—Original Article—

Autoimmune pancreatitis: Imaging features

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ABSTRACT

Background and Objectives: Autoimmune pancreatitis (AIP) remains a difficult disease to diagnose before treatment, particularly if presenting as a focal mass lesion. The purpose of this multicenter retrospective study is to analyze imaging features of histologically confirmed AIP to determine the additional diagnostic value of contrast-enhanced ultrasound (CEUS), contrast-enhanced endoscopic ultrasound (CE-EUS), and elastography to B-mode features. **Patients and Methods:** We report on a retrospective data collection of 60 histologically confirmed cases of AIP in comparison to 16 patients with pancreatic adenocarcinomas (PDAC). All CE (-E) US examinations were assessed by two independent readers in consensus. The role of CEUS and CE-EUS for pancreatic evaluation was defined according to the 2011 European Federation of Societies for Ultrasound in Medicine and Biology guidelines. **Results:** After injection of ultrasound (US) contrast agents, most AIP lesions displayed focal or diffuse isoenhancement (86.6%) in the arterial phase, while most of the PDAC lesions (93.7%) were hypoenhancing ($P < 0.01$). During the late phase, most AIP lesions were hyper-(65%) or iso-enhancing (35%), while most PDAC lesions were hypoenhancing (93.7%). CE-EUS was performed in a subset of ten patients and showed hyperenhancement in all AIP cases. Most focal AIP lesions ($n = 27$, 79.4%) were stiffer than the surrounding pancreatic parenchyma. **Conclusions:** In this study, percutaneous and endoscopic contrast enhanced harmonic US techniques consistently revealed diffuse and focal types of AIP to have features consistent with vascularized lesions. Differentiation from the typically hypovascularized pancreatic adenocarcinoma was possible with CE (-E) US evaluation.

Key words: Autoimmune pancreatitis, contrast-enhanced ultrasound, contrast-enhanced endoscopic ultrasound, guideline

INTRODUCTION

Autoimmune pancreatitis (AIP) is an infrequently recognized disorder of presumed autoimmune etiology and accounting for up to 10% of chronic pancreatitis cases.[1,2] The earliest case of AIP was described in 1961 by Sarles *et al.*[3] The term AIP was first used in 1995 by Yoshida *et al.* to describe chronic pancreatitis associated with a Sjogren-like syndrome.[4]

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AIP can occur as a primary pancreatic disorder or in association with other systemic disorders of presumed autoimmune etiology including IgG4 cholangitis, salivary gland disorders, mediastinal fibrosis, retroperitoneal fibrosis, tubulointerstitial disease, and inflammatory bowel disease (IgG4 systemic disease).[5] According to the International Consensus Diagnostic Criteria (ICDC) for AIP, there are 2 subtypes.[1,6] The histological features of type 1 AIP are known as lymphoplasmacytic sclerosing pancreatitis, while type 2 AIP is characterized by a distinct histology termed idiopathic duct-centric pancreatitis (IDCP) with granulocytic epithelial lesions.[6-8] Type 1 AIP is recognized to be the pancreatic manifestation of IgG4-related systemic disease, characterized by elevated IgG4 serum levels.[8,9] This form of AIP presents predominantly with obstructive jaundice in elderly males; both pancreatic and extrapancreatic manifestations respond to steroid therapy. It has been suggested that a clinical diagnosis of type 1 AIP can be made without need for a histology sample.[10-12]

In contrast, IDCP (type 2 AIP) is diagnosed at a younger age (mean age at diagnosis is 40 years).[13] Further, IDCP is without gender bias and clinical presentations are limited to the pancreas. IDCP is usually not associated with IgG4 activity.[1,6] Response to steroids is excellent, as in type 1, but type 2 AIP patients rarely relapse.[14] While certain features are considered diagnostic, types 1 and 2 cannot be reliably distinguished by imaging.[7,15]

Three patterns of AIP distribution are recognized in the literature: focal, multifocal, and diffuse.[16] Focal tumor-like AIP is less common than diffuse disease and manifests as a focal mass, often within the pancreatic head. Clinically, focal AIP masses can be confused with pancreatic carcinoma or lymphoma. AIP is finally diagnosed in 2.5%–3.8% of patients undergoing resection for suspected pancreatic cancer.[17-21] Correctly distinguishing AIP from pancreatic cancer can help avert the consequences of progressive disease and unnecessary surgery, especially in focal tumor-like forms.

