

Endoscopic ultrasound characteristics of pancreatic lymphoepithelial cysts: A case series from a large referral center

Kunal S. Dalal, John M. DeWitt, Stuart Sherman, Harvey M. Cramer¹, Temel Tirkes², Mohammad A. Al-Haddad³
Department of Medicine, Division of Gastroenterology and Hepatology, Indiana University School of Medicine, Departments of ¹Pathology and Laboratory Medicine and ²Radiology, Indiana University School of Medicine, Indianapolis, Indiana, USA, ³Cleveland Clinic Abu Dhabi, Digestive Disease Institute, Abu Dhabi, UAE

ABSTRACT

Background and Objectives: Lymphoepithelial cysts (LECs) of the pancreas are benign lesions that can mimic cystic neoplasms on imaging. Endoscopic ultrasound (EUS) features have not been well described. We aimed to describe the clinical and EUS characteristics of LECs and the present outcomes of management at a high-volume referral center. **Materials and Methods:** We identified patients who underwent EUS and were found to have LECs based on fine-needle aspiration (FNA) cytology or surgical pathology from existing databases. EUS features, imaging characteristics, and pathology results were described. **Results:** Sixteen patients were found to have 17 LECs. The mean size was 33 mm ± 15 mm. Locations within the pancreas included 10 lesions in the tail, 3 in the body, 1 in the uncinate process; the remaining 3 were exophytic. Six lesions were anechoic, 6 were hypoechoic, and 5 had mixed echogenicity. Nine lesions had mixed solid/cystic components, 7 were purely cystic, and 1 was solid. Cyst fluid was thick or viscous in six cases and thin in three. Eleven patients had diagnostic cytopathology. Six patients ultimately underwent surgery due to symptoms, nondiagnostic FNA, or other clinical concerns for malignancy. **Conclusions:** Pancreatic LECs have variable morphology and echogenicity on EUS, but the appearance of a cyst with variable solid and cystic components combined with the appearance of thick, turbid, and viscous aspirate should raise suspicion for an LEC. The majority of patients with LECs at our center avoided surgery for LECs on the basis of diagnostic EUS-FNA.

Key words: Endoscopic ultrasound (EUS), lymphoepithelial cyst (LEC), pancreatic cyst

INTRODUCTION

Lymphoepithelial cysts (LECs) of the pancreas are benign lesions with no malignant potential. The imaging appearance can mimic other cystic neoplasms, and therefore distinguishing LECs and

other benign lesions from those with malignancy or malignant potential is important. This is underscored by the fact that pancreatic cysts are

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Dalal KS, DeWitt JM, Sherman S, Cramer HM, Tirkes T, Al-Haddad MA. Endoscopic ultrasound characteristics of pancreatic lymphoepithelial cysts: A case series from a large referral center. *Endosc Ultrasound* 2016;5:248-53.

Access this article online

Quick Response Code:



Website:

www.eusjournal.com

DOI:

10.4103/2303-9027.187879

Address for correspondence

Dr. Mohammad Al-Haddad, Cleveland Clinic Abu Dhabi, PO Box 112412, Abu Dhabi, UAE. E-mail: alhaddm@clevelandclinicabudhabi.ae

Received: 2015-09-18; **Accepted:** 2016-01-06

increasingly detected due to the widespread use of cross-sectional imaging.^[1] However, literature describing imaging and clinical features of LECs is limited to case reports and small case series. Thus, features of such lesions may be less known compared to other lesions of the pancreas.

Clinical and imaging findings of LECs are typically nonspecific. Definitive diagnosis has traditionally relied on surgical histopathology following resection. It has been shown that benign cysts are often indistinguishable from cystic neoplasms on pre-operative imaging, and therefore the patients often undergo unnecessary resection.^[2] Carcinoembryonic antigen (CEA) levels may also be elevated in fluid aspirated from confirmed LECs,^[3,4] which may initially raise the suspicion for a mucinous neoplasm. Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) cytopathology may help diagnose LECs,^[5] but cyst cytology may be difficult to interpret due to contamination of the aspirate by intestinal tissue with mucinous and glandular epithelium.^[6] Additionally, the absence of classic cytological findings of LEC does not exclude the diagnosis.^[7]

EUS may be able to further characterize such lesions based on morphology and cyst fluid analysis. While EUS features of LECs have been previously described,^[4,5] there remains an overall dearth of literature pertaining to EUS findings. Additional studies are needed to better characterize the EUS features of these lesions in order to lend support for their diagnosis and to help avoid unnecessary surgery. In this series, we describe the clinical and EUS characteristics of LECs confirmed on cytology and/or surgical pathology, and present outcomes of management at a high-volume referral center.

