdomen at 120 min after injection. The plasma glucose level before PET imaging was less than 150 mg/dl in all patients.

FDG uptake was first evaluated visually. A region of interest (ROI) was placed over the entire area of any abnormal FDG uptake. SUVmax (maximum ROI activity/injected dose/body weight) was then computed at the early and delayed periods.

Statistical analysis

Statistical analysis was performed using Mann-Whitney test. A level of $p<0.05$ was accepted as statistically significant. All patients provided their written informed consent for these tests.

RESULTS

FDG uptake was observed in the pancreas of all AIP and PC patients. There were no significant differences between AIP and PC in early SUVmax (3.5±0.9 (mean±SD), range 2.2-5.2 vs. 4.8±1.9, range 2.7-8.8), delayed SUVmax (4.2±1.3, range 2.2-5.4 vs. 5.5±2.3, range 3.1-10.2), and the ratio of delayed to early SUVmax (1.1±0.1, range 0.8-1.3 vs. 1.1±0.9, range 0-1.3). However, the highest early SUVmax was 5.2 in AIP cases, and 5 PC cases had SUVmax values greater than 5.2. The SUVmax decreased with time in 2 AIP patients, but in no PC patients. The uptake area in the pancreas was wide in 4 AIP patients, with diffuse change (**Figure 1**) or segmental change in the pancreatic body and tail. Skipped uptake in the pancreas was detected only in 2 AIP patients (**Figure 2A and B**) (**Table 1**).

Abnormal extrapancreatic FDG uptake was observed in 5 AIP patients, in the hilar lymph nodes (n=4), mediastinal lymph nodes (n=2), abdominal lymph nodes (n=2) (**Figure 3A**), and bilateral swollen salivary glands (n=2) (**Figure 4**). Three PC patients showed abnormal extrapancreatic FDG uptake in the abdominal lymph nodes.

After steroid therapy, the abnormal FDG uptake in the pancreas disappeared almost completely in two patients, and the FDG uptake in the hilar, mediastinal and abdominal lymph nodes decreased in one patient (**Figure 3B**). SUVmax in the pancreas was decreased after steroid therapy.

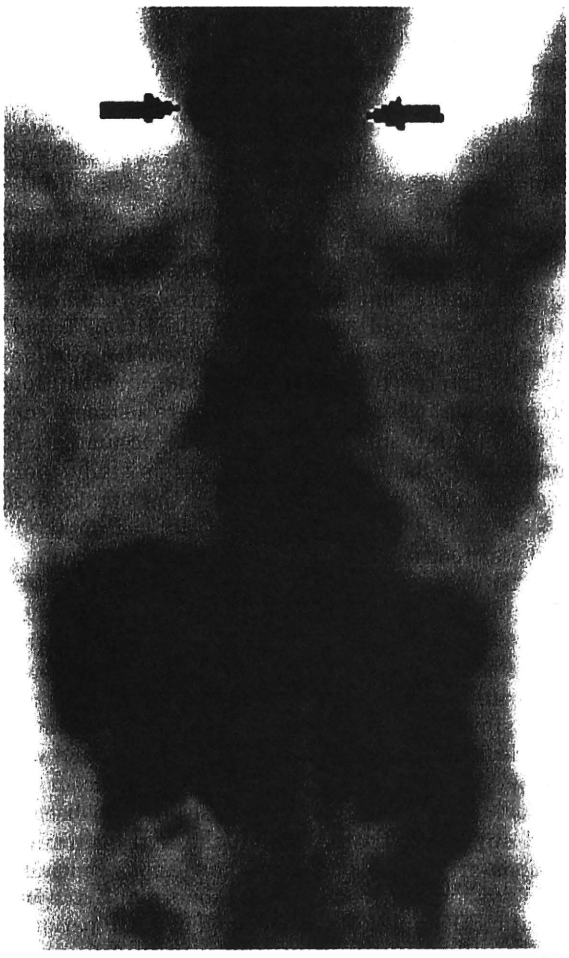

FIGURE 4
Whole-body FDG PET coronal MIP image of an AIP patient (Case 2) showing pathologic FDG uptake in the bilateral submandibular glands (arrows) and hilar lymph nodes as well as in the pancreas.

TABLE 1 PET Findings of Patients with Autoimmune Pancreatitis

Case	Swelling of the pancreas	Uptake pattern	SUVmax Early	SUVmax Delay	SUVmax* Early	SUVmax* Delay
1	diffuse	diffuse	4.2	5.0 (1.19)	2.0	1.7 (0.85)
2	diffuse	skipped	3.9	4.8 (1.21)		
3	head	segmental	3.3	4.3 (1.30)		
4	head	segmental	2.8	3.1 (1.10)	2.1	1.9 (0.90)
5	head	segmental	2.7	2.2 (0.81)		
6	body, tail	diffuse	3.4	4.2 (1.23)		
7	body, tail	skipped	2.6	3.1 (1.19)		
8	body, tail	segmental	4.4	5.4 (1.22)		
9	body, tail	segmental	2.2	2.4 (1.09)		
10	tail	segmental	5.2	5.1 (0.98)		

( ): the ratio of delayed SUVmax to early SUVmax
*: after steroid therapy

DISCUSSION

Since AIP responds dramatically to steroid therapy, an accurate diagnosis of AIP is required. However, it is sometimes difficult to differentiate AIP from PC. As it is usually difficult to take adequate specimens from the pancreas, AIP is currently diagnosed based on a combination of clinical, laboratory, and imaging studies (1,11). FDG-PET/CT is a sensitive modality for the diagnosis of malignancies. Since FDG uptake is caused by increased glucose utilization of tumor cells and is also observed at inflammatory sites (3,4), FDG uptake is observed in AIP as well as in PC. This study aimed to evaluate the clinical utility of FDG-PET/CT for the management of AIP patients, with special emphasis on differentiating AIP from PC.

