J Gastroenterol 2009; 44:154–159
DOI 10.1007/s00535-008-2294-2

Journal of Gastroenterology

Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography

Noriyuki Hoki[1], Nobumasa Mizuno[1], Akira Sawaki[1], Masahiro Tajika[1], Reiko Takayama[1], Yasuhiro Shimizu[2], Vikram Bhatia[3], and Kenji Yamao[1]

[1] Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
[2] Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan
[3] Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India

Background. Revised clinical criteria for autoimmune pancreatitis (AIP) have been proposed by the Research Committee of Intractable Disease of the Pancreas and the Japan Pancreas Society. These criteria require distinguishing AIP from neoplastic lesions. However, this can be difficult, and patients often undergo surgery on the basis of suspected pancreatic cancer (PC). ***Methods.*** AIP was diagnosed in 25 patients at the Aichi Cancer Center Hospital (ACCH) according to the revised AIP criteria. In each patient, endoscopic ultrasonography (EUS) was used to describe the conventional pancreatic parenchymal and ductal features of chronic pancreatitis (Sahai criteria), and other abnormal features, namely, diffuse hypoechoic areas (DHAs), diffuse enlargement (DE), focal hypoechoic areas (FHAs), focal enlargement, bile duct wall thickening (BWT), lymphadenopathy, and peripancreatic hypoechoic margins (PHMs). We compared these features between 25 patients with AIP and 30 patients with pancreatic cancer resected at ACCH. ***Results.*** Few conventional EUS features of chronic pancreatitis (CP) were seen in patients with AIP (mean, 2.0 features). Frequencies of DHA, DE, BWT, and PHM were significantly higher in AIP than in PC. DHAs, DE, and FHAs resolved after steroid treatment. ***Conclusions.*** Novel EUS features of AIP are useful in distinguishing AIP from PC and for following the effects of steroid therapy.

Key words: pancreatic cancer, autoimmune pancreatitis, lymphadenopathy, bile duct wall thickening

Introduction

The first description of pancreatitis with hypergammaglobulinemia was published by Sarles et al. in 1961.[1] Japanese investigators first proposed the concept of "autoimmune pancreatitis" (AIP) in 1995 to describe features of a diffusely enlarged pancreas, narrowed pancreatic duct on imaging, presence of hypergammaglobulinemia and autoimmune autoantibodies, fibrotic changes with lymphocytic infiltration on histopathology, and a therapeutic response to steroids.[2] The current diagnosis of AIP is based on the diagnostic criteria proposed by the Japan Pancreas Society in 2002.[3] AIP has since been described quite often, although mostly in Japanese-language publications. However, with the increasing recognition of a large number of patients with AIP, some with atypical manifestations, revised criteria for AIP were proposed by the Research Committee of Intractable Disease of the Pancreas and the Japan Pancreas Society. The 2006 criteria for diagnosis of AIP mandate the presence of diffuse or localized narrowing of the main pancreatic duct on endoscopic retrograde cholangiopancreatography and diffuse or localized enlargement of the pancreas on transabdominal ultrasonography (TUS), computed tomography (CT), or magnetic resonance imaging.[4] Parenchymal imaging changes are not described in detail by the revised criteria, which rely heavily on TUS. On TUS, pancreatic enlargement in patients with AIP is usually described as hypoechoic, sometimes with scattered echogenic spots.

Endoscopic ultrasonography (EUS) can reveal pancreatic parenchymal and ductal features in much more detail than any other existing imaging modality, owing to the lack of intervening bowel gas and the use of high-frequency transducers. We therefore studied AIP patients with EUS and sought novel imaging features that would suggest a diagnosis of AIP. In addition, we compared the results between AIP patients and patients

Received: October 13, 2007 / Accepted: September 4, 2008
Reprint requests to: K. Yamao

with pancreatic cancer (PC), which is often part of the differential diagnosis of AIP because their clinical and imaging features overlap. We also studied the evolution of EUS features of AIP with steroid treatment, and we propose a new scoring system for this disease.

