

Pancreatic lymphoepithelial cysts express CEA and can contain mucous cells: potential pitfalls in the preoperative diagnosis

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Pancreatic lymphoepithelial cysts are rare benign cysts that cannot be reliably differentiated from neoplastic mucinous cysts preoperatively. Although elevated cyst fluid carcinoembryonic antigen (CEA) levels support a diagnosis of a mucinous cyst, the finding of increased CEA levels in lymphoepithelial cysts prompted this study. Nine resected lymphoepithelial cysts were examined for expression of CEA, carbohydrate antigen (CA) 19-9, CK7, p63, PAS-D and a panel of mucins. The pathology data were correlated with clinical information, including serum, cyst fluid and imaging studies. By computed tomography scan, although most lymphoepithelial cysts appeared cystic, 23% were described as masses. The endoscopic ultrasound findings were variable, but the lymphoepithelial cysts tended to be hypoechoic cystic lesions or masses. On cytology, 44% of the cysts had squamous cells, 67% had glandular cells and 56% had atypical cells. The cysts were resected because of size ≥ 3 cm (89%), symptoms (44%) and/or elevated cyst fluid CEA levels (33%). The cyst fluid CEA levels in the three cysts tested were >450 ng/ml. Histopathologically, all cysts were lined by mature, stratified squamous-type cells and produced keratin. Mucous cells were present in 78% of the cysts. The immunohistochemical profile of the squamous lining was CK7+, p63+, MUC1+, MUC4+, MUC2-, MUC5AC- and MUC6-. Even though lymphoepithelial cysts are lined by squamous-type epithelium, all our resected lymphoepithelial cysts expressed CEA and/or CA19-9, many contained mucous cells, and three exhibited markedly elevated cyst fluid CEA levels. Although cyst fluid CEA levels >200 ng/ml support the diagnosis of mucinous neoplasms, this study emphasizes the need for clinicians and pathologists to recognize that lymphoepithelial cysts can mimic neoplastic mucinous cysts clinically, radiographically and on cyst fluid CEA analysis.

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Pancreatic lymphoepithelial cysts are rare, benign cysts that are typically lined by mature, keratinizing squamous epithelium with surrounding lymphoid tissue. These cysts tend to occur in middle- to older-aged men (male/female ratio 4:1 with a mean age of 56 years).¹ Lymphoepithelial cysts can be unilocular

or multilocular, can occur throughout the pancreas and often protrude outside the pancreas. The mean size of resected lymphoepithelial cysts is 4.7 cm, but cysts up to 17 cm in size have been reported.² Although easy to diagnose on a resection specimen, any cysts in the pancreas, including lymphoepithelial cysts, can pose diagnostic challenges preoperatively.

Most lymphoepithelial cysts are found incidentally on imaging studies performed for unrelated reasons. When characteristic features are present, computerized tomography (CT) and magnetic resonance imaging (MRI) can help support the diagnosis of lymphoepithelial cyst. However, imaging studies

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cannot consistently separate lymphoepithelial cysts from neoplastic mucinous cysts, such as mucinous cystic neoplasms and intraductal papillary mucinous neoplasms. Fine needle aspiration (FNA) can also support the diagnosis of a lymphoepithelial cyst when squamous cells or keratinous material is present, but FNA can yield inconclusive results, especially if atypical glandular cells are present.

Cyst fluid analysis can be a helpful tool in distinguishing neoplastic (mucinous) from nonneoplastic (nonmucinous) cysts. Several markers, such as carcinoembryonic antigen (CEA), cancer antigen 72-4, carbohydrate antigen (CA) 19-9, fluid viscosity, amylase and lipase, have been extensively studied. Currently, measurement of cyst fluid CEA appears to be the most useful marker to discriminate between mucinous and nonmucinous cysts.³ In a recently proposed algorithm for the diagnosis of pancreatic cysts, if a cystic neoplasm is suspected on endoscopic ultrasound and there is no solid component, a cyst fluid CEA level >200 ng/ml supports the diagnosis of a mucinous neoplasm.³

Using cyst fluid CEA as a discriminating test has its limitations, including known false-positive results. Several case reports have noted elevated levels of both CEA and CA19-9 in lymphoepithelial cysts.⁴⁻⁹ This is an important diagnostic pitfall in lymphoepithelial cysts that needs to be further addressed, as patients who have any suspicion of harboring a neoplastic cyst often have the cyst resected. In this study, we reviewed a series of nine lymphoepithelial cysts that were resected at our institution. We correlated the preoperative imaging findings, FNA cytology results and cyst fluid analysis with the postoperative histopathological findings. We also further investigated the potential cause for elevated CEA and CA19-9 in lymphoepithelial cysts.

Materials and methods

We searched the University of Pittsburgh Medical Center Department of Pathology surgical pathology files for patients with a final diagnosis of lymphoepithelial cyst from 2002 to 2009. This query yielded nine resected lymphoepithelial cysts. The gross descriptions of the lesions were reviewed, along with demographic information about the patients including sex and age. Corresponding cytology diagnoses were reviewed, as were serum and cyst fluid CEA and CA19-9 levels if obtained before resection.

