9 Other Cystic Lesions of the Pancreas

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Introduction

Pancreatic cyst lesions encompass a wide variety of entities ranging from nonneoplastic to neoplastic lesions with cystic degeneration (Table 9.1). The cysts can show significant overlap in terms of imaging findings as well as clinical features. Cytology along with cyst fluid analysis plays a pivotal role in the preoperative characterization of these lesions. However, some lesions, especially the uncommon ones, may not be diagnosed accurately resulting in unnecessary surgery. This chapter will discuss the various aspects of pancreatic cystic lesions (other than the neoplastic mucinous cysts) including the clinical features, imaging findings, pathologic features, molecular genetics, and management.

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Table 9.1 Pancreatic cyst classification

Neoplastic cysts
Intraductal papillary mucinous neoplasm
Mucinous cystic neoplasm
Serous cystic neoplasm
Neoplasms with cystic degeneration
Solid pseudopapillary neoplasm
Pancreatic neuroendocrine tumor
Pancreatic ductal adenocarcinoma
Acinar cell carcinoma
Nonneoplastic cysts
Pseudocyst
Lymphoepithelial cyst
Epidermoid cyst of the accessory spleen
Dermoid cyst
Squamoid cyst of the pancreatic ducts
Retention cyst
Enterogenous duplication cyst
Endometriotic cyst
Other
Acinar cell cystadenoma (cystic acinar transformation)

Other Neoplastic Cysts of the Pancreas

Serous Cystadenoma

Clinical Features

Though uncommon, serous cystadenomas (SCAs) constitute one of the most frequent benign cystic neoplasms of the pancreas. They mostly occur in the body or tail of the pancreas. The mean age of presentation is 60 years, and the majority (67–80%) of patients are women. They also occur in 35–90% of patients with von Hippel-Lindau (VHL) syndrome. Multifocality or diffuse involvement of the pancreas is typically seen in VHL syndrome. Many are asymptomatic and are discovered incidentally.

Symptoms may include abdominal pain, palpable mass, nausea and vomiting, and weight loss [1, 2]. With lesions that are >4 cm in size, symptoms are reportedly more frequent [3].

Imaging Findings

Serous adenomas can be microcystic, macrocystic, oligocystic (<10% of cases), mixed (micro-macrocystic), or solid. Microcystic serous cystadenoma (SCA) typically appears as an isolated, lobulated, well-marginated, multilocular lesion on computed tomography scan/magnetic resonance imaging (MRI). It comprises of a cluster of multiple small cysts separated by thin septa. The typical imaging finding of a honeycomb appearance with a central stellate scar with sunburst pattern of calcifications is seen in only 20% of cases. Branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) may also present in a polycystic pattern, simulating the microcystic SCAs.

Macrocystic SCAs are characterized by fewer cysts that are larger in size (>2 cm in diameter) or even one single cyst. The macrocystic SCAs can be particularly difficult to distinguish from mucinous cystic neoplasms and BD-IPMNs. If the patient has a history of pancreatitis, another differential diagnostic consideration is a pseudocyst.

The mixed micro-macrocystic type shows a combination of features of both microcystic and macrocystic types. The solid SCAs consist of small cysts which are separated by multiple, thick fibrous septa [4, 5].

Pathologic Features

Gross Findings Typically, SCAs are single masses that are well circumscribed and average 6 cm in diameter. They do not communicate with the pancreatic ducts. Classically, the cut surface is sponge-like with numerous small cysts (just few mm in diameter) filled with clear, serous fluid. The center of the neoplasm may show a dense fibrous scar with thin septa radiating to the periphery. The scar may also be calcified. Unlike the microcystic SCAs, the macrocystic ones tend to be located in the head of the pancreas.

Histology The cysts are lined by a single layer of cuboidal or flat epithelium with clear cytoplasm. The cytoplasm is clear due to the presence of abundant intracellular glycogen. Occasionally, the epithelial lining cells can exhibit eosinophilic granular cytoplasm. The nuclei are round to ovoid with inconspicuous nucleoli. The lining epithelium is closely associated with underlying fibrovascular stroma with a rich capillary network (Fig. 9.1). Intracystic papillae may develop that lack fibrovascular cores.

Solid serous adenomas show similar cytology, but the cells tend to be arranged in small acini. Solid serous adenomas may be difficult to distinguish from metastatic renal cell carcinoma, pancreatic neuroendocrine tumor (PanNET), and clear cell sugar tumor. In patients with VHL, the neuroendocrine tumors can exhibit clear cells and closely mimic SCAs [1, 2].