Patients and methods

Patient characteristics

AIP was diagnosed in 25 patients at Aichi Cancer Center Hospital (ACCH) between January 1997 and December 2006. Fourteen of these patients had been referred with a diagnosis of PC for staging or surgical treatment. All these patients met the 2006 revised criteria for the diagnosis of AIP. The EUS examination was performed by experienced endosonographers with an echoendoscope (GF-UCT240, GF-UE260, or GF-UM240, Olympus, Tokyo, Japan), and the image analysis was done by N.H., N.M., and K.Y. A total of 30 PCs were resected at ACCH between January 2004 and December 2005. All these patients had a final histological diagnosis of adenocarcinoma. The EUS features of the patients with PC were compared with those of the AIP patients.

EUS findings

We used the Sahai EUS criteria to describe the parenchymal and ductal changes in patients with AIP.[5] The parenchymal features included hyperechoic foci, hyperechoic strands (Fig. 1A), lobularity, cysts, and shadowing calcifications. The ductal features included dilation, irregularity, hyperechoic duct margins, and visible side branches.

We also defined other EUS features of AIP that are not included in the conventional criteria. These abnormal findings included diffuse hypoechoic areas (DHAs) (Fig. 1B), diffuse enlargement (DE) (Fig. 1B), focal hypoechoic areas (FHAs) (Fig. 1C), focal enlargement (FE) (Fig. 1D), extrahepatic bile duct wall thickening (BWT) (Fig. 1E), lymphadenopathy (LN) (Fig. 1F), peripancreatic hypoechoic margins (PHM) (Fig. 1G), and a duct-penetrating sign (DPS). DHA, FHA, BWT, LN, and PHM are defined in Table 1. In cases of AIP, we also compared pancreatic images before and after the administration of corticosteroid therapy.