The histology of all eight cases was reviewed and a representative formalin-fixed paraffin-embedded tissue block from each case was selected and serially sectioned. One section of each block was stained with hematoxylin and eosin. The remaining serial sections were stained with PAS-D, CEA, CA19-9, CK7, p63 and the mucins MUC1, MUC2, MUC4, MUC5AC and MUC6 (see Supplementary Table 1 for

antibody clones and dilutions). Standard automated immunohistochemistry was performed using the Ventana BenchMark XT system for CEA, CA19-9, CK7 and p63. Standard manual immunohistochemistry was performed for the mucins according to the vendor's instructions and previously published methods.¹⁰ All histochemical and immunohistochemical stained sections were reviewed and the expression profiles of the lining of the cysts were recorded.

Results

The clinical data are summarized in Table 1. Six of the patients (67%) were male and the mean age was 58 (range 40–75) years. Five (56%) of the patients were symptomatic; three patients presented with abdominal pain and/or nausea, one patient presented with weight loss, and one patient with a concomitant pancreatic cancer presented with jaundice. In the remaining four patients, the cysts were found incidentally. Serum CEA and CA19-9 levels were measured preoperatively in six and five patients, respectively. In one patient (without cancer), the serum CEA level was elevated to 6.4 ng/ml (mean 2.7 ng/ml, range 1–6.4 ng/ml). Serum CA19-9 levels were elevated in three cases (mean 123.8 U/ml, range 4–509 U/ml). Of note, the patient with pancreatic cancer also had an elevated CA19-9 level, but his level was excluded from the analysis.

The location and macroscopic descriptions of the cysts are shown in Table 2. Most of the lymphoepithelial cysts were located in the neck/body (56%), with the remainder in the head (22%) and tail (22%). Four (44%) of the cysts were exophytic or appeared to be within the peripancreatic soft tissue. Eight (89%) of the cysts were ≥ 3 cm with a mean cyst size of 4.4 cm and range of 2.5–10 cm. Five were multilocular (56%) and four were unilocular (44%). One patient with a lymphoepithelial cyst in the body (LEC2) had pancreatic ductal adenocarcinoma in the head.

Eight patients had both CT and endoscopic ultrasound imaging studies performed; one patient only had a CT scan. The results and impression

Table 1 Clinical information

	<i>Sex</i>	<i>Age (years)</i>	<i>Presentation</i>	<i>Serum CEA (ng/ml)</i>	<i>Serum CA19-9 (U/ml)</i>
LEC1	M	58	Weight loss	2.5	51.9
LEC2	M	58	Jaundice	1.2	N/A
LEC3	M	75	New right upper abdominal pain	N/A	188
LEC4	F	41	Epigastric pain	N/A	N/A
LEC5	F	40	Epigastric pain, nausea	3.7	13.9
LEC6	M	75	Incidental	1	4
LEC7	F	59	Incidental	1.3	N/A
LEC8	M	66	Found 8 years prior	6.4	509
LEC9	M	50	Found 2 years prior	N/A	N/A

LEC, lymphoepithelial cyst; N/A, not available.

Table 2 Description of the lymphoepithelial cysts

	<i>Cyst location</i>	<i>Cyst size (cm)</i>	<i>Multilocular</i>	<i>FNA fluid description</i>	<i>Cyst contents on gross</i>	<i>Cyst fluid CEA (ng/ml)</i>
LEC1	Peripancreatic, neck/body	10	No	Cloudy, brown	Not reported	N/A
LEC2	Pancreatic body	3.2	No	Not reported	Not reported	N/A
LEC3	Peripancreatic, head	3	Yes	Mucoid	Ivory, cheesy	N/A
LEC4	Pancreatic neck/body	5	Yes	Yellow, watery	White, yellow, soft	45–493 ^a
LEC5	In/near pancreatic body	3	Yes	Thick, opaque, whitish	Not reported	N/A
LEC6	Pancreatic tail	3	Yes	Thick, mucinous, foamy	Heterogenous, cheesy	N/A
LEC7	Pancreatic head	6.7	No	Mucinous	Loose, tan, pasty, keratinaceous	N/A
LEC8	Pancreatic neck/body	3.5	Yes	Tan, cloudy	Friable, gray-yellow material	112 830 ^b
LEC9	Pancreatic tail, exophytic	2.5	No	Opaque, brownish-green	Brown viscous material	678–1091

LEC, lymphoepithelial cyst; N/A, not available.

^aInitial analysis revealed a normal cyst fluid CEA level; a study repeated 8 months later revealed an elevated CEA level.

^bObtained at an outside institution.

