Cystic Lesions of the Pancreas

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Introduction

In recent years, the diagnosis of cystic lesions of the pancreas (CLPs) has increased dramatically due to the widespread use of cross-sectional radiologic imaging technologies [1]. In the radiology literature, the prevalence of CLPs on computed tomography (CT) and magnetic resonance imaging (MRI) is estimated to range between 2.4 and 14 % [2–4]. Furthermore, small CLPs have been reported iwith a high frequency (up to 39 %) during screening of asymptomatic individuals with a high risk of pancreatic malignancy [5]. A recent population-based study demonstrated that the overall frequency of detecting malignancy in CLPs at 2.9 % in patients surveyed for known pancreatic cysts, with an annual incidence of 0.4 % per year [6]. Based on the presence of epithelial tissue, the World Health Organization (WHO) classifies) CLPs into epithelial and non-epithelial lesions [7]. Inflammatory pancreatic fluid collections (pancreatitis-associated pseudocysts) are not considered true cysts due to the absence of an epithelial component.

A combination of clinical and imaging findings in addition to cyst fluid markers can help appropriately classify CLPs. In this chapter we will expand on each one of the main types of epithelial CLPs, including the commonly encountered types in clinical practice from the mucinous and nonmucinous subtypes.

Mucinous Cystic Lesions of the Pancreas

Mucinous CLPs are mucin-producing neoplasms, which are composed of two distinct groups: intraductal papillary-mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Despite the fact that mucinous CLPs are considered premalignant, many of them remain indolent and do not exhibit an aggressive biological behavior. Because of this malignant potential, however, mucinous CLPs require a baseline investigation to assess the risk of malignant transformation and the interval for follow-up. Furthermore, these tumors sometimes need surgical resection if already malignant at the time of diagnosis or strongly suspected to be so based on preoperative

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testing. Therefore, it is necessary to distinguish between mucinous and nonmucinous CLPs prior to making final management recommendations.

Intraductal Papillary-Mucinous Neoplasms

Histopathologic Features

IPMNs are defined as intraductal papillary mucin-producing neoplasms, arising in the main pancreatic duct or its major branches [7]. Based on the WHO classification, IPMNs are histologically categorized as benign, borderline, or malignant; the malignant ones encompass noninvasive and invasive lesions [7]. According to the consensus on the pathologic classification [8], IPMNs are categorized based on the presence or absence of invasive adenocarcinoma in the resected specimen due to its impacts on local recurrence and patient survival. In addition, the consensus suggested classifying noninvasive IPMN into low-grade dysplasia (adenomas in the previous classification), moderate dysplasia (borderline tumors in the previous classification), or high-grade dysplasia (carcinoma in situ), based on the maximal degree of dysplasia in the lining epithelium. From a pathological and morphological perspective, IPMNs can be classified as main-duct (MD-IPMN), branched-duct (BD-IPMN), or mixed IPMN [9]. Macroscopically, IPMNs exhibit various degrees of main- or side-branch ductal dilation with mucin-filled cystic cavities [7]. The lining of the lesion may be smooth or exhibit classic papillary growth. The histopathologic hallmark of IPMN is the intraductal proliferation of columnar mucin-producing cells [7]. The premalignant papillary projections within IPMN lesions can be categorized into four histopathological subtypes: the gastric, intestinal, pancreatobiliary, and oncocytic subtypes [10, 11]. The gastric subtype is the most common variant seen in BD-IPMN, which often demonstrates benign behavior, whereas the intestinal subtype is the most common type in MD-IPMN and has a higher malignant potential compared to the gastric type. The pancreatobiliary subtype is less commonly seen but could be considered a highly dysplastic variant of the gastric type, which typically exhibits aggressive biological behavior once it becomes invasive. The oncocytic subtype, on the other hand, typically displays noninvasive behavior. Most invasive carcinoma arising from IPMN presents as either the tubular or colloid type. The histological and biological behavior of the tubular type is similar to the common ductal adenocarcinoma. The colloid type contains pools of mucin intervening between scant carcinoma cells, which usually predicts a better prognosis.

