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A Comparative Study of Endoscopic Ultrasonography and Histopathology Images for the Diagnosis of Early Chronic Pancreatitis

Masanari Sekine, MD, PhD, Akira Tanaka, MD, PhD,† Maho Akimoto, MD,† Takaya Miura, MD,* Junichi Fujiwara, MD,* Hiroshi Noda, MD, PhD,‡ Toshiki Rikiyama, MD, PhD,‡ Hirohide Ohnishi, MD, PhD,§ and Hirosato Mashima, MD, PhD**

Objective: The concept of early chronic pancreatitis (ECP) and its diagnostic criteria were first proposed by Japan, using endoscopic ultrasonography (EUS) findings for diagnosis. However, these findings have not been supported by pathological findings. We aimed to examine the association between the EUS and pathological findings of the same area of the pancreas.

Methods: In 12 patients who underwent pancreaticoduodenectomy for distal bile duct cancer without accompanying pancreatitis, a comparative analysis between preoperative EUS and pathological findings was performed. The part of the pancreas adjoining the portal vein was evaluated.

Results: In 7 cases, abnormal EUS findings included in the diagnostic criteria for ECP were seen; the correlation of the accuracy of lobularity seen on EUS compared with the pathological findings of the pancreatic parenchyma (inflammatory cell infiltration, atrophy of acinar cells, and fibrosis) was high (83.3%–91.7%). Pancreatic duct findings revealed that the accuracy of the hyperechoic margin of the pancreatic duct on EUS compared with pathological findings (wall thickness of pancreatic duct) was high (83.3%).

Conclusions: Endoscopic ultrasonography findings for ECP, according to Japan's 2019 revised criteria, lobularity, and the hyperechoic margin of the pancreatic duct may highly correspond to the pathological findings of chronic inflammation.

Key Words: early chronic pancreatitis, endoscopic ultrasonography, histopathology, lobularity, hyperechoic margin of the pancreatic duct

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Chronic pancreatitis (CP) is an irreversible, progressive inflammatory disease of the pancreas caused by multiple factors.[1–3] The progression of irregular fibrosis and parenchymal exfoliation characteristically leads to pancreatic exocrine/endocrine dysfunction. In patients with CP, the average life expectancy is approximately 10 years lower than that in healthy individuals; a higher incidence rate of pancreatic cancer is also shown to be problematic.[4] However, therapeutic intervention during early CP (ECP) was reported to aid in recovery to normal in an animal model.[5] Thus, therapeutic interventions at an early stage are considered important, leading the Japanese to be the first in the world to propose the concept of ECP in 2009.[6] The "new mechanistic definition" of CP was proposed by Whitcomb et al in 2016 and in the conceptual model, ECP was defined as the reversible pathological condition of a preceding stage of "completed irreversible CP."[3] Therefore, the diagnosis of ECP prevents irreversible progression; in addition, therapeutic interventions prevent complications, leading to an improvement in the prognosis. For diagnosis, endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP) imaging is needed. However, ERCP carries a risk of pancreatitis; at present, it is not performed with the aim of diagnosis in actual clinical settings. Magnetic resonance cholangiopancreatography represents a newly introduced modality in the 2019 diagnostic criteria; a magnetic field strength of 3.0T has been recommended to capture an image of the pancreatic branch ducts in detail. Collecting cases in the future is important regarding usefulness. Therefore, in the current situation, imaging by EUS is used for the diagnosis of ECP in almost all cases. Endoscopic ultrasonography findings of the diagnostic criteria for early-stage CP were slightly modified in 2019.[7] They define CP as the presence of 2 or more of the 4 findings, including the following (1) or (2): (1) hyperechoic (nonshadowing) foci or strands, (2) lobularity, (3) hyperechoic margin of the pancreatic duct, and (4) dilated pancreatic branch ducts. However, these were partially extracted from the Rosemont classification based on clinical experience; that is, pathological evidence was not included.[8] The association between EUS images and pathological changes, such as early-stage inflammation and fibrosis, in the pancreas remains unclear. Although symptoms for ECP have not been observed in clinical settings, similar EUS image findings of ECP have been frequently encountered. In addition, histological findings have not been included in the diagnosis of ECP, because histological findings of ECP have not been clarified. Therefore, the present study aimed to examine the association between the EUS and histopathology images by comparing the same area of the pancreas.