Table 3 Imaging findings

	<i>CT findings</i>	<i>CT impression</i>	<i>Endoscopic ultrasound findings</i>	<i>Endoscopic ultrasound impression</i>
LEC1	Large cystic lesion in the tail with mural nodularity	Not given	Hypoechoic, heterogeneous mass with thin wall extrinsic to the pancreas near neck/body	Lymphoepithelial cyst, pseudocyst, mesenteric cyst, other
LEC2	Multicystic lesion superior to the body	Not given	Hypoechoic and heterogeneous mass in body of pancreas with adjacent cystic structures	Not given
LEC3	Complex cystic mass within the head	Favor a cystic neoplasm	Hypoechoic and heterogeneous lesion in the portacaval region	Unclear relationship to the pancreas
LEC4	Hypodense mass near superior aspect of the neck	Serous cyst, mucinous cyst or exophytic carcinoma	Anechoic, distally enhancing lesion (suggestive of a cyst) with thin outer wall and a few thickly septated compartments; one contains an intrinsic mass	Possible oligocystic serous cystadenoma or mucinous cyst
LEC5	Multicystic low-density lesion within the head	Could be a benign or malignant neoplasm	Oval hypoechoic and homogenous mass with well-defined borders projecting from or adjacent to the pancreatic body	Duplication cyst, pseudocyst or endocrine neoplasm
LEC6	Complex exophytic cystic mass	Not given	Complex exophytic mass budding off the pancreas; more solid than cystic with hypoechoic/anechoic areas	Highly suspicious of a neoplasm
LEC7	Complex cyst	Not given	Very large, round mass replacing much of the head of the pancreas with mixed echogenicity	Not given
LEC8	Large hypovascular mass superior to the head	Most likely a lymph node mass	Not done (CT-guided FNA was performed)	Not given
LEC9	Exophytic water density cystic lesion off the tail	Mucinous cystic neoplasm; intraductal papillary mucinous neoplasm	Single fluid-filled lesion within pancreas with internal debris	Intraductal papillary mucinous neoplasm, pseudocyst

LEC, lymphoepithelial cyst; CT, computerized tomography; FNA, fine needle aspiration.

of the imaging studies are summarized in Table 3. By CT, seven (78%) of the lymphoepithelial cysts were described as cystic lesions, but two were described as noncystic masses. The endoscopic ultrasound findings were variable. The lymphoepithelial cysts appeared hypoechoic and heterogeneous ($n = 3$), hypoechoic and homogeneous ($n = 1$), anechoic with an intrinsic mass ($n = 1$), as complex masses with mixed echogenicity ($n = 2$) and as a single fluid-filled lesion with internal debris ($n = 1$).

All of the nine cases had FNA cytology performed. The descriptions of the cyst fluid are listed in Table 2

and the FNA cytology results are summarized in Table 4. On cytological examination, four cases (44%) had squamous cells (Figure 1a) or squamous debris (Figure 1b), five (56%) had macrophages (Figure 1a) or histiocytes, three (33%) had acellular (nonkeratin) debris, and one case (11%) had lymphocytes. Of note, six cysts (67%) had glandular cells and five (56%) had atypical cells present (Figure 1c). Only three patients had cyst fluid analysis for CEA (see Table 2), and in all three cysts, the CEA level was markedly elevated (to 493 ng/ml, 1091 ng/ml and >100 000 ng/ml). The indications for surgery are

Table 4 FNA cytology results, impression and reason for surgery

	<i>FNA cytology results</i>	<i>Cytological impression</i>	<i>Reason for surgery</i>
LEC1	Atypical cells present. Nucleated and anucleated squamous epithelial cells and degenerated debris present	Benign cyst with squamous features favored; malignancy cannot be entirely excluded	Cyst size > 3 cm; symptomatic
LEC2	Atypical cells present; abundant squamous debris, clusters of pancreatic acinar cells and rare atypical glandular epithelial cells	No definite evidence of malignancy	Cyst size > 3 cm; removed during resection for known cancer
LEC3	Atypical cells present; hypocellular specimen with atypical glandular epithelial cells; possibly cyst contents	LEC, abscess and possibly a mucinous cyst; uncertain malignant potential	Cyst size ≥ 3 cm; symptomatic
LEC4	Initial FNA: lymphocytes, few macrophages, debris and bland epithelial cells; no squames. Repeat FNA 11 months later: bland glandular cells, histiocytes with rare multinucleated histiocytes, debris and small lymphocytes	Initial FNA: not a mucinous cyst. Repeat FNA: epithelial cells may represent cyst lining; no high-grade dysplasia	Cyst size > 3 cm; symptomatic; cyst fluid CEA > 200 ng/ml
LEC5	Initial FNA: abundant debris including anucleate squames, bland glandular cells, stromal cells. Repeat FNA 3 months later: mostly anucleate squames and few macrophages	Squamous cyst	Cyst size ≥ 3 cm; symptomatic
LEC6	Abundant acellular debris, bland epithelium and one cluster of atypical epithelium; no squames	Not given	Cyst size ≥ 3 cm; solid component on endoscopic ultrasound
LEC7	Sheets of epithelium, one focus of squames	Likely GI contaminant	Cyst size > 3 cm
LEC8	Histiocytes and proteinaceous material (outside hospital)	LEC	Cyst size > 3 cm; cyst fluid CEA > 200 ng/ml
LEC9	Atypical glandular cells and macrophages	Cyst contents	Cyst fluid CEA > 200 ng/ml

LEC, lymphoepithelial cyst; FNA, fine needle aspiration.

also listed in Table 4. Eight (89%) of the cysts were removed because they exceeded 3 cm in diameter and/or were symptomatic and one cyst (2.5 cm) was removed because of concern for a mucinous cystic neoplasm with cyst fluid CEA > 600 ng/ml.