Clinical Characteristics

MD-IPMN and mixed-type IPMN are slightly more prevalent in men [9, 12], with a peak age of incidence in the sixth to seventh decade (Table 4.1) [12, 13]. IPMNs are slightly more frequently seen in the pancreatic head. The majority of patients with IPMNs are asymptomatic and most BD-IPMNs are incidentally diagnosed on imaging studies [12, 14]. However, IPMNs can present with symptoms such as abdominal pain, jaundice, weight loss, diabetes, steatorrhea, and pancreatitis [14]. Recently, a multicenter case-control study identified possible risk factors relevant for the development of IPMN, including a previous history of diabetes, especially with insulin use, chronic pancreatitis, and family history of pancreatic ductal adenocarcinoma [15]. The overall malignancy risk in MD-IPMN has been reported as up to 92 % in surgical patients, with most studies placing this between 40 and 50 % [16–20]. In BD-IPMN, this risk varied in surgical literature but is believed to be 20 % or less [16, 18, 20, 21]. Nevertheless, many experts believe that these reported risks are inflated, citing selection bias in these mostly surgical series.

It is believed that IPMN lesions grow slowly and follow an adenoma-to-carcinoma sequence [22]. Based on the 2006 international consensus guidelines [23], clinical factors associated with invasive cancer in patients with IPMNs include jaundice and weight loss, intramural nodules, progressive dilation of the main duct, and positive cytology on fine-needle aspiration (FNA).

Table 4.1 Clinical and histopathologic features of the different types of cystic pancreatic neoplasms

	IPMNs	MCNs	SCNs	cPNETs	SPTPs
Age range	60s–70s	50s–70s	60s–70s	50s–60s	30s
Gender	Male > Female	Female > Male	Female > Male	Male = Female	Female > Male
Presentations	Mostly asymptomatic with BD-IPMNs	Asymptomatic if small Pain/weight loss if larger	Frequently asymptomatic	Nonfunctioning lesions and often asymptomatic	Asymptomatic or abdominal pain
Macroscopic findings	Various degrees of ductal dilation in MD-IPMNs; mucin-filled cystic cavity in BD-IPMNs	A smooth surface and a fibrous pseudocapsule with variable thickness septations	A few/numerous small cysts filled with serous fluid around a central fibronodular core	A single locule, surrounded by a rim of neoplastic parenchyma, filled with clear to straw-colored fluid	Cystic areas of hemorrhage and necrosis with a well-defined fibrous pseudocapsule
Microscopic findings	Intraductal proliferation of columnar mucin-producing cells	Benign: no mitosis Malignant: changes of high-grade intraepithelial neoplasia or invasive adenocarcinoma	A single layer of cuboidal or flattened epithelial cells with clear cytoplasm; positive PAS staining	Monotonous cells with granular chromatin and plasmacytoid morphology, positive synaptophysin and chromogranin A stains	Pseudopapillary structures composed of tumor cells surrounding small central vessels
Location	Head > body, tail	Body, tail > head	Body, tail ≥ head	Body, tail > head	Throughout the pancreas

MD-IPMN main duct intraductal papillary mucinous neoplasm, *SB-IPMN* side branch intraductal papillary mucinous neoplasm, *cPNETs* cystic neuroendocrine tumors of the pancreas, *SPTPs* solid pseudopapillary tumors of the pancreas, *PAS* periodic acid Schiff

Although BD-IPMN is associated with a lower risk of malignancy, PDAC has been reported concomitantly in patients with BD-IPMN [24–26]. Those cancers were detected in a location distant from the IPMN lesion. During follow-up, the 3- and 5-year rates of IPMN-concomitant PDAC occurrence were 4.0 % and 8.8 %, respectively [24]. However; the natural history of IPMN remains unclear due to the rather short span of follow-up, which is less than 6 years in most published studies [27–30].