MATERIALS AND METHODS

Subjects

This was a retrospective, pilot, and single-center study. The subjects comprised 12 patients diagnosed with bile duct cancer, who had undergone preoperative EUS and pancreaticoduodenectomy at Saitama Medical Center, Jichi Medical University, Japan.

Endoscopic Ultrasonography

EU-ME2/GF-UCT260 (Olympus Corp, Tokyo, Japan) was used for all patients under sedation using midazolam. Two operators performed EUS; 1 operator was a board-certified fellow of the Japan Gastroenterological Endoscopy Society, and the Japan

From the Departments of *Gastroenterology, †Pathology, and ‡Surgery, Saitama Medical Center, Jichi Medical University, Saitama; and §Japan Organization of Occupational Health and Safety, Kawasaki, Japan.

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Address correspondence to: Masanari Sekine, MD, PhD, Department of Gastroenterology, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma-cho, Omiya-ku, Saitama City, Saitama, 330-8503, Japan (e-mail: msekine@jichi.ac.jp).

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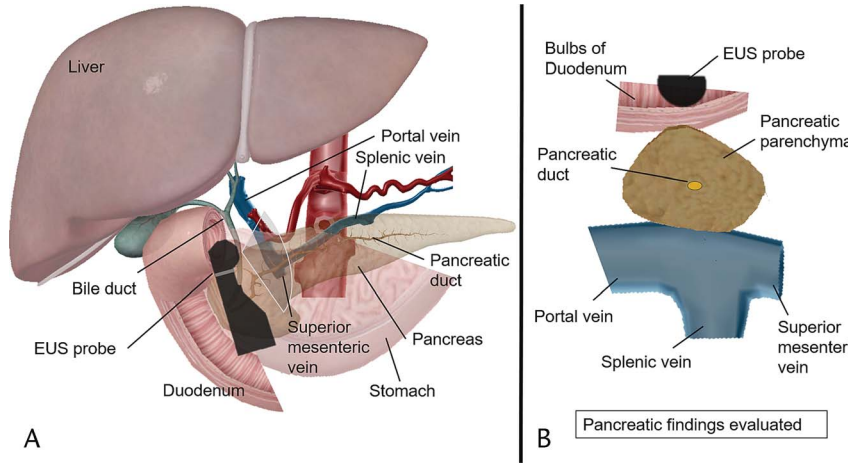


FIGURE 1. Assessment method in EUS. A, Transitional view of pancreas with EUS from duodenal bulb. Assessment is performed at the site adjoining the confluence (portal vein, splenic vein, and superior mesenteric vein) in the short-axis view of pancreas. B, Schematic diagram visualized by EUS. The pancreas surrounded by the duodenal wall, portal vein, and superior mesenteric vein is used for assessment.

Pancreas Society with more than 1000 experiences using EUS, and the other was a board-certified fellow of the Japan Gastroenterological Endoscopy Society with more than 300 experiences using EUS. The former used video-recorded images to evaluate the EUS findings. The findings similar to ECP by EUS were assessed in accordance with Japan's 2019 clinical diagnostic criteria for CP.[7] Four criteria, for the assessment of the pancreatic parenchyma (hyperechoic foci [nonshadowing] or strands [Hyp] and lobularity [Lob]), and for the pancreatic duct (hyperechoic margin of the pancreatic duct [H-MPD] and dilated side branches of the pancreatic duct [Dil]), were classified and scored as − (absent) or + (present). Concerning the EUS findings (overall), the presence of 2 or more of the 4 findings, including either Hyp or Lob, was scored as + (present) and otherwise as − (absent).

To assess the EUS images and the pathological findings in the same area, the findings of the pancreas adjoining the portal vein as observed from the duodenal bulb were used (Fig. 1).

Surgical Procedure

Pancreaticoduodenectomy accompanied by standard lymphadenectomy was performed in all the patients. The pancreatic dissection line was at the left edge or just above the portal vein. A frozen section diagnosis of the pancreatic stump was performed in 8 patients.

Histological Evaluation

The extracted portion of the pancreas in the pancreaticoduodenectomy is adjacent to the notch of the portal vein. Formalin-fixed and paraffin-embedded specimens of pancreatic stumps, on which a frozen section diagnosis was performed, were prepared, and an assessment was performed (Fig. 2). In the remaining 4 cases, a frozen section diagnosis was not performed. For comparison, the assessable specimen closest to the pancreatic body was used in such cases.