Cytology Usually, the cytologic interpretation is descriptive or nondiagnostic due to lack of sufficient cellularity. When present,

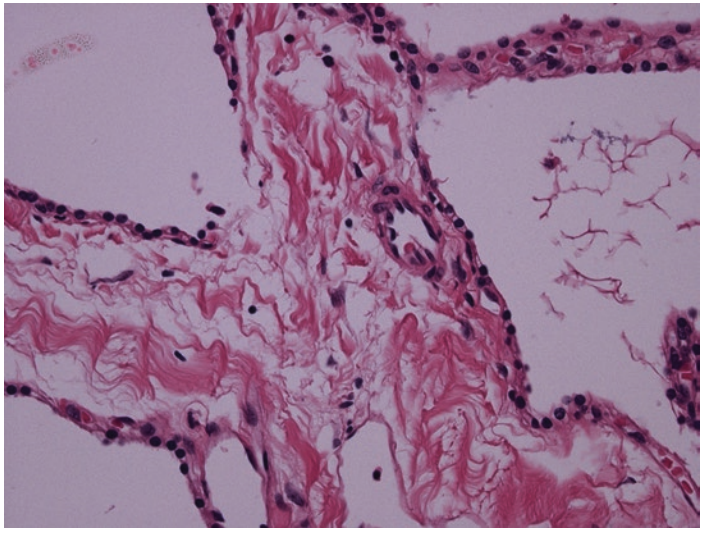


Fig. 9.1 Histology of serous cystadenoma reveals bland cuboidal epithelium with interspersed fibrovascular septa (hematoxylin-eosin stain, 400×)

the neoplastic cells are cuboidal with moderately abundant granular to clear, non-mucinous cytoplasm and round nuclei with fine chromatin (Fig. 9.2). The background is usually hemorrhagic and may contain hemosiderin-laden macrophages. A close mimicker of the SCA is a cystic PanNET. In contrast to the SCA, the PanNET cells tend to exhibit a finely stippled "salt and pepper" chromatin. SCAs can also be mistaken for pseudocysts and for neoplastic mucinous cysts owing to contaminating gastrointestinal epithelium and mucin [6, 7].

Although periodic acid-Schiff (PAS) and PAS/diastase stains could help identify the glycogen in SCA cells and inhibin immunohistochemistry is reportedly helpful in their identification, the aspirates are mostly paucicellular and inadequate for additional studies [8]. Another diagnostic pitfall is that inhibin can show positive staining in PanNETs with clear cell features [9].

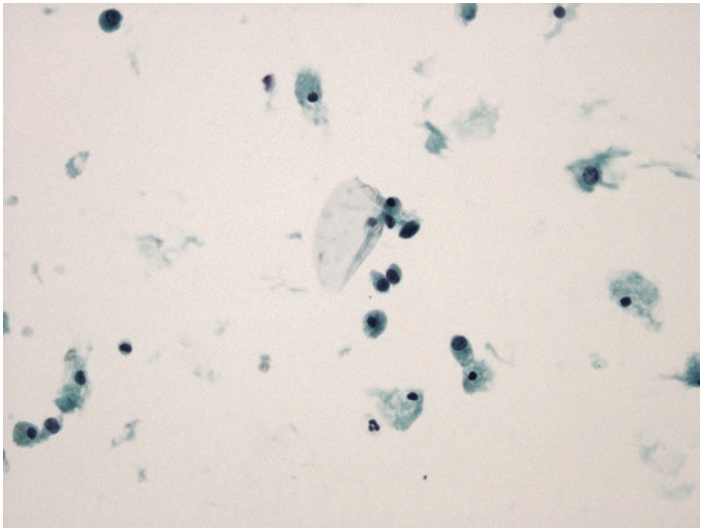


Fig. 9.2 Fine needle aspirate of serous cystadenoma is usually paucicellular. The lesional epithelium is composed of cuboidal cells with non-mucinous cytoplasm and round nuclei with fine chromatin (Papanicolaou stain, ThinPrep, 400×)

Cyst Fluid Biochemistry

SCAs typically have low carcinoembryonic antigen (CEA) (<5 ng/ml) and amylase (<250 IU/L) levels [6].

Molecular Genetics

Mutations or loss of heterozygosity in the *VHL* gene has been identified in 67% of SCAs [10].

Management

Majority of SCAs follow a benign course, and risk of malignant transformation is minimal. Most patients can be followed by serial imaging. The usual indications for resecting SCAs are to alleviate symptoms or when the diagnosis is uncertain and a malignant process/transformation cannot be excluded [2].