Radiological Findings

On CT imaging, MD-IPMN demonstrates diffuse or focal dilation of the main pancreatic duct with possible intraductal heterogeneous densities, representing mucin or intraductal tumor growth (Table 4.2) [31]. BD-IPMN can be either unifocal or multifocal [14, 32]. MRI technology is better suited to outline the morphology of the main duct and its side branches, as well as determine the presence of septations, mural nodules, or mass [31, 33]. IPMN lesions usually appear as well-circumscribed uni- or multiloculated hyperintensities on T2-weighted (W) images (Fig. 4.1a). On magnetic resonance cholangiopancreatograhy (MRCP), a communication between the cystic lesion and the main pancreatic duct (Fig. 4.1b) or its side branches can be often demonstrated in BD-IPMN. MCNs and BD-IPMNs may be difficult to differentiate on imaging alone since both can appear as simple unilocular cystic lesions, with variable cystic wall thickness [34]. Communication with a side branch of the main pancreatic duct is the hallmark of BD-IPMNs but is not always seen. Mucinous cystic neoplasms, on the other hand, rarely exhibit any communication with the pancreatic ductal system. Intramural filling defects seen on imaging of BD-IPMNs can be either mucin or mural nodules. Based on earlier studies [33, 35–40], CT or MRI features associated with malignancy in IPMNs include lesion size more than 3 cm, main duct dilation more than 6 mm, irregularly thickened wall, mural nodule larger than 5 mm, ductal wall enhancement, common bile duct dilation, and bulging papilla. A recent meta-analysis evaluated imaging features for differentiating malignant from benign BD-IPMNs [41] and found that the presence of mural nodules was the most suggestive finding for malignancy [odds ratio (OR), 6.0], followed by main pancreatic duct dilatation (OR, 3.4), thick septum or cyst wall (OR, 2.3), and cyst size greater than 3 cm (OR, 2.3). According to the 2012 international consensus guidelines for the management of IPMNs and MCNs [42], "high-risk stigmata" included enhanced solid component and the size of main pancreatic duct ≥10 mm, or "worrisome features," including cyst o≥3 cm, thickened enhanced cyst walls, nonenhanced mural nodules, the main pancreatic duct size of 5–9 mm, abrupt change in the main pancreatic duct caliber with distal pancreatic duct atrophy, and lymphadenopathy.

EUS Morphology

The classic endoscopic finding of fish-mouth appearance of the papilla, which is characterized by the presence of mucin exuding from a patulous major or minor papilla (Fig. 4.2) with or without papillary tissue protrusion (fish-egg appearance), is diagnostic of MD-IPMN. EUS characteristics include a macrocystic morphology of the cyst, with or without septations, which could communicate with a dilated pancreatic duct (MD or BD) (Fig. 4.3, Table 4.3) [43]. A mucin nodule may be seen (Fig. 4.4). The differential diagnosis of a unilocular pancreatic cyst on EUS includes commonly macrocystic serous cystic neoplasm, mucinous cystic neoplasm, and inflammatory cyst [44]. Other less common differential diagnoses include cystic solid tumor (neuroendocrine or solid pseudopapillary) and lymphoepithelial cyst. Previous retrospective studies reported a strong association between the presence of a mural nodule (height >10 mm, lateral spread >15 mm) and malignancy in BD-IPMN [45, 46].

Due to the difficulty in differentiating such tumors based on morphology alone, FNA is generally recommended in this case to accrue fluid for cytology and tumor markers. The integration of cyst fluid cytology and tumor markers for the appropriate classification of CLPs is discussed elsewhere in this book.

Table 4.2 Radiological characteristics of the different types of cystic pancreatic neoplasms

	IPMNs	MCNs	SCNs	cPNETs	SPTPs
CT	MD-IPMNs: diffuse or focal dilatation of MPD with intraductal heterogeneous densities	Solitary lesion consisting of a thick enhancing wall, ± septation, ± peripheral calcification, ± mural nodules	Polycystic, honeycomb or oligocystic pattern, with septations, ± central scar ± calcifications	A cystic lesion with peripheral arterial enhancement ± a solid component	A solid part in the periphery with central cystic component, surrounded by well-demarcated capsule
	BD-IPMNs: unifocal or multifocal cystic lesions				
MRI	MD-IPMN: diffusely or segmentally dilated main pancreatic duct; BD-IPMN: Well-circumscribed single or multiloculated hyperintensity on T2W	Round, homogeneous, with high signal intensity on T2W, with regular rim enhancement on delayed T1W	Microcystic with honey comb appearance and central scar on T2W or macrocystic, unilocular or oligolocular on T2W. Enhancement of thin septations radiating from a central scar on gadolinium-T1W	Homogenous unilocular, thick wall lesion on T2W. Wall enhancement in arterial phase on gadolinium-T1W	High and low signal intensity with thick fibrous capsule. Heterogeneous peripheral capsule enhancement on T1W post-gadolinium
MRCP	Cyst usually communicating with pancreatic duct	Cyst rarely communicating with pancreatic duct	No communication with the pancreatic duct	No communication with the pancreatic duct	No communication with the pancreatic duct

