

Ultrasound imaging features of isolated pancreatic tuberculosis

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ABSTRACT

Background and Objectives: Isolated pancreatic tuberculosis (PTB) is extremely rare worldwide. The purpose of this multicenter retrospective study is to analyze imaging features of histologically confirmed isolated PTB in order to determine the diagnostic features of the new methods contrast enhanced ultrasound (CEUS), ultrasound elastography and contrast enhanced endoscopic ultrasound (CE-EUS). **Patients and Methods:** We report on a retrospective data collection of 12 cases of PTB confirmed by histology or cytology. All examinations were interpreted by two independent readers in consensus. CEUS, CE-EUS and ultrasound elastography were performed according to the European Federation of Societies for Ultrasound in Medicine and Biology guidelines. **Results:** In PTB patients the common bile duct was never dilated. Multiple retroperitoneal lymph nodes are the second important B-mode ultrasound feature detected in 75% of PTB patients. CE-EUS was performed in three PTB patients demonstrating hyperenhancement. On elastography, all PTB lesions were markedly stiffer than surrounding pancreatic parenchyma. **Conclusions:** Here we report the first time on CEUS and elastography features of PTB. PTB had some typical imaging features with iso- or hyperenhancement on CE(E) US. PTB is markedly stiffer on elastography. If clinicians are aware of clinical features of PTB and conduct appropriate investigations with multiple modalities including B-mode ultrasound, CEUS, and EUS guided fine needle aspiration, diagnosis of PTB without laparotomy is possible and the disease can be effectively treated with anti-tuberculous drugs.

Key words: Contrast enhanced endoscopic ultrasound, contrast enhanced ultrasound, elastography, guidelines, pancreatic tuberculosis

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How to cite this article: Dong Y, Jürgensen C, Puri R, D’Onofrio M, Hocke M, Wang WP, *et al.* Ultrasound imaging features of isolated pancreatic tuberculosis. *Endosc Ultrasound* 2018;7:119-27.

Access this article online

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DOI:

10.4103/2303-9027.210901

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Received: 2016-10-24; **Accepted:** 2016-11-30; **Published online:** 2017-07-17

INTRODUCTION

Extra-pulmonary tuberculosis (TB) is an emerging clinical problem worldwide, including dissemination to the gastrointestinal tract,^[1-3] liver,^[4] spleen and mesenteric lymph nodes.^[5-8] Pancreatic TB (PTB) is an extremely rare disease, which usually occurs as a complication of miliary TB in immunodeficiency individuals.^[9,10] PTB has been little reported in the literature over the past few decades and its clinical characteristics remain unclear.^[11-14]

The accurate preoperative diagnosis of PTB is clinically challenging because it is difficult to differentiate from other tumorous and non-tumorous lesions. Isolated PTB is extremely rare worldwide. It can mimic carcinoma, lymphoma, cystic neoplasia, retroperitoneal tumors, pancreatitis or pseudocysts.^[15] Due to the paralleling clinical presentations and imaging findings in pancreatic TB and pancreatic neoplasm, and patients exhibiting a wide spectrum of non-specific complaints, the majority of the cases are diagnosed after surgical exploration for presumed pancreatic malignancy.^[16,17] Accurate diagnosis may avoid delays in treatment and unnecessary surgery.^[18]

Solitary pancreatic involvement of TB may present with variable radiological manifestations.^[19,20] The imaging picture of this chronic infection may be revealed as variable pancreatic lesions, including pancreatic cystic neoplasm, such as serous cystadenoma.^[21] It is often difficult to differentiate PTB mimicking cystic neoplasms from benign or malignant pancreatic cystic neoplasms.^[19,22,23] Until now, non-invasive imaging studies such as B-mode ultrasound (BMUS), computed tomography (CT) and magnetic resonance imaging (MRI) can only localize a focal lesion in the pancreas. However non-surgical imaging diagnosis of PTB continues to be a challenge.

Contrast enhanced ultrasound (CEUS) is a safe and accurate imaging method to evaluate the vascularity of pancreatic lesions, which improves the characterization of pancreatic masses.^[24] As a first line examination, CEUS performed immediately after the detection of a pancreatic mass at BMUS, providing a significant improvement in diagnostic accuracy.^[24,25] The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines and recommendations on the clinical practice of CEUS updated 2011 on non-hepatic applications included the use of CEUS in focal

pancreatic lesions.^[26] With the review of literature, there is no report about CEUS features of pancreatic TB.