MATERIALS AND METHODS

At a single tertiary referral center, EUS, surgical, and cytology databases were accessed and retrospectively reviewed to identify the appropriate patients. All the patients who were diagnosed with pancreatic LECs based on definitive cytopathology or surgical resection pathology between 2004 and 2014 were included in this case series. Each EUS procedure was performed by one of six endosonographers. The EUS images of the LECs were pulled and retrospectively reviewed by an expert endosonographer (MAH) blinded to the original EUS reports to assess for

the size, location, border, echogenicity, internal components, and presence of septations. Similarly, reports from computed tomography (CT) or magnetic resonance imaging (MRI) acquired before EUS were retrospectively reviewed by a radiologist to determine the location and other radiological features including exophytic appearance. The results of any imaging studies performed in patients managed nonoperatively were also reviewed to assess for changes in the size or morphology of the lesions. Cyst fluid physical characteristics as well as cyst fluid amylase and CEA levels were also retrieved when available. The Institutional Review Board of our medical center approved this study.

FNA cytology results were reviewed and confirmed by an expert cytopathologist. The presence of anucleated and/or nucleated squamous cells admixed with a variable number of lymphocytes in a background of keratinaceous and/or amorphous debris on FNA smears was considered diagnostic of an LEC [Figure 1].^[5,8] In cases where FNA cytology was nondiagnostic, surgical resection pathology reports were reviewed to confirm the diagnosis of LEC.

RESULTS

Sixteen patients (12 males; mean age 57 ± 13 years) with 17 confirmed LECs underwent EUS (1 patient was found to have 2 distinct LECs) [Table 1]. Presenting symptoms included: Abdominal pain in six patients and weight loss in two patients; eight patients were asymptomatic with incidental lesions on cross-sectional imaging performed for unrelated indications. Reports from imaging obtained prior to EUS were available in 13 patients (CT in 6, MRI in 2, and both in 5 patients), accounting for 14 lesions. On CT or MRI, lesions were predominantly located in the tail ($N = 8$) or body ($N = 5$); nine of these lesions were exophytic

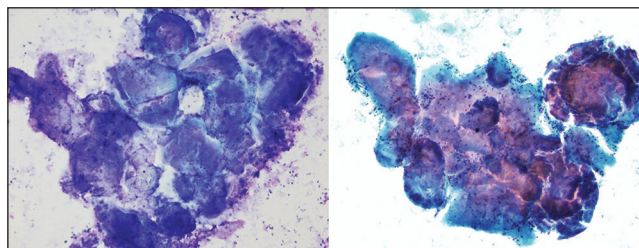


Figure 1. Cytology smear of an aspirate from a lymphoepithelial cyst (case 7): anucleated and nucleated squamous cells are noted in the background admixed with a variable number of lymphocytes. (1A: Diff Quick, 10 \times ; 1B: Papanicolaou stain, 10 \times)

but originated from the tail or body of the pancreas (Figure 2 for representative CT images of case 5).

On EUS [Table 1], the mean LEC size was 33 ± 15 mm. Location of LECs within the pancreas were as follows: 10 were in the tail, 3 in the body, 1 in the uncinate process, and 3 were described as exophytic (2 in the body and 1 in the tail). Borders were well-defined in 16 and poorly defined in 1. Echogenicity was described as anechoic in 6, hypoechoic in 6, and mixed in 5 patients. Representative EUS images are shown in Figure 3.