MD-IPMN main duct intraductal papillary mucinous neoplasm, *SB-IPMN* side branch intraductal papillary mucinous neoplasm, *cPNETs* cystic neuroendocrine tumors of the pancreas, *SPTPs* solid pseudopapillary tumors of the pancreas, *PAS* periodic acid Schiff

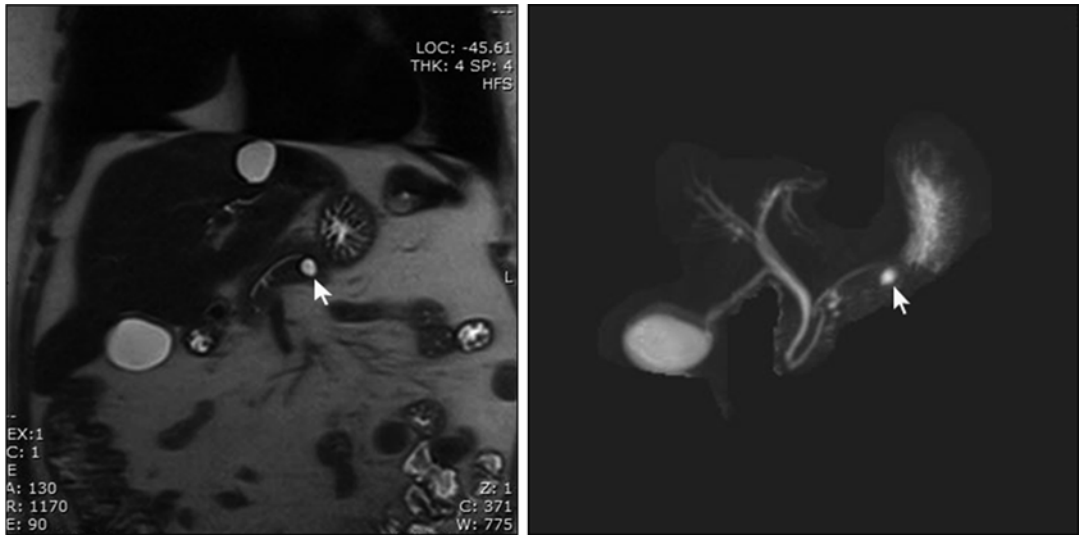

Fig. 4.1 Radiological characteristics of side-branch IPMNs. (**a**) MRI of a 35-year-old asymptomatic female patient shows a 9-mm cystic lesion (*white arrow*), in close proximity to the main pancreatic duct. (**b**) Communication between the pancreatic cyst and the main pancreatic duct seen on MRCP (*white arrow*)

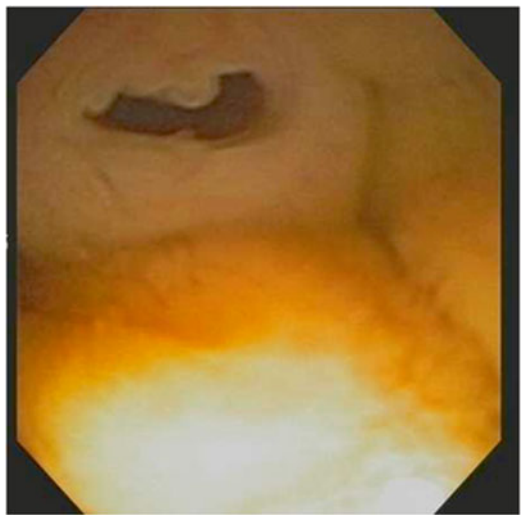

Fig. 4.2 Endoscopic finding of fish-mouth appearance of the major papilla, characterized by the presence of mucin exuding from a patulous papilla in a patient with main-duct IPMN