It has been reported that the sensitivity of FDG uptake was 83% (6)-100% (10) in AIP and 73% (10)-

96% (12) in PC, but FDG uptake was observed in all AIP and PC patients in the present study. Similar to the report by Ozaki *et al.* (10), there were no significant differences between AIP and PC in SUVmax and the ratio of delayed to early SUVmax. However, the highest early SUVmax was 5.2 in AIP cases, SUVmax was greater than 5.2 in 5 PC cases, and the SUVmax decreased with time only in 2 AIP cases. An early SUVmax greater than 5.2 suggests that PC is more likely, while SUVmax that decreases with time suggests that AIP is more likely. Ozaki *et al.* (10) also reported that the typical FDG-PET findings for AIP are an irregular contour, longitudinal shape, heterogeneous accumulation, and multiple localization, whereas those for PC are a smooth contour, nodular shape, homogeneous accumulation, and solitary localization. In the present study, there was no difference in contour, but the uptake area was wide in 4 AIP patients, and skipped uptake in the pancreas was detected only in 2 AIP patients.

AIP is sometimes associated with various extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, and lymphadenopathy. Since the histopathological findings, such as abundant infiltration of IgG4-positive plasma cells, are very similar in the pancreas and in the extrapancreatic lesions of AIP patients, and they respond well to steroid therapy, we proposed a new clinicopathological entity of IgG4-related sclerosing disease, and suggested that AIP and the extrapancreatic lesions are pancreatic and other lesions reflecting this systemic disease (1,13). Abnormal extrapancreatic FDG uptake was observed in 5 AIP patients, including the hilar lymph nodes, mediastinal lymph nodes, abdominal lymph node, and salivary glands. FDG-PET can easily show all of the active inflammatory sites throughout the entire body at once in patients with IgG4-related systemic disease. Although stenosis of the bile duct due to sclerosing cholangitis is the most frequent extrapancreatic lesion of AIP (1,14), FDG-PET/CT did not show FDG uptake in the stenotic bile duct of 5 AIP patients. This might be due to the fact that the lesion was too small to depict FDG-PET/CT.

After steroid therapy, the abnormal FDG uptake in the pancreas and the hilar, mediastinal, and abdominal lymph nodes disappeared almost completely. For tapering or stopping steroid therapy, there is currently no optimal marker. FDG-PET/CT appears to have the potential to assess the disease activity of AIP and its extrapancreatic lesions, and it may provide a useful monitoring marker for tapering or stopping steroid therapy.

In conclusion, FDG-PET/CT may be helpful to differentiate AIP from PC by assessing FDG-uptake patterns in the pancreas and extrapancreatic lesions, it may have the potential to assess the disease activity of AIP and its extrapancreatic lesions, and it may be useful as a monitoring marker for tapering or stopping steroid therapy.

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GUIDELINES FOR CLINICAL PRACTICE

Endoscopic approach for diagnosing autoimmune pancreatitis

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Abstract

It is of utmost importance to differentiate autoimmune pancreatitis (AIP) from pancreatic cancer (PC). Segmental AIP cases are sometimes difficult to differentiate from PC. On endoscopic retrograde cholangio pancreatography, long or skipped irregular narrowing of the main pancreatic duct (MPD), less upstream dilatation of the distal MPD, side branches derived from the narrowed portion of the MPD, absence of obstruction of the MPD, and stenosis of the intrahepatic bile duct suggest AIP rather than PC. Abundant infiltration of IgG4-positive plasma cells is frequently and rather specifically detected in the major duodenal papilla of AIP patients. IgG4-immunostaining of biopsy specimens obtained from the major duodenal papilla is useful for supporting a diagnosis of AIP with pancreatic head involvement. On endoscopic ultrasonography (EUS), hyperechoic spots in the hypoechoic mass and the duct-penetrating sign suggest AIP rather than PC. EUS and intraductal ultrasonography sometimes show wall thickening of the common bile duct even in the segment in which abnormalities are not clearly observed with cholangiography in AIP patients. EUS-guided fine needle aspiration, especially EUS-guided Tru-Cut biopsy, is useful to diagnose AIP, as well as to exclude PC.

Key words: Autoimmune pancreatitis; Pancreatic cancer; Endoscopic retrograde cholangiopancreatography; Endoscopic ultrasonography-Fine needle aspiration; IgG4

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INTRODUCTION

Autoimmune pancreatitis (AIP) is a recently identified clinical entity of pancreatitis in which it is suspected that autoimmune mechanisms are involved in the pathogenesis. AIP is characterized clinically by elderly male preponderance, frequent initial symptom of obstructive jaundice without pain, occasional association with impaired pancreatic endocrine or exocrine function, various extrapancreatic lesions, and a favorable response to steroid therapy. AIP is characterized radiologically by irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas; and serologically by elevation of serum IgG, or IgG4 levels, and the presence of some autoantibodies. Histopathological characteristics are dense lymphoplasmacytic infiltration with fibrosis and obliterative phlebitis in the pancreas[1-3]. Since there is currently no diagnostic serological marker, and as it is usually difficult to take adequate specimens from the pancreas, AIP is currently diagnosed based on a combination of clinical, laboratory, and imaging studies[4-6]. In 2006, the Japan Pancreas Society proposed the "Clinical