Internal components within the lesion were also characterized by EUS. Nine lesions had mixed solid/cystic components (of which 2 were mostly solid and 1 had calcifications), 7 were purely cystic (2 had internal debris), and 1 was solid with no cystic components. Internal septations were noted in 6 (5 with thin or incomplete septations and 1 with thick septations); septations were suggested on imaging in two additional cases, but were not confirmed on EUS. No wall nodularity or pancreatic ductal dilation was noted on EUS, though a mural nodule was seen on MRI in one lesion.

When adequate cyst fluid was aspirated, its consistency was described as thick, mucoid, and/or viscous in six cases and thin in three cases; color was clear in three cases and turbid/opaque in three cases [Table 2]. Median cyst fluid CEA ($N = 5$) and amylase ($n = 6$) were 2.4 ng/mL (range 1.3-13,088) and 100 U/mL (range 5-1111), respectively. Eleven LECs (from 11 distinct patients) were diagnosed on the basis of characteristic FNA cytology [Table 2]. In these cases, cytologic exam of the aspirated cyst fluid revealed a combination of nucleated or anucleated squamous cells, keratinous debris, and a variable number of lymphocytes (ranging from scattered to numerous). In a diagnostic FNA case, cholesterol crystals were seen as well. Six cases from five patients had nondiagnostic cytology (five cases with findings of benign, indeterminate cysts based on FNA alone and one case with hypocellular aspirate); the diagnosis of LEC in these cases was established by subsequent surgical resection pathology [Figure 4].

Six patients accounting for seven cysts ultimately underwent surgical resection by laparoscopic or open distal pancreatectomy. Two of these patients (totaling 3 cysts) required surgery for abdominal pain attributed to



Figure 2. Axial contrast enhanced image from a 65-year-old male patient (case 5) performed in arterial (a) and venous (b) phases through the cystic lesion (arrow). Images demonstrate a well-defined exophytic lesion in the body of the pancreas. Postcontrast CT density is 18 Hounsfield units, compatible with a mildly complex cyst. There is no internal enhancement, nodularity, or septation

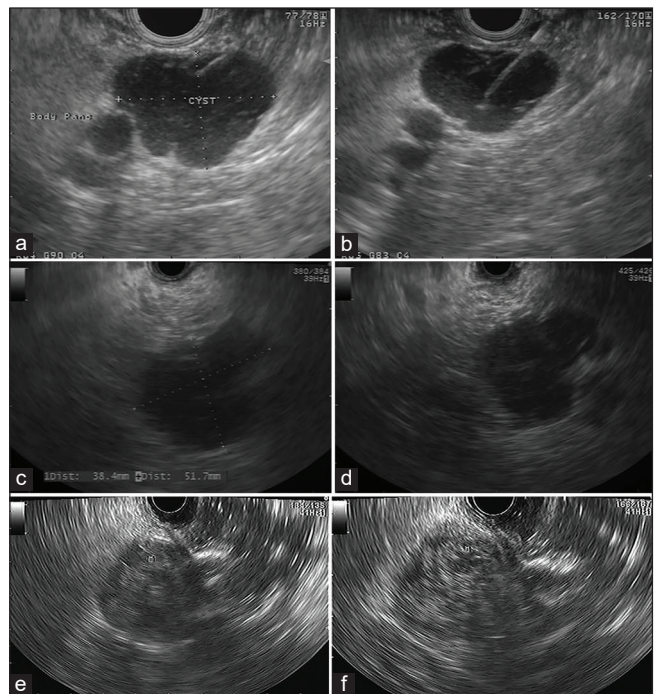


Figure 3. EUS findings. Case 5 (A+B): Anechoic cyst with lobulated contour and thin, incomplete septations; FNA needle seen in B. Case 8 (C+D): Hypoechoic cyst with irregular contour. Case 9 (E+F): Cyst with mixed echogenicity, regular contour, and internal debris