Mucinous Cystic Neoplasms

Histopathologic Features

MCNs are defined as cystic epithelial neoplasms with no communication with the pancreatic ductal system and are composed of columnar, mucin-producing epithelium, supported by ovarian-type stroma [7]. These tumors are usually associated with extracellular mucin production with variable degrees of cyst wall epithelial atypia. The histopathologic hallmark of MCN is the presence of ovarian stroma underlying the mucinous columnar cyst epithelium and is required to differentiate this tumor from IPMN [47]. Similar to IPMNs, MCNs are classified as noninvasive (low-grade dysplasia, moderate dysplasia, and high-grade dysplasia) and invasive lesions. Gross morphology demonstrates a round mass with a smooth surface and a fibrous pseudocapsule with variable thickness and frequent calcifications [7]. Histologically, MCNs exhibit columnar epithelium with basally located nuclei and absent or minimal mitosis, whereas mucinous cystadenocarcinomas show changes of high-grade intraepithelial neoplasia (nuclear stratification, severe nuclear atypia, and frequent mitoses), which are usually focal [7].

Clinical Characteristics

Females are more frequently affected with MCNs, particularly in their fifth to seventh decades

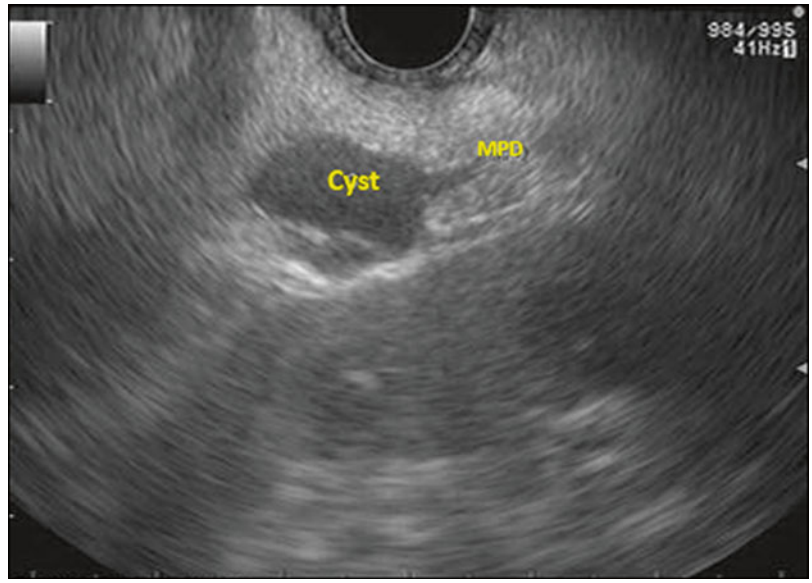

Fig. 4.3 EUS morphology of SB-IPMNs. A 14-mm × 12-mm cystic lesion was identified in the pancreatic tail in a 66-year-old male presenting with abdominal pain. The cyst was found to communicate with the main pancreatic duct through a small side branch, suggestive of branched duct IPMN

Table 4.3 EUS morphology in the different types of cystic pancreatic neoplasm

	IPMNs	MCNs	SCNs	cPNETs	SPTPs
Typical features	Fish-mouth appearance on endoscopy. Macrocystic, septated cyst with dilated PD (main or side branch)	Macrocystic cyst with a visible wall	A well-demarcated lesion with multiple small fluid-filled cavities, ± central calcified scar	Uni- or multilocular lesion with a visible wall	Well-defined, mixed echogenicity lesion, ± internal or peripheral calcifications
Echogenicity	Anechoic	Anechoic	Usually anechoic Hypoechoic if solid variant	Anechoic, hypoechoic, or mixed	Anechoic, hypoechoic, or mixed
Wall thickness	Thin	Mostly thick	Thin	Mostly thick	Mostly thick
Septation	Yes	Yes	Yes	Yes	No
Nodule	Mucin aggregation; ± true soft tissue mural nodule	± Mural nodule	Rare	± Mural nodule	± Mural nodule
Communication with the pancreatic duct	Usually seen	Rarely seen	Not seen	Not seen	Not seen

