ORIGINAL ARTICLE

Gut and Liver, Vol. 12, No. 5, September 2018, pp. 591-596

Contrast-Enhanced Endoscopic Ultrasound for Differentially Diagnosing Autoimmune Pancreatitis and Pancreatic Cancer

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Background/Aims: Differentially diagnosing focal-type autoimmune pancreatitis (f-AIP) and pancreatic cancer (PC) is challenging. Contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) may provide information for differentiating pancreatic masses. In this study, we evaluated the usefulness of CEH-EUS in differentiating f-AIP from PC. **Methods:** Data were collected prospectively and analyzed on patients who underwent CEH-EUS between May 2014 and May 2015. Eighty consecutive patients were diagnosed with f-AIP or PC. PC and f-AIP were compared for enhancement intensity, contrast agent distribution, and internal vasculature. **Results:** The study group comprised 53 PC patients and 27 f-AIP patients (17 with type-1 AIP [15 definite and two probable], two with probable type-2 AIP, and eight with AIP, not otherwise specified). Hyper- to iso-enhancement in the arterial phase (f-AIP, 89% vs PC, 13%; p<0.05), homogeneous contrast agent distribution (f-AIP, 81% vs PC, 17%; p<0.05), and absent irregular internal vessels (f-AIP, 85% vs PC, 30%; p<0.05) were observed more frequently in the f-AIP group. The combination of CEH-EUS and enhancement intensity, absent irregular internal vessels improved the specificity (94%) in differentiating f-AIP from PC. **Conclusions:** CEH-EUS may be a useful noninvasive modality for differentially diagnosing f-AIP and PC. Combined CEH-EUS findings could improve the specificity of CEH-EUS in differentiating f-AIP from PC. **(Gut Liver 2018;12:591-596)**

Key Words: Autoimmune pancreatitis; Contrast media; Endosonography; Biopsy, fine-needle; Pancreatic neoplasms

INTRODUCTION

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis that responds well to corticosteroids.[1,2] Diagnosing AIP is challenging and should be achieved through a comprehensive evaluation of clinical, radiological, serologic, and pathological evidence, as there is currently no single reliable diagnostic modality.[3] In particular, diagnosing focal-type AIP (f-AIP) is difficult due to its clinical mimicry of pancreatic cancer (PC). The inadvertent resection of a benign pancreatic mass is associated with serious consequences because pancreatic surgery has a considerable risk of severe adverse events, and a misdiagnosis could evoke a lawsuit. Although endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can provide crucial pathological evidence for excluding a suspected pancreatic malignancy, this modality has limitations in diagnosing f-AIP. EUS-FNA may provide insufficient tissue architecture data to allow for a histological diagnosis.[4] In addition, large-caliber (e.g., 19-gauge) needle to acquire histological sample has limitations, for example, difficulty accessing and precisely targeting a specimen, depending on the location of the mass.[5]

Contrast enhancement can be performed simultaneously during a conventional EUS session for identifying and correctly targeting a lesion.[6] Furthermore, dynamic ultrasound images could provide additional information regarding the characteristics of a pancreatic mass. Recent evidence supports the additive role of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) in the differential diagnosis of pancreatic masses.[7-10] Until now, there have been few studies to evaluate the CEH-EUS findings of f-AIP, particularly in the differential diagnosis

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Received on August 30, 2017. Revised on November 12, 2017. Accepted on December 26, 2017. Published online April 27, 2018
pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl17391
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from PC. In the present study, we aimed to evaluate the additive value of CEH-EUS in the differentiation of f-AIP from PC.

MATERIALS AND METHODS

1. Patients

Data for consecutive patients who underwent CEH-EUS for the differential diagnosis of a pancreatic mass previously detected by abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging from May 2014 to May 2015 were analyzed. The study group comprised 53 PC patients and 27 AIP patients (17 with type 1 AIP [15 definite and two probable], two with probable type 2 AIP, and eight with AIP, not otherwise specified) (Table 1). The f-AIP was diagnosed based on the International Consensus Diagnostic Criteria (ICDC) for AIP.[3] To diagnose AIP, the ICDC use five cardinal features of AIP: pancreatic parenchymal and ductal imaging, serology, other organ involvement, histology, and steroid responsiveness. All PC were finally diagnosed by histology including EUS-FNA or pancreatic resection specimen. All of 53 PC patients undergone surgery. PC with metastatic or advanced stage was excluded. This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 20150818). Informed consent was obtained from all patients.