Solid Pseudopapillary Neoplasm

Clinical Features

Solid pseudopapillary neoplasm (SPN) of the pancreas is a neoplasm of uncertain lineage that tends to undergo hemorrhagic cystic degeneration. It is predominantly seen in young women (mean age being 28 years). They can be asymptomatic and found incidentally on imaging performed for other indications. If symptomatic, the presenting symptoms include abdominal pain, early satiety, nausea, and vomiting [11].

Imaging Findings

On imaging, the tumor is well demarcated and variably solid and cystic. It typically appears as a mixed-density lesion with solid component peripherally and cystic component more centrally. Calcification may be seen at the periphery of the lesion. On MRI, SPNs usually have variable signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and a hypointense rim on both T1- and T2-weighted images. Hemorrhage appears as areas of high signal on T1-weighted images and low signal on T2-weighted images [12].

Pathologic Features

Gross Findings SPNs appear as solitary masses that are well demarcated from the surrounding pancreas. Cut surface is yellow to brown with solid and cystic areas and zones of hemorrhage.

Histology and Cytology SPNs are characterized by loosely cohesive tumor cells that surround hyalinized to myxoid stroma containing thin-walled blood vessels (Fig. 9.3). There are foci of hemorrhage, and solid areas may contain tumor cell aggregates with cholesterol clefts surrounded by foreign body giant cells. The tumor cells show moderately abundant eosinophilic or clear cytoplasm. The nuclei are indented or grooved and exhibit fine chromatin (Fig. 9.4). Intracellular and/or extracellular hyaline globules may be present. Histologic features such as perineural invasion, vascular invasion, and infiltration of the surrounding structures do not appear to correlate with the biologic behavior of the neoplasm [11].

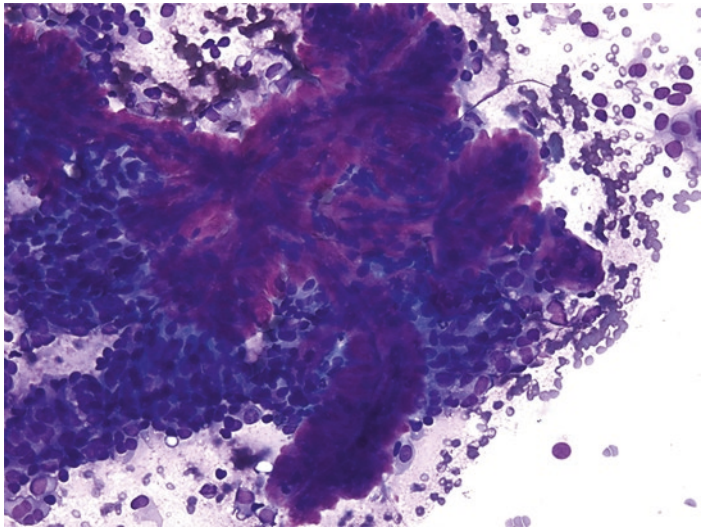


Fig. 9.3 Solid pseudopapillary neoplasm with metachromatic hyalinized fibrovascular cores surrounded by loosely cohesive monotonous neoplastic cells (Diff-Quik stain, 200×)

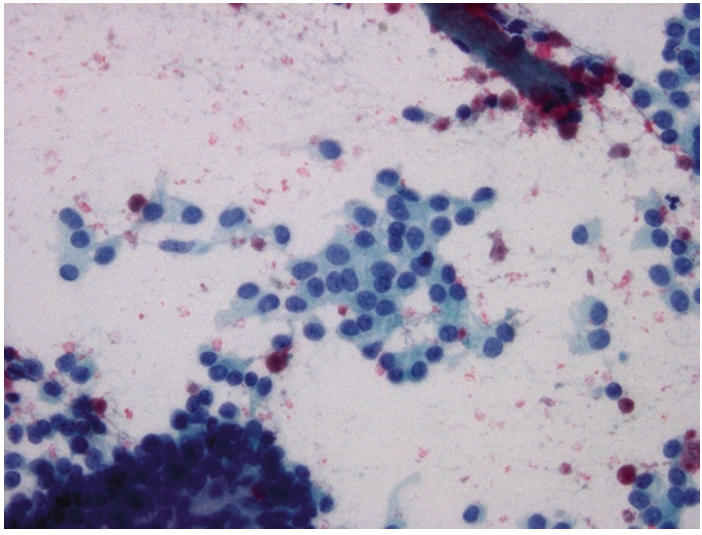


Fig. 9.4 Neoplastic cells of solid pseudopapillary neoplasm exhibit moderate amount of cytoplasm with round to oval nuclei with fine chromatin. Nuclear grooves may not be conspicuous (Papanicolaou stain, 400×)

Immunohistochemistry

The tumor cells characteristically reveal nuclear and cytoplasmic staining with β-catenin (Fig. 9.5). Due to alterations of the catenin-cadherin complex, the tumor cells do not demonstrate a membranous expression pattern with E-cadherin. Instead, there is either complete loss of staining or cytoplasmic/nuclear staining [13, 14]. Another recently described immunohistochemical marker for SPN is lymphoid enhancer binding factor 1 (LEF1). LEF1 shows strong and diffuse nuclear expression in SPNs (Fig. 9.6) [15].

