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ORIGINAL ARTICLE

Utility of Contrast-Enhanced Harmonic Endoscopic Ultrasonography to Diagnose Pancreaticobiliary Maljunction

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Abstract

Background Detection of a common channel outside the duodenal wall is important in diagnosing pancreaticobiliary maljunction (PBM). The present study evaluated the utility of contrast-enhanced harmonic endoscopic ultrasonography (CH-EUS) in diagnosing PBM.

Methods This single-center retrospective study enrolled 45 patients who were diagnosed with PBM or high confluence of pancreatobiliary ducts (HCPBD) between January 2007 and December 2021. The diagnostic sensitivities of contrast-enhanced computed tomography (CE-CT), magnetic resonance imaging (MRI), and CH-EUS for diagnosing PBM were analyzed. Imaging findings were evaluated by two reviewers blinded to the clinicopathological results.

Results Based on diagnostic criteria, 33 patients were diagnosed with PBM and 12 with HCPBD. Compared with the patients with HCPBD, those with PBM had significantly longer common channel (12.5 mm vs. 8.1 mm, $P=0.018$) and common bile duct (13.0 mm vs. 8.6 mm, $P=0.049$) lengths. The κ-coefficients for differentiating PBM and HCPBD were 0.871 between CE-CT and MRI, 0.330 between CE-CT and CH-EUS, and 0.611 between MRI and CH-EUS. The diagnostic sensitivity of CH-EUS (95.2%) was higher than that of CE-CT (83.3%) and MRI (82.8%), although the differences were not statistically significant.

Conclusion CH-EUS may be useful for the diagnosis of PBM.

Keywords Contrast-enhanced harmonic endoscopic ultrasound · Endoscopic ultrasonography · Pancreatobiliary ducts · Pancreaticobiliary maljunction · Pancreaticobiliary

Abbreviations

CH-EUS	Contrast-enhanced harmonic endoscopic ultrasonography
CI	Confidence interval
CE-CT	Contrast-enhanced computed tomography
EUS	Endoscopic ultrasonography
ERCP	Endoscopic retrograde cholangiopancreatography
HCPBD	High confluence of pancreatobiliary ducts
MPR	Multiplanar reconstruction
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PBM	Pancreaticobiliary maljunction
SSFSE	Single-shot fast spin-echo

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital anatomic anomaly, in which the pancreatic and bile ducts merge outside the duodenal wall, resulting in the mutual backflow of pancreatic juice and bile and causing various pathological conditions, including biliary tract cancer [1]. The frequency of biliary cancer in adults with PBM has been reported to range from 22 to 42%, with a diagnosis of PBM being an indication for prophylactic surgical treatment [1]. PBM can be diagnosed by direct cholangiography techniques, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage procedure, as well as by less invasive methods such as magnetic resonance

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imaging (MRI), computed tomography (CT), and endoscopic ultrasonography (EUS) (Supplementary Fig. 1) [2].

PBM is characterized anatomically by a long common channel outside the duodenal wall, but must be differentiated from high confluence of pancreatobiliary ducts (HCPBD), a similar disease in which the common channel lies within the duodenal wall (Supplementary Fig. 2) [3]. Although CT or MRI is generally used to differentiate PBM from HCPBD, these methods may have difficulty in detailed assessments around the duodenal wall. EUS may be useful in these patients, as it clarifies the positional relationship between the duodenal muscle layer and intrapancreatic bile duct by injecting air or saline solution into the duodenum in real time [3]. Contrast-enhanced harmonic EUS (CH-EUS) has recently been reported useful in the diagnosis of pancreaticobiliary diseases [4–7]. To our knowledge, however, no studies to date have evaluated the ability of CH-EUS to diagnose PBM. The present cross-sectional study therefore compared the abilities of CH-EUS, CT, and MRI to diagnose PBM.

Patients and Methods

Study Design

This was a single-center, comparative, retrospective study. The study protocol was approved by the Ethics Committee of the Kindai University Faculty of Medicine (approval number: R05-198). All enrolled subjects provided informed consent. All procedures were performed in accordance with relevant guidelines and regulations.

The primary study endpoints were the comparative sensitivities of contrast-enhanced CT (CE-CT), MRI (including magnetic resonance cholangiopancreatography [MRCP]), and CH-EUS in the diagnosis of PBM by detecting a common channel outside the duodenal wall. The secondary endpoints were the concordance rates between pairs of imaging modalities in determining a diagnosis of PBM or HCPBD.