The purpose of this multicenter retrospective study is to analyze imaging features of histologically confirmed PTB in order to describe diagnostic features of CEUS, ultrasound elastography and contrast enhanced endoscopic ultrasound (CE-EUS).

PATIENTS AND METHODS

Patients

We report on a retrospective data collection of 12 cases of PTB confirmed by histology or cytology. The average age at diagnosis was 54 ± 11 years (37–70 years). Six patients were male and six were female [Table 1].

Based on traditional imaging modalities (CT, MRI and conventional BMUS), the pre-EUS diagnoses included autoimmune pancreatitis in two patients, cystadenoma in two patients, pancreatic adenocarcinomas (PDAC) in five patients, neuroendocrine tumor in one patient, metastasis lesion in one patient and lymphoma in one patient. All lesions were histologically confirmed as PTB by surgical biopsies or via EUS - fine needle aspiration (FNA).

Table 1. Baseline characteristics of pancreatic tuberculosis and pancreatic ductal adenocarcinoma patients

Characteristic	PTB patients (n=12)	PDAC patients (n=22)
Age (year)		
Mean±SD	54±11	54±14
Range	37-70	60-74
Male/female	6/6	14/8
Underlying disease		
Known tuberculosis	3	/
Lung cancer	1	/
HIV positive	1	
No	7	22
Symptoms		
Abdominal pain	2	4
Jaundice	2	14
Incidental finding	8	2
Weight loss	/	2
Histological results		
Surgery	/	22
Core needle biopsy during operation	9	/
Fine needle biopsy	3	

PTB: Pancreatic tuberculosis, PDAC: Pancreatic ductal adenocarcinoma, HIV: Human immunodeficiency virus, SD: Standard deviation, /: number = 0

Since PDAC is the most important differential diagnosis, twenty-two patients with histopathologically proven PDAC were analyzed as peer group.

Examination technique

Conventional ultrasound and CEUS were performed in all patients with one of six ultrasound systems: Philips iU22 unit (Philips Bothell, WA, USA; C5-1 convex array probes, 1–5 MHz), or LOGIQ E9 (GE Healthcare, Milwaukee, WI, USA; C1-5 convex array probes, 1–5 MHz) or Hitachi (Hi vision EUB-6500, Preirus, Ascendus; C715 convex array probes, 1–5 MHz), 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 ultrasound contrast agent SonoVue was injected at a dose of 2.4 mL, immediately followed by an injection of 10 mL sodium chloride solution. Images were recorded for 3 min after contrast agent injection.

CE-EUS and EUS elastography were performed as recently described using longitudinal echoendoscopes EG-3870 UTK and Hitachi platforms (HI vision EUB-6500, Preirus, Ascendus).^[27]

Three patients were assessed by the acoustic radiation force impulse (ARFI) technology using Acuson S2000™ equipment with Virtual Touch™ Quantification software (VTQ) for the assessment of pancreatic lesions' stiffness by obtaining the shear wave velocity (SWV). Ten measurements of ARFI VTQ were made in each suspected pancreatic lesion. The SWV was expressed in m/s. The depth of measurement ranged from 4.5 cm to 5.5 cm from skin.

Imaging Evaluation (contrast enhanced ultrasound, endoscopic ultrasound, elastography)

All examinations were interpreted by two independent readers (15 and 20 years of experience with pancreatic CEUS imaging) who were blinded to the clinical and pathologic data. CEUS enhancement pattern of PTB was evaluated according to the 2011 EFSUMB guidelines.^[26,28] The CEUS features of isolated PTB lesions were compared to the surrounding normal pancreatic parenchyma.

The VTQ values of SWV measurements were presented as the mean, median, standard deviation range.

Final diagnoses, treatment and clinical follow up

The final diagnosis of nine PTB patients was achieved by core needle biopsy (18-gauge 20-cm single-use biopsy needles; Temno, Germany, or BioPince, Pflugbeil, Germany) as part of workup for a preoperative confirmation of pancreatic carcinoma. In another three PTB patients, fine needle biopsy was performed during EUS.