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[48–50]. The tumors occur most frequently in the pancreatic body and tail [13]. MCNs can be incidentally found [47]; however, they can present with abdominal pain, palpable mass, and weight loss, particularly in association with large lesions [9, 13]. Pancreatitis is infrequent with MCNs but can be seen in up to 10–20 % of cases [48, 51, 52]. A recent study demonstrated factors predictive of high-grade dysplasia and/or invasive carcinoma in MCNs, which included the presence of symptoms, obstructive jaundice, and elevated serum CEA and CA 19-9 [53]. Although MCNs have malignant

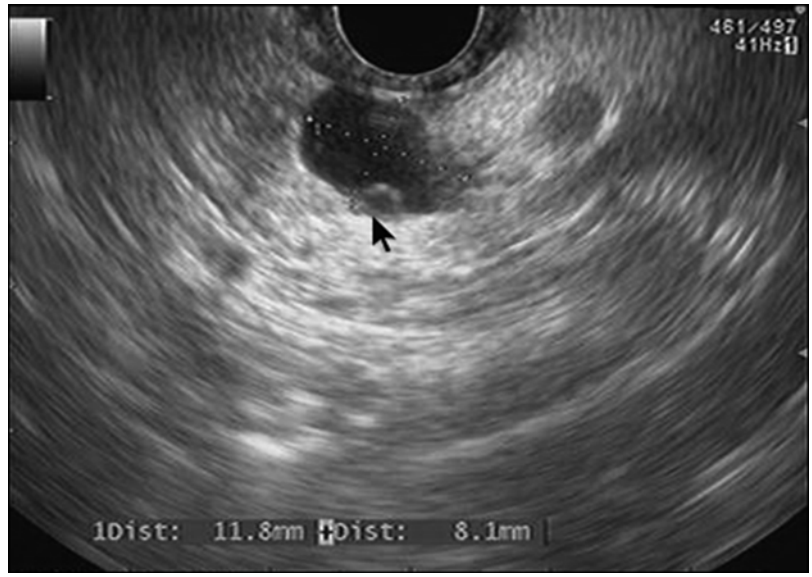

Fig. 4.4 EUS morphology of IPMNs. A 12-mm × 8-mm cystic lesion with mucin aggregate (*black arrow*; this was suspicious for soft tissue mural nodule on MRI) within the fluid-filled cavity of the cyst, consistent with SB-IPMN. Mucin "balls" typically have a hyperechoic rim and hypoechoic core

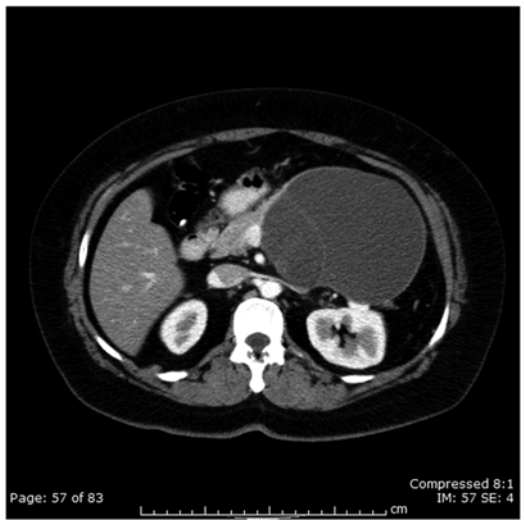

Fig. 4.5 Radiological characteristics of MCNs. CT demonstrated a large 11-cm septated cystic lesion in the pancreatic tail in a middle-aged female patient presenting with left upper quadrant discomfort

potential, they carry a lower overall risk of malignancy in comparison with MD-IPMNs [47]. In a study of 163 patients undergoing surgery, the prevalence of malignancy in such tumors was found to be 17.5 % (5.5 % with carcinoma in situ and 12 % with invasive cancer) [51].