The histological features of the lymphoepithelial cysts are shown in Figure 2. All resected cysts were lined, at least focally, by mature, stratified squamous cells; three cysts were predominantly denuded. Keratin was also present, at least focally, in all of the cysts. Beneath the squamous lining, eight cysts (89%) had the characteristic dense lymphoid tissue with scattered germinal centers; one cyst had a markedly fibrotic wall with scattered lymphoid follicles. In six cases (67%), there were focal-to-diffuse areas where the cyst lining resembled transitional epithelium with a layer of plump cells without keratohyaline granules at the surface. Four (44%) of the cysts had scattered sebaceous glands. Of particular interest was the presence of goblet-shaped mucous cells within the superficial layer of the cyst lining in seven (78%) of the cysts; the only cysts that did not contain these mucous cells were two of the cysts that were predominantly denuded and this could represent a false-negative finding. These mucous cells were rare (one to two individual cells or small clusters of cells) in three cysts, scattered (> 2 foci of cells present in < 30% of the cyst lining) in three cysts, and diffuse (scattered cells present in over 30% of the cyst lining) in one

cyst. These mucous cells stained strongly for PAS after diastase (see Figure 3).

The results of the special stains, including the mucin expression profiles, are summarized in Supplementary Table 2 and representative photomicrographs are shown in Figure 3. CK7 (normally expressed in simple epithelium, including ductal epithelium and urothelium) and p63 (normally expressed in squamous epithelium and urothelium) were expressed in the squamous lining of all nine cysts (100%); CK7 tended to label the surface, whereas p63 labeled the basal cells. Interestingly, all nine (100%) cysts expressed either CEA or CA19-9 (patchy to diffuse staining) in the surface squamous cells; CEA and CA19-9 were both expressed in seven (78%) cases. One of the two predominantly denuded cysts did not show convincing expression of CEA, but was positive for CA19-9, whereas the other predominantly denuded cyst expressed CEA but not CA19-9. The mucous cells were variably positive for CEA and CA19-9 (see Figure 3). With regard to the mucins, primarily surface labeling of squamous cells was seen with MUC1 and MUC4 (100%); MUC2 and MUC6 were negative in all nine cysts. MUC5AC labeled the mucous cells, so it was positive in seven (78%) of the cases; in two cases, the MUC5AC labeling was very focal. The mucous cells also expressed MUC4, but they were negative for MUC1, MUC2 and MUC6.