In all patients with PTB, clinical follow-up to 12 months confirmed the diagnosis.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Continuous parameters such as the mean \pm standard deviation and the Chi-square test and Fisher's exact test were used to compare categorical parameters between groups. $P < 0.05$ was considered statistically significant.

Institutional board approval

Institutional Board Approval was obtained.

RESULTS

Conventional ultrasound

On conventional BMUS, all 12 cases of PTB were detected as isolated hypoechoic focal pancreatic lesions. All PDAC lesions were detected as hypoechoic focal pancreatic lesions in the pancreatic head [Figure 1].

A pathologically dilated common bile duct (CBD) was common in PDAC lesions (86.3%), but not in PTB lesions ($P < 0.05$).

Multiple retroperitoneal lymph nodes were detected in 75% PTB patients, but not in PDAC patients [Table 2].

Contrast enhanced ultrasound

In six patients, CEUS was performed. After contrast agent injection as well as during the late phase, all six PTB lesions (100%) and most of the PDAC lesions (86.3%) were hypoenhancing ($P > 0.05$) on CEUS. In the arterial phase iso- or hyperenhancement was seen in six patients comparing to the surrounding tissue.

Contrast enhanced endoscopic ultrasound

CE-EUS was performed in three patients with PTB demonstrating hyperenhancement in all cases. All 22 cases of PDAC were hypoenhancing in CE-EUS.

Elastography

EUS elastography was performed in five PTB lesions, all of them were markedly stiffer than surrounding pancreatic parenchyma [Figure 2].

VTQ were performed in three PTB lesions, mean SWV were 3.66 ± 1.21 m/s, which were stiffer than the surrounding pancreas parenchyma (1.08 ± 0.70 m/s) [Table 3].

DISCUSSION

Epidemiology

TB of the abdomen is seen in 12% of patients with miliary TB.^[29,30] PTB, which was first reported by

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

Characteristic	PTB lesions (n=12), n (%)	PDAC lesions (n=22), n (%)
Location		
Head/neck	7 (58.3)	22 (100)
Body	2 (16.7)	0
Tail	3 (25.0)	0
Common bile duct		
Dilated (>8 mm)	0	19 (86.3)
Normal	12 (100)	3 (13.6)
Size of focal pancreatic lesion (mm)		
Mean±SD	36.5±14.2	61.9±10.4
Range	20-65	52-87
Hypervascular in CDI	2 (16.7)	0
Retroperitoneal lymph node enlargement	9 (75)	0

CDI: Color Doppler imaging, PTB: Pancreatic tuberculosis, PDAC: Pancreatic ductal adenocarcinoma, SD: Standard deviation

Auerbach in 1944, is extremely rare.^[31] The incidence of pancreatic TB is reported to be <4.7% worldwide. Pancreatic TB most often occurs as a complication of miliary TB. The low frequency of pancreatic TB may be partly due to the biological resistance of the pancreas to tubercular infection. Pancreatic enzymes, including lipases and deoxyribonucleases, have antimycobacterial effects.^[32]

Pancreatic TB is a common opportunistic infection in human immunodeficiency virus (HIV)-positive patients and is considered to be an acquired immunodeficiency syndrome defining illness.^[15] The proposed mechanism for the spread of pancreatic TB are as follows: the ingestion of mycobacterial organisms, the spread from the GI tract to the lymphatics, and then directly to the adjacent abdominal organs;^[33] or the hematogenous or lymphatic dissemination from a remote focus.^[32]

Clinical features

The clinical presentation of pancreatic TB is insidious and non-specific. Common symptoms and signs include abdominal pain, weight loss, nausea/vomiting, fever, abdominal mass^[9,33] and obstructive jaundice.^[1,19]

Intra-abdominal TB frequently involve abdominal lymph nodes, the spleen, the peritoneum, the liver, and the gastrointestinal tract.^[15] However, even in HIV infected patients, TB of the pancreas is relatively rare with an incidence of 0.46% based on ultrasound findings.^[20] Insolated primary pancreatic TB is particularly rare.

