

## REVIEW

# Is Preoperative Diagnosis Possible? A Clinical and Radiological Review of Lymphoepithelial Cysts of the Pancreas

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### Summary

Lymphoepithelial cysts of the pancreas are rare lesions found mainly in middle-aged men. They are usually benign and have no clear natural history except one study linking their occurrence with HIV infection. Nevertheless, they often cause enormous psychological stress to patients as they tend to mimic pancreatic neoplasms which are known to carry poor prognosis. The authors have therefore assessed the published literature from PubMed in order to determine whether lymphoepithelial cysts can be diagnosed preoperatively using novel imaging techniques. Based on our findings, it is evident that three-dimensional computed tomography scans, in-phase and out-of phase magnetic resonance imaging studies, and endosonography have enabled better characterization of pancreatic lymphoepithelial cysts than a decade ago. Endoscopic ultrasound-guided fine needle aspiration has also added considerably to the promise of preoperative diagnosis. Thus, the authors can affirm that despite surgical excision of the cyst with pathological examination being the gold standard for diagnosis, it is possible that a combination of the modern imaging techniques and/or minimally-invasive approach can enable patients avoid unnecessary surgery in the future.

### Introduction

Lymphoepithelial cysts of the pancreas are rare lesions comprising 0.5% of all pancreatic cysts [1]. First described in 1985 by Luchtrath and Schriefers [2], these cysts averages 6 cm (range: 1 to more than 15 cm), and are mostly multiloculated or unilocular with septations. Unlike pancreatic pseudocysts, lymphoepithelial cysts are considered true cysts, since they are lined by stratified squamous epithelium and surrounded by mature lymphocytes [3]. Most reports show that they predominantly affect middle age men who either present with non-specific symptoms or no symptom at all [4, 5]. The most common complaint in symptomatic cases is abdominal pain. Anorexia, fever and weight loss have also been reported [3]. Although they can involve any part of the pancreas, studies show that pancreatic lymphoepithelial cysts mainly affect the tail.

The mechanism leading to pancreatic lymphoepithelial cysts is unclear. Their diagnoses are also challenging as they have no specific serological marker to distinguish them from other pancreatic cysts. A case report by Sewkani *et al.* in 2010 showed that lymphoepithelial cysts can present with a rise in levels of carbohydrate antigen (CA 19-9) as well as weight loss, mimicking malignant pancreatic neoplasms [6]. The perception among specialists has therefore been that preoperative diagnosis cannot be carried out with accuracy in the absence of surgical resection [7]. However, there remains the necessity among clinicians to thoroughly investigate and ascertain the true nature of pancreatic cysts once they are discovered on abdominal imaging [8, 9, 10]. To our knowledge, the challenging aspect of pancreatic LECs has always been the inability to preoperatively distinguish them from pseudocysts, cystic neoplasms and intraductal carcinomas. Therefore, this review was conducted with the aim of presenting not only the key clinical features of these cysts, but also the present radiological findings that can help differentiate them from other pancreatic pathologies.

### Epidemiology

According to Adsay *et al.* (2002), lymphoepithelial cysts constitute about 0.5% of all pancreatic cysts [5]. Other case reports also show that they have

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**Abbreviations** EBV: Epstein-Barr virus

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preponderance for males, mainly after the 5<sup>th</sup> decade of life [11, 12, 13]. The ratio of males to females has been approximated as between 4:1 to 6:1, and is in contrast with pancreatic mucinous cystic neoplasms which are far more common in women [14].

### Etiology

Lymphoepithelial cysts are not unique to the pancreas, but have also been described in the parotid, submandibular and thyroid glands, as well as the lungs and cervical regions [15]. The etiologies of these cysts, however, tend to differ by location. For instance, cystic lesions of the head and neck have been linked to viral and/or systemic illnesses. Specifically, the associations between lymphoepithelial cysts of the parotid gland with HIV infection, Sjogren syndrome and lymphomas are well-established in the literature [5].