Other markers that are helpful in the diagnosis of SPNs are CD10 and PR (Fig. 9.7). CD10 and PR may be expressed in a minority of pancreatic neuroendocrine tumors, but their expression tends to be focal in these tumors. SPNs may show focal and weak reactivity with cytokeratin in 10–74% of cases. They are usually positive for CD56 and may exhibit focal and weak reactivity with synaptophysin but are negative for chromogranin [13, 14].

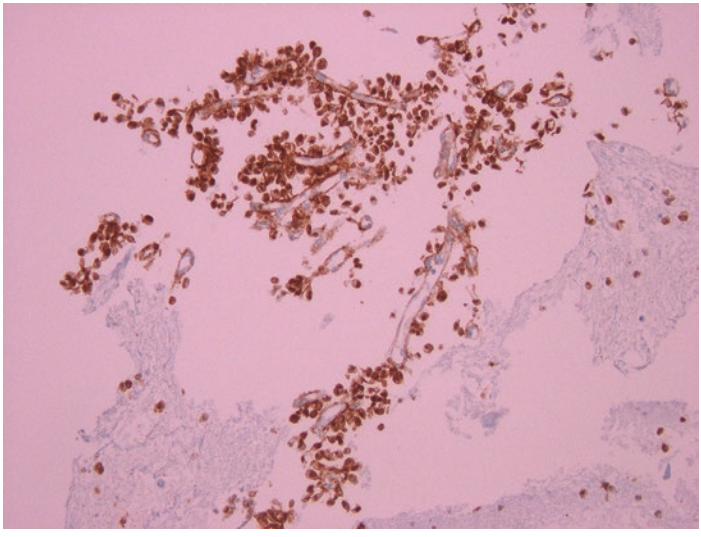


Fig. 9.5 Beta-catenin immunohistochemistry in solid pseudopapillary neoplasm reveals nuclear and cytoplasmic staining (200×)

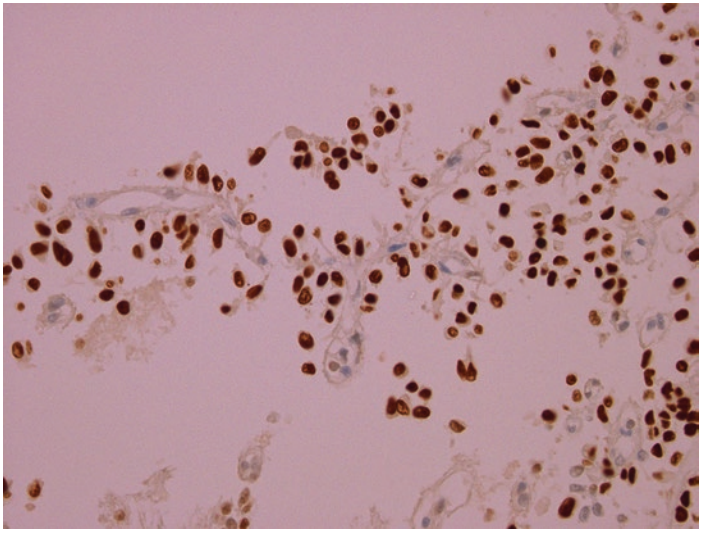


Fig. 9.6 LEF1 immunohistochemistry in solid pseudopapillary neoplasm reveals nuclear staining (400×)

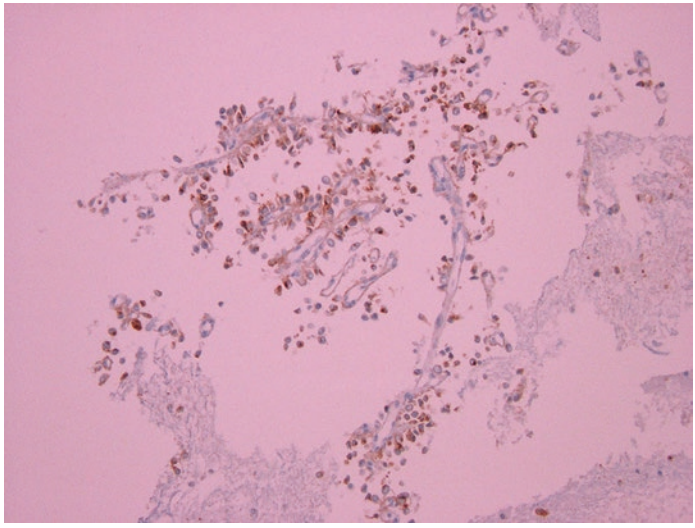


Fig. 9.7 CD10 immunohistochemistry in solid pseudopapillary neoplasm reveals cytoplasmic staining (200×)

Molecular Genetics

SPNs exhibit somatic mutations in the β-catenin (CTNNB1) gene in 95% of cases [10].