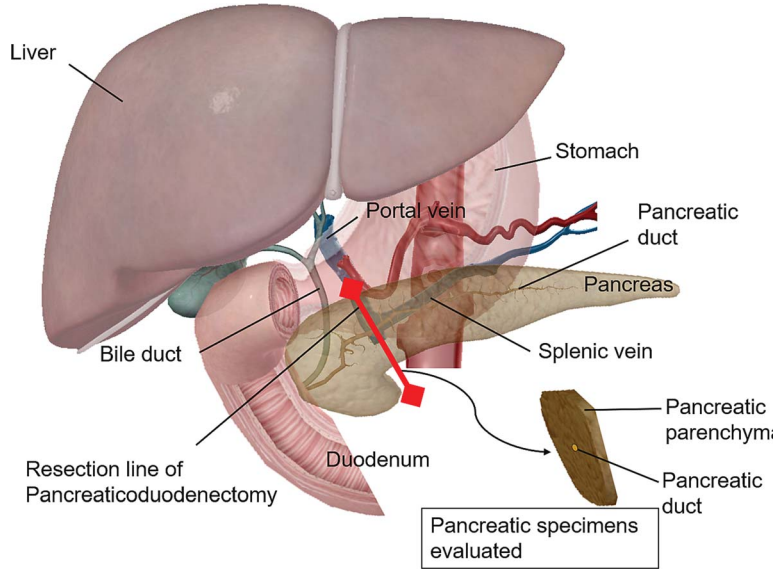


FIGURE 2. Assessment method in collected specimens. The resection line in pancreaticoduodenectomy is placed above the portal vein; an assessment is performed by operating a short-axis segment of the pancreatic stump for frozen section diagnosis.

TABLE 1. Patient Characteristics

Sex, male/female, n	10:2
Age, mean (range), y	75.3 (60–82)
p-AMY, mean (range), U/L	33.2 (18–89)
Alcohol use, mean (range), g	25.8 (0–45)
Epiabdominal and/or back pain continued, positive/negative	0:12
History of acute pancreatitis, positive/negative	0:12
Calcification of pancreatic parenchyma and/or duct in CT, positive/negative	0:12
Diagnosis	
Cholangiocarcinoma (Bd)	8
Cholangiocarcinoma (Bp)	1
Cholangiocarcinoma (Bp-Bd)	1
Intraductal papillary neoplasm of the bile duct	1
Atypical epithelium of bile duct	1

Bd indicates distal bile duct; Bp, perihilar bile duct.

Two experienced pathologists of the Japan Society of Pathology evaluated the histological findings independently. When the decisions were divided, they discussed and decided on the final diagnosis. The characteristic histological findings of CP as designated in Japan's clinical diagnostic criteria in 2009 and 2019 represent exfoliation of the pancreatic parenchyma and fibrosis. These are generally assessed with the degree of intralobular and interlobular fibrosis shown by Ammann et al.[9] In previous studies, the assessment of the pancreatic parenchyma included acinar cell atrophy (atr), inflammatory cell infiltration (inf), and fibrosis (fib). Assessment of the pancreatic duct involved analysis of the wall thickness (t-MPD).[10,11] These were classified as negative (−) or positive (+). The pathological findings (overall) were classified as present (+) when any of the 4 criteria was present and otherwise as absent (−).

Statistical Analysis

Endoscopic ultrasonography and histopathology findings in the 12 cases were classified into absent (−) and present criteria (+). The variance of the EUS and histopathology findings was analyzed using the χ^2 test. In addition, P values (<0.05) of the EUS and histopathology findings were calculated using linear regression analysis. Data were analyzed using the statistical software EZR Version 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[12]

Ethical Aspects

The study was approved by the ethics committee of Saitama Medical Center, Jichi Medical University (register code: S18-147) and conducted in accordance with the Declaration of Helsinki.

RESULTS

Patient Characteristics

The patient characteristics are shown in Table 1. The patients had undergone pancreaticoduodenectomy for bile duct tumors. Endoscopic ultrasound had been performed before surgery; therefore, effects such as accompanying pancreatitis and tumor invasion had not been observed in the pancreas. Abdominal computed tomography scan had also shown no CP findings, such as pancreatic parenchymal calcification. The alcohol consumption among the patients was 25.8 g/d on average, and 6 patients did not drink. The average pancreatic amylase level (p-AMY) was 33.2 U/L and a higher p-AMY level than normal (reference range, 21–64 U/L) was seen in 4 patients.