On the other hand, the causes of pancreatic lymphoepithelial cysts are largely unknown and their relationships with salivary gland lymphoepithelial cysts are still debatable. An *in situ* hybridization study by Schwarz and Weiss failed to show any Epstein-Barr virus (EBV) positive cells in pancreatic lymphoepithelial cysts. This is significant because lymphoepithelial cysts of the parotid gland have been associated with HIV and EBV-related lymphomas [16]. So far, only a recent incidental report by Bédard *et al.* has suggested a possible association between pancreatic lymphoepithelial cysts and HIV infection [17]. These authors described two cases found on abdominal CT scan and noted that one of the lymphoepithelial cysts resolved with the initiation of antiretroviral therapy.

### Histopathogenesis of Lymphoepithelial Cysts

The definitive mechanism leading to pancreatic lymphoepithelial cysts is still unknown, but several hypotheses are in the literature as to their origin [18, 19, 20]. Some authors have proposed that lymphoepithelial cysts represent squamous metaplasia

of an obstructed intrapancreatic duct, which subsequently protrudes into a peripancreatic lymph node [4, 20]. Although possible squamous metaplasia in the uninvolved pancreatic tissue is a relatively uncommon finding in these pancreata [5]. In addition, some investigators have suggested that these cysts may develop from ectopic pancreatic tissues in the peripancreatic lymph nodes [4, 20, 21, 22, 23]. A study by Arai *et al.* (1992) identified possible lymphoepithelial cyst precursors in these nodes [22]. This theory might explain the often extrinsic location of lymphoepithelial cysts and the fact that benign ectopic pancreatic tissues have been found throughout these lesions [24, 25]. Moreover, others have proposed that pancreatic lymphoepithelial cysts originate from misplaced branchial cleft cysts fused with pancreatic anlage during embryogenesis [2, 25]. This proposition was first suggested by Luchtrath and Schiefers, and has since been supported by histological similarity between pancreatic lymphoepithelial cysts and branchial cleft cysts of the neck [2, 26].

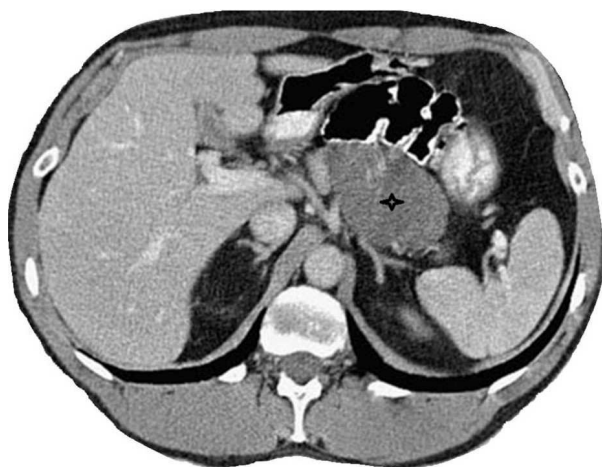
### Clinical Presentation

Lymphoepithelial cysts of the pancreas are asymptomatic in about 40% of cases and are mostly found during radiological work-up for other intra-abdominal diseases [8, 27, 28]. Some patients are also diagnosed with these cysts after being referred for further evaluation of isolated levels of elevated CA 19-9 [27, 28, 29]. Occasionally, they may present with non-specific abdominal pain and other symptoms such as diarrhea, anorexia, weight loss, nausea, and vomiting [13, 14]. As previously stated, typical patients are mostly men in their fifth decade of life [30].