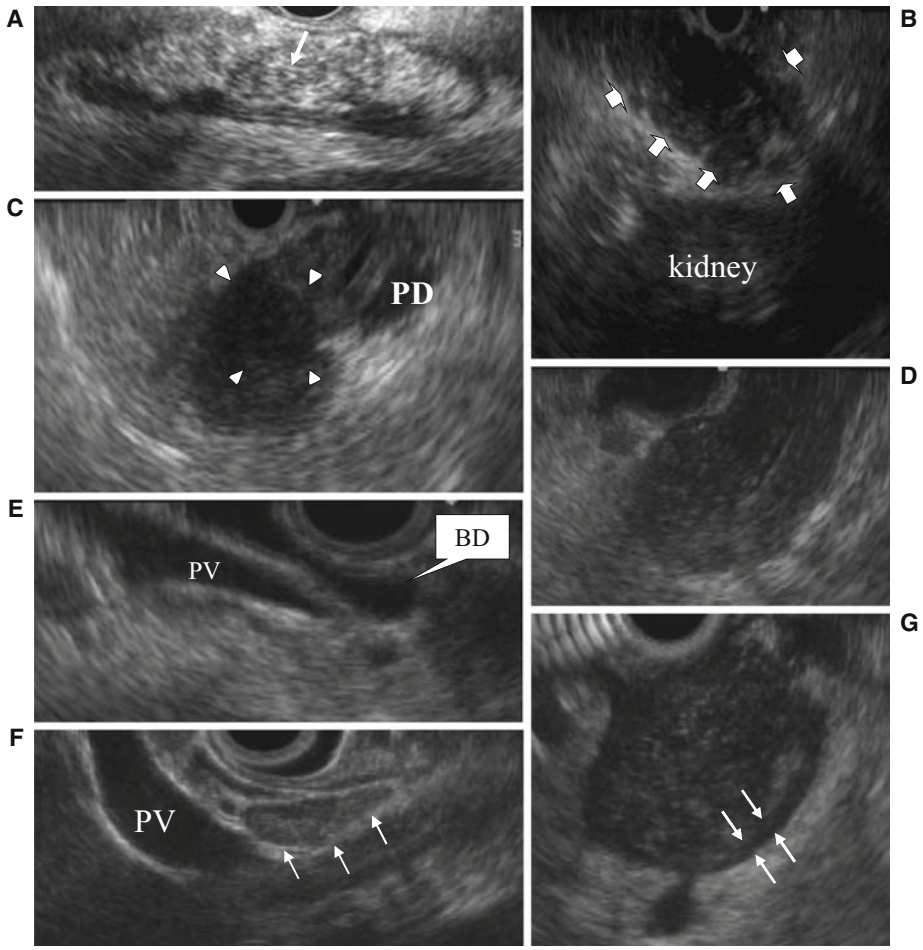

Fig. 1. **A** Endoscopic ultrasound (EUS) image showing hyperechoic foci and hyperechoic strand (*arrow*) in an autoimmune pancreatitis (AIP) patient. **B** EUS image showing a diffuse hypoechoic area and diffuse enlargement (*arrows*). **C** EUS image showing a focal hypoechoic area (*arrowheads*). *PD*, pancreatic duct. **D** EUS image showing focal enlargement. **E** EUS image showing bile duct wall thickening. *PV*, portal vein; *BD*, bile duct. **F** EUS image showing lymphadenopathy (*arrows*). **G** EUS image showing a peripancreatic hypoechoic margin (*arrows*)

Table 1. Abnormal EUS findings in AIP

DHA or FHA	Pancreatic parenchyma displays lower echogenicity than the renal cortex
BWT	The hypoechoic layer on the internal aspect of the bile duct is clearly thickened
LN	Lymph node diameter >10 mm
PHM	A capsule-like hypoechoic rim defined on CT

EUS, endoscopic ultrasonography; AIP, autoimmune pancreatitis; DHA, diffuse hypoechoic area; FHA, focal hypoechoic area; BWT, bile duct wall thickening; LN, lymphadenopathy; PHM, peripancreatic hypoechoic margin; CT, computed tomography

Table 2. Patient characteristics

	Patients with AIP ($n = 25$)	Patients with PC ($n = 30$)	P
Age, years (median, range)	65 (52–76)	64 (38–75)	NS*
Sex (male/female)	21/4	16/14	0.015**
DM	14	7	0.003**
Alcohol abuse	2	1	NS*
Biliary drainage	8	14	NS**
Steroid treatment	17	0	—
Operation	0	30	—
Location (head/body/tail/diffuse)	10/0/1/22	22/6/2/0	<0.001**
Mass size (≤2 cm/>2 cm)	4/7	8/22	NS**

PC, pancreatic cancer; DM, diabetes mellitus; NS, not significant
* t test
** χ-squared test

We propose a novel scoring system for differentiating EUS features between AIP and PC. With this scoring system, findings more frequently associated with AIP (DHA, DE, BWT, PHM, and DPS) are worth +1 point each and those more frequently associated with PC (FHA and FE) are worth –1 point each.

Statistical analysis was done with Student's t test, χ-squared test, and Fishers' exact test, with the significance level set at 0.05.

Results

Comparison of clinical characteristics between AIP and PC

The clinical characteristics of patients with AIP and PC are summarized in Table 2. The age distribution was equivalent in the two groups. Frequencies of alcohol abuse and biliary drainage did not differ significantly between the groups, but male sex and diabetes mellitus (DM) were significantly more frequent in patients with AIP than in those with PC. Patients with AIP had both diffuse and focal changes. By using EUS, a focal mass was detected in 11 patients with AIP and in all patients with PC.

EUS features of AIP

The conventional EUS features of chronic pancreatitis (CP) as seen in the 25 AIP patients are summarized in Table 3. The Sahai EUS criteria for AIP are not sensitive for the diagnosis of AIP. Fourteen of 25 patients (56%) met the conditions for <3 Sahai criteria, eight met those for three criteria, three those for four criteria, and none met the conditions for more than four criteria. The mean number of EUS features of CP among patients with AIP was 2.28 (range, 0–4; SD, 1.1). Thus, on the basis of EUS features of CP, all patients with AIP were classified as normal or displaying mild disease. Comparisons of AIP images among TUS, CT, and EUS are summarized in Table 4. EUS was far superior to TUS and CT for revealing LN and DPS. DHA and BWT were also better detected by EUS than by other modalities. Conversely, CT was far superior to EUS for detecting the rim on a PHM.

Table 3. Sahai criteria and number of AIP patients fulfilling each criterion ($n = 25$)

	No. of patients (%)
Ductal features	
Dilation	3 (12)
Irregularity	10 (40)
Hyperechoic wall	9 (36)
Side branch visible	0
Parenchymal features	
Hyperechoic foci	8 (32)
Hyperechoic strands	14 (56)
Lobularity	2 (8)
Cysts	4 (16)
Calculi	4 (16)

Comparison of EUS features between AIP and PC

Table 5 summarizes the EUS features of AIP and PC. The tumors in eight patients with PC were <2 cm in diameter, and these patients showed no focal enlargement of the pancreas. DHA, DE, BWT, PHM, and DPS were significantly more common in patients with AIP than in patients with PC. FHA and FE were significantly more common in patients with PC than in AIP patients.