Patients

The present study enrolled 45 patients who were diagnosed with PBM or HCPBD based on Japanese diagnostic criteria for PBM 2013 [2] between January 2007 and December 2021. All included patients were evaluated at least once by two of the three imaging modalities, CE-CT, MRI, and CH-EUS. Patients not evaluated by at least two modalities were excluded.

CE-CT

Intravenous CE-CT imaging was performed using a two-phase CT (Toshiba X-vigor; Toshiba Medical System, Tokyo, Japan) or a 64-channel multidetector CT scanner (Discovery CT750 HD or LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA). In the former modality, 100 mL of Iopamiron (iopamidol; Nihon Schering, Osaka Japan), with an iodine concentration of 370 mg/mL, was injected, followed by dynamic acquisition in the early arterial (30 s) and portal (60 s) phases. In the latter modality, patients underwent a non-contrast-enhanced scan, followed by injection of nonionic contrast material containing 300–370 mg/mL iodine (510 mg iodine per kg body weight) for 30 s [7]. Early arterial phase scanning was started manually 10 s after the attenuation value in the region of interest in the abdominal aorta reached over 200 HU (about 30 s after the injection). The late arterial, portal venous and equilibrium phases were scanned at 40, 55, and 150 s, respectively. The CT images were reviewed mainly in late arterial phase of multiplanar reconstruction (MPR), at thicknesses of 3 mm and 5 mm, by two readers (S.W. Im and T. Hyodo) who were blinded to the clinicopathological results.

MRI

MRI was performed using a 3.0 T system (Achieva: Philips Medical Systems, Best, The Netherlands) or either of two 1.5 T systems (Signa Excite HDxt, GE Healthcare; and Gyroscan Intera Nova, Philips Medical Systems). Axial and coronal breath-hold single-shot fast spin-echo (SSFSE) or half-Fourier acquisition SSFSE T2-weighted, 2D thick-slab SSFSE MRCP, 3D MRCP, T1-weighted dual-echo, b800 diffusion-weighted images, and T2-weighted images acquired with fat-suppressed turbo spin-echo sequence were obtained [8]. T2-weighted and MRCP images were mainly evaluated, with all images analyzed by the same blinded radiologists (S.W. Im and T. Hyodo) who evaluated the CT images.

CH-EUS

Patients underwent EUS and CH-EUS using an echoendoscope developed for CH-EUS (GF-UC240, GF-UCT240, or GF-UCT260; Olympus Medical Systems, Tokyo, Japan), with the images analyzed using ALOKA Pro-Sound α10, Pro-Sound F75, or ARIETTS 850 (Fujifilm Healthcare, Tokyo, Japan). Following normal EUS, the imaging mode was switched to the extended pure harmonic detection mode, which synthesized the filtered second-harmonic components with signals obtained from the phase shift for contrast-enhanced harmonic imaging. The transmitting frequency and mechanical index were 4.7 MHz and 0.3, respectively [4].

The ultrasound contrast agent used for CH-EUS was Sonazoid® (GE Healthcare), which consists of perfluorobutane microbubbles surrounded by a lipid membrane. Just before performing CH-EUS, the contrast agent was reconstituted

with 2 mL of sterile water. A bolus injection of 15 μL Sonazoid® per kg body weight in a 2-mL syringe was administered at a speed of 1 mL/s through a 22-gauge cannula placed in the antecubital vein, followed by 10-mL saline solution to ensure that all contrast agents were introduced into the circulation. CH-EUS was started approximately 60 s after the injection of contrast medium. All CH-EUS videos were stored and individually reviewed by two blinded EUS endoscopists (K. Kamata and H. Tanaka), each of whom had performed > 1000 CH-EUS procedures for differentiating PBM from HCPBD.

Final Diagnosis

PBM was differentiated from HCPBD based on their diagnostic criteria, as determined by blinded re-evaluation of the images [2]. PBM was defined as the presence of a long common channel outside the duodenal wall on any of the imaging methodologies, whereas HCPBD was defined as the presence of a common channel ≥ 6 mm long within the duodenal wall and the absence of a common channel outside the duodenal wall on any of the imaging methods. Thus, the case of discrepancy between each imaging diagnosis was defined as PBM.