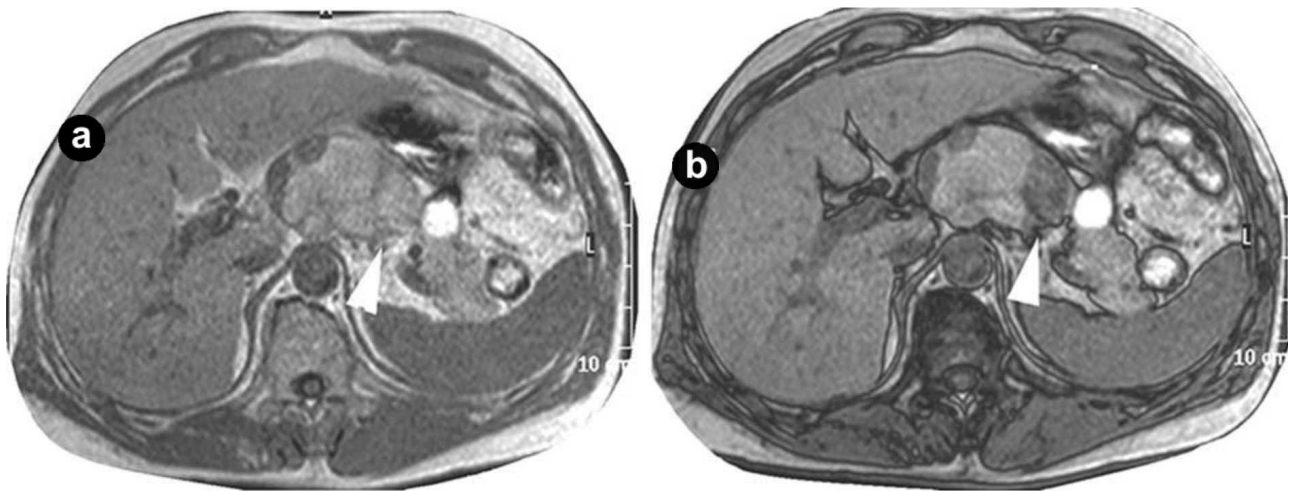
### Diagnosis

Due to the close resemblance between pancreatic lymphoepithelial cysts and other macrocystic lesions of the pancreas, their accurate diagnosis has posed a great challenge to both radiologists and clinicians alike [31]. This difficulty has also been compounded by reports showing that lymphoepithelial cysts can present with increased levels of pancreatic tumor biomarkers such as carbohydrate antigen (CA 19-9) and carcinoembryonic antigen (CEA) [12, 32]. Nevertheless, concerning serum biomarkers, a recent study by Madan *et al.* has suggested that an aspirated pancreatic cystic fluid CEA of more than 800 ng/mL should necessitate surgical enucleation [33].

CT imaging has been attempted by several authors to evaluate pancreatic lymphoepithelial cysts with variable descriptions in the literature. For instance, some authors have characterized these lesions as well-circumscribed, low attenuating masses with thin enhancing rims, septations and focal calcifications [34]. On the other hand, Toumi *et al.* [13] described pancreatic lymphoepithelial cysts on CT scan as lobulated, non-enhancing and sharply demarcated lesions with focal calcifications, often in the absence of pancreatic ductal dilatation or atrophy (Figure 1). In



**Figure 1.** An axial CT image showing a large, hypodense lymphoepithelial cyst with internal septations within the tail of the pancreas. (Reproduced with permission from Toumi *et al.* [13]).



**Figure 2.** An image showing in-phase (a.) and out-of-phase (b.) MRI with significant decrease of MR intensity in the lymphoepithelial cyst. (Reproduced with permission from Kudo *et al.* [8]).

addition, while most cases of lymphoepithelial cysts are either multicystic or unilocular with thin septations [34], the lymphoepithelial cyst case reported by Neyman *et al.* (2005) was not only unilocular, but also lacked septations, clear wall enhancements, or regions of fat attenuation [35]. Thus, pancreatic lymphoepithelial cysts may have papillary projections, small solid components, wall calcifications and/or thin wall enhancements on conventional CT imaging [26, 34]. This variation has led some authors to argue that three-dimensional computed tomography (3D-CT) scan, rather than the conventional scan, may be better suited to differentiate lymphoepithelial cysts from other lesions of the pancreas [35]. So far, this assertion has been supported by a recent study which showed that when compared to serous cystadenomas and mucinous cystadenomas, lymphoepithelial cysts had a predominantly extra-pancreatic 3D location and higher precontrast CT attenuation. Moreover, they were noted to be smaller and more frequently microlobulated than mucinous cystadenomas [36].