2. Standard and CEH-EUS techniques

A radial or linear echoendoscope (GIF-UE260, GIF-UCT260; Olympus, Tokyo, Japan) and a ProSound alpha-10 ultrasound processor (Aloka, Tokyo, Japan) were used in this study. Under conscious sedation with midazolam, the patients underwent standard B-mode EUS scanning of the pancreas prior to CEH-EUS. After focused scanning of the pancreatic mass to determine the location, size, and echogenicity, the echoendoscope was steadily positioned on the mass lesion. SonoVue (Bracco SpA, Milan, Italy) was used for contrast enhancement. After a 2.4-mL intravenous bolus injection of SonoVue, followed by a 5-mL saline flush, CEH-EUS scanning of the solid pancreatic mass and the surrounding parenchymal structure was performed.[11] An additional 2.4-mL bolus injection of SonoVue was used to obtain a conclusive diagnosis if the enhancement was unsatisfactory. The extended pure harmonic detection mode, which combines the receiving frequencies of filtered fundamental and second harmonic components with a transmitting frequency of 3.4 MHz, was used for CEH-EUS.[11-13] The initial baseline CEH image was acquired in the pre-contrast phase, and subsequent real-time CEH-EUS images were continuously observed for 3 minutes of the contrast-enhanced phase.

Table 1. Baseline Patient Characteristics

Characteristic	f-AIP (n=27)	PC (n=53)	p-value
Age, yr	58 (32–87)	61 (35–77)	0.660
Sex			<0.05
Male	20	26	
Female	7	27	
Pancreatic mass characteristics			
Mass size, cm	2.5 (1–4)	2.5 (1–6)	0.783
Location			0.943
Head	13	27	
Body to tail	14	26	
Type of AIP			-
Type I	17	-	
Type II	2	-	
NOS	8	-	

Data are presented as median (range) or number.
f-AIP, focal-type autoimmune pancreatitis; PC, pancreatic cancer; NOS, not otherwise specified.

3. Definitions

The enhancement intensity was defined as hyper to iso- or hypo-enhancement. Hyper- to iso-enhancement was defined when enhancement intensity is superior or similar to the adjacent normal parenchyma.[14] Prominent increase of echogenicity compared to the pre-contrast phase echogenicity of mass was also defined as hyperenhancement. The contrast agent distribution was defined as homogeneous or heterogeneous. Even distribution of contrast similar to normal parenchyma was defined as homogeneous. Heterogenous distribution was defined as uneven spread of contrast with multifocal filling defects. The peak of intensity and homogeneity of enhancement was defined when full flare up of enhancement was reached regardless of arterial or venous phase. The internal vascular structure was assessed for the presence of irregularities (tortuosity and abrupt disruption) during the arterial phase.[15]

Three endoscopist (T.J.S., D.W.O, and M.K.C.) reviewed the 3 minutes of recorded CEH-EUS footage including arterial (10 to 30 seconds) and venous (30 to 120 seconds) phases. They determined the enhancement intensity, contrast agent distribution, internal vascular structure without any information of previous pathologic and cross-sectional imaging diagnosis. The reviewers were blinded to the final diagnosis of each pancreatic tumor.

4. Statistical analysis

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the CEH-EUS findings for differentiating f-AIP from PC were estimated. To identify independent predictors, a backward logistic regression method of binary logistic regression was used to build a multivariate model of the CEH-EUS pattern. Differences in CEH-EUS findings were considered significant with p-value less than 0.05. Inter-observer agreement was assessed by k statistics. Agreement was interpreted as poor (k<0.20), fair (k<0.21–0.40), moderate (k<0.41–0.60), good (k<0.61–0.80), or very good (k<0.81–1.0).

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

The baseline characteristics of the patients and their pancreatic mass features are listed in Table 1. Patient age and the median mass size did not significantly differ between the two groups, although there were more males in the f-AIP group. B-mode EUS scanning revealed a hypoechoic solid mass in all cases of f-AIP and PC. No adverse events were observed during the CEH-EUS procedure.