Imaging is of utmost importance for differential diagnosis, therapeutic monitoring, follow-up, and early identification of AIP. Imaging modalities include contrast-enhanced computed tomography (CE-CT) and CE magnetic resonance (CE-MR) imaging for pancreatic parenchymal lesion localization and characterization, endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRCP) to assess duct involvement, and more recently positron emission tomography (PET) imaging to assess extrapancreatic involvement. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) may be used to obtain histologic specimens from the pancreas; when the diagnosis of AIP has been established, surgery may be avoided.[22-25] However, recent studies do not show a reduction of unnecessary surgery of benign lesions masquerading as pancreatic adenocarcinomas (PDAC) despite more aggressive investigation of focal pancreatic lesions of uncertain etiology using state-of-the-art imaging techniques and EUS-FNA.[19,26,27]

Conventional ultrasound (US) can visualize a pancreatic mass or alterations of pancreatic parenchyma during pancreatitis, but unfortunately, many lesions cannot be characterized by US alone. Over the years, contrast-enhanced US (CEUS) has proved valuable in the characterization of pancreatic lesions, leading to improvement of its diagnostic capability.

In 2008, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) first included pancreatic applications of CEUS in its guidelines.[28,29] The role of CEUS for pancreatic evaluation was strengthened in the 2011 EFSUMB guidelines,[11,30] in which the first recommendation was the characterization of ductal adenocarcinoma (recommendation level: A; 1b). Other recommendations included differentiation between pseudocysts and cystic tumors (recommendation level: A; 1b); differentiation of vascular-solid from avascular-liquid/necrotic components (recommendation level: A; 1b); improvement of definition of dimensions and margins, including relationships with adjacent vessels (recommendation level: B; 2b); distinction between solid and cystic lesions, thus providing information for the choice of the next imaging modality (*i.e.*, magnetic resonance imaging (MRI) and/or endoscopic US for cystic lesions), resulting in better management of patients (recommendation level: C; 5); diagnosis of indeterminate cases at CT (recommendation level: C; 5). CEUS is conclusive in about 90% cases and should be considered a first-line imaging method in clinical practice.[28]

The purpose of this multicentered retrospective study is to analyze imaging features of histologically confirmed AIP to determine the added diagnostic value of CEUS, elastography, and other techniques.

PATIENTS AND METHODS

Patients

We report on a retrospective data collection of 60 histologically confirmed cases of AIP. The average age at diagnosis was 47 years (19–81 years). Forty patients were male and 20 were female [Table 1].

The suspected diagnosis was AIP in 37 patients, on the bases of imaging appearance (CT, MRI, and conventional abdominal US) and IgG4 serum values. Nine masses were interpreted as pancreatic carcinoma by CT or MRI. Sixteen patients with histopathologically proved PDAC were also analyzed.

Examination technique

Conventional US and CEUS were performed in all patients with one of six US systems: Philips iU22 unit (Philips Bothell, WA, USA; C5-1 convex array probes, 1–5MHz), or LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA; C1-5 convex array probes, 1–5MHz), or Hitachi (Hi vision EUB-6500, Preirus, Ascendus; C715 convex array probes, 1–5MHz), or SIEMENS (Acuson Sequoia or S2000), or Toshiba (Aplio platinum 500; Aplio CV, convex array probes 3–6 MHz). CEUS was performed using contrast harmonic real-time imaging at a low MI 0.05–0.30. The US contrast agent SonoVue® (Bracco SpA, Milan, Italy) was used at a dose of 1.5–2.4 mL, immediately followed by an injection of 10 mL sodium chloride solution. Images were recorded for 3 min after contrast agent injection.