Statistical Analysis

Continuous variables were expressed as the median and range and analyzed by *t* tests. Categorical variables were expressed as percentages and analyzed by Fisher's exact tests. Disagreements between the two reviewers on blinded, independent readings of CE-CT, MRI, and CH-EUS imaging results were resolved by re-evaluation by both reviewers together until agreement was reached. The diagnostic sensitivities of CE-CT, MRI, and CH-EUS for PBM were calculated, along with their 95% confidence intervals (CIs) and compared by Fisher's exact tests. The consistency between assessments of imaging modalities was evaluated by calculating their κ-coefficients and 95% CIs, with κ-coefficients > 0.8, > 0.6, and > 0.4 indicating excellent, good, and moderate agreement, respectively. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) and a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Baseline Characteristics

Evaluation of the imaging results in the 45 included patients showed that 33 were diagnosed with PBM and 12 with HCPBD, with none of these patients being unclassifiable. The baseline characteristics of these 45 patients are shown in Table 1. Patients with PBM had significantly longer common channel (12.5 mm vs. 8.1 mm, $P = 0.018$) and common bile duct (13.0 mm vs. 8.6 mm, $P = 0.049$) lengths than patients with HCPBD. Biliary cancer was observed only in five patients with PBM. Three patients were diagnosed with PBM during the further evaluation for cholangiocarcinoma, and one was diagnosed with PBM at the same time as the diagnosis of gallbladder cancer. The other patient did not wish to undergo surgery after diagnosis of PBM, but developed gallbladder cancer 4 years later. Common bile duct dilatation ≥ 10 mm was observed in 22 (66.7%) of the 33 patients with PBM, all of whom were suspected of congenital biliary dilation. The Todani classification of the bile duct cysts in these 22 patients was I-a in one patient, I-c in 17, and IV-A in four [9].

Table 1 Patient characteristics

	Total ($n = 45$)	PBM ($n = 33$)	HCPBD ($n = 12$)	*P* value*
Age, years	59 (4–84)	57 (4–76)	70.5 (15–84)	0.279
Male: female, *n*	16: 29	10: 23	6: 6	0.296
Surgical case, *n*	35	27	8	0.418
Common channel length, mm	12.0 (6.0–24.0)	12.5 (7.0–24.0)	8.1 (6.0–16.4)	0.018
Common bile duct length, mm	13.0 (3.0–42.0)	13.0 (3.0–42.0)	8.6 (6.0–23.0)	0.049
Comorbidities				
Gallstone, *n*	5	3	2	0.598
Bile duct stone, *n*	2	2	0	1.000
Cholangiocarcinoma, *n*	3	3	0	0.553
Gallbladder cancer, *n*	2	2	0	1.000

HCPBD high confluence of pancreatobiliary ducts; *PBM* pancreaticobiliary maljunction

*For comparisons between the PBM and HCPBD groups

Table 2 Diagnostic results of imaging modalities

$n=34$		MRI	
		PBM	HCPBD
CE-CT	PBM	21	1
	HCPBD	1	11
$n=22$		CE-CT	
		PBM	HCPBD
CH-EUS	PBM	13	5
	HCPBD	1	3
$n=23$		MRI	
		PBM	HCPBD
CH-EUS	PBM	13	4
	HCPBD	0	6

CE-CT contrast-enhanced computed tomography; *CH-EUS* contrast-enhanced harmonic endoscopic ultrasonography; *HCPBD* high confluence of pancreatobiliary ducts; *MRI* magnetic resonance imaging; *PBM* pancreaticobiliary maljunction

Table 3 Diagnostic sensitivity of imaging modalities for PBM

	Sensitivity	*P* value*
CE-CT, % [95% CI]	83.3 (25/30) [66.0–93.1]	0.381
MRI, % [95% CI]	82.8 (24/29) [65.0–92.9]	0.380
CH-EUS, % [95% CI]	95.2 (20/21) [75.6–100.9]	

CE-CT contrast-enhanced computed tomography; *CH-EUS* contrast-enhanced harmonic endoscopic ultrasonography; *CI* confidence interval; *MRI* magnetic resonance imaging; *PBM* pancreaticobiliary maljunction