2. CEH-EUS findings

Regarding enhancement intensity and contrast agent distribution, hyper- or iso-enhancement in the arterial phase (f-AIP [89%] vs PC [13%], p<0.05) and homogenous contrast agent distribution (f-AIP [81%] vs PC [17%], p<0.05) were more frequently observed in cases of f-AIP (Table 2, Fig. 1). In differentiating f-AIP from PC, the sensitivity and specificity of hyper- to iso-enhancement in the arterial phase were 89% and 87%, and those of homogenous contrast agent distribution were 81% and 83%, respectively. The internal vascular structure was visualized during the arterial phase of contrast enhancement (10 to 30 seconds). Tortuous or disrupted irregular internal vessels were more frequently detected in cases of PC and considered as negative findings (AIP [15%] vs PC [70%], p<0.05) (Fig. 2). The inter-observer agreement in the analysis of CEH-EUS findings was good (enhancement intensity, k=0.79; contrast agent distri-

Table 2. CEH-EUS Patterns in f-AIP and PC

CEH-EUS findings	f-AIP (n=27)	PC (n=53)	p-value
Enhancement intensity in the arterial phase			<0.05
Hyper to iso-enhancement	24 (89)	7 (13)	
Hypo-enhancement	3 (11)	46 (87)	
Contrast agent distribution			<0.05
Homogenous	22 (81)	9 (17)	
Heterogenous	5 (19)	44 (83)	
Irregular internal vessels			<0.05
Negative	23 (85)	16 (30)	
Positive	4 (15)	37 (70)	

Data are presented as number (%).
CEH-EUS, contrast-enhanced harmonic endoscopic ultrasound; f-AIP, focal-type autoimmune pancreatitis; PC, pancreatic cancer.

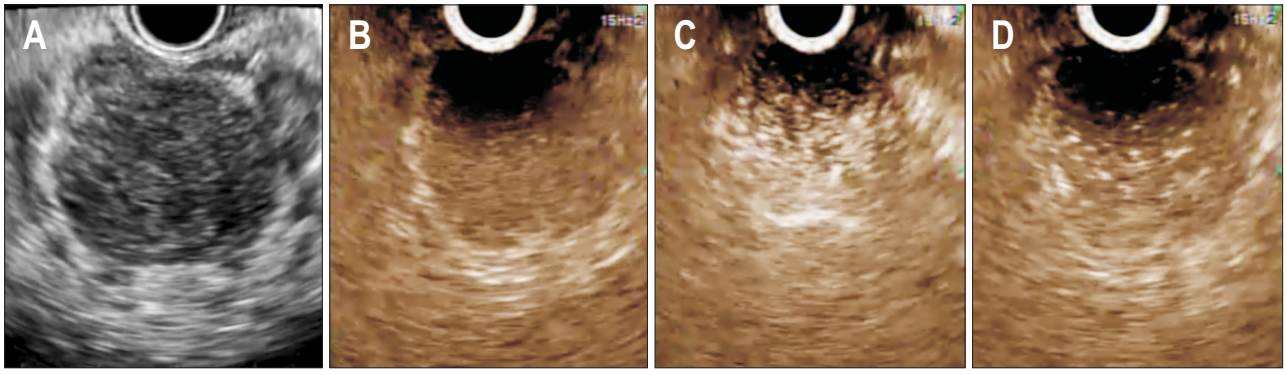

Fig. 1. Contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) of focal-type autoimmune pancreatitis. (A) Hypoechoic mass at the pancreatic head (B mode). (B) Pre-contrast secondary harmonic image. (C) Hyperenhancement of the mass in the arterial phase (20 seconds). (D) Washout in the venous phase (30 seconds).