Table 1. Baseline characteristics of autoimmune pancreatitis and pancreatic ductal adenocarcinoma patients

Characteristic	AIP patients (*n*=60)	PDAC patients (*n*=16)
Age (year)		
Mean±SD	47±15	64±10
Range	19-81	50-84
Male/female	40/20	6/10
Underlying disease		
IgG4 related disease	6	-
Inflammatory bowel disease	2	-
Symptoms		
Abdominal pain	12	-
Acute pancreatitis	10	-
Jaundice	22	13
Incidental finding	16	-
Weight loss	-	3
Type (I, II)		
Type I	6	-
Type II	54	-
Type (focal, diffuse)		
Focal	34	-
Diffuse	26	-
Histological results		
Surgery	9	16
Core needle biopsy	35	-
Fine needle biopsy	16	-

AIP: Autoimmune pancreatitis, PDAC: Pancreatic ductal adenocarcinoma, SD: Standard deviation

CE-EUS was performed using longitudinal echoendoscopes EG-3870 UTK and Hitachi platforms (HI vision EUB-6500, Preirus, Ascendus).[31] Intravenous injection of 4.8 mL SonoVue® was performed according to the guidelines of the EFSUMB.[11,30]

Imaging evaluation (contrast-enhanced ultrasound, endoscopic ultrasound, and elastography)

All examinations were interpreted by two independent readers (10 and 15 years of experience with CEUS imaging) who were blinded to the clinical and pathologic data. The role of CEUS for pancreatic evaluation was defined according to the 2011 EFSUMB guidelines. [11,30] The CEUS features of focal tumor-like lesions were compared to the surrounding normal pancreatic parenchyma.

After identification of the pancreatic lesion by conventional B-mode EUS, EUS-elastography was immediately followed. Sonoelastographic strain values are measured and displayed relative to the surrounding tissue, which serves as an internal reference standard. Calculation of the tissue elasticity distribution is carried out in real time and the examination results are displayed in color as a transparent overlay on the conventional B-mode image.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, United States of America). The Chi-square test and Fisher's exact test were used to compare categorical parameters between the groups. Continuous parameters were presented as the mean ± standard deviation, and Student's *t*-test was used. $P < 0.05$ was considered statistically significant.

Institutional Board Approval

Institutional Board Approval was obtained. Informed consent was obtained from each patient.

RESULTS

Final diagnoses, treatment, and clinical follow-up

All 60 lesions were histologically defined as AIP. Twelve of 60 AIP patients were treated conservatively after standard steroid treatment for AIP. Nine AIP patients underwent resection for a preoperative diagnosis of pancreatic carcinoma.

The final diagnosis was achieved by either histology using transabdominal (percutaneous) US-guided core needle biopsy (18-gauge 20-cm single-use biopsy needles; Temno, Germany, or BioPince, Pflugbeil, Germany) (n = 35), cytology with immunostaining of IgG4 (n = 16) or surgical resection with histopathological analysis of pancreatic tissue (n = 9).

In all patients with suspected AIP, clinical follow-up to 12 months was established.

Conventional ultrasound

On conventional B-mode US (BMUS), 34 cases were detected as focal "tumor-like" AIP lesions, and 26 cases were detected as diffusely hypoechoic in the whole pancreas. Among 34 focal AIP lesions, 24 (70.6%) were detected on the head of the pancreas. All PDAC lesions were detected in the pancreatic head.

Most AIP lesions (93.3%) and all PDAC lesions (100%) were hypoechoic on BMUS ($P > 0.05$). A pathologically dilated common bile duct was more common in PDAC lesions (100%) than in AIP lesions (68.3%) [Table 2].