Xia *et al.*^[9] have summarized characteristic features of PTB as follows: (1) mostly occurs in young people,

Table 3. Typical imaging findings of pancreatic tuberculosis and pancreatic ductal adenocarcinoma lesions

Characteristic	PTB	PDAC
B mode ultrasound		
Pancreatic enlargement	Common	Rare
CBD and pancreatic duct dilatation	Rare	Common
Enlarged peripancreatic lymph nodes	Common	Rare
Contrast enhanced ultrasound		
Arterial phase	Iso or hyperenhancement	Hypoenhancement
Late phase	Hypoenhancement	Hypoenhancement
Endoscopic ultrasound		
Echogenicity	Circumscript echofree areas	Hypoechoic
Margin of lesion	Less sharply demarcated	Sharply demarcated
Peripancreatic pseudocysts	Common	Rare
Contrast enhanced endoscopic ultrasound	Hyperenhancement	Hypoenhancement
Ultrasound elastography	Markedly stiffer than surrounding tissue	Stiffer than surrounding tissue
Endoscopic ultrasound elastography	Stiffness depending on the stage of tuberculosis	Stiffer than surrounding tissue

PTB: Pancreatic tuberculosis, PDAC: Pancreatic ductal adenocarcinoma, CBD: Common bile duct



Figure 1. Circumscript pancreatic tuberculosis using transcutaneous B-mode

especially female; (2) have past history of TB or come from endemic zone of TB; (3) often present with epigastric pain, fever, and weight loss; and (4) ultrasound or CT scan show pancreatic mass and peri-pancreatic nodules, some with focal calcification.

Imaging features

Pancreatic TB can be classified radiologically as follows: The most common form is mass-forming (with or without diffuse pancreatic enlargement) and accounts for 94.4% of cases. Additionally, there is a diffuse and a small, nodular type. The masses can be radiographically similar to pancreatic tumors, autoimmune pancreatitis, abscesses, lymphomas, or pseudocysts.^[5,15,27,34-40]

B-mode ultrasound

Conventional ultrasound usually depicts a focal hypoechoic lesions at or adjacent to the pancreas,^[11,14,41,42] heterogeneously hypo-isoechoic lesions (primarily in the head of the pancreas), diffuse enlargement of the pancreas and enlarged peripancreatic and other abdominal lymph nodes.^[43]

An important image finding in PTB is the normal appearing CBD and the pancreatic duct, even if the mass is located centrally in the head of the pancreas. This is in contrast to pancreatic adenocarcinoma, where the pancreatic duct is dilated in centrally located tumors.^[16] Pancreatic TB should be suspected in patients with associated lymphadenopathy in the portohepatic and para-aortic regions.^[29]

The diffuse form of PTB is characterized by pancreatic enlargement with narrowing of the main pancreatic duct and heterogeneous enhancement.^[44]

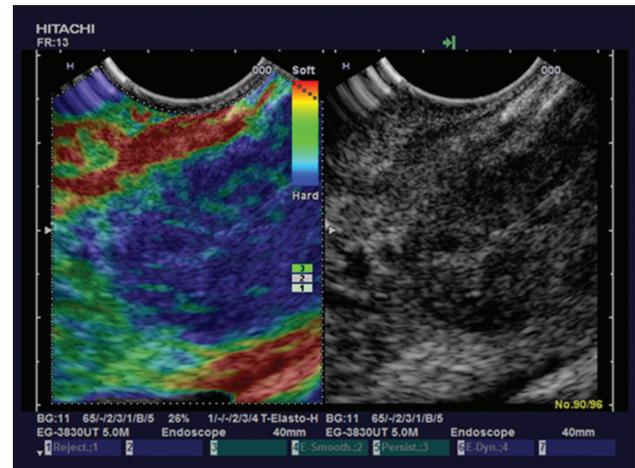


Figure 2. Pancreatic tuberculosis using endoscopic ultrasound elastography with stiff tissue diffusely infiltrating the pancreas

Endoscopic ultrasound

PTB usually manifests as circumscript echoless areas with a solid impressing or semiliquid but echoic inner content. In contrast to pancreatitis the surrounding reactive changes are less prominent. Peripancreatic pseudocysts may be another manifestation of PTB mimicking complicated chronic pancreatitis.