*Compared with the results of CH-EUS

Image Evaluations

Of the 45 patients, 34 underwent both CE-CT and MRI, 22 underwent both CE-CT and CH-EUS, and 23 underwent both MRI and CH-EUS (Table 2). The κ-coefficients for differentiating PBM from HCPBD were 0.871 (95% CI 0.587 to 0.964) between CE-CT and MRI, 0.340 (95% CI − 0.029 to 0.518) between CE-CT and CH-EUS, and 0.629 (95% CI 0.269 to 0.629) between MRI and CH-EUS. Thus, CE-CT and MRI showed excellent agreement and MRI and CH-EUS showed good agreement. Twenty-eight patients underwent both EUS and CH-EUS. Their results were in perfect agreement in determining PBM or HCPBD. On the other hand, significant differences were identified in the clarity of the common channel between the two modalities on a 5-point scale evaluation (1, Poor; 2, Average; 3, Good; 4, Very good; 5, Excellent) by five blinded reviewers, each of whom had performed > 1000 CH-EUS procedures (Supplementary Table 1).

Of the 33 patients with PBM, 30, 29, and 21 were evaluated by CE-CT, MRI, and CH-EUS, respectively (Table 3). The diagnostic sensitivities of CE-CT and MRI were comparable (83.3% [25/30] vs. 82.8% [24/29], $P=1.000$), whereas the diagnostic sensitivity of CH-EUS (95.2% [20/21]) was higher than that of CE-CT ($P=0.381$) and MRI ($P=0.380$), although the differences were not significant. One patient with PBM, who underwent a B-I operation, could not be diagnosed by EUS, with imaging of the ampulla of Vater area being somewhat poor. That patient could be diagnosed with PBM only by CE-CT. In one patient, CE-CT and MRI failed to detect a common channel outside the duodenal wall, whereas CH-EUS was able to detect this channel, leading to a diagnosis of PBM (Fig. 1). CH-EUS of this patient showed a well-defined duodenal lumen, with the confluence of the bile and pancreatic ducts being located within the pancreas.

Nineteen patients underwent all the three modalities (Supplementary Table 2). In those patients, the κ-coefficients for differentiating PBM from HCPBD were 0.774 (95% CI 0.339 to 0.937) between CE-CT and MRI, 0.379 (95% CI − 0.032 to 0.580) between CE-CT and CH-EUS, and 0.627 (95% CI 0.206 to 0.627) between MRI and CH-EUS. Sixteen out of 19 patients had PBM. The diagnostic sensitivities of CE-CT and MRI for PBM were consistent (75.0% [12/16]), whereas the diagnostic sensitivity of CH-EUS (93.8% [15/16]) was higher than that of CE-CT and MRI, although the differences were not significant ($P=0.333$) (Supplementary Table 3). Thus, these subgroup analyses showed similar trends to the overall.

Discussion

The diagnostic criteria for PBM include an abnormally long common channel, but this channel need not be outside the duodenal wall [2]. Some reports using cholangiography have defined a long common channel as being ≥ 10 mm or ≥ 15 mm in length [10, 11], whereas another study reported a cut-off value of ≥ 8 mm [12]. In addition, autopsy studies have shown that the length of the common channel in patients with PBM varies from 1 to 12 mm [13]. Thus, there are no clear criteria for "abnormally long" channels. The diagnostic criteria recommend that common channel length be determined by MRCP or 3D-drip infusion cholecystocholangiography with CT [2]. The latter method, however, has inherent disadvantages, including the side effects of contrast agents and the inability of this method to visualize the pancreatic ducts [14]. Thus, the common channel being located outside the duodenal wall is an important criterion in the definition of PBM. Some patients with long common channels that may have been classified originally as having PBM, however, may have been classified as having HCPBD