The Findings of EUS and Histopathology

The scores for the EUS and the histopathology findings in each patient are displayed in Table 2. In the present study, Dil was not observed. There were 7 cases with abnormalities detected by EUS, 6 of which had anomalies in the histopathology findings. On the other hand, in the event of no abnormal EUS findings, anomalies were not seen in the extracted pancreatic specimens.

Representative Case Presentation

Here, we present the 2 representative cases. Case 8 was free from both abnormal EUS and pathological findings. Case 10 had multiple abnormal findings in both EUS and pathology.

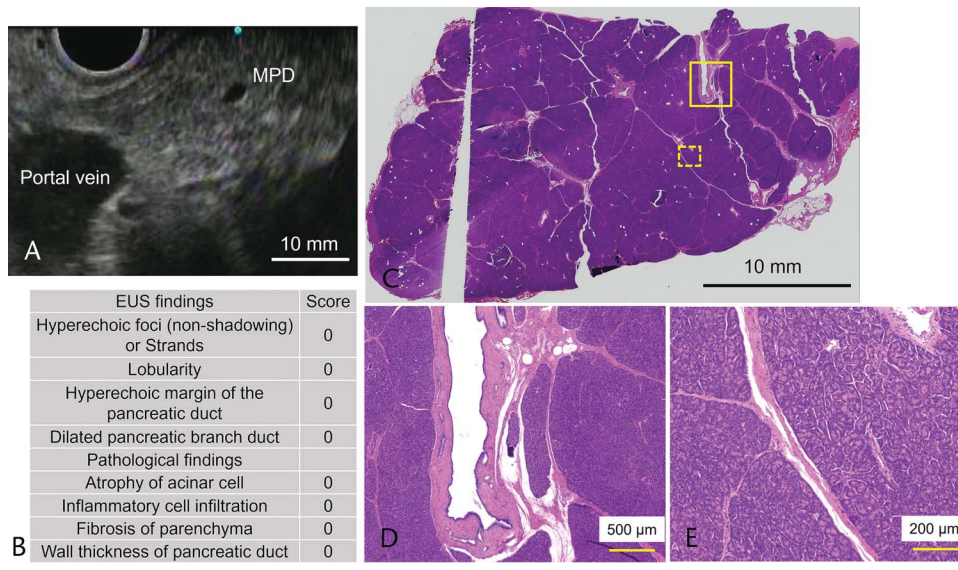
TABLE 2. The EUS and the Pathological Findings

	EUS Findings (Overall)*	Hyp	Lob	H-MPD	Dil	Pathological Findings (Overall)†	Fib	Atr	Inf	t-MPD
Case 1	+	+	+	+	−	+	+	−	−	−
Case 2	+	+	+	+	−	+	−	+	−	+
Case 3	−	−	−	−	−	−	−	−	−	−
Case 4	−	−	−	−	−	−	−	−	−	−
Case 5	+	+	−	+	−	+	−	−	−	+
Case 6	+	+	−	+	−	+	+	−	−	+
Case 7	+	+	−	+	−	−	−	−	−	−
Case 8	−	−	−	−	−	−	−	−	−	−
Case 9	−	−	−	−	−	−	−	−	−	−
Case 10	+	+	+	+	−	+	+	+	+	+
Case 11	−	−	−	−	−	−	−	−	−	−
Case 12	+	+	+	−	−	+	+	+	+	−

*Endoscopic ultrasonography findings (overall): the presence of 2 or more of the 4 findings (Hyp, Lob, H-MPD, Dil), including Hyp or Lob, was scored as present (+) and otherwise as absent (−).

†Pathological findings (overall): the presence of any of the 4 criteria (fib, atr, inf, t-MPD) was scored as present (+) and otherwise as absent (−).

Fib indicates fibrosis; Atr, acinar cell atrophy; Inf, inflammatory cell infiltration.