Management

SPNs are considered as low-grade malignancies. Complete surgical resection can cure as many as 95% of patients. Metastasis to the peritoneum or liver may be encountered in 5–15% of cases [11].

Cystic Pancreatic Neuroendocrine Tumor (PanNET)

Cystic PanNETs are similar in sex distribution and can occur over a wide age range (23–91 years; mean, 52 years) just like their solid counterparts. Cystic PanNETs are mostly located in the tail of the pancreas. On imaging, these are unilocular cysts which can be difficult to differentiate from other pancreatic cysts [16]. On EUS, these tend to be thick-walled cysts [17].

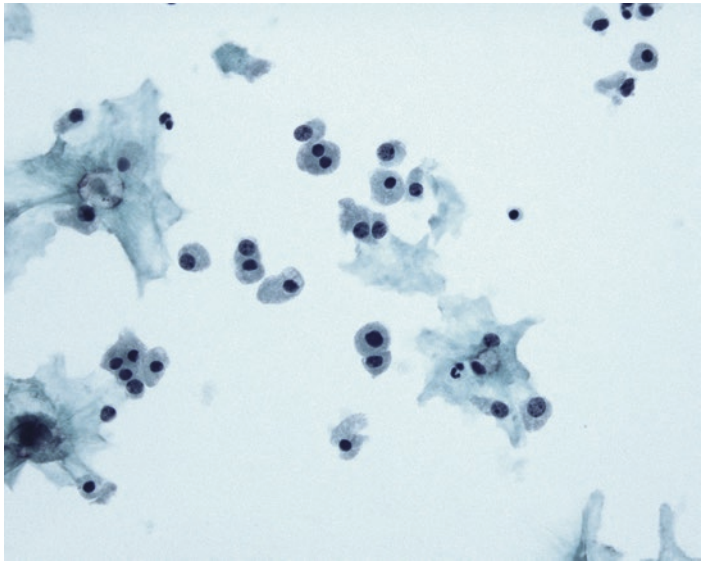


Fig. 9.8 Fine needle aspirate of cystic pancreatic neuroendocrine tumor reveals polygonal neoplastic cells with eccentrically placed nuclei and coarsely stippled chromatin in a background of histiocytes (Papanicolaou stain, ThinPrep, 400×)

Histologically, the cystic PanNETs are well demarcated and surrounded by a thin to thick fibrous capsule. The individual cells are typical of neuroendocrine morphology being characterized by monotonous polygonal cells with amphophilic to eosinophilic cytoplasm and eccentrically placed nuclei with stippled chromatin. Mitotic figures tend to be rare, and tumor necrosis is unusual [16]. Cytology can make a specific diagnosis of cystic PanNET in as many as 71% of instances (Fig. 9.8). Immunohistochemistry for chromogranin and synaptophysin can assist in the differential diagnosis with SCAs and cystic acinar cell tumors [18]. A Ki-67 proliferation index is usually low in these tumors (range, 0.2–11%; mean, 1.8%) [16].

Cyst fluid CEA (range, 0.2 to >500 ng/mL; mean, 29.5 ng/mL) and amylase (mostly <500 U/L) levels are typically low in cystic PanNETs [18]. In terms of biologic behavior, several studies have

shown that cystic PanNETs have less aggressive biologic behavior as compared to the solid ones [16, 19, 20].

Nonneoplastic Cysts

Pseudocyst

Clinical Features and Imaging Findings

Most patients with pseudocysts have a history of prior pancreatitis. On imaging, it is a thin-walled unilocular cyst that frequently has internal debris and lacks a mural nodule. The adjoining pancreas may show features of pancreatitis. It should be emphasized that patients with IPMNs and other neoplastic pancreatic cysts can also present with acute pancreatitis.

Cytology

The aspirate mostly contains neutrophils and histiocytes (which could be hemosiderin laden). Extracellular yellow pigment has been reported in as many as 31% of pseudocyst samples and is considered to be a combination of hematoidin and bile pigment (Fig. 9.9). Occasionally, necrotic fat cells can be identified.