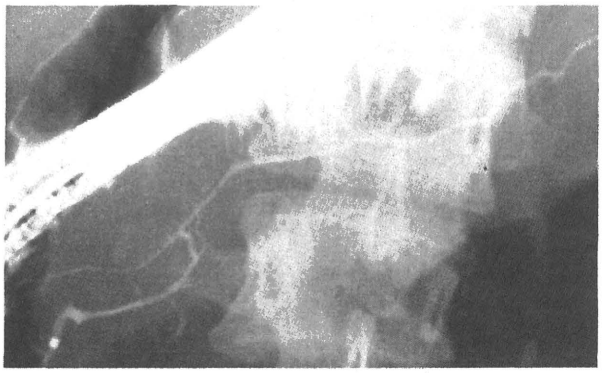

Figure 1 Diffuse irregular narrowing of the main pancreatic duct of an AIP patient on ERP.

Diagnostic Criteria for Autoimmune Pancreatitis"[4]. It contained three items: (1) radiological imaging showing diffuse or localized enlargement of the pancreas and diffuse or segmental irregular narrowing of the MPD; (2) laboratory data showing abnormally elevated levels of serum gammaglobulin, IgG or IgG4, or the presence of autoantibodies; and (3) histological findings showing marked interlobular fibrosis and prominent lymphoplasmacytic infiltration in the pancreas. To make the diagnosis of AIP, criterion 1 is mandatory, and either criterion 2 or criterion 3 must be present.

AIP responds dramatically to steroid therapy and therefore to avoid unnecessary surgery, an accurate diagnosis of AIP is required. The most important disease that should be differentiated from AIP is pancreatic cancer (PC)[1-3,7]. Serum IgG4 levels are elevated most frequently in AIP patients. However, the sensitivity of elevated serum IgG4 levels in AIP patients is reported to be 73%-80%[8,9], and elevation of serum IgG4 level is detected in some cases of PC[10,11]. In particular, AIP forming a mass-like lesion in the head of the pancreas is sometimes difficult to differentiate from locally advanced pancreatic head cancer. Based on our experience with 50 cases of AIP, this review focuses on the endoscopic approach for diagnosing AIP, with special emphasis on differentiating AIP from PC.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Diffuse irregular narrowing of the MPD on endoscopic retrograde cholangiopancreatography (ERCP) is one of the radiological features rather specific to AIP (Figure 1). PC rarely shows this pancreatogram. However, some AIP patients show segmental narrowing of the MPD (Figure 2A), which is rather difficult to differentiate from stenosis of the MPD in PC. In our series[12], the length of the narrowed portion of the MPD on endoscopic retrograde pancreatography (ERP) was 6.7 ± 3.2 (mean ± SD) cm in AIP patients, which was significantly longer than in PC patients (2.6 ± 0.8 cm; $P < 0.001$). The length of the narrowed portion of the MPD on ERP was longer than 3 cm in 76% of AIP patients, which was significantly

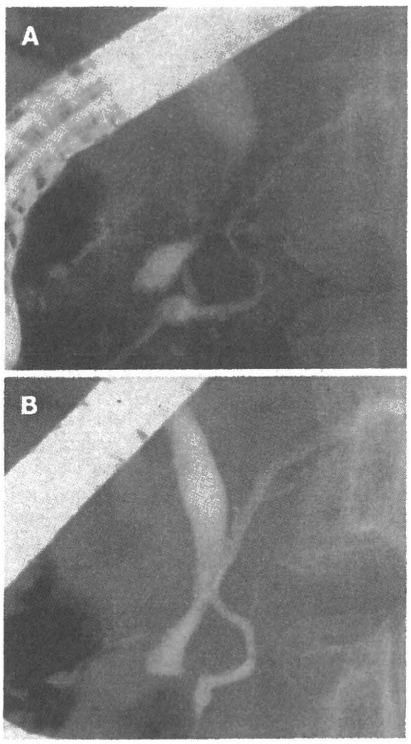

Figure 2 ERCP findings of an AIP patient. A: Segmental narrowing of the main pancreatic duct and stenosis of the lower bile duct before steroid therapy; B: After steroid therapy, stenosis of the main pancreatic duct and bile duct is improved.

higher than in PC patients (20%; $P < 0.001$). In AIP patients, the degree of narrowing of the MPD varied in the same patient, and skipped, narrowed lesions of the MPD were detected in 35% of our AIP patients, but in none of our PC patients ($P < 0.001$). In AIP patients with segmental narrowing of the MPD, upstream dilatation of the distal MPD was less often noted than in PC. The maximal diameter of the upstream MPD on ERP was 2.9 ± 0.7 mm in segmental AIP patients, which was significantly smaller than in pancreatic head cancer patients (7.1 ± 1.9 mm; $P < 0.001$). The maximal diameter of the upstream MPD was smaller than 5 mm in 94% of segmental AIP patients, significantly higher than in PC patients (18%; $P < 0.001$). Side branches were more frequently derived from the narrowed portion of the MPD in AIP patients (65%) than in PC patients (25%; $P < 0.036$). Obstruction of the MPD was detected more often in PC patients (60%) than in AIP patients (6%; $P < 0.001$).