Radiological Findings

CT typically shows a unilocular cystic lesion in the pancreatic body or tail, with or without septations and a thick enhancing wall (Fig. 4.5). Peripheral calcifications can be present in 15–23 % and occasionally can be linear, taking the shape of an eggshell [48, 52]. Mural nodules within MCN on CT scan strongly suggest malignancy [52]. MCN appears round, homogeneous, with high signal intensity on T2W MRI (Fig. 4.6), with regular rim enhancement on delayed T1W images [54]. MRCP usually demonstrates no communication between the cyst and the pancreatic ductal system [31, 54].

EUS Morphology

MCNs presents as a macrocystic lesion with a visible wall and septations of variable thickness on EUS (Fig. 4.7a) [13, 43]. A solid component (Fig. 4.7b) or mural nodule (Fig. 4.7a) may be seen. Peripheral calcifications can be present focally or as a rim but are only seen in up to 15 % of lesions [48]. Mucinous cystadenocarcinomas are more likely to appear as a hypoechoic cystic/solid mass or complex cyst and are frequently

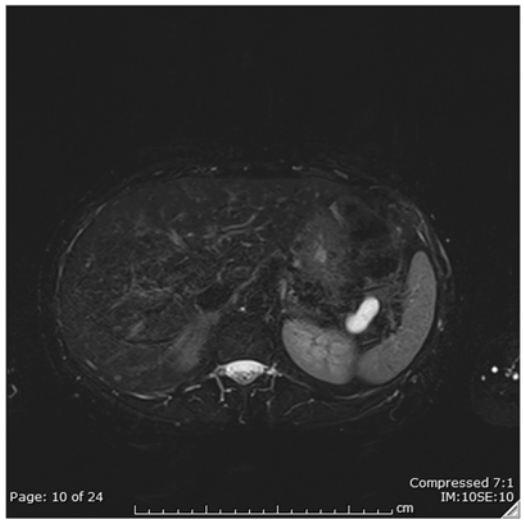

Fig. 4.6 Radiological characteristics of MCNs. T2-weighted MRI showed a round, homogeneous cyst with high signal intensity in the pancreatic tail. EUS-FNA of this lesion confirmed the mucinous nature due to an elevated cyst fluid CEA and the presence of a low-clonality K-ras mutation

associated with a dilated main pancreatic duct upstream from the lesion [55]. Furthermore, regional lymphadenopathy can be seen during EUS examination in malignant lesions [56].

Nonmucinous Cystic Lesions of the Pancreas

Nonmucinous CLPs vary greatly in their clinical, radiologic, and EUS characteristics due to variable underlying pathologies. Serous cystadenomas (SCAs) are the most commonly encountered nonmucinous true cystic tumors of the pancreas. Other nonmucinous pure cystic or mixed solid–cystic tumors such as pancreatic neuroendocrine tumors (PNETs) and solid pseudopapillary tumors of the pancreas (SPTPs) will be discussed in this chapter as well.