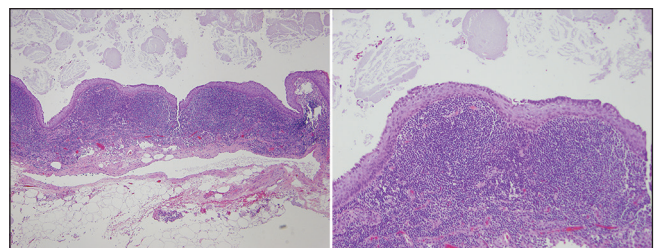


Figure 4. Histopathology from a resected LEC (case 7). Cyst cavity is lined by squamous epithelium and a dense subepithelial rim of lymphoid tissue. External cyst “capsule” consisting of fibrous and adipose tissue is present. Intraluminal keratin and formed laminae are seen in 4A (H&E stain, 4×). Higher magnification demonstrating the stratified squamous epithelium and dense subepithelial lymphoid tissue is shown in 4B (H&E stain, 10×)

the cyst (cases 7 and 10). In another patient (case 4), FNA cytology was diagnostic for LEC; however,

Table 1. Imaging and EUS features of pancreatic LECs

Case no.	Sex	Age at EUS	Pre-EUS imaging	Location on imaging	Size on EUS (mm)	Location in pancreas on EUS	EUS findings
1	F	43	CT	tail*	50×30	body [†]	well-defined, anechoic, cystic
2	F	84	n/a		40×32	body [†]	well-defined, anechoic, thin outer wall, cystic, and thin/incomplete septations
3	F	44	CT	body*	30×18	tail [†]	well-defined, anechoic, cystic with internal solid debris
4	F	66	n/a		18×8	tail	well-defined, mixed echogenicity, heterogenous, calcified, mixed solid/cystic
5	M	65	CT	body*	22×18	body	well-defined, anechoic, cystic, thinly septated with two compartments
6	M	48	CT/MRI	tail	28×28	tail	well-defined, hypoechoic, heterogenous, cystic
7	M	65	MRI	body*	29×23	body	well-defined, hypoechoic, cystic with internal debris, thin/incomplete septations with few compartments
8	M	56	CT	uncinate process	50×30	uncinate process	poorly defined, hypoechoic, heterogenous, mixed solid/cystic, incomplete septations
9	M	50	CT/MRI	tail*	36×33	tail	well-defined, mixed echogenicity with hyperechoic foci, heterogenous, cystic with mostly solid components
10 [†]	M	37	CT	tail*	24×20	tail	well-defined, mixed echogenicity, mixed solid/cystic
11 [†]	M	37	CT	tail*	25×20	tail	well-defined, mixed echogenicity, mixed solid/cystic
12	M	73	MRI	tail	23×9	tail	well-defined, hypoechoic, cystic component not seen
13	M	54	CT/MRI	tail	28×24	tail	well-defined, hypoechoic, heterogenous, mixed solid/cystic but mostly solid, thin septations
14	M	40	CT/MRI	tail*	6×7	tail	well-defined, anechoic with hyperechoic attenuation deep to cyst, cystic
15	M	58	CT	body*	nos	tail	well-defined, hypoechoic, mixed solid/cystic, thick septations with multiple small cystic lesions
16	M	62	CT/MRI	body	58×42	body	well-defined, anechoic, complex mass, mixed solid/cystic with internal debris
17	M	52	n/a		60×45	tail	well-defined, mixed echogenicity, mixed solid/cystic

*Exophytic on imaging/EUS, [†]Denotes same patient, n/a: Not available, nos: Not otherwise specified

Table 2. FNA and cytology features

Case no.	Aspirate description	Cytologic description	Diagnosed by	Surgical resection
1	blood-tinged, thin, colorless	Scattered benign lymphocytes	FNA	No
2	opaque, blood-tinged, thin	Numerous lymphocytes	FNA	No
3	clear, yellow, thin	Benign lymphocytes and benign epithelium	FNA	No
4	nos	Fragment of squamous epithelium and underlying lymphoid cells	FNA	Yes*
5	clear, white, slightly viscous	Benign nucleated and anucleated squamous epithelial cells, keratinous debris, rare scattered lymphocytes	FNA	No
6	nos	Keratin debris, lymphocytes, squamous epithelium	FNA	No
7	thick, turbid, white	Occasional acute inflammatory cells, abundant proteinaceous debris, scattered cholesterol crystals	Surgical pathology	Yes
8	bloody	Abundant nucleated squamous cells, scant lymphocytes	FNA	No
9	liquid, serosanguinous, somewhat thick, mucoid	Abundant anucleated squamous cells, macrophages, crystalline and scattered inflammatory cells	FNA	No
10 [†]	turbid, white, slightly viscous	Anucleate squames	Surgical pathology	Yes
11 [†]	nos	Anucleate squames	Surgical pathology	Yes
12	nos	Hypocellular, fragments of contaminating epithelium	Surgical pathology	Yes*
13	nos	Hypocellular, amorphous debris	Surgical pathology	Yes*
14	clear, slightly viscous	Numerous lymphoid cells, macrophages; no epithelial component	FNA	No
15	mucoid-type material	Abundant squamous epithelial cells	Surgical pathology	Yes*
16	nos	Abundant debris and anucleate squamous cells	FNA	No
17	nos	Low cellularity, anucleate squamous cells, keratinaceous debris, cholesterol crystals, scattered lymphocytes	FNA	No