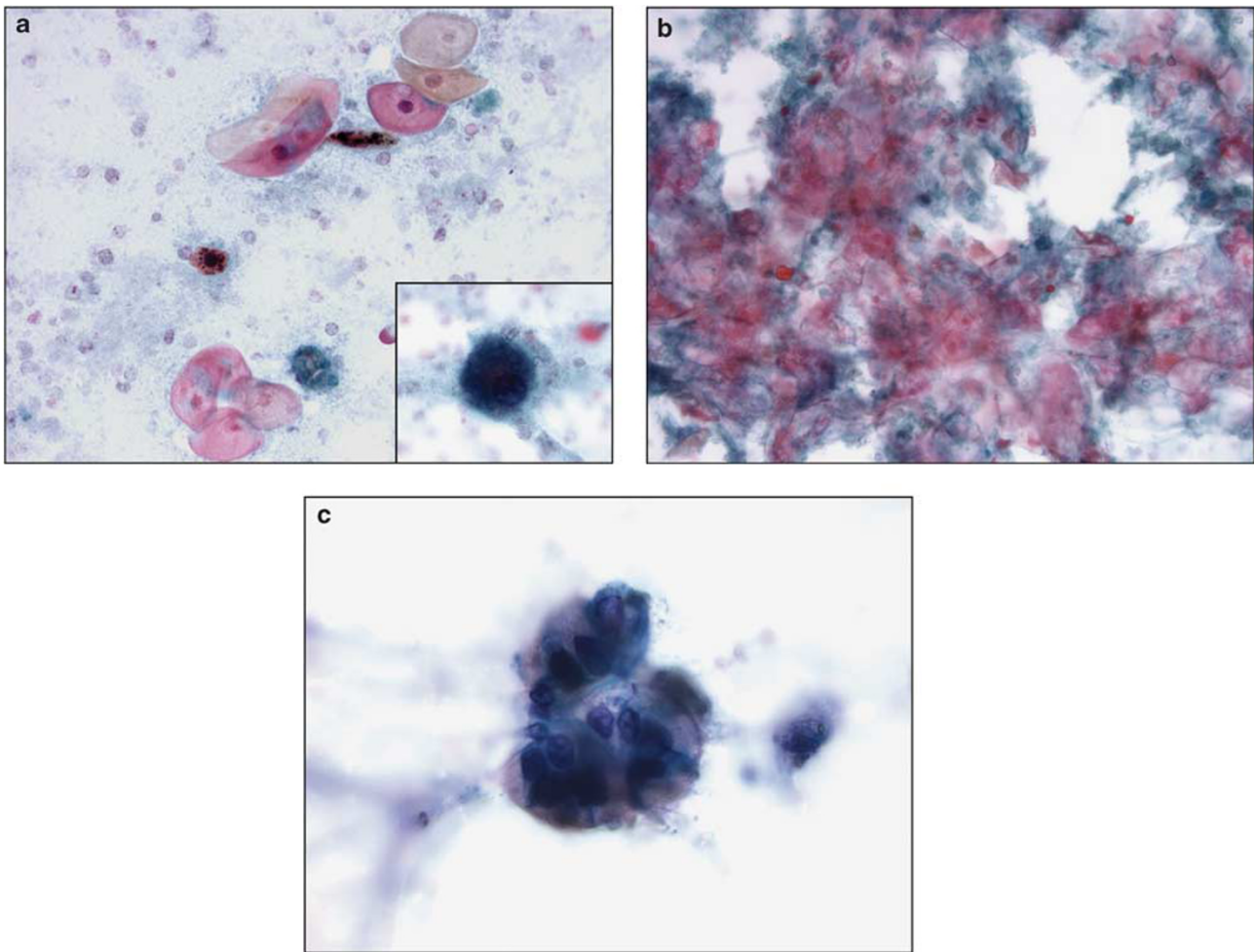


Figure 1 Cytological features of lymphoepithelial cysts. Characteristic features include (a) mature squamous cells (some with keratohyaline granules), macrophages (inset) and (b) anucleate squamous cells with keratinous debris (Papanicolaou stains). (c) This cell cluster is an example of the atypical glandular cells that can be encountered by these cyst aspirates (Papanicolaou stain); it is not known whether these glandular cells represent the mucous cells that can be present within the squamous lining of lymphoepithelial cysts. Lymphocytes are also often seen in cytological aspirates of lymphoepithelial cysts, but they were not common finding in our study.

Discussion

The pancreatic cyst lined by squamous epithelium with surrounding lymphoid tissue was first described by Luchtrath and Schriefers in 1985,¹¹ who noted the microscopic similarity of the cyst to the branchial cleft cyst of the lateral neck. The term lymphoepithelial cyst of the pancreas was proposed by Truong *et al*¹² in 1987. Lymphoepithelial cysts are uncommon benign lesions that are easily diagnosed on resection specimens. They are not, however, easily diagnosed preoperatively.

Lymphoepithelial cysts pose a diagnostic dilemma in the preoperative workup of patients with pancreatic cysts because they can mimic more common neoplastic mucinous cysts based on imaging, cytological and cyst fluid studies. Distinguishing lymphoepithelial cysts from other cysts, such as pseudocysts and mucinous cysts, can be challenging on imaging studies. Features that support a lymphoepithelial cyst include visualization of a

multilocular cyst on the surface of the pancreas with decreased attenuation (low Hounsfield units) on CT, hyperintensity on T1-weighted MRI, granular hypointensity on T2-weighted MRI and internal heterogeneous hyperechogenicity on ultrasound, findings that likely reflect the lipid and keratin contents of the cysts.^{13,14} However, lymphoepithelial cysts can have nonspecific and even misleading imaging features. The cysts can be unilocular and not obviously located on the surface of the pancreas. In our series, almost one-half (44%) of the cysts were unilocular and more than one-half (56%) of the cysts were located within the pancreas. By CT, lymphoepithelial cyst can appear to have solid components (due to dense keratinous material), or appear as a hypoechoic mass with an enhancing rim.^{15,16} By ultrasonography, lymphoepithelial cysts can appear solid or solid and cystic.^{15,16} Hence, although imaging studies provide information on size, location, presence or absence of solid components, and other physical descriptions,