On endoscopic retrograde cholangiography, stenosis of the lower bile duct was detected frequently in both AIP and PC patients (Figure 2A). Brushing cytology of the stenotic biliary lesion and cytology of the bile via an endoscopic nasobiliary drainage tube inserted to manage jaundice, are useful to differentiate AIP from pancreatic or biliary cancer. Stenosis of the intrahepatic bile duct was detected in a few AIP patients, but it was not detected in PC patients. When AIP patients develop stenosis in the intrahepatic bile duct, the cholangiographic appearance is similar to that of primary sclerosing cholangitis

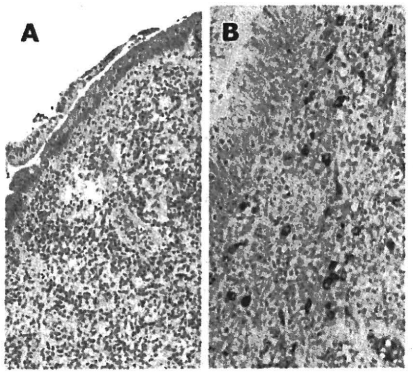

Figure 3 Immunohistochemistry of biopsy specimen taken from the major duodenal papilla of an AIP patient. A: HE staining showing significant lymphoplasmacytic infiltration; B: IgG4 immunostaining showing significant infiltration of IgG4-positive plasma cells (10 ≥ 10/HPF).

(PSC)[13,14]. A long stricture was detected in the hepatic hilar region in AIP patients involving the intrahepatic bile ducts, but the diffusely distributed, beaded and pruned-tree appearance, that is usually detected in PSC patients was not detected in AIP patients[12,13]. Stenosis of the hilar bile duct in AIP patients should be also differentiated from cholangiocarcinoma at the hepatic hilus, these diseases can be differentiated by the absence of the pancreatic abnormalities in patients with cholangiocarcinoma at the hepatic hilus.

Both pancreatic and biliary lesions improve 2-4 wk after starting oral steroid therapy (initial prednisolone dose: 30 mg/d) (Figure 2B). A poor response to steroid therapy should raise the possibility of PC and the need for re-evaluation of the diagnosis.

ENDOSCOPIC OBSERVATION AND BIOPSY OF THE MAJOR DUODENAL PAPILLA

The major duodenal papilla is sometimes swollen in AIP patients[15]. In our series, swelling of the major duodenal papilla was detected endoscopically in 24% (12/50) of AIP patients. Histologically, dense lymphoplasmacytic infiltration and fibrosis is detected in the swollen major duodenal papilla (Figure 3A), similar to that seen in the pancreas of AIP patients. Furthermore, abundant infiltration of IgG4-positive plasma cells in the papilla is frequently and specifically detected in AIP patients. In our study of IgG4-immunostaining in biopsy specimens from the major duodenal papilla[16,17], severe infiltration of IgG4-positive plasma cells [≥ 10/HPF (high power field)] was observed in the major duodenal papilla of all 8 AIP patients with pancreatic head involvement (Figure 3B). Moderate infiltration of IgG4-positive plasma cells (9-4/HPF) was detected in 1 patient with pancreatic head cancer, but there were also rare (≤ 3/HPF) IgG4-positive plasma cells infiltrating the major duodenal papilla in 2 AIP patients who only had pancreatic body and/or tail involvement, in 9 patients

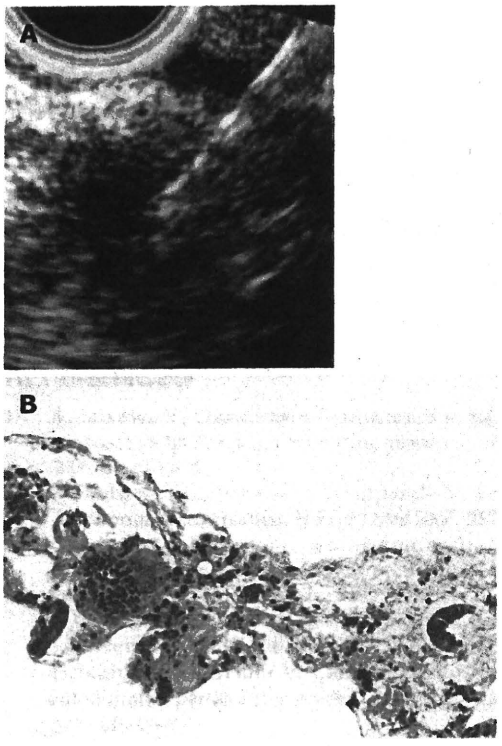

Figure 4 A hypoechoic mass in an AIP patient. A: Endoscopic ultrasonography finding. EUS-FNA was performed to this mass lesion; B: Histology of the specimen gained by EUS-FNA (HE).

with pancreatic cancer, and in 10 patients with papillitis. IgG4-immunostaining of biopsy specimens obtained from the major duodenal papilla is useful for supporting a diagnosis of AIP with pancreatic head involvement. After steroid therapy, the swollen major duodenal papilla decreases on endoscopy, and the number of IgG4-positive plasma cells in repeat biopsy specimens from the major duodenal papilla decreases.