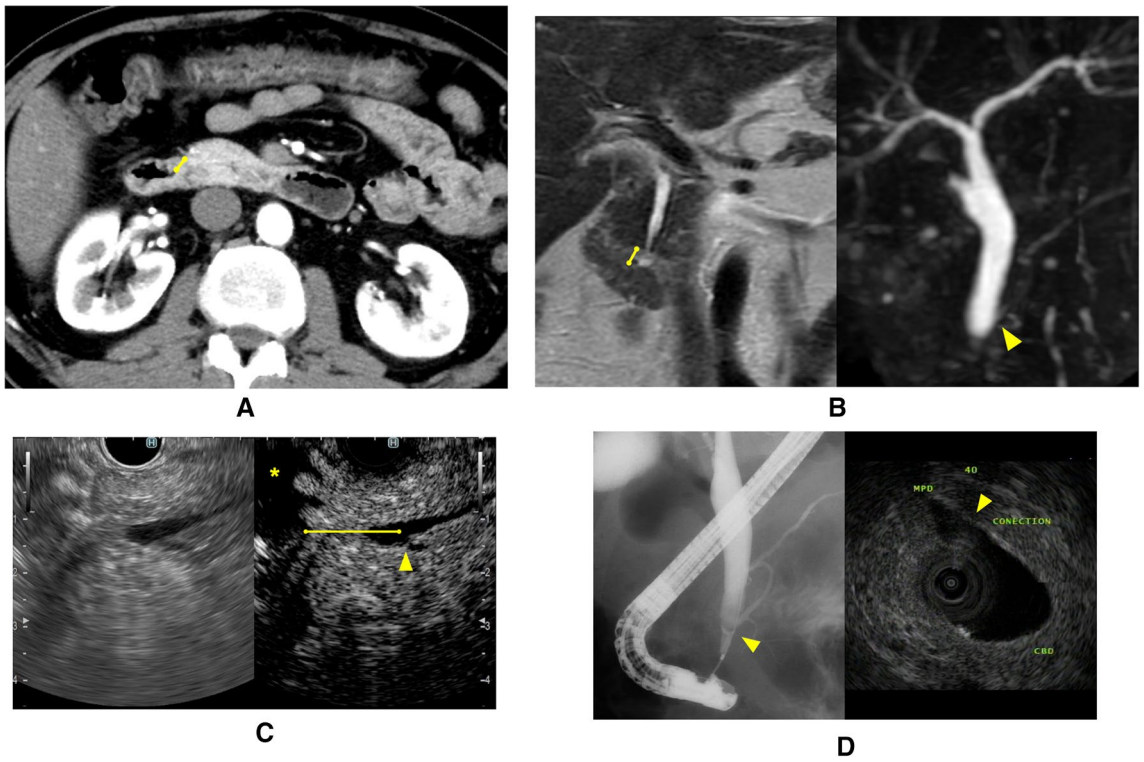

Fig. 1 **a** CE-CT image. The common channel within the duodenal wall measured 4.8 mm in length (yellow line). **b** MR T2-weighted (left side) and MRCP (right side) images. The common channel within the duodenal wall measured 7.4 mm in length (yellow line). MRCP also showed the confluence of the pancreatic and biliary ducts (arrowhead). **c** CH-EUS image (left side; monitor mode, right side; contrast mode). The duodenal lumen (*) was clearer in contrast mode than in monitor mode. The common channel outside the duodenal wall measured 19.2 mm in length (yellow line). The distance from the confluence of the pancreatic and biliary ducts (arrowhead) to the ampulla of Vater orifice was easy to measure. **d** ERCP (left side) and intraductal ultrasonography (right side) images showing the confluence of the pancreatic and biliary ducts (arrowhead)

in the present study. Nevertheless, differences were observed in the patient profiles of the two groups, including differences in common bile duct and common channel lengths and the frequency of biliary cancer.

Various imaging modalities have been used to diagnose PBM. For example, ERCP is excellent at delineating the confluence of the bile and pancreatic ducts and, when combined with intraductal ultrasonography, has high diagnostic accuracy [15]. ERCP, however, is an invasive method associated with several complications. Noninvasive methods, such as CT and MRI, are currently used to diagnose PBM [16]. CT delineates the pancreatic parenchyma and duodenal wall, allowing differentiation between PBM and HCPBD, with CT using MPR images having diagnostic sensitivities for PBM of 58–100% in adults and 20% in children [17]. The MPR of CE-CT images in late arterial phase is considered appropriate for the diagnosis of PBM. This method shows high contrast between the pancreas and pancreaticobiliary duct, and moderate contrast between the pancreas and duodenal wall, making it easy to identify the boundary between the pancreas and duodenum. Although MPR is optimized by making a section orthogonal to the wall of the duodenal papillary region, it is sufficient to evaluate the relationship between the confluences of the pancreaticobiliary ducts and the duodenal wall in coronal sections. The delineation of duodenal lesions on CT may be improved by imaging methods that use a radiopaque contrast or foaming agent in the right anterior oblique position to dilate the duodenal lumen and stretch the duodenal wall, but the usefulness of these methods in diagnosing PBM is unknown [18].