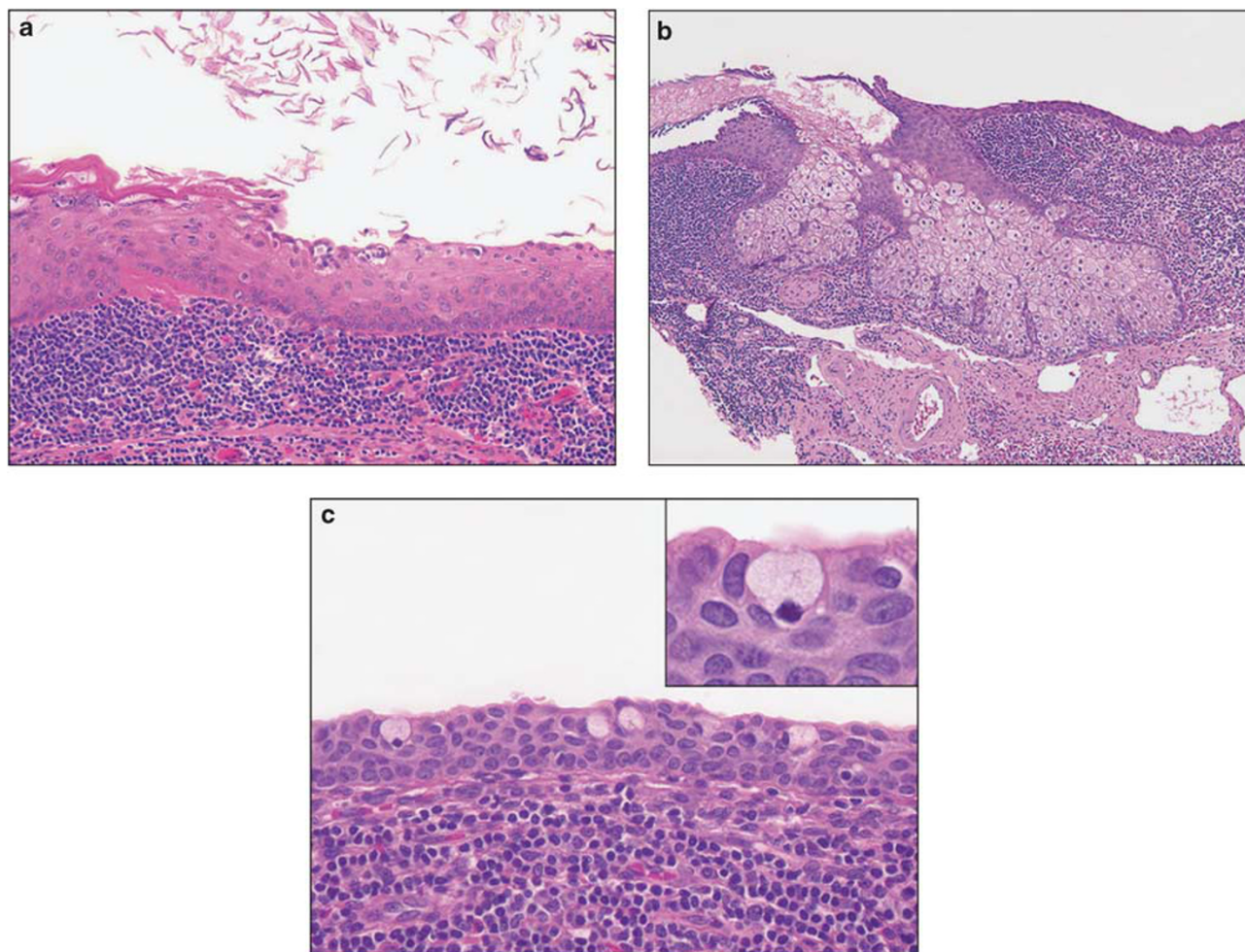


Figure 2 Histological appearance of lymphoepithelial cysts. (a) All cysts were lined by mature, stratified squamous epithelium, produced keratin (at least focally) and most (89%) contained the characteristic dense lymphoid tissue beneath the epithelial lining. (b) Four (44%) cysts had focal sebaceous differentiation. (c) Surface mucous cells were noted in seven (78%) of the cysts.

they cannot rule in or out malignant or premalignant lesions.

Cytological analysis of pancreatic cyst contents obtained by FNA is an insensitive test because only small number of cells are typically present in the fluid.^{17,18} If squamous epithelium, keratin debris and lymphocytes are seen in the absence of worrisome features, a diagnosis of lymphoepithelial cyst can be made. In our series of lymphoepithelial cyst, only four cases (44%) had squamous cells or squamous debris and only one case (11%) had lymphocytes. To add to the difficulty of the cytological diagnosis, 67% of the cysts in our study had glandular cells and in five of these cases (56% overall), atypical cytological features were present. Additionally, 33% of these cysts contained mucus or mucoid material. Overall, on the basis of the results of cytology, squamous cysts or lymphoepithelial cysts were in the differential diagnosis of 44% of our cases.

Cyst fluid analysis is another test that can assist in the preoperative diagnosis of a pancreatic cyst.

There are numerous studies in the literature that demonstrate the utility of cyst fluid analysis to distinguish neoplastic (mucinous) from nonneoplastic (nonmucinous) cysts. Currently, measurement of cyst fluid CEA appears to be the most useful discriminatory marker.³ If a cystic neoplasm is suspected on endoscopic ultrasound and there is no solid component, a cyst fluid CEA level >200 ng/ml supports the diagnosis of a mucinous neoplasm.³ Only three patients in our study had cyst fluid analysis performed, yet all three cysts had markedly elevated cyst fluid CEA levels, well above the 200 ng/ml cutoff that would support the presence of a mucinous cyst. Although our study was initiated because of this interesting observation (elevated CEA levels in lymphoepithelial cysts), this phenomenon has been reported, primarily in case reports in the literature.^{4–9} However, the source of the elevated CEA has not been previously systematically studied. It is interesting to note that CEA can be elevated in the cyst fluid of lymphoepithelial cysts of the head and neck,^{19,20} but this