ENDOSCOPIC ULTRASONOGRAPHY AND INTRADUCTAL ULTRASONOGRAPHY

Endoscopic ultrasonography (EUS) imaging of AIP shows hypoechoic enlargement of the pancreas with hypoechoic spots. A lobular outer gland margin of the pancreas or a hyperechoic pancreatic ductal margin, which is frequently detected in alcoholic chronic pancreatitis, is rarely observed in AIP patients. A hypoechoic mass lesion detected in segmental AIP patients is difficult to differentiate from PC (Figure 4A). Hyperechoic spots in a hypoechoic mass and the duct-penetrating sign suggest AIP rather than PC. Hyperechoic spots may correspond to compressed pancreatic ducts. The lower bile duct, corresponding to the stenotic portion on ERCP, shows marked wall thickening with a smooth configuration of the outermost layer on EUS and intraductal ultrasonography (IDUS)[18]. This finding suggests that the bile duct wall thickening itself causes the biliary stenosis, and that it is not caused by extrinsic compression from inflamma-

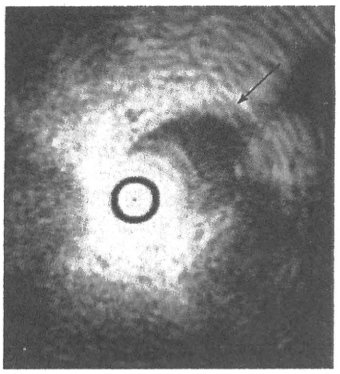

Figure 5 Intraductal ultrasonography finding of an AIP patient showing wall thickening of the common bile duct without stenosis (arrow).

tory pancreatic tissue in AIP. EUS and IDUS sometimes show wall thickening of the common bile duct even in the segment in which abnormalities are not clearly observed on cholangiography in AIP patients (Figure 5)[19].

ENDOSCOPIC ULTRASONOGRAPHY-GUIDED FINE NEEDLE ASPIRATION AND ENDOSCOPIC ULTRASONOGRAPHY-GUIDED TRU-CUT BIOPSY

Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) can be safely performed at the same time as diagnostic EUS, and it will become an established technique to evaluate pancreatic masses. In segmental AIP cases, EUS-FNA is useful to exclude the possibility of PC. The presence of cellular stromal fragments with prominent lymphocytosis either within the stroma or in the background can support a clinical diagnosis of AIP (Figure 4B)[20]. Furthermore, the presence of many IgG4-positive plasma cells in the aspirated specimen examined by IgG4-immunostaining provides more support for the diagnosis of AIP. However, cytological examination of EUS-FNA specimens is sometimes insufficient for diagnosing AIP due to the small sample and lack of tissue architecture. To overcome the limitations of needles which only allow cytological review, large caliber cutting biopsy needles have been developed that acquire samples in which tissue architecture can be assessed and histological examination performed. Endoscopic ultrasonography-guided Tru-Cut biopsy (EUS-TCB) acquires core specimens that preserve tissue architecture and permit histological review and diagnosis of AIP. Histological features vary, but the most common finding is fibrosis and an intense inflammatory cell infiltrate comprised mostly of lymphocytes and plasma cells, usually surrounding medium- and large-sized interlobular ducts accompanied by an obliterative phlebitis predominantly involving venules. According to a Mayo Clinic study, TCB specimens were considered diagnostic or strongly suggestive in 12/14 AIP patients[21].

CONCLUSION

It is most important to differentiate AIP from PC. Long or skipped narrowed portions with side branches of the main pancreatic duct without upstream dilatation, and stenosis of the intrahepatic bile duct on ERCP suggest AIP rather than PC. IgG4-immunostaining of biopsy specimens obtained from the major duodenal papilla is useful for supporting a diagnosis of AIP with pancreatic head involvement. On EUS, hyperechoic spots in a hypoechoic mass and the duct-penetrating sign suggest AIP rather than PC. EUS-FNA, especially EUS-TCB, is useful to diagnose AIP, as well as to exclude PC.

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Autoimmune pancreatitis -diagnosis and treatment-

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Abstract

Autoimmune pancreatitis (AIP) is a newly described entity with characteristic clinical, radiological, serological, and histological features, in which autoimmune mechanisms seem to be involved in pathogenesis. As AIP responds dramatically to steroid therapy, accurate diagnosis of AIP is necessary to avoid unnecessary laparotomy or pancreatic resection. It is importance to misdiagnose pancreatic cancer as AIP as well as to misdiagnose AIP as pancreatic cancer. In the absence of a diagnostic serological marker for AIP, its diagnosis rests on identifying unique patterns of abnormalities. Japanese criteria are based on the minimum consensus features of AIP and aim to avoid misdiagnosis of malignancy. They contain 3 items: (1) enlargement of the pancreas and narrowing of the main pancreatic duct; (2) high serum gammaglobulin, IgG, or IgG4, or the presence of autoantibodies; (3) histological findings of lymphoplasmacytic infiltration and fibrosis in the pancreas. For diagnosing AIP,

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the presence of the imaging criterion is essential. Other clinical characteristics of AIP are elderly male preponderance, fluctuating obstructive jaundice without pain, occasional association with diabetes mellitus and extrapancreatic lesions, and favorite responsiveness to oral steroid therapy. Elevation of serum IgG4 levels and infiltration of abundant IgG4-positive plasma cells in various organs are rather specific in AIP patients. Oral steroid is the standard treatment for AIP.