Contrast-enhanced ultrasound

After contrast agent injection, most AIP lesions displayed focal or diffuse isoenhancement (86.6%) in the arterial phase [Figure 1]. Meanwhile, most PDAC lesions (93.7%) were hypoenhancing ($P < 0.01$).

During the late phase, most AIP lesions were hyper-(65%) or iso-enhancing (35%), while most PDAC lesions were hypoenhancing (93.7%) [Table 3].

Contrast-enhanced endoscopic ultrasound

CE-EUS was performed in a subset of ten patients diagnosed with AIP and showed hyperenhancement in all cases [Figure 2]. All 16 cases of PDAC were hypoenhancing in CE-EUS.

Elastography

US elastography was performed in 34 cases of focal AIP lesions and in all PDAC lesions. Among all focal AIP lesions, 8 were softer than the surrounding parenchyma while the majority of focal AIP lesions (n = 27, 79.4%) and all PDAC lesions (n = 16) were stiffer than the surrounding pancreatic parenchyma.

DISCUSSION

AIP is a rare disease often found in people with a history of autoimmune diseases. According to the International Association of Pancreatology,[1] AIP is characterized by diffuse or focal inflammation of the pancreas, optionally with obstructive jaundice, a dense lymphoplasmacytic infiltrate and fibrosis (histologically) and a dramatic response to corticosteroid treatment (therapeutically).[1,13] In 30%–40% of AIP, a focal tumor-like pancreatic mass is found, hampering differentiation from pancreatic cancer.[32] Unique immunological features[33,34] as well as genetic predisposing factors[35-37] have been identified.

The ICDC are presently evaluated as the most sensitive and specific criteria for diagnosing AIP.[38] These criteria are composed of five cardinal features including (1) imaging of the pancreatic parenchyma, (2) serology, (3) other organ involvement, (4) histology, and (5) response to steroid therapy.[1,6]

IgG4 ≥135 mg/dL is the most sensitive and specific serum marker for type 1 AIP (sensitivity: 86%; specificity to AIP against PDAC: 96%). However, it is unspecific[39] and may also be increased in patients with PDAC (10%, 13/135).[40] However, the level of

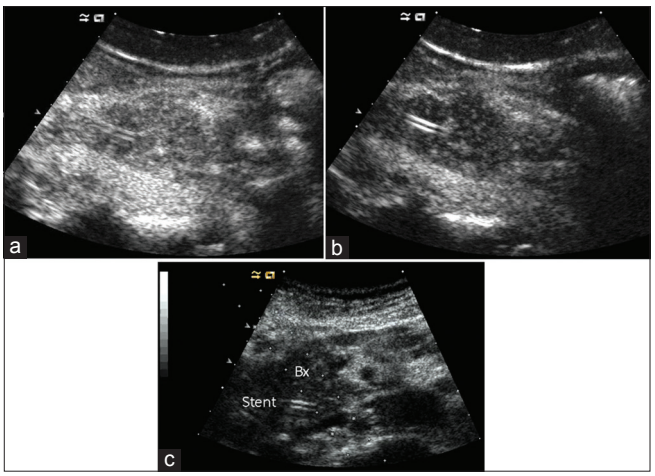

Figure 1. Focal autoimmune pancreatitis isoenhancing in comparison to the surrounding pancreatic parenchyma in the arterial phase (a) and hypoenhancing (wash-out) in the venous phase (b). Ultrasound-guided core biopsy is performed to confirm diagnosis (c). The stent is visualized in all images. Bx: Transcutaneous biopsy guidance

Table 2. Comparison of B-mode ultrasound findings between autoimmune pancreatitis and pancreatic ductal adenocarcinoma lesions

Characteristic	AIP lesions (*n*=60)	PDAC lesions (*n*=16)
Location (%)		
Head/neck	24 (40)	16 (100)
Body	4 (6.7)	0
Tail	6 (10)	0
Diffuse	26 (43.3)	0
Common bile duct (%)		
Dilated (>8 mm)	41 (68.3)	16 (100)
Normal	19 (31.7)	0
Size of focal AIP (mm)		
Mean±SD	28.5±11.9	67.5±12.8
Range	2-50	52-90
Echogenicity (%)		
Hyperechoic	2 (3.3)	0
Hypoechoic	56 (93.3)	16 (100)
Isoechoic	2 (3.3)	0
Hypervascular in CDI	24 (40)	0