The cytologic findings in a pseudocyst can be associated with several diagnostic pitfalls. Contaminating gastrointestinal tract epithelium can result in a false interpretation of a neoplastic mucinous cyst. Additionally, a pseudocyst can reveal the presence of Alcian blue- and mucicarmine-positive material that can result in the misinterpretation of a neoplastic mucinous cyst. Clusters of ductal epithelium with reactive atypia can also be encountered which may be mistaken for malignancy. These cells may have enlarged nuclei with nuclear overlap but usually lack anisonucleosis to the extent of 1:4, and nuclear membranes tend to be smooth (Figs. 9.10 and 9.11).

The cytologic findings in a pseudocyst tend to be nonspecific and can overlap many a time with a neoplastic mucinous cyst.

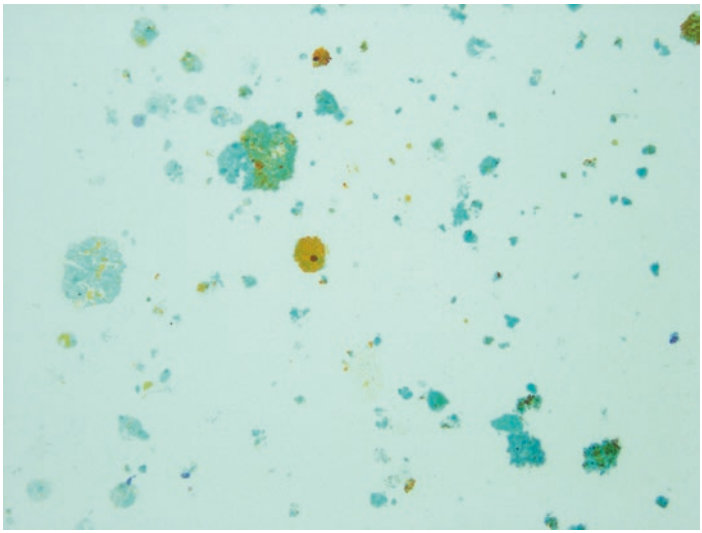


Fig. 9.9 Fine needle aspirate of pseudocyst usually reveals nonspecific findings. The presence of a yellow pigment is suggested as a surrogate marker for pseudocysts (Papanicolaou stain, ThinPrep, 200×)

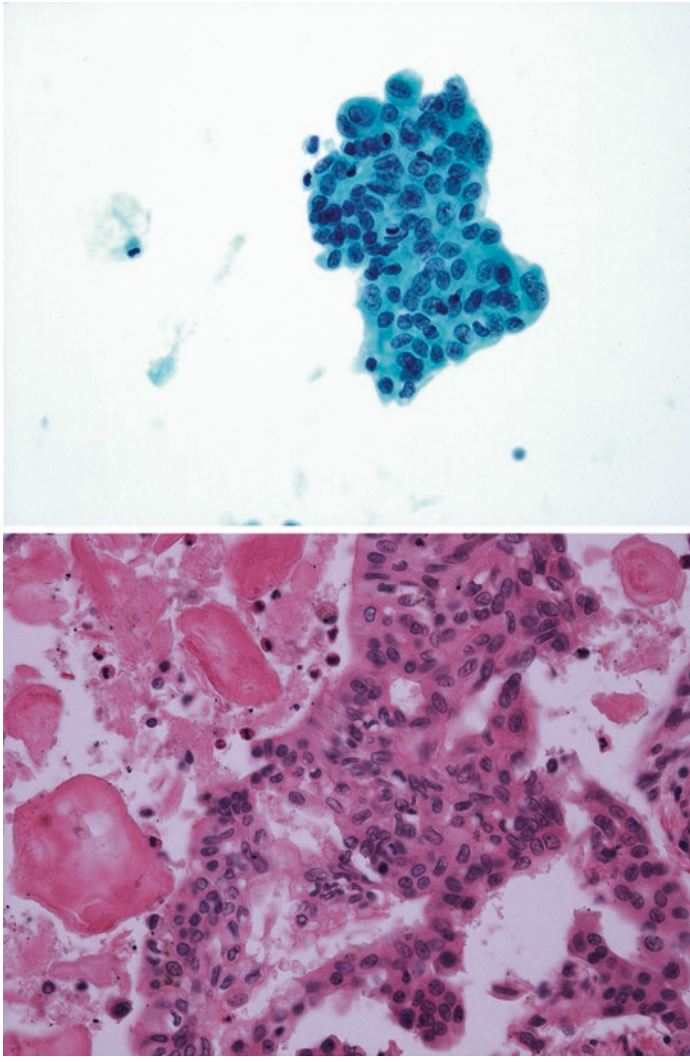
However, when interpreted in conjunction with appropriate clinical findings (a prior history of pancreatitis), imaging studies, and cyst fluid biochemistry, they support the diagnosis of a pseudocyst. The primary role of cytology in such instances is to exclude malignancy.