Introduction

Autoimmune pancreatitis (AIP) is a newly described entity, in which autoimmune mechanisms seem to be involved in pathogenesis (1). Although AIP has become a distinct entity recognized worldwide, precise pathogenesis or pathophysiology remains unclear. AIP has many clinical, radiological, serological and histopathological characteristics. However, in the absence of a diagnostic serological marker for AIP, AIP should be diagnosed currently on the basis of combination with these unique patterns of abnormalities. It is uppermost importance to misdiagnose AIP as pancreatic cancer (2). AIP dramatically responds to oral prednisolone therapy (3). This review focuses on diagnosis and treatment of AIP, based on our experience of 60 AIP cases.

Clinical features of AIP

AIP is diagnosed more commonly in elderly males. The mean age of the patients is 66.4 years (range, 25-83 years) and the male-to-female ratio is 4.2:1 in our series. Typical presentation with severe abdominal pain and clinically acute pancreatitis is rarely seen. Obstructive jaundice due to associated sclerosing cholangitis occurs frequently. The jaundice sometimes fluctuates. Failure of pancreatic exocrine or endocrine function is frequently seen. Up to 50% of AIP patients present with glucose intolerance. The diagnoses of diabetes mellitus and AIP are made simultaneously in many cases, but some cases show exacerbation of preexisting diabetes mellitus with the onset of AIP (4).

AIP patients frequently have various extrapancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis and retroperitoneal fibrosis (5). Sclerosing cholangitis is most frequently associated with AIP. Stenosis of the lower bile duct is usually detected. When stenosis is found in the intrahepatic or the hilar hepatic bile duct, the cholangiographic appearance is very similar to that of primary sclerosing cholangitis (6). Swelling of the bilateral salivary glands was detected in 23% of AIP patients. Hydronephrosis due to retroperitoneal fibrosis was detected in 4 AIP patients. All these extrapancreatic lesions show similar histopathological findings to those in the

pancreas and also respond well to steroid therapy (4-7).

Diagnostic criteria of AIP

Japanese "Diagnostic Criteria for Autoimmune Pancreatitis" were revised in 2006 (8). They contain three items: (1) radiological imaging showing diffuse or localized enlargement of the pancreas and diffuse or segmental irregular narrowing of the main pancreatic duct; (2) laboratory data demonstrating high serum gammaglobulin, IgG, or IgG4 or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor; and (3) histological examination of the pancreas showing marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells. Diagnosis of AIP is established when criterion 1, together with either criterion 2 and/or criterion 3, are fulfilled. The presence of the imaging criterion is essential for diagnosing AIP. These criteria are based on the minimum consensus features of AIP to avoid a misdiagnosis pancreatic cancer as far as possible.

On ultrasonography (US), an enlarged hypoechoic pancreas is characteristically detected in AIP (**Fig. 1**). On dynamic computed tomography (CT), there is delayed enhancement of the enlarged pancreatic parenchyma. Typical AIP cases

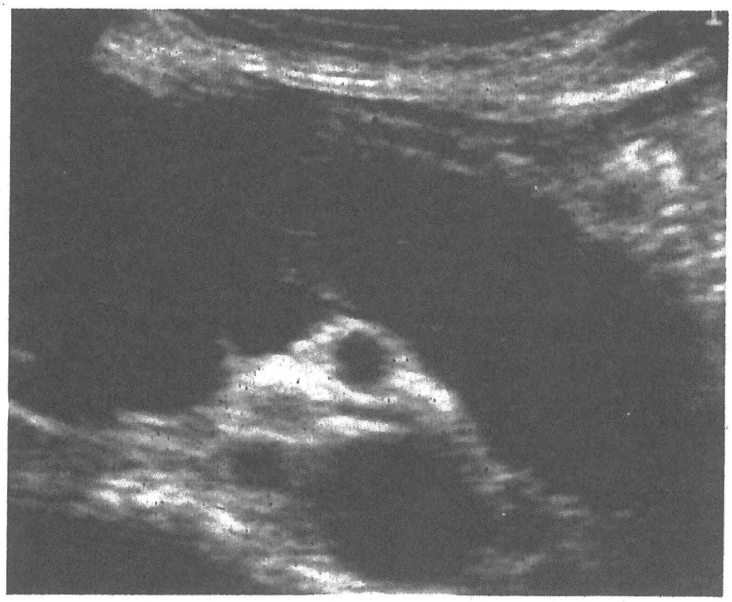

Fig. 1. Ultrasonography of a patient with autoimmune pancreatitis showing a diffusely enlarged hypoechoic pancreas.

show diffuse enlargement of the pancreas, the so-called sausage-like appearance. A capsule-like rim surrounding the pancreas, which appears as a low density on CT, is specifically detected in some cases. Pancreatic calcification or pseudocyst is rarely seen. Some cases show a focal enlargement of the pancreas, similar to that seen with pancreatic cancer. Endoscopic retrograde cholangiopancreatography (ERCP) discloses an irregular, narrow (<3 mm in diameter) main pancreatic duct (**Fig. 2**). In patients with segmental narrowing, absence of upstream dilatation of the main pancreatic duct is characteristic. Stenosis of the extrahepatic or intrahepatic bile duct is frequently observed. Marked wall thickening of the extrahepatic bile duct or gallbladder is sometimes detected on US or endoscopic ultrasonography (EUS). Magnetic resonance cholangiopancreatography does not adequately show the narrow portion of the main pancreatic duct, but it can adequately demonstrate stenosis of the bile duct with dilatation of the upper biliary tract.