CDI: Color Doppler imaging, AIP: Autoimmune pancreatitis, PDAC: Pancreatic ductal adenocarcinoma, SD: Standard deviation

Table 3. Comparison of contrast-enhanced ultrasound imaging features between autoimmune pancreatitis and pancreatic ductal adenocarcinoma lesions

Characteristic	AIP lesions (*n*=60)	PDAC lesions (*n*=16)	*P*
Arterial phase			
Early hyperenhancement	6 (10)	0	0.01
Isoenhancement	52 (86.6)	1 (6.3)	0.04
Hypoenhancement	2 (3.4)	15 (93.7)	0.02
Late phase			
Hyperenhancement	39 (65)	0	0.03
Isoenhancement	21 (35)	1 (6.3)	0.04
Hypoenhancement	0	15 (93.7)	0.02

AIP: Autoimmune pancreatitis, PDAC: Pancreatic ductal adenocarcinoma

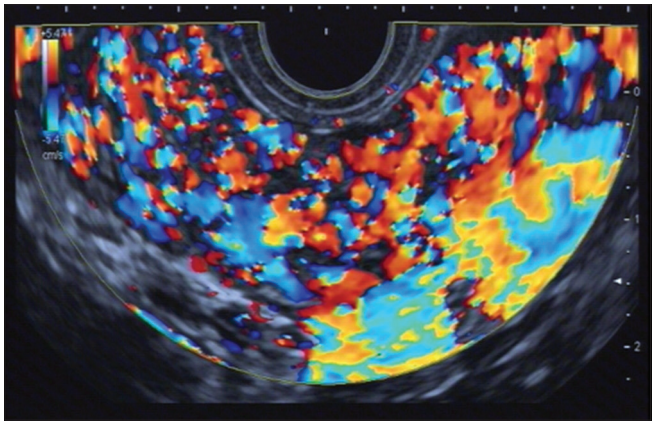

Figure 2. Diffuse autoimmune pancreatitis using radial endoscopic ultrasound (color Doppler). Note the homogenously hypervascular pancreatic parenchyma

serum markers usually correlates with the autoimmune activity (IgG4, soluble interleukin-2 receptor, *etc.*)[41,42] and elevated levels of serum IgG are often detected in patients with AIP relapse.[43,44] Therefore, serum markers may be useful for the clinical follow-up of patients with type 1 AIP.[45-47] The sensitivity of a combination of nonspecific serum markers (IgG + ANA + RF) is 91% and thus similar to that of IgG4, but the specificity (61%) is significantly lower than for IgG4 alone.[39]

The presence of other organ involvement and the patient's responsiveness to steroids is highly suggestive of AIP. Imaging showing pancreatic enlargement helps to further confirm the diagnosis.[8,48,49]

Three types of AIP can be distinguished based on morphological patterns: diffuse, focal, and multifocal. Diffuse disease is the most common type. Focal disease is less common than diffuse disease and manifests as a focal mass. In 20%–30% of patients, there is mass-like enlargement of the head with tail atrophy. Peripancreatic lymphadenopathy is seen in 25% of patients. Focal disease tends to be relatively well demarcated, and when present, upstream dilation of the main pancreatic duct is typically milder than what is observed in patients with pancreatic carcinoma. Multifocal involvement can also be evident.[16,50]

Conventional US is often the first imaging exam performed in the presence of any abdominal symptom. However, in the focal and multifocal forms of AIP, only the affected regions of the pancreas appear hypoechoic. This appearance is not specific but very often AIP are hypervascular [Figure 2]. Color Doppler is often not helpful for the diagnosis.