EUS findings	Score
Hyperechoic foci (non-shadowing) or Strands	0
Lobularity	0
Hyperechoic margin of the pancreatic duct	0
Dilated pancreatic branch duct	0
Pathological findings	
Atrophy of acinar cell	0
Inflammatory cell infiltration	0
Fibrosis of parenchyma	0
Wall thickness of pancreatic duct	0

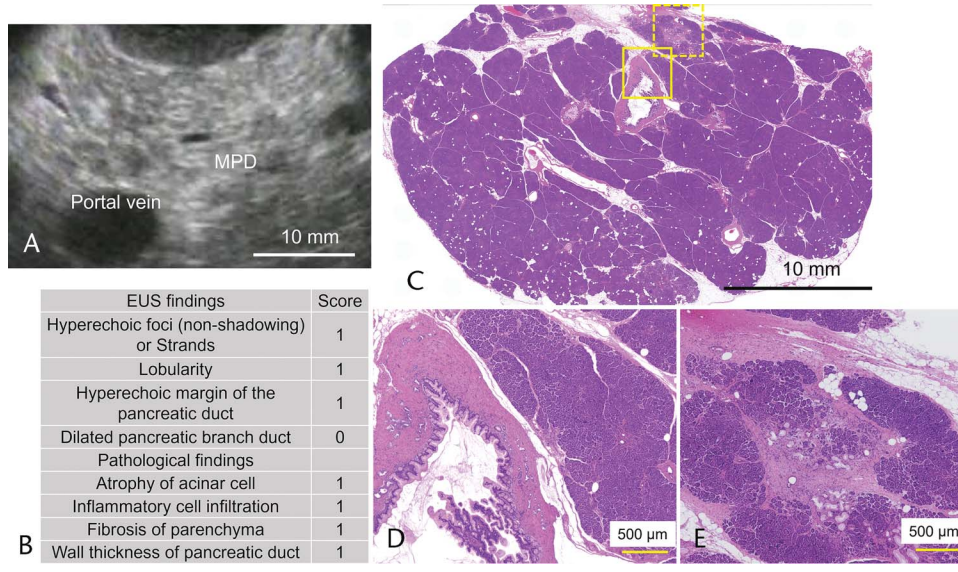
FIGURE 3. A representative case without abnormal EUS or pathological findings (case 8). A, EUS image. B, Scoring of EUS and pathological findings. C, A loupe image. D, The rectangle (solid line) in (C), showing no MPD thickening. E, The rectangle (dotted line) in (C), showing no inflammation in pancreatic parenchyma.

Case 8 (Fig. 3) is a 71-year-old man who underwent pancreaticoduodenectomy for distal bile duct cancer. There was no history of alcohol use or acute pancreatitis. A mild elevation in pancreatic enzymes (p-AMY = 72 U/L) was observed. There were no findings suggesting chronic inflammation in the EUS or the pathological images.

Case 10 (Fig. 4) is an 82-year-old woman who underwent pancreaticoduodenectomy for distal bile duct cancer. There was no history of alcohol use or acute pancreatitis. The levels of pancreatic enzymes were within the normal range (p-AMY = 50 U/L). An EUS showed Lob, Hyp, and H-MPD. The pathological findings also included inf, atr, fib, and t-MPD.

Comparison Between the EUS Findings and the Histopathology Findings

Next, the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of each EUS finding corresponding to the pathological findings were analyzed (Table 3). In Table 3, the sensitivity, specificity, and accuracy between the EUS findings (overall) and the pathological findings (overall) were high (100% [12 of 12], 83.3% [10 of 12], and 91.7% [11 of 12], respectively). Subsequently, the 2 EUS findings of the pancreatic parenchyma (Hyp and Lob) were analyzed in each corresponding pathological finding. An analysis of Hyp to



EUS findings	Score
Hyperechoic foci (non-shadowing) or Strands	1
Lobularity	1
Hyperechoic margin of the pancreatic duct	1
Dilated pancreatic branch duct	0
Pathological findings	
Atrophy of acinar cell	1
Inflammatory cell infiltration	1
Fibrosis of parenchyma	1
Wall thickness of pancreatic duct	1

FIGURE 4. A representative case with multiple abnormal EUS and pathological findings (case 10). A, EUS image. B, Scoring of EUS and pathological findings. C, A loupe image. D, The rectangle (solid line) in (C), showing MPD thickening. E, The rectangle (dotted line) in (C), showing inflammatory cell infiltration, acinar cell atrophy, and fibrosis in pancreatic parenchyma.