*Malignancy suspected based on indeterminate clinical or imaging findings, [†]Denotes same patient, nos: Not otherwise specified

clinical suspicion for a neuroendocrine tumor remained high due to symptomatic hypoglycemia, thus this patient underwent surgical resection. Surgical pathology confirmed LEC in this patient. The remaining three patients underwent surgery for suspected malignancy based on indeterminate clinical and imaging findings and nondiagnostic FNA cytology; one underwent exploratory surgery after imaging suggested a malignant right adrenal lesion with liver invasion (case 12); one was found to have a hypermetabolic focus in and adjacent to the pancreatic cyst (case 13); one had benign FNA cytology, although mutational analysis on the aspirated fluid was performed at a commercial laboratory and revealed several allelic imbalances suggestive of malignancy (case 15). Of the 10 patients who did not have surgical resection, 4 had subsequent imaging available a median 39 months (range 19-62) after EUS; all 4 showed stable (3 cases) or decreased (1 case) cyst size.

DISCUSSION

EUS-FNA is generally recommended for the evaluation of pancreatic cysts detected on imaging to better characterize these lesions and to avoid unnecessary surgical resection of benign cysts.^[6] In the current EUS-based case series, which is the largest to date, we found that the majority of patients with LECs at our center avoided surgery for these benign lesions on the basis of diagnostic EUS-FNA.

In our series, the majority of patients were middle-aged males, with a male:female ratio of 3:1 and a mean age of 57 years. Our patient demographic was similar to that described by Yanagimoto *et al.*, who reviewed 106 cases of LECs and found the mean age of presentation to be 56 years, with a male:female ratio of 4:1.^[9] The majority of our patients were asymptomatic, while abdominal pain was the most common presenting symptom as has been previously described by others.^[9-11]

Four patients underwent surgery for suspicion of malignancy including one with diagnostic FNA for LEC and three with nondiagnostic cytology. Asymptomatic patients with nondiagnostic cytology who have EUS and cytology features suggestive of an LEC may benefit from observation rather than surgical resection.

We found that EUS morphology of LECs varies considerably from a predominantly solid to purely cystic or a mixed solid/cystic appearance. Lesions were mostly well defined, predominantly anechoic or

hypoechoic, and often exophytic on pre-EUS imaging, which should raise the pre-EUS probability of LEC. In our series, the majority of the lesions were localized to or exophytic from the tail of the pancreas, whereas previous studies have reported equal distribution throughout the pancreas.^[9,10]

In a prior EUS-based case series of nine patients, Nasr *et al.* similarly demonstrated diverse sonographic characteristics of LECs on EUS.^[4] The majority of the LECs in that series appeared hypoechoic and solid, with subtle posterior enhancement suggestive of a cystic component. This agrees with our findings of several cases with mixed solid/cystic components. Also, while the majority of our cases had hypoechoic or anechoic cysts on EUS, five cases were noted to have mixed hypo or hyper-echogenicity and another three cases were noted to have echogenic internal debris. Hypoechoic lesions with hyperechoic content has been described in cases outside our series,^[5] thus internal debris within the cyst likely account for mixed echogenicity seen in our cases.