Contrast-enhanced ultrasound

Here we described for the first time the imaging features of CEUS. CEUS reveals heterogeneous enhancement pattern. Non-enhancement in the necrotic zones and hyperenhancement in the most active zones. In the arterial phase PTB showed typically iso- or hyperenhancement comparing to the surrounding tissue, which is the most important feature to differentiate PDAC [Figure 3].

Endoscopic ultrasound using elastography

Here we described for the first time the imaging features of endoscopic elastography. Depending on the stage diffuse infiltration of TB of the pancreas reveals stiffer tissue compared to the surrounding healthy pancreatic parenchyma if the infiltration is circumscript. In contrast to ductal adenocarcinoma the focal pancreatic lesion is less sharply demarcated. In addition, lymphoma may show less stiff tissue. In the case of diffuse tuberculous infiltration of the whole organ this shows stiff tissue a finding which is similar to autoimmune pancreatitis.^[5-8,45-49] The lymph node findings are similar to the lung.^[50]

Computed tomography and magnetic resonance imaging

In cases of PTB, contrast enhanced CT may show a sharply delineated mass in the pancreatic head with

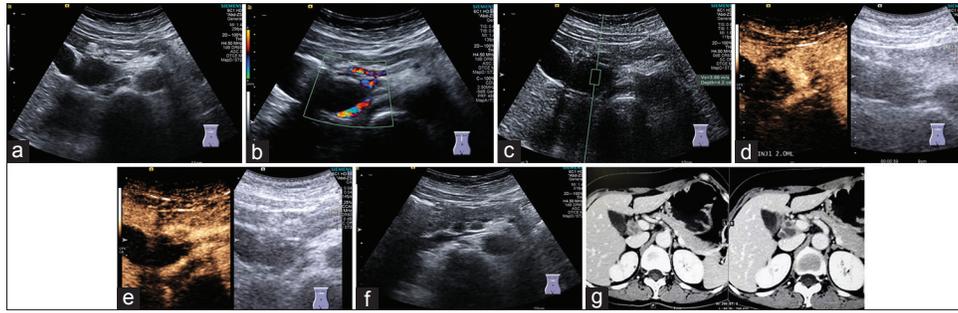


Figure 3. Pancreatic tuberculosis in B_mode (a), color Doppler flow imaging (b) and ultrasound elastography with Virtual Touch™ Quantification measurement (c). On contrast enhanced ultrasound arterial phase (d) and portal venous phase (e), the focal pancreatic lesion was partially septa enhanced. Lymphadenopathies were detected both on B-mode ultrasound (f) and computed tomography (g)

irregular margins and peripheral enhancement. However these features are not specific for PTB.^[51]

MRI demonstrated multinodular masses which were low signal intensity in T1 weighted image and high signal in T2, with non-enhanced internal necrotic foci and peripheral enhancement.^[18]

On both CT and MRI, it is most commonly described as a heterogeneous, lobulated, and multicystic mass. Pancreatic TB is appearing with hypodensity on CT, and low signal intensity on T1-weighted images; it varies from hypo to hyper signal intensity on T2-weighted images.^[19,44] Pancreatic TB typically has a thick rim enhancement and internal septa enhancement on postcontrast images.^[52] Such image characteristics on CT and MRI are similar, if not identical, to those of pancreatic neoplasia, making the radiologic diagnosis of pancreatic TB to be a challenge.

Positron emission tomography - computed tomography

An increase in F-18 fludeoxyglucose (FDG) uptake is seen in malignancy as well as in inflammation. In the case of pancreatic TB, the lesions are composed of cells with an elevated level of glucose metabolism-epithelioid cells, Langhans giant cells and lymphocytes—consecutively resulting in a high F-18 FDG uptake.^[17]

Enhanced ultrasound guided fine needle aspiration

The diagnosis of pancreatic TB has traditionally been based on biopsy samples taken during surgery. More recently, studies employing EUS-guided FNA for preoperative diagnosis showed some promising results.^[18,29,53-55] Recommendations have been reported in the EFSUMB guidelines.^[56-65]

EUS offers a superior tissue contrast and a higher local regional resolution compared to CT or MRI. In contrast to percutaneous FNA, EUS-guided FNA has a higher diagnostic accuracy of 76.2% for pancreatic TB, which is comparable to that for pancreatic cancer.^[53] The diagnostic accuracy of EUS-FNA was reported to be 76%–95% for pancreatic cancer and 46% for focal inflammation.^[66] EUS guided FNA may be useful in the diagnosis of an undetermined pancreatic lesion. Resulting, a laparotomy can be avoided when TB is diagnosed.