Ancillary Studies

The amylase level is >250 IU/ml in pseudocysts, and CEA tends to be low [21].

Management

Pseudocysts mostly resolve spontaneously. However, when they are associated with complications and large size, drainage is indicated. Drainage could be endoscopic, percutaneous, or surgical [22].



Figs. 9.10 and 9.11 Reactive ductal atypia in fine needle aspirate and excision of pseudocyst. The ductal epithelial cells show mild crowding with mild degree of anisonucleosis, fine chromatin, and smooth nuclear membranes (Papanicolaou stain, ThinPrep, 400×) (hematoxylin-eosin stain, 400×)

Lymphoepithelial Cyst (LEC)

Clinical Features and Imaging Findings

Lymphoepithelial cysts of the pancreas are rare, benign cysts that are lined by keratinizing squamous epithelium with adjoining lymphoid tissue. They usually occur in older men with male to female ratio of 4:1. The patients may be asymptomatic or may present with abdominal pain.

They can be intrapancreatic or peripancreatic and can be exophytic. On CT, a multilocular cyst on the surface of the pancreas with decreased attenuation is supportive of a lymphoepithelial cyst. LECs demonstrate hypointensity on T2 imaging and a high signal intensity on T1-weighted images. On EUS, these can appear as predominantly solid or multilocular or unilocular cysts. The imaging findings can be nonspecific and can overlap with other pancreatic cysts including pseudocysts and neoplastic mucinous cysts.

Cytology

The aspirate may be viscous, thick milky, creamy, or frothy. The cytologic smears are predominantly composed of keratinous debris and a variable number of anucleated and nucleated squamous cells. Plate-like cholesterol crystals may also be seen. Lymphocytes are usually sparse (Figs. 9.12 and 9.13). The differential diagnosis includes epidermoid cyst of the accessory spleen and dermoid cyst. The presence of contaminating gastrointestinal tract epithelium may be mistaken for neoplastic mucinous epithelium, and these cysts may be erroneously diagnosed as neoplastic mucinous cysts.

Ancillary Studies

The CEA level can be markedly elevated in lymphoepithelial cysts, and this is probably due to the expression of CEA by the squamous epithelium and presence of mucous cells in the lining epithelium of the cyst. As a result, lymphoepithelial cysts may be difficult to distinguish from neoplastic mucinous cysts.

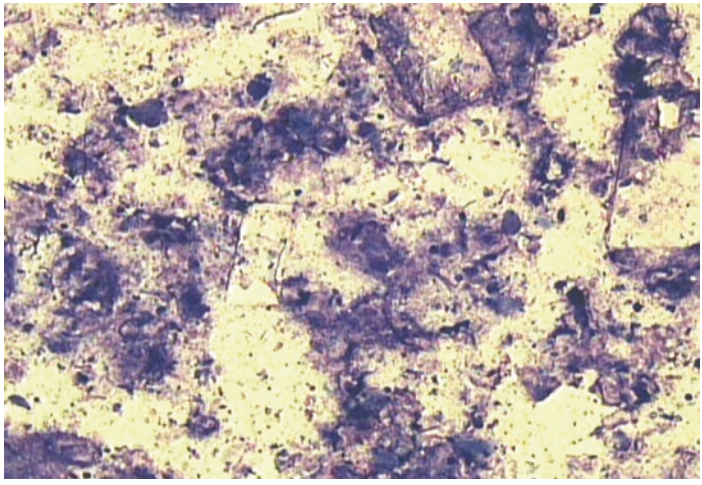


Fig. 9.12 Fine needle aspirate of lymphoepithelial cyst showing keratinous debris and cholesterol crystals (Diff-Quik stain, 100×)