CEUS allows complete real-time and dynamic evaluation of all contrast enhancement phases. CEUS can successfully visualize fine vessels in pancreatic lesions and may play a pivotal role in the depiction and differential diagnosis of pancreatic tumors.[51,52] CEUS may influence the choice of further examinations, as well as being useful in obtaining an immediate and faster diagnosis.[51,53-56] Dynamic CEUS might have an impact for differentiating PDAC from AIP.[57] A recent meta-analysis indicated that the sensitivity (0.89), specificity (0.84), and diagnostic odds ratio (61.12) show the merits of CEUS for characterizing and differentiating PDAC from other pancreatic diseases.[58]

As recently has been shown, the excellent discriminatory accuracy of CEUS and CE-EUS also applies for small solid pancreatic lesions measuring ≤15 mm.[31] CEUS should be used first line for characterizing neoplastic pancreatic lesions.[2,59] EUS findings of AIP include diffuse hypoechoic pancreatic enlargement, bile duct wall thickening, and peripancreatic hypoechoic margins.[5,60,61] Hocke *et al*. reported that CE-EUS revealed a unique vascularization pattern, making it possible to discriminate between AIP and malignant lesions; AIP typically shows hypervascularization whereas pancreatic cancer was hypovascularized.[62,63]

Elastography has been proven to be helpful for the diagnosis of AIP. The elastographic pattern of AIP is characteristic for tumor-like lesions with a unique pattern of small spotted, mainly blue, color signals that are evenly spread over the head and body of the pancreas. Therefore, the whole organ and not just the suspicious lesion demonstrate altered tissue stiffness.[64]

AIP is usually first suggested by an imaging study such as contrast-enhanced CT or MRI. Progressive enhancement of a diffusely enlarged pancreas at dynamic CT and MRI is reported to be characteristic of AIP.[65-67] Decreased enhancement of the pancreatic gland in the early phase, and moderate and persisting delayed enhancement in the late phase are found in 90% of the cases, a finding due to fibrosis.[68] This enhancement patter could be shown also by PDAC due to rich fibrosis related to high desmoplastic reaction. CEUS, lacking the possibility of fibrosis contrast materials accumulation using a blood pool contrast agent, could therefore be superior to CT in the differential diagnosis by viewing PDAC as hypovascular and AIP as isovascular as reported in the present study.

PET/CT scans provide no beneficial information for differentiating between AIP and malignancy[69] but can act as an assessment of corticosteroid therapy on AIP.

At MRI, the affected pancreas is diffusely, focally or multifocally enlarged, hypointense on T1-weighted images, slightly hyperintense on T2-weighted images, with heterogeneously diminished enhanced in the early phase and diffuse slight delayed enhancement in the late phase,[60,70-72] A low-signal capsule-like rim surrounds the diseased parenchyma,[73] along with absence of parenchymal atrophy and peripancreatic fluid, dilatation of the duct proximal to the site of stenosis and sharp demarcation of the abnormality.[74] MRCP is a less accurate alternative to ERCP in evaluating pancreatic ductal changes.[75,76] The intrapancreatic common bile is the most commonly involved segment. Less frequently, multifocal intrahepatic biliary strictures may occur in AIP patients.[61,65,77] ERCP typically shows a (long) stricture of the pancreatic duct without significant associated dilatation.[70,73]

CONCLUSIONS

AIP is characterized by an early and late phase iso- or hyper-enhancement in CE(-E)US in more than 90% of cases. Therefore, CE(-E)US provides complementary diagnostic information which has the potential to improve discrimination in the differential diagnosis from PDAC, particularly when applied to focal tumor-like AIP. However, due to the fact that iso- and hyper-enhancement is also observed in pancreatic neoplasms other than PDAC (e.g., neuroendocrine tumor, and metastases), final diagnosis has to be predicated by comprehensive appreciation of several diagnostic criteria including clinical, biochemical, morphological, and histopathological features.[78-84]

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Conflicts of interest
There are no conflicts of interest.

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