Definitive diagnosis of PTB is made by demonstrating caseating granulomas, acid fast bacilli on Ziehl–Nelson staining or the presence of *Mycobacterium tuberculosis* DNA by a polymerase chain reaction in the tissue obtained from the lesion.^[9]

Differential diagnoses

Pancreatic TB most commonly presents as a solitary lesion with multiple cystic components. The main differential diagnoses of pancreatic solid-cystic masses include cystic neuroendocrine tumor, mucinous cystadenocarcinoma, serous cystadenoma, solid pseudopapillary neoplasm and cystic degeneration of pancreatic adenocarcinoma. Pancreatic TB should also be considered in the differential diagnosis of pancreatic solid-cystic mass lesions.^[29] From clinical reviews, between 60% and 100% cases of PTB were initially diagnosed as having pancreatic cancer^[9,12] and between 45% and 86% required surgery to confirm the diagnosis.^[13,22]

Interestingly, though commonly seen in pancreatic cancer, pancreatic ductal dilatation is seldomly found in pancreatic TB. Nagar *et al.*^[23] recommended to take TB of the pancreas as a differential diagnosis for pancreatic masses associated with peripancreatic lymphadenopathy.

On CEUS, ductal adenocarcinoma is reported to be hypovascular in a percentage from 73% to 93%.^[67,68] A multicenter study named PAMUS reported the high accuracy of CEUS in characterizing pancreatic masses, declaring that solid pancreatic lesions were correctly characterized in respect to pathology with an accuracy of 91.7% and pancreatic ductal adenocarcinoma was correctly characterized with an accuracy of 87.8%.^[69] A specificity of 100% for trans-abdominal CEUS diagnosis of ductal adenocarcinoma with a sensitivity of 90% is reported.^[70,71]

Management of pancreatic tuberculosis

Management of pancreatic TB is based on anti-tubercular treatment for 6–12 months, with complete clinical and radiologic response.^[30]

No definitive guidelines are available in literature regarding the role of reimaging. Singh *et al.*^[51] have suggested radiological follow-up to document regression of the mass but time intervals are not exactly specified. They have suggested that if radiological improvement does not occur even after anti-tubercular treatment, the mass has to be resected for histological confirmation. However, there is no data available on co-existing pancreatic carcinoma with TB. Xia *et al.*^[9] have done a follow-up CT scan in 11 of 16 patients and found complete resolution in all, though time was variable between 78 and 186 days with a mean of 132 days. Therefore, we conclude that a repeat imaging at the end of anti-tubercular treatment and thereafter at regular intervals will help us to monitor and understand the natural process of the disease.

If the diagnosis is delayed, pancreatic TB can be fatal; the disease has a 10.8% mortality rate (which is comparable to the mortality rate of 9.1% in immune-competent patients).^[15] However, pancreatic TB responds well to standard ATDs.

Weaknesses of our study

Weaknesses of our retrospective and non-comparative study include the retrospective data acquisition and the non-comparative character of reported imaging features.

CONCLUSIONS

TB of the pancreas is rare, with a wide range of non-specific clinical presentation and image features overlapping with those seen in pancreatic neoplasia. To our best knowledge, our paper had a comparatively

large number of histopathological-proven PTB patients partially examined with new technologies so far not reported in the literature. Imaging diagnosis of PTB represents a diagnostic challenge. On BMUS PTB most commonly presents as a solitary lesion with multiple enlarged peripancreatic lymph nodes and without dilatation of the CBD. In the arterial phase of CE(E) US PTB showed iso- or hyperenhancement comparing to the surrounding tissue, which is the most important feature to differentiate PDAC. Additionally, PTB was markedly stiffer than the surrounding pancreatic tissues on (endoscopic) ultrasound elastography.

However, if clinicians are aware of its clinical and imaging features and conduct appropriate investigations with multiple modalities including BMUS, CEUS, and EUS guided FNA, diagnosis of PTB without laparotomy is possible and the disease can be effectively treated with anti-tuberculous drugs.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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