TABLE 3. The Sensitivity, Specificity, Accuracy, PPV, NPV, and *P* Values Between Items of the EUS Findings and the Pathology Findings

	Sensitivity, %	Specificity, %	Accuracy, %	PPV, %	NPV, %	*P*
EUS findings (overall)* and pathological findings (overall)†	100	83.3	91.7	85.7	100	0.00054
Hyp and the following:						
inf	100	50	58.3	28.6	100	0.57
atr	100	55.6	66.7	42.9	100	0.47
fib	100	62.5	75	57.1	100	0.14
Lob and the following:						
inf	100	80	83.3	50	100	0.085
atr	100	88.9	91.7	75	100	0.0034
fib	75	87.5	83.3	75	87.5	0.017
H-MPD and t-MPD	100	75	83.3	66.7	100	0.063

*Endoscopic ultrasonography findings (overall): the presence of 2 or more of the 4 findings (Hyp, Lob, H-MPD, dilated side branches), including either Lob or Hyp, was scored as present and otherwise as absent.

†Pathological findings (overall): The presence of any of the 4 criteria (fib, atr, inf, t-MPD) was scored as present (+), and otherwise as absent (−).

the 3 pathological findings of the pancreatic parenchyma (inf, atr, and fib) reflected high sensitivity and NPV (100%, 100%, respectively), with low specificity, accuracy, and PPV (range, 50%–62.5%, 58.3%–75%, and 28.6%–57.1%, respectively; Table 3), indicating the high false-positive rate of Hyp. In contrast, the sensitivity, specificity, accuracy, and NPV of Lob to the same 3 pathological findings (inf, atr, and fib) were high (range, 75%–100%, 80%–88.9%, 83.3%–91.7%, and 87.5%–100%, respectively), whereas PPV was relatively low (range, 50.0%–75.0%). Last, an analysis of the sensitivity, specificity, accuracy, and NPV of H-MPD in EUS findings compared with those of t-MPD in the pathological findings showed high values (100%, 75%, 83.3%, and 100%, respectively), similar to the result for Lob.

A linear regression analysis of the previous results showed that the relations between Lob and 2 pathological findings of the pancreatic parenchyma (atr and fib) were significant ($P = 0.0034$ and $P = 0.017$). The hyperechoic margin of the pancreatic duct in EUS and wall thickness of the pancreatic duct in pathology tended to be related, but not significantly. As a whole, the association between EUS findings (overall) and pathological findings (overall) was significant ($P = 0.00054$).

These results demonstrate that Lob and H-MPD reflect the histopathology images of chronic inflammation in the pancreatic tissue. In contrast, Hyp was not shown to sharply reflect the analyzed pathology because of its high false-positive rate. In addition, NPV was high in all the findings; normal EUS findings resulted in conventional pathology criteria.

DISCUSSION

In this study, we analyzed the EUS findings of the diagnostic criteria for ECP and compared them with the pathological findings for the disease. Other than symptoms of ECP, we sometimes encounter abnormal EUS findings similar to them. Using surgical specimens for bile duct cancer, not accompanying pancreatitis, we could compare the EUS images and histopathology from almost the same site of the pancreas. In 6 of 12 patients, we were able to detect abnormal EUS findings, which were associated with chronic inflammation in pathology.

Japan's 2009 clinical diagnostic criteria for early-stage CP were modified in 2019[7] and now state that cases must display at least 3 of the following signs and symptoms: (1) persistent upper abdominal or back pain, (2) abnormal levels of pancreatic enzymes in the blood/urine, (3) pancreatic exocrine dysfunction, (4) continuing alcohol intake of over 60 g/d or abnormality in pancreatitis-related genes, and (5) a history of acute pancreatitis. In addition, the cases satisfying EUS, ERCP, or MRCP findings and displaying ECP are defined as confirmed cases, whereas those only satisfying 2 of the 5 conditions and satisfying EUS/ERCP/MRCP findings are defined as suspected cases.

Endoscopic ultrasonography displays high spatial resolution; it is expected to identify changes in the pancreatic parenchyma and the duct in CP, whereas ERCP and MRCP indicate only the morphological changes of the pancreatic duct. The study of CP using EUS was first reported in 1986.[13,14] Although many studies have reported diagnoses of CP, the classification of the clinical progression and severity using EUS has not always been consistent.[15–17] To resolve this, a new classification system using EUS, the Rosemont classification, was prepared in the Consensus Conference on the EUS Evaluation of Chronic Pancreatitis held in April 2007.[3] In this system, EUS findings are rated and assessed by adding weight (major A, major B, minor) to some of the previous data consistent with, suggestive of, or indeterminate for CP, as well as for normal. Early CP was considered an indeterminate form of CP. In the 2009 clinical diagnostic criteria for CP, the following 7 findings were adopted as EUS imaging findings of ECP: (*a*) lobularity with honeycombing (major B in the Rosemont classification), (*b*) lobularity without honeycombing (minor), (*c*) hyperechoic foci without shadowing (minor), (*d*) stranding (minor), (*e*) cyst (minor), (*f*) dilated side branches (minor), and (*g*) hyperechoic main pancreatic ductal margin (minor). The diagnostic criteria were modified in 2019, and lobularity and hyperechoic foci (nonshadowing) or strands, dilated side branches, and hyperechoic margin of the pancreatic duct were retained.