Hypergammaglobulinemia (>2.0 g/dl), elevated serum IgG levels (>1800 mg/dl) and presence of autoantibodies including antinuclear antibody and rheumatoid factor are detected in about half of AIP patients, respectively. Serum IgG4 levels are rather significantly and specifically high (>135 mg/dl) in AIP patients. The sensitivity of elevated serum IgG4 levels is about 80% in our series. Elevation of serum IgG4 levels was reported

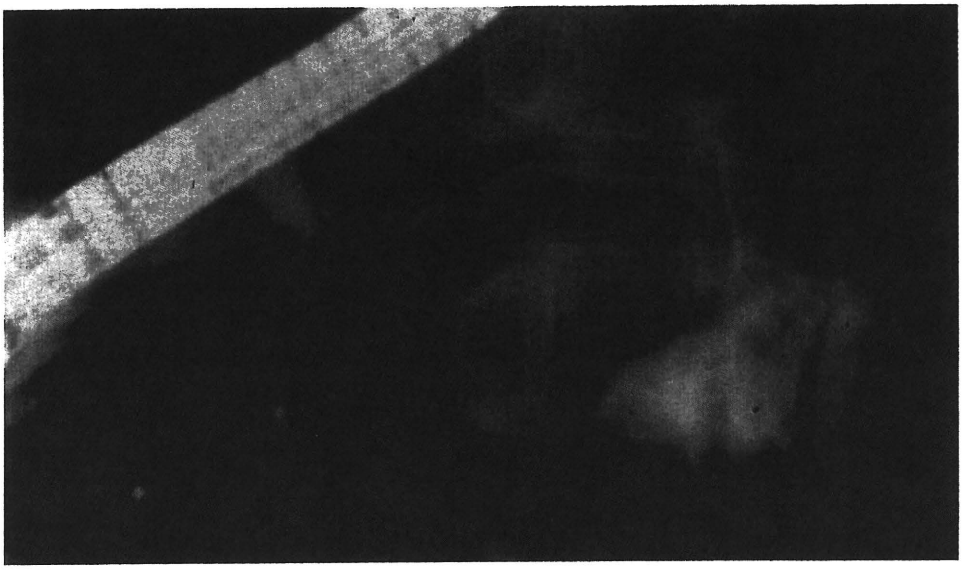

Fig. 2. : Endoscopic retrograde pancreatography showing diffuse irregular narrowing of the main pancreatic duct.

in a patient with pancreatic cancer (9).

The histological finding of AIP is characteristic, that is, dense lymphoplasmacytic infiltration with fibrosis of the pancreas. Pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration. Another characteristic histological finding is obliterative phlebitis involving minor and major veins, including the portal vein. Such an inflammatory process widely and intensely involves the contiguous soft tissue, peripancreatic retroperitoneal tissue, and the thickened wall of the bile duct and gallbladder (4,7,8).

Immunohistochemically, infiltrating inflammatory cells in the pancreas consist of CD4- or CD8-positive T lymphocytes and IgG4-positive plasma cells. Dense infiltration of IgG4-positive plasma cells in the pancreas is not observed in chronic alcoholic pancreatitis or pancreatic cancer. Infiltration of abundant IgG4-positive plasma cells is also detected in various organs such as peripancreatic retroperitoneal tissue, major duodenal papilla, biliary tract, intrahepatic periportal area, salivary glands, gastric mucosa, colonic mucosa, lymph nodes and bone marrow of AIP patients. We suggested that AIP might be a pancreatic lesion of IgG4-related systemic disease (4,8).

Strategy for differentiating between AIP and pancreatic cancer

To make an algorithm for clinical management of a mass-like lesion on pancreas head with special emphasis on differentiating between AIP and pancreatic cancer, we examined serological and radiological features of 17 AIP patients and 70 patients with pancreatic cancer (10). Based on these data, we chose the following six imaging findings suggesting AIP rather than pancreatic cancer, which can be objectively and accurately evaluated. They were enhancement of the enlarged pancreas on CT; a capsule-like rim on CT; narrowed portion of the main pancreatic duct ≥ 3-cm-long on ERP; skipped lesions of the main pancreatic duct on ERP; a maximal diameter of < 5 mm of the upstream main pancreatic duct on ERP; and the presence of extrapancreatic lesions, such as salivary gland swelling, retroperitoneal mass, and stenosis of the intrahepatic bile duct on CT or ERC. MRCP can also be used to examine the presence of these findings assessed on ERP or ERC.

Many cases with a mass-like lesion on pancreas head present with obstructive jaundice; endoscopic or percutaneous trashepatic biliary drainage is usually done initially. At that time, cytological examination of the bile or pancreatic duct should be performed as soon as possible to confirm

or rule out malignancy. In cases with no positive imaging factors for AIP, surgery should be considered under the provisional diagnosis of pancreatic cancer. When there is at least 1 positive imaging factor for AIP, serum IgG4 levels should be measured. When serum IgG4 levels are elevated (more than 135 mg/dl), in cases with more than 2 positive imaging factors, indication of steroid therapy should be considered under the provisional diagnosis of AIP, while in cases with 1 positive imaging factor, biopsy guided by ultrasound or EUS- guided fine needle aspiration (EUS-FNA) should be done for histological examination. Indication of steroid therapy should be considered under the provisional diagnosis of AIP in patients without evidence of cancer on histological examination, while those who are cancer-positive should have surgery. In patients with normal serum IgG4 levels who have more than 3 positive imaging factors, indication of