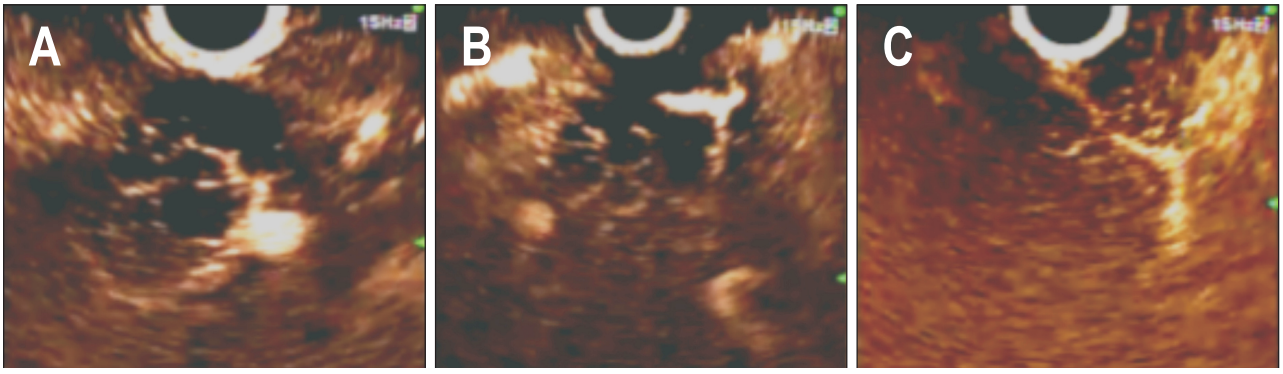

Fig. 2. Pancreatic cancer vascular patterns visualized by contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS). Irregular and abrupt vessel disruptions were observed during CEH-EUS.

bution, k=0.91; absent irregular internal vessels, k=0.93).

3. Diagnostic yield for differentiating f-AIP and PC

The sensitivity, specificity, accuracy, and positive and negative predictive values of individual CEH-EUS findings for differentiating f-AIP and PC are listed in Table 3. Hyper- to iso-enhancement, absent irregular internal vessels were identified as independent factors by backward stepwise method in the multivariate logistic regression analysis (Table 4). The most specific CEH-EUS finding was hyper- to iso-enhancement without irregular internal vessels (specificity, 94%) for differentiating f-AIP and PC (Table 3).

Table 3. Sensitivity, Specificity, and Accuracy of CEH-EUS for Differentiating f-AIP and PC

CEH-EUS findings	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %
A*	89	87	88	77	94
B†	81	83	83	71	90
C‡	85	70	75	59	90
A+B	89	83	85	73	94
B+C	67	92	84	82	84
A+C	74	94	88	87	88
A+B+C	89	87	88	77	94

CEH-EUS, contrast-enhanced harmonic endoscopic ultrasound; f-AIP, focal-type autoimmune pancreatitis; PC, pancreatic cancer; PPV, positive predictive value; NPV, negative predictive value.
*A, enhancement intensity; †B, contrast agent distribution; ‡C, absent irregular internal vessels.

DISCUSSION

Recent studies have shown that CEH-EUS could be useful for the differential diagnosis of pancreatic masses. Although CEH-EUS findings specific for PC such as hypoenhancement with a heterogeneous pattern have been reported (Fig. 3),[11,12] there have been few reports on CEH-EUS findings of f-AIP. Therefore, we attempted to identify CEH-EUS findings that could support a differential diagnosis between f-AIP and PC. In the present study, we focused on the CEH-EUS-based diagnosis of f-AIP and its differential diagnosis with PC. We evaluated the sensitivity, specificity and accuracy of each CEH-EUS finding and those of combinations of these findings for differentially diagnosing f-AIP and PC. We found that hyper- to iso-enhancement in the arterial phase, homogenous contrast agent distribution, absent irregular internal vessels were significantly more frequent in cases of f-AIP. Those findings could be valuable for distinguishing f-AIP from PC. The combination of two independent CEH-EUS findings (enhancement intensity and absent irregular internal vessels) showed high specificity (94%) and positive predictive value (87%) (Table 3). We also suggest that CEH-EUS findings can provide valuable evidence for diagnostic steroid trial, particularly when pathological evidence is unavailable or inconclusive.

Cross-sectional imaging modalities are essential for the characterization and differential diagnosis of solid pancreatic masses. However, pathological confirmation may be necessary because there may be certain ambiguities and overlap of cross-sectional imaging findings between f-AIP and PC. EUS-guided tissue acquisition can provide pathological evidence for

Table 4. Univariate and Multivariate Analyses for Differentiating f-AIP from PC

CEH-EUS findings	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Enhancement intensity	52.6 (12.5–221.8)	<0.001	45.9 (9.2–229.1)	<0.001
Contrast agent distribution	21.5 (6.4–72.0)	<0.001	-	-
Absent irregular internal vessels	13.3 (4.0–44.7)	<0.001	10.9 (2.7–55.4)	0.004

f-AIP, focal-type autoimmune pancreatitis; PC, pancreatic cancer; CEH-EUS, contrast-enhanced harmonic endoscopic ultrasound; OR, odds ratio; CI, confidence interval.