More recently, endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (EUS-FNA) studies have shown great promise in preoperative studies of pancreatic lymphoepithelial cysts that could potentially eliminate the need for surgical diagnosis [9, 37]. According to Sewkani *et al.* (2010), lymphoepithelial cysts typically appear on EUS as hypoechoic cystic lesions which are either unilocular or multilocular [3]. Rarely, the debris within these cysts may give hyperechoic appearance on ultrasound imaging [38]. Proponents of EUS-FNA attest to its minimally-invasive nature, and also to the cystic fluid contents of lymphoepithelial cysts which can readily be differentiated from those of pseudocysts or malignant cystic neoplasms. Aspirates containing squamous epithelial materials rich in lymphocytes are almost pathognomonic for lymphoepithelial cyst [3]. On the contrary, malignant cystic neoplasms rarely have lymphoid reactions and often do not form sub-epithelial bands like lymphoepithelial cysts. A

retrospective study by Nasr *et al.* reported that of the 9 patients who underwent EUS-FNA, 6 patients avoided surgery based on cytological results alone [39]. The unresolved concern with EUS-FNA is that in case of a cystic neoplasm, it may cause dissemination of malignant cells through fluid leakage from the cyst [40, 41]. Zielińska-Pajak *et al.* (2008) also noted that while FNA is useful for differentiating pancreatic lymphoepithelial cysts from other cysts, in the absence of squamous epithelial material rich in lymphocytes, it may be difficult to ascertain the true cytological picture of the aspirate [42].

In magnetic resonance imaging (MRI) studies, a pancreatic lymphoepithelial cyst lesion has been described as a solid, homogeneously hypointense mass on T1-weighted images. When gadolinium contrast is administered, the rim enhances while the hypointensity of the central core remains constant [27, 43]. A unique “cheerios-like” appearance of lymphoepithelial cysts on T2-weighted MRI studies has also been reported [30].

Kudo *et al.* (2011) recently showed that in-phase and out-of-phase MRI scans can greatly distinguish lymphoepithelial cysts from other cystic lesions of the pancreas, signaling a significant step towards preoperative diagnosis [8]. This novel approach depends on the phase difference caused by the variation in resonance frequency of hydrogen protons in water and fat. A similar intensity between in-phase and out-of-phase is observed if the tissue includes only water or fat. On the other hand, co-existence of water and fat leads to major signal reduction of out-of-phase MRI *versus* in-phase MRI. The authors observed that in cases of pancreatic mucinous cystic tumors or intraductal papillary neoplasms, there were no differences in intensity between in-phase and out-of-phase MRI scans. However, with lymphoepithelial cysts, a gap of signal reduction was evident between the out-of-phase MRI compared with in-phase MRI, confirming the co-existence of fat and water in these cysts [8] (Figure 2).

The authors can confirm that although significant improvements in imaging and characterization of pancreatic lymphoepithelial cysts have occurred over the last decade, major successes in preoperative diagnosis have only been sparsely reported. Thus, surgical excision with pathological examination is still used to confirm the diagnosis.