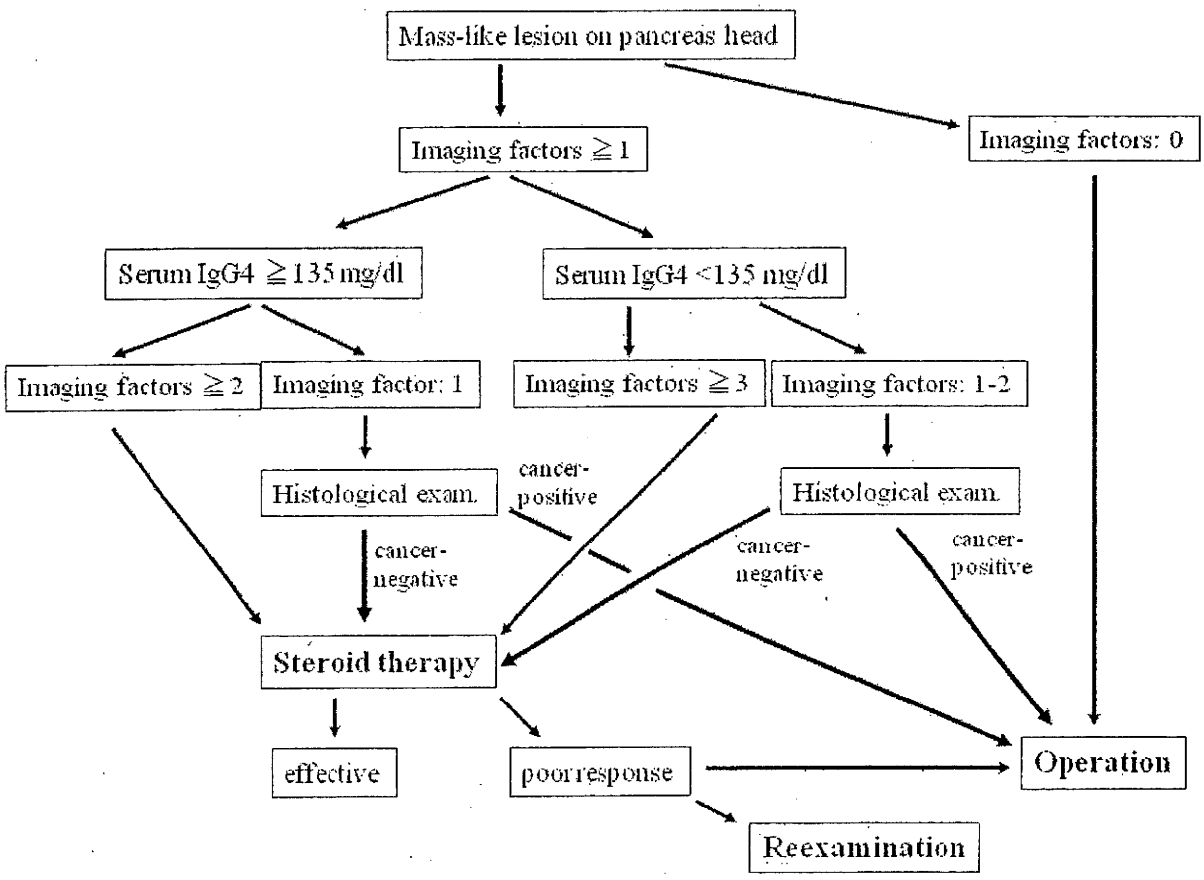

Fig. 3. : An algorithm for management of a mass-like lesion on pancreatic head, with special emphasis on differentiating between autoimmune pancreatitis and pancreatic cancer (10).

steroid therapy should be considered, while cases with 1 or 2 positive imaging factors should be biopsied for histological examination. Since AIP responds so readily to steroid therapy, a poor response to steroid therapy suggests pancreatic cancer and the need for further reexamination, including laparotomy (Figure 3) (10).

Treatment and prognosis

Before steroid therapy is started, endoscopic or percutaneous transhepatic biliary drainage must be done in cases with obstructive jaundice, and glucose levels must be controlled in cases with diabetes mellitus. Oral predonisolone is usually initiated at 0.6 mg/kg/day and it is tapered by 5 mg every 1-2 weeks. Serological and imaging tests are followed periodically after commencement of steroid therapy. Usually, pancreatic size is normalized within a few weeks, and biliary drainage becomes unnecessary. Patients in whom complete radiological improvement is documented can stop their medication. To prevent relapses without complete discontinuation of steroid, continued maintenance therapy with prednisolone 2.5 mg-5 mg/day is sometimes required. In half of steroid-treated patients, impaired exocrine or endocrine function improved. Some AIP patients relapse during maintenance therapy or after stop of steroid medication, and should be retreated with high-dose steroid therapy. The indications for steroid therapy in AIP include obstructive jaundice due to stenosis of the bile duct or the presence of other associated systemic diseases, such as retroperitoneal fibrosis. Steroid therapy is also effective for sclerosing cholangitis which relapses after surgery (3,11).

The long-term prognosis of AIP is not well known. It is reported that recurrent attacks of AIP resulted in pancreatic stone formation in some cases (12).

Conclusion

AIP has many clinical, serological, morphological, and histopathological characteristic features. AIP should be diagnosed carefully based on combination of these findings. In an elderly male presenting obstructive jaundice and pancreatic mass, AIP should be considered as one of differential diagnoses to avoid unnecessary surgery. AIP shows reversible improvement with oral steroid therapy.

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