Total scores of each of our patients with AIP and PC according to the proposed novel scoring system are shown Table 6. Scores for AIP and focal AIP were significantly higher than scores for PC. When a score of ≥0 was used to indicate AIP, the sensitivity of the scoring system was 76% and specificity was 96%. In comparison, when a score ≥1 was used for AIP, sensitivity was 68% and specificity was 100%. This scoring system should therefore be very useful. However, for patients with focal AIP, a score ≥0 showed a sensitivity of only 45% and a specificity of 96%.

Table 4. Comparison of AIP findings among TUS, CT, and EUS

Finding	No. of patients (%)			*P**
	TUS	CT	EUS	
DHA	16 (64)	—	22 (88)	NS
DE	14 (56)	15 (60)	15 (60)	NS
FHA	11 (44)	9 (36)	11 (44)	NS
FE	11 (44)	9 (36)	10 (40)	NS
BWT[a]	3/17 (18)	6/21 (29)	9/17 (53)	NS
LN	1 (4)	2 (8)	18 (72)	<0.001
PHM/rim	5 (20)	13 (52)	5 (20)	<0.05
DPS	1 (4)	0 (0)	6 (24)	<0.01

TUS, transabdominal ultrasonography; DE, diffuse enlargement; FE, focal enlargement; DPS, duct-penetrating sign
[a]Excluding patients in whom plastic stents were inserted
*χ-squared test or Fisher's exact test

Evolution of EUS findings for AIP after steroid therapy

Steroids were administered to 13 patients who also underwent EUS at least twice. Table 7 shows the changes in EUS findings after a follow-up for 3 to 26 months (mean, 5 months). After steroid therapy, DHA and DE persisted in only 31% and 8% of these patients, respectively, and diffuse pancreatic changes were decreased significantly (Table 7), whereas FHA and FE were undetectable in all patients. BWT and LN persisted to some degree in almost all patients. Steroid therapy normalized parenchymal findings, but extrapancreatic findings did not change.

Discussion

Many patients with AIP have been identified in Japan since it was first described.[1] As a result, AIP is now classified as a general disease associated with an autoimmune disorder. In 2006, revised criteria were proposed.[4] However, until now, AIP has been diagnosed in Japan mainly according to characteristic pancreatic duct features. In contrast, the Korean diagnostic criteria for AIP include a good response to steroid therapy,[6] and the Mayo Clinic criteria include histological evidence.[7]

The first EUS device for gastrointestinal use was developed specifically to image the pancreas.[8] These early studies focused on the technical feasibility of EUS to detect small pancreatic carcinomas in pancreatic images.[9] Raimondo et al.[10] have attempted to diagnose early chronic pancreatitis using EUS, but a gold standard procedure has not yet been established so a diagnosis by EUS alone is insufficient.

We initially attempted to evaluate the pancreatic features of AIP by EUS with the Sahai criteria. The threshold for diagnosing CP based on EUS can vary (e.g., >3, >4, or >5 features),[11] and an increasing score indicates a greater severity of changes in chronic pancreatitis. Our patients with AIP fulfilled on average 2.0 Sahai criteria, indicating mild changes toward CP. Thus, the features

Table 5. Comparison of EUS findings between AIP and PC

Image	Patients with AIP (%) (n = 25)	Patients with PC (%) (n = 30)	*P**
DHA	22 (88)	7 (23)	<0.001
DE	15 (60)	0 (0)	<0.001
FHA	11 (44)	30 (100)	<0.001
FE	10 (40)	22 (74)	<0.05
BWT[a]	9/17 (53)	1/16 (6)	<0.01
LN	18 (72)	15 (50)	NS
PHM	5 (20)	0 (0)	<0.05
DPS	6 (24)	0 (0)	<0.05

[a]Excluding patients in whom plastic stents were inserted
*χ-squared test or Fisher's exact test