Studies associated with the pathological findings of ECP are limited.

It is therefore important to compare the findings of EUS and pathology in ECP. However, regarding the assessment of fibrosis, Varadarajulu et al[18] and Albashir et al[19] report EUS findings to be beneficial, whereas Chong et al,[20] LeBlanc et al,[21] and Trikudanathan et al[22] report the contrary. Several problems exist in comparing EUS and pathological findings. First, collecting a normal pancreatic tissue sample is ethically difficult. Second, for the proper pathological assessment of the pancreatic parenchyma, the optimal site needs to be assessed by EUS. Savides et al[23] reported that pancreatitis was difficult to assess in ventral pancreatic parenchyma using EUS. In addition, pancreatitis caused by cancer is required to be excluded. Therefore, in the present study, we used the data of cases of bile duct cancer.

Unlike pancreatic cancer, the resection site for a pancreaticoduodenectomy matches the notch of the portal vein, permitting pathological assessment at the corresponding site. Thus, a comparison between the EUS findings and the pathological findings of the region adjoining the portal vein can be performed. Moreover, the notch of the portal vein belongs to the dorsal pancreas.

The analysis of EUS findings and histopathology data indicated that both Lob and Hyp, corresponding to the changes in pancreatic parenchyma, showed high sensitivity and NPV. However, the specificity and accuracy of Lob were high, whereas those of Hyp were low. The present study indicated that in the EUS findings, Lob reflected the pathological changes, featuring chronic inflammation of the pancreatic parenchyma, especially atrophy of the acinar cells and fibrosis. Previous studies showed that Hyp is not a specific finding in the diagnosis of CP; however, it is observed when CP has been histologically proven.[14,15] This was similar to the results of the present study. Hyperechoic foci (nonshadowing) or strands might be an earlier marker for chronic inflammation than Lob but probably contain the pathological changes from other causes like alcohol use or smoking.[24] Furthermore, H-MPD of the EUS findings were indicative of t-MPD in the pathological findings. The wall thickness of the pancreatic duct in pathological findings might mean perilobular fibrosis and/or periductal fibrosis.[25] Lob and H-MPD were considered extremely useful as the EUS imaging findings of ECP. The results suggested that the addition of major and minor classifications like the Rosemont classification of CP may increase the imaging accuracy of EUS. In addition, if changes in the EUS findings from early to CP are clarified, the degree of progression to CP may become predictable.

The limitations of the study are as follows: (1) this is a single-institution retrospective investigation, (2) the number of cases is small (n = 12), and (3) EUS and histopathological findings were evaluated by "all or none" method, which is presence or absence of the findings. Considering the distribution of EUS findings, Hyp was diffuse or scattered, and Lob was sparse. In histological findings, fib and atr were sparse in most of the positive cases but scattered in some cases. Inflammatory cell infiltration was sparse in all positive cases. These EUS and histological abnormal findings were spotty in some cases, but when the area of anomalies was less than 1% of the total, it was scored as absent. The number of cases is insufficient to provide definitive information from the data.

Observing the cases of bile duct cancer not affecting the pancreas, the EUS images and pathological data were comparable at the same site of the pancreas. In the future, the analysis should be performed in a multicenter prospective study featuring a larger number of cases. An assessment of the extent and distribution of each finding should be included in the study. In addition to clarifying the correlation between the EUS and pathological findings of ECP, the analysis of age, drinking history, sex, body mass index, as well as the preparation of a new scoring system may allow an increase in the accuracy of diagnostic criteria.

Conclusions

Using Japan's 2019 clinical diagnostic criteria for ECP, the EUS findings for Lob and H-MPD strongly reflect the pathological findings of chronic inflammation. Evaluating the significance of each EUS finding may facilitate the accurate diagnosis of ECP.

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