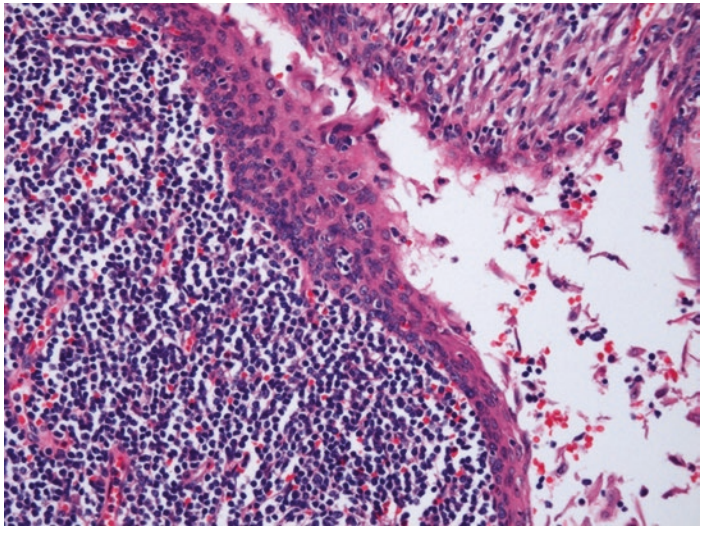


Fig. 9.13 Histology of lymphoepithelial cyst showing benign stratified squamous epithelial lining with an accompanying lymphoid infiltrate (hematoxylin-eosin stain, 200×)

Management

Asymptomatic patients are managed conservatively. It may be difficult to make a definitive diagnosis of lymphoepithelial cyst preoperatively. The cyst may be surgically resected due to the patient's symptoms or to exclude a premalignant/malignant cyst [23, 24].

Epidermoid Cyst of the Accessory Spleen

An epidermoid cyst arising within an intrapancreatic accessory spleen is a rare occurrence. These are almost exclusively located in the tail of the pancreas with size ranging from 1.5 to 11.5 cm and can be unilocular or multilocular. It has been hypothesized that these cysts may arise due to mesothelial inclusion with squamous metaplasia, as a by-product of a teratoma, or due to communication between the pancreatic ducts and an intrapancreatic accessory spleen.

On contrast-enhanced CT scan, the periphery of these lesions may show the same enhancement as that of the spleen in the arterial phase. On MRI, the cystic contents show high signal intensity on both T1- and T2-weighted images.

Histologically, the cyst is lined by keratinizing or nonkeratinizing stratified squamous epithelium and is surrounded by normal splenic tissue. A fine needle aspiration (FNA) of an epidermoid cyst within an intrapancreatic accessory spleen can yield only inflammatory debris, but the presence of mature squamous epithelial cells with lack of malignant-appearing cells can assist in the differential diagnosis [25–27].

Retention Cyst

Obstruction and fibrosis of the pancreatic duct can result in upstream dilatation resulting in a retention cyst. The cyst lining epithelium is composed of low cuboidal or attenuated mucinous epithelium. The finding of an obstruction of the pancreatic duct can aid in the diagnosis of a retention cyst.

Squamoid Cyst of the Pancreatic Ducts (SCOP)

In 2007, Othman et al. reported a distinct type of squamous-lined pancreatic cyst termed squamoid cyst of the pancreatic ducts (SCOP). These are unilocular cystic dilatation of the ducts that usually contain muco-proteinaceous acidophilic acinar secretions forming concretions that suggests the role of a localized obstruction in their pathogenesis. No evidence of pancreatitis is present, however. The epithelial lining ranges from attenuated, flat squamoid to transitional to stratified squamous cells without keratinization. On immunohistochemistry, the cells forming the basal/parabasal region express p63, and the surface cells are positive for MUC-1 and MUC-6 (which are also expressed by intercalated duct cells). SCOP is thought to be a metaplastic cystic transformation beginning in the intercalated ducts [28]. Recently, Hanson et al. reported that SCOPs could be associated with elevated CEA levels and may be difficult to distinguish preoperatively from mucinous cysts [29].

Acinar Cell Cystadenoma

Acinar cell cystadenoma is a rare, benign cystic lesion of the pancreas. It may be detected incidentally or can present with abdominal pain. Imaging reveals a unilocular or multilocular cyst that may be located anywhere in the pancreas. Whether it is neoplastic or nonneoplastic is not clearly understood. Some authors have suggested alternative terminology, that is, cystic acinar transformation, for this entity.

Histologically, the cysts are lined by acinar cells (with apical bright-red zymogen granules) and ductal epithelium. No cytologic atypia, mitoses, necrosis, infiltrative growth, or associated invasive carcinoma is identified. Mucinous epithelium, akin to gastric foveolar-type epithelium, can also be seen.

On cytology, the acinar cells could be misinterpreted as PanNET cells derived from a neoplastic mucinous cyst or an adenocarcinoma. PAS with diastase stain can help highlight the apical cytoplasmic granules of an acinar cell cystadenoma. On immunohistochemistry, the acinar cells are positive for trypsin

and chymotrypsin and negative for neuroendocrine markers (synaptophysin, chromogranin, and CD56). Ki-67 labeling index is reportedly low (1–2%).

Cyst fluid CEA levels may be elevated and are probably due to the presence of mucinous epithelium in acinar cystadenomas. Amylase levels are elevated with a reported range of 73–252,788 U/L and a mean of 45,847.5 U/L [30, 31].

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