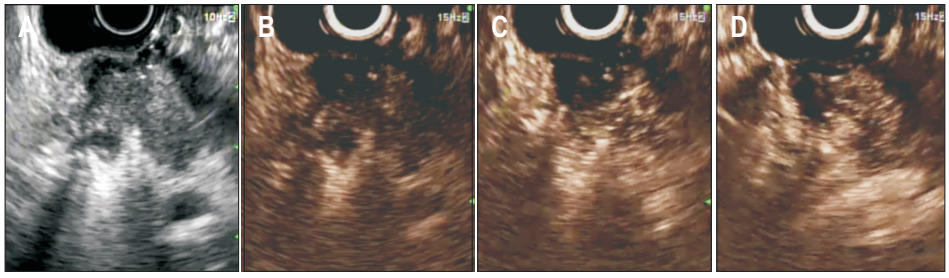

Fig. 3. Contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) of pancreatic cancer. (A) Hypoechoic mass at the pancreatic head (B mode). (B) Pre-contrast secondary harmonic image. (C) Heterogeneous hypoenhancement of the mass in the arterial phase (25 seconds). (D) Persistent venous phase hypoenhancement (50 seconds).

the diagnosis or exclusion of PC and may provide histological evidence suggestive of AIP. Unfortunately, diagnosing AIP based on cytology or histology also has certain limitations. A cytology-based evaluation does not provide sufficient histological and immunohistochemical characteristic evidence for diagnosing AIP.[16-19] In fact, even in core biopsy specimens the full spectrum of lymphoplasmacytic sclerosing pancreatitis was only observed in 26% to 44%.[2,20] In a recently published study, EUS-FNA was non-diagnostic in 44% of patients who had a definitive diagnosis of AIP based on ICDC guidelines prior to EUS-FNA.[21] Although new EUS-guided core biopsy needles with enhanced flexibility and improved tissue acquisition have been developed, it is challenging to access with core biopsy needle for some lesions. Considering the limitations of cross-sectional imaging and EUS-guided tissue acquisition, CEH-EUS can play an important role in obtaining valuable evidence for differentiating between f-AIP and PC.

CEH-EUS is a contrast-specific imaging procedure that is superior to B-mode or contrast-enhanced Doppler EUS (CED-EUS).[11,22] CEH-EUS can provide better real-time images of the fine internal vasculature without any blooming or motion artifacts. Hocke *et al*.[15] reported certain vascularity-based endosonographic criteria for differentiating between malignant and benign disease. An irregular appearance of arterial vessels in the contrast-enhanced power Doppler mode was suggested as a specific finding of PC, and a regular appearance of vessels was suggested as a specific finding of chronic pancreatitis. In this study, we found that irregular internal vessels were more frequently detected in cases of PC (AIP [15%] vs PC [70%], $p<0.05$).

Imazu *et al*.[23] suggested the use of quantitative echo intensity, time intensity curve, and maximal intensity gain measurements to depict changes in the signal intensity over time. However, the observation of these findings would require specialized software, and an inappropriate region-of-interest setting could lead to inaccurate estimations.[24] We were intended to analyze the enhancement patterns in casual setting without dedicated software. Additional study using objective analyzing technique is necessary.

CEH-EUS can be performed noninvasively without radiation exposure by simply adding a contrast agent during a conventional EUS exam. SonoVue—a second-generation ultrasound contrast agent—contains poorly soluble phospholipid-stabilized microbubbles of sulfur hexafluoride.[22] The toxicity of and potential for an allergic reaction to SonoVue are minimal, and the risk of emboli is clinically insignificant.[22,24] No adverse events due to SonoVue use were observed in any of the 80 patients in the present study.

This study has several limitations. First, this study did not include other benign pancreatic tumors, such as neuroendocrine tumors or solid pseudopapillary neoplasm. We only focused on differentiating between f-AIP and PC because PC should be the first diagnosis of exclusion when f-AIP is suspected and steroid trial is considered. Further investigation is required to assess the clinical value of CEH-EUS for the differential diagnosis of f-AIP from other benign pancreatic tumors. Second, small case volume may limit the validation of diagnostic performance of CEH-EUS. Further prospective study with large number of patients is needed.

In conclusion, CEH-EUS may be a valuable noninvasive modality for the differential diagnosis of f-AIP and PC; for this purpose, a combination of CEH-EUS findings can provide more improved specificity.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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