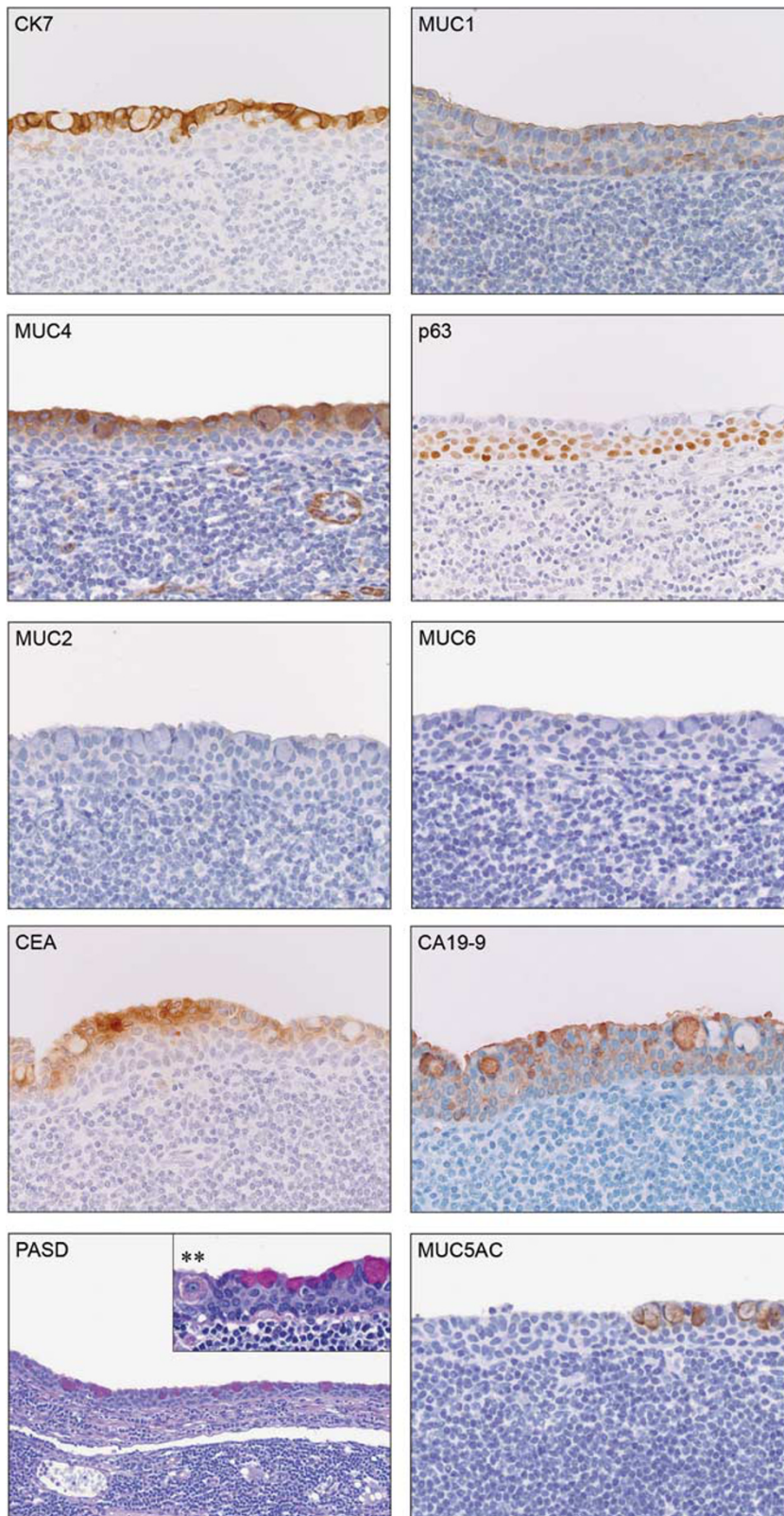


Figure 3 Typical immunohistochemical profile of lymphoepithelial cysts (these photographs were obtained from LEC4). The squamous cells were positive for CK7, MUC1 and MUC4 in all nine (100%) cysts. All cysts (100%) were also positive for p63 and negative for MUC2 and MUC6. Of interest, the squamous lining of all nine (100%) cysts expressed CEA and/or CA19-9; seven (87%) cysts expressed both CEA and CA19-9. The mucous cells were positive for PAS-D, MUC5AC, MUC4 and CK7, variably positive for CEA and CA19-9, and negative for MUC1 and MUC2 (**macrophages are weakly positive for PAS-D).

finding does not pose the same diagnostic challenge as it does in pancreatic cysts.

By thoroughly examining the resected lymphoepithelial cysts both histologically and immunohistochemically, we made two observations that could account for the elevated CEA levels. First, we noticed that the squamous lining of lymphoepithelial cysts can contain goblet-shaped mucous cells. This observation has not been well documented. The presence of rare goblet cells was noted (but not well described) in only one pancreatic lymphoepithelial cyst in the literature.²¹ However, mucous cells and glandular/columnar epithelium can be a feature of lymphoepithelial cysts in the head and neck region.^{22,23} It is possible that these mucous cells have been overlooked in lymphoepithelial cysts of the pancreas because of their scant number and patchy distribution. Although it is possible that these MUC5AC-positive mucous cells could produce CEA, they were variably positive for CEA immunohistochemically and they were only present as a few cells scattered throughout the cyst lining. Hence, it is unlikely that these mucous cells are responsible for the marked elevation in CEA that is observed in some lymphoepithelial cysts. It is possible, though, that these cells could appear in cytological aspirates of lymphoepithelial cysts and contribute to misclassification of the cyst as a mucinous or potentially neoplastic cyst (Figure 1c).