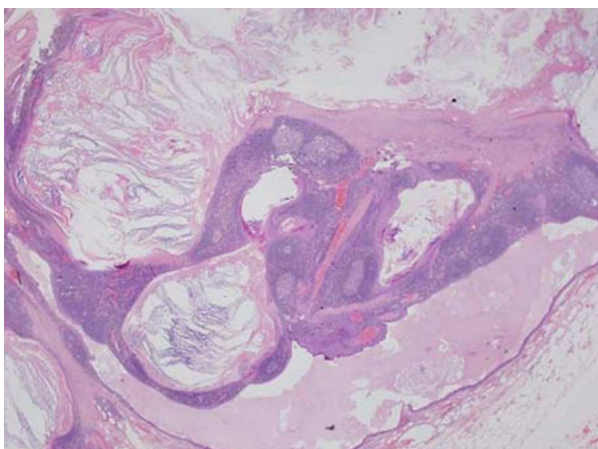
A gross pancreatic lymphoepithelial cyst mass has been described as pink, friable, and filled with keratinous yellowish-white material [13, 28]. Histological examination classically shows a true cyst lined by stratified squamous-type epithelium and surrounded by a dense band of lymphoid tissues with germinal centers [44] (Figure 3). Mucous cells have also been reported in up to 78% of these cysts [6, 13].

**Management of Pancreatic Lymphoepithelial Cysts**

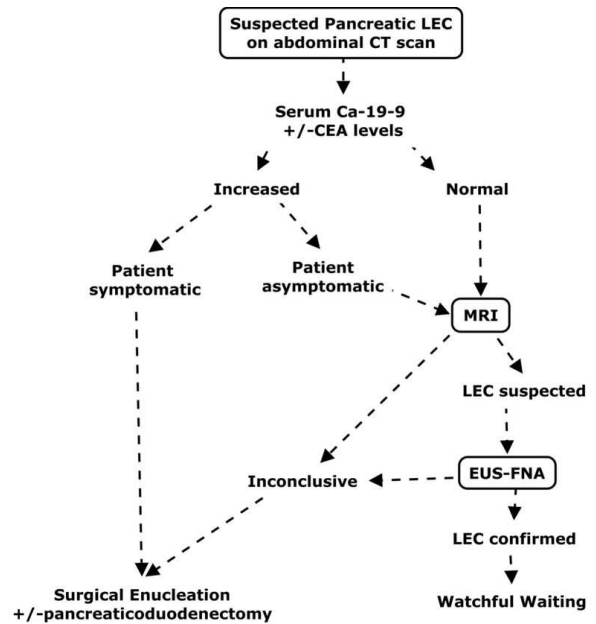
The management approach to pancreatic lymphoepithelial cysts largely depends on whether or not they are preoperatively diagnosed. Based on our review, watchful waiting may be all that is needed in cases where EUS-guided FNA or MRI is strongly suggestive of an lymphoepithelial cyst [3, 39]. On the other hand, surgical enucleation is both diagnostic and therapeutic, and should be done if the cyst is greater than 3 cm and/or the patient also has symptoms suggestive of a neoplasm [6, 26]. When indicated, Toumi *et al.* recently reported that laparoscopic surgical intervention is as effective as conventional laparotomy, with the added benefit of less blood loss and decreased length of hospital stay [45]. The authors have proposed an algorithm for the management of lymphoepithelial cysts shown in Figure 4.

**Prognosis**

Pancreatic lymphoepithelial cysts are benign and we found no report of their malignant transformation or recurrence after surgical resection [3, 31]. They can therefore be managed conservatively with excellent outcomes [14].



**Figure 3.** Microscopic picture of pancreatic lymphoepithelial cyst showing lymphoid nodules with germinal centers outside the cyst's thin, keratinized epithelial lining. (Reproduced with permission from England and Allen [44]).



**Figure 4.** Proposed algorithm for diagnosis and management of lymphoepithelial cysts (LEC).

**Conclusion**

lymphoepithelial cysts of the pancreas are benign and rare. However, since they often mimic pancreatic cystic tumors, their preliminary diagnosis is crucial to help patients avoid the psychological and surgical stress that come with pancreatic neoplasms. Up until now, the best diagnostic approach has been surgical removal and analysis. Nevertheless, based on our review, we can affirm that with 3D-CT scans, in-phase and out-of-phase MRI scans, and EUS-guided FNA studies preoperative diagnosis is possible. The cost-effectiveness of using these techniques in tandem and their availability remain the major limitation.

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**Conflict of interest** None

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