Table 6. Comparison of novel scoring system scores between AIP and PC

	Score mean ± SD (range)		
PC (n = 30)	–1.4 ± 0.6 (–2 to 0)	*	**
Focal AIP (n = 11)	–0.3 ± 1.2 (–2 to 2)		
AIP (n = 25)	1.4 ± 1.8 (–2 to 4)		

* $P < 0.01$
** $P < 0.001$

Table 7. EUS findings for AIP before and after steroid therapy

EUS image	Patients (%) (n = 13) Pretherapy	Post-therapy	P*
DHA	13 (100)	4 (31)	<0.001
DE	9 (69)	1 (8)	<0.01
FHA	5 (38)	0 (0)	<0.05
FE	3 (23)	0 (0)	NS
BWT[a]	4/9 (44)	7/10 (70)	NS
LN	11 (85)	9 (69)	NS
PHM	2 (15)	0 (0)	NS

[a] Excluding patients in whom plastic stents were inserted
* χ-squared test or Fisher's exact test

of AIP did not change like those of CP, indicating that the Sahai criteria alone are inadequate for evaluation of AIP.

The characteristic EUS findings of AIP have been reported as diffuse enlargement, a frankly hypoechoic pancreas, or a solitary hypoechoic mass, a dilated or sclerotic appearance of the pancreatic duct, and a dilated common bile duct.[12] Additionally, Hyodo and Hyodo[13] reported that EUS imaging showed swelling of the whole pancreas with spotty bright echoes and a thickened bile duct wall in the five patients with AIP that they studied. We therefore paid attention to other abnormal findings on pancreatic imaging, namely DHA, DE, FHA, FE, BWT, LN, and PHM, as characteristic features of AIP. LN and DPS were seen on EUS significantly more frequently than on TUS or CT. DHA and BWT tended to be seen more frequently on EUS, but the differences were not significant. Only peripancreatic hypoechoic margins indicating a rim were seen more frequently on CT (Table 4). No patients showed PHM only by EUS. EUS was therefore superior to TUS and CT for pancreatic and extrapancreatic imaging, except in the case of PHM. Over half of our patients with AIP displayed DHA, DE, BWT, and LN. In contrast, fewer than half of the patients with AIP showed FE or FHA. The frequency of LN was the same for both AIP and PC. Given these focal changes and LN, many patients with focal AIP have undergone surgery owing to a misdiagnosis of PC.[14–16] In patients with LN, AIP should be suspected along with PC. We also tried to distinguish between AIP and PC by using other abnormal findings. DHA, DE, BWT, and PHM were more characteristic of AIP than of PC (Table 5). Among patients who underwent pancreaticoduodenectomy, 10.6% had only benign disease according to pathological findings and almost all of them underwent resection because of a clinical suspicion of malignancy.[14] In particular, patients with AIP were all thought to harbor malignancy. These findings indicate that it is necessary to distinguish AIP from PC. Other features judged abnormal by EUS were useful for differentiating these patients. The novel scoring system proposed herein should be very useful for the diagnosis of AIP.

Potential errors in judgment might be avoided by more aggressive attempts at EUS-guided fine-needle aspiration (EUS-FNA) in selected patients when the diagnosis remains in doubt. We performed EUS-FNA in all 25 patients with AIP and determined the clinical course of follow-up.

Steroids are supposed to be effective in AIP.[17] However, Sahai scores of our patients with AIP were not particularly high. We were therefore unable to evaluate the features of AIP using the Sahai criteria alone. DE, DHA, and FHA disappeared after steroid therapy.

These features were considered changeable, although some features identified by EUS remained. BWT and LN persisted for an average of 5 months. We did not determine whether these changes could be controlled by long-term therapy.

We evaluated pancreatic features in detail and could differentiate AIP from PC. The Sahai criteria were not critical to this process. AIP and PC must be distinguished to prevent unnecessary surgery for PC in patients with AIP. The present study showed that EUS can visualize in detail the pancreatic parenchyma along with duct and lymph nodes around the pancreas and the extrahepatic bile duct. Thus, EUS is a practical method for distinguishing malignant pancreatic disease from AIP.

Acknowledgments. This work was supported by the Research Committee of Intractable Pancreatic Diseases (M. Otsuki, Chairman), provided by Ministry of Health, Labour and Welfare of Japan.

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