Second, we found that the squamous cells themselves expressed both CEA and CA19-9. The squamous lining in all nine (100%) of our cases expressed one or both these markers. The three cysts in our study that had markedly elevated cyst fluid CEA levels also had strong, patchy CEA labeling of the squamous lining, suggesting that the squamous lining is the source of the elevated cyst fluid CEA levels. CEA is a glycoprotein that is typically expressed by endodermally derived tissues and adenocarcinomas. Although the expression of CEA by squamous epithelium can occur,^{24,25} its expression in the squamous lining of lymphoepithelial cysts has been previously reported in only two case reports.^{7,26} CA19-9 is a high-molecular-weight glycoprotein that is frequently expressed in gastrointestinal adenocarcinomas, but its expression has been reported in nonneoplastic squamous mucosa and in three lymphoepithelial cysts (two of the same cysts with CEA expression).^{7,8,26,27} As proposed by Kaiserling *et al*,⁷ the labeling of the squamous lining of lymphoepithelial cyst by both CEA and CA19-9 suggests that the cyst lining is derived from the exocrine pancreas. This theory could also explain the presence of rare mucinous cells within the lining of the cysts. Alternatively, as sebaceous glands can be seen in lymphoepithelial cyst (44% of our cysts had sebaceous glands), the squamous lining of lymphoepithelial cyst may be derived from ectodermal elements with aberrant expression of CEA and CA19-9.

We also studied the mucin profile of lymphoepithelial cysts. Mucins are heavily glycosylated, high-molecular-weight glycoproteins that are commonly expressed in epithelial cells. Currently, about 20 mucin (*MUC*) genes have been identified and/or sequenced.²⁸ Their expression is relatively specific to the types of cells or tissue. For example, MUC2 is a goblet cell mucin predominantly expressed in the intestine.²⁹ Normal adult pancreas expresses MUC1 and MUC6, but not MUC2 and MUC5AC. MUC1 is expressed in the intercalated ductal cells³⁰ while MUC6 is exhibited in centroacinar cells.³¹ MUC4 is absent or minimally expressed in the normal pancreas.³² Interestingly, mucins are differentially expressed in mucinous cysts of the pancreas; MUC5AC is consistently expressed in the epithelial lining of pancreatic mucinous cysts; MUC2 is expressed in intestinal-type epithelial lining; and both MUC1 and MUC6 are expressed in pancreaticobiliary and oncocytic epithelial lining.^{33,34}

The mucin expression profile of lymphoepithelial cysts has not been described previously in the literature. In our study, MUC1 and MUC4 were positive in all cysts and MUC2 and MUC6 were negative in all cysts. MUC5AC was at least focally expressed in 78% of the cysts (scattered mucous cells were positive, but the squamous epithelium was negative); thus its usefulness in ruling in or out a lymphoepithelial cyst is limited. However, the pattern of expression of mucin proteins in lymphoepithelial cysts provides insight into the pathogenesis of these cysts.

As MUC1 and MUC4 are expressed in the normal stratified epithelium,^{32,35} pancreatic squamous metaplasia³⁶ and in squamoid cysts of the pancreas,³⁷ the presence of MUC1 and MUC4 in our study suggests that lymphoepithelial cysts may originate from the pancreatic duct with squamous metaplasia and cystic formation, or alternatively, from epithelial remnants in peripancreatic lymph nodes.² The scattered mucous cells could represent remnant ductal epithelial cells. Interestingly, there may be an additional component of transitional metaplasia. The overall immunohistochemical profile of the squamous lining of lymphoepithelial cysts (CK7 +, p63 +, MUC1 +, MUC4 +, MUC2 -, MUC5AC - and MUC6 -) is identical to that seen in normal urothelium.³⁸ Regardless of what specific pathogenic mechanism is involved in creating lymphoepithelial cysts, these cysts have a mixed squamous–transitional–ductal phenotype that results in the expression of CEA and CA19-9.

Lymphoepithelial cysts of the pancreas have clinical, radiographic and cytological features that can lead to the misdiagnosis of these lesions preoperatively. Even though these cysts are lined by squamous epithelium, our series of resected lymphoepithelial cysts revealed that many (78%) of these lesions contained at least focal mucous cells (which could appear as atypical cells on cytological

analysis) and that all (100%) demonstrated expression of CEA and/or CA19-9 on the surface of the squamous epithelium (which could account for the elevated cyst fluid CEA levels). The cysts in our study were resected because of size ≥ 3 cm (89%), symptoms (44%) and/or elevated cyst fluid CEA levels (33%), all features concerning for neoplastic mucinous cysts. Although a cyst fluid CEA level >200 ng/ml generally supports the diagnosis of a mucinous neoplasm, such as a mucinous cystic neoplasm or intraductal papillary mucinous neoplasm, this study emphasizes the need for clinicians and pathologists to recognize that lymphoepithelial cysts can mimic neoplastic mucinous cysts clinically, radiographically and on cyst fluid CEA analysis.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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