On the basis of gross cyst fluid appearance, thick, turbid, and viscous appearing fluid was suggestive of LECs, as reported in 6 out of 10 cases in this series. Similarly, Nasr *et al.* showed that a thick milky, creamy, or frothy aspirate should raise suspicion for LECs.^[4] Cyst fluid CEA and amylase levels were highly variable in our series, as has been previously demonstrated.^[3,4] Therefore, these may not be useful markers.

In a single patient in our series, two distinct LECs were ultimately diagnosed based on surgical pathology, though preoperative FNA cytology described a differential diagnosis for a benign cyst including a dermoid or epidermoid cyst (cases 10 and 11). EUS reports of pancreatic dermoid cysts are rare, with isolated case reports describing a multilocular hypoechoic appearance^[12] or complex, honeycomb lesion with histiocytes, benign epithelial cells, and lymphocytes seen on cytology.^[13] The ability to discern LEC from other benign cysts on EUS, particularly dermoid and epidermoid cysts, can be difficult and requires further studies.

With the frequent detection of pancreatic cysts on imaging, it is likely that LECs will be increasingly reported and characterized in the literature. We anticipate that EUS will continue to play an important

role in conjunction with cross-sectional imaging and FNA cytology to differentiate the benign lesions from malignant ones, and help avert surgery in asymptomatic patients. The appearance of an exophytic cyst with variable solid and cystic components combined with the appearance of thick, turbid, and viscous aspirate should raise suspicion for an LEC.

Financial support and sponsorship

Nil.

Conflicts of interest

None relevant to this manuscript.

REFERENCES

1. Lee KS, Sekhar A, Rofsky NM, *et al.* Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 2010;105:2079-84.
2. Assifi MM, Nguyen PD, Agrawal N, *et al.* Non-neoplastic epithelial cysts of the pancreas: A rare, benign entity. *J Gastrointest Surg* 2014;18:523-31.
3. Centeno BA, Stockwell JW, Lewandrowski KB. Cyst fluid cytology and chemical features in a case of lymphoepithelial cyst of the pancreas: A rare and difficult preoperative diagnosis. *Diagn Cytopathol* 1999;21:328-30.
4. Nasr J, Sanders M, Fasanella K, *et al.* Lymphoepithelial cysts of the pancreas: An EUS case series. *Gastrointest Endosc* 2008;68:170-3.
5. Ahlawat SK. Lymphoepithelial cyst of the pancreas. Role of endoscopic ultrasound guided fine needle aspiration. *JOP* 2008;9:230-4.
6. Karim Z, Walker B, Lam E. Lymphoepithelial cysts of the pancreas: The use of endoscopic ultrasound-guided fine-needle aspiration in diagnosis. *Can J Gastroenterol* 2010;24:348-50.
7. Renou C, Giovannini M, Monges G, *et al.* Pitfalls of cyst fluid findings obtained by endoscopic ultrasonography fine-needle aspiration on a pancreatic lymphoepithelial cyst. *Am J Gastroenterol* 2007;102:213-5.
8. Mandavilli SR, Port J, Ali SZ. Lymphoepithelial cyst (LEC) of the pancreas: Cytomorphology and differential diagnosis on fine-needle aspiration (FNA). *Diagn Cytopathol* 1999;20:371-4.
9. Yanagimoto H, Satoi S, Toyokawa H, *et al.* Laparoscopic distal pancreatectomy for a pancreatic lymphoepithelial cyst: Case report and review of literature. *JOP* 2013;14:664-8.
10. Sewkani A, Purohit D, Singh V, *et al.* Lymphoepithelial cyst of the pancreas: A rare case report and review of literature. *Indian J Surg* 2010;72:427-32.
11. Adsay NV, Hasteh F, Cheng JD, *et al.* Lymphoepithelial cysts of the pancreas: A report of 12 cases and a review of the literature. *Mod Pathol* 2002;15:492-501.
12. Urata T, Izumi Y, Takekuma Y, *et al.* A case of dermoid cyst of the pancreas. *Nihon Shokakibyō Gakkai Zasshi* 2012;109:1791-8.
13. Lyons DA, Coberly EA, Hammoud GM, *et al.* Case report of pancreatic dermoid cyst: Can fine needle aspiration make the diagnosis? *JOP* 2013;14:653-6.