MRCP is a noninvasive method that can substitute for ERCP, with the diagnostic rate of MRCP for PBM ranging from 63 to 82% [19, 20]. Although the location of the confluences of the pancreaticobiliary ducts and the duodenal wall can be determined from T2-weighted images of coronal sections alone, it often requires determination in reference to MRCP. The diagnostic performance of MRI may be improved by dynamic MR with secretin stimulation [17]. However, the possibility of bovine spongiform encephalopathy has led to the avoidance of biologic products, and porcine secretin is no longer used in most countries. The U.S. Food and Drug Administration approved the use of human synthetic secretin (ChiRhoStim®) in 2004, and its usefulness has since been reaffirmed.

CT and MRI have difficulties in accurately measuring common channel length and identifying confluences in certain situations. These include (1) when the anatomic location of the duodenum and peristalsis make it difficult to control collapse and dilation or wall thickness, even when using foaming agents, antispasmodics, and/or re-positioning; (2) when difference in the contrast between the duodenal wall and pancreas is poor, making it difficult to identify the boundary; (3) when measurements are erroneous, varying by 1–2 mm; and (4) when the secretion of digestive juices leads to opening of the ampulla of Vater, thereby altering the length of the common channel.

By contrast, EUS has high spatial resolution and can clearly observe areas around the duodenal wall, with the diagnostic performance of EUS for PBM being 85–100% [21–23]. There are two types of EUS, radial and convex, but their relative ability to diagnose PBM is unclear. Although CH-EUS involves invasive endoscopic procedures, the rate of side effects of ultrasound contrast is extremely low [24]. Compared with CE-CT and MRI, EUS has the potential to control for collapse and dilation or wall thickness by real-time observation and by lifting duodenal collapse. Furthermore, CH-EUS can enhance the ability to differentiate between the duodenal wall and pancreas by using contrast to clearly delineate the duodenal lumen, wall, and pancreatic parenchyma with contrast. Whereas CE-CT and MRI produce similar results in differentiating PBM from HCPBD, CH-EUS often provides different results than the other two modalities. EUS had the highest sensitivity in diagnosing PBM, although differences between imaging modalities were not statistically significant in the present study.

The present study had several limitations, including its retrospective design and inclusion of a relatively small number of patients. Moreover, some of these patients were not evaluated by all three imaging modalities, thus complicating comparisons. Second, the standard against which these modalities were compared was based on an overall diagnostic imaging evaluation that also considered the results of blind readings. Therefore, there may be biases in calculating the sensitivity of each diagnostic imaging modality and in comparing these sensitivities. Third, because there was a one-to-one correspondence between the common channel being depicted outside the duodenal wall and the definitive diagnosis of PBM, the positive predictive value and specificity of the imaging diagnosis should each be 100%; thus, only diagnostic sensitivity was evaluated. Finally, the superiority of CH-EUS over EUS was not demonstrated for the differential diagnosis of PBM and HCPBD, although CH-EUS clearly delineated the common channel in comparison with EUS.

In conclusion, identification of a common channel outside the duodenal wall should be regarded as an objective indicator for the diagnosis of PBM. Despite each imaging modality having own advantages and disadvantages, CH-EUS may be useful in the diagnosis of PBM. Additional studies, however, are needed to confirm these findings.

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Author's contributions Tomohiro Yamazaki contributed toward study concept and design, acquisition, analysis, and interpretation of data, statistical analysis, and drafting of the manuscript; Ken Kamata contributed toward critical revision of the manuscript for important intellectual content, blind reading of endoscopic ultrasonography images, and study supervision; Tomoko Hyodo and Sung-Woon Im contributed toward blind reading of CT and MRI images; Hidekazu Tanaka contributed toward blind reading of endoscopic ultrasonography images; Akihiro Yoshida and Tomohiro Fukunaga contributed toward data collection and blind reading of endoscopic ultrasonography images; Shunsuke Omoto contributed toward critical revision of the manuscript for important intellectual content; Kosuke Minaga contributed toward critical revision of the manuscript for important intellectual content and blind reading of endoscopic ultrasonography images; Mamoru Takenaka contributed toward study supervision and final approval of the submitted manuscript and blind reading of endoscopic ultrasonography images; Masatoshi Kudo contributed toward study supervision and final approval of the submitted manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest with respect to this study.

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