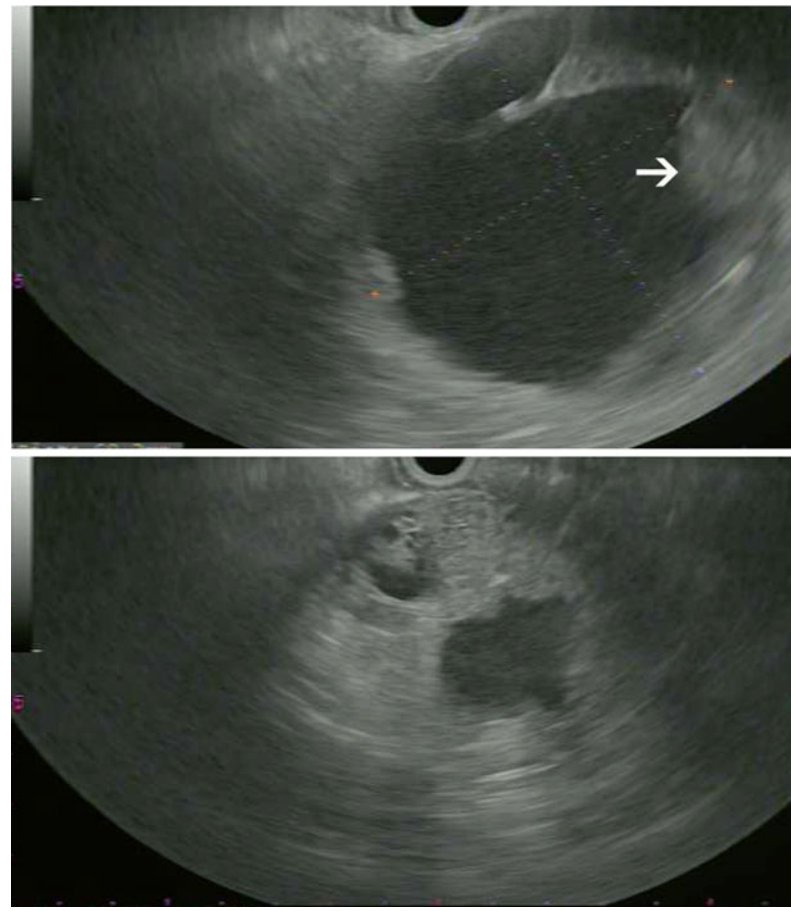

Fig. 4.7 EUS morphology of MCN. (**a**) A mixed cystic–solid septated 70-mm ×70-mm lesion was seen in the pancreatic tail with thickened wall and mural nodules (*white arrow*) within the cavity, not communicating with the pancreatic duct. (**b**) A tangential view through the cyst demonstrates the thickened wall and septum

Serous Cystadenomas

Histopathologic Features

SCAs are defined as cystic epithelial neoplasms composed of glycogen-rich, ductular-type epithelial cells that produce a watery fluid similar to serum [7]. Gross pathology often demonstrates a few or numerous small cysts filled with serous fluid around a central fibrous core with fine septations (central scars) [7]. By histology, the cysts are lined with a single layer of cuboidal or flattened epithelial cells with a clear cytoplasm. The periodic acid–Schiff stain is positive due to their intracytoplasmic glycogen [7]. Morphologically, microcystic SCAs (typically with individual cysts measuring less than 5 mm in size) are more common, whereas the macroscopic variant (over 2 cm in size) is relatively infrequent. Microcystic tumors are usually well delineated with multiple small fluid-filled cavities, which are separated by thin septa and lined with cuboidal epithelial cells [14]. Macrocystic SCAs may not be indistinguishable from MCNs or BD-IPMNs based on morphology alone. The presence of any intramural nodules, cyst wall thickening, floating debris, mucin, or associated pancreatic duct dilation or communication can indicate a mucinous lesion [55, 57].

Clinical Characteristics

SCAs frequently occur in females around the sixth to seventh decade of life [9, 13, 58] and are believed to be predominantly located in the pancreatic body and tail [9, 12]. However, a 2012 multicenter study from Japan reported a similar distribution in the pancreas head (39 %), body (35 %), and tail (22 %) [58]. Patients are usually asymptomatic, with SCAs being an incidental finding on imaging studies [13, 58]. Among symptomatic patients, abdominal pain is the most common presentation (12 %) [58], but other symptoms include back pain, jaundice, pancreatitis, or palpable mass [9, 12, 58]. Malignant SCAs of the pancreas are very rare, and these tumors are therefore considered to have a negligible malignant potential [59–61]. A recent study showed a steady rate of growth of pancreatic SCAs over time, with an estimated time of doubling in size of 12 years [62].

Radiological Findings

SCAs can appear as polycystic (70 %), honeycomb (20 %), or oligocystic (<10 %) on imaging [63]. On CT, the polycystic lesion is characterized by multiple cysts measuring 2 cm or smaller with septations (Fig. 4.8) [63]. A central scar may be seen on delayed-phase imaging [64]. The honeycomb appearance is described as numerous subcentimeter cysts, separated by fibrous septa [31, 63]; however, this may appear as a well-delineated mass with mixed attenuation and a sharp interface with vascular structures on CT scan [63]. The oligocystic pattern is recognized by fewer large cysts measuring >2 cm, which may appear like MCNs or BD-IPMNs [63]. T2W MRI can demonstrate a microcystic (cysts <2 cm) morphology with a honeycomb appearance and central scar or a macrocystic (cysts >2 cm) oligocystic pattern (unilocular or bilocular; Fig. 4.5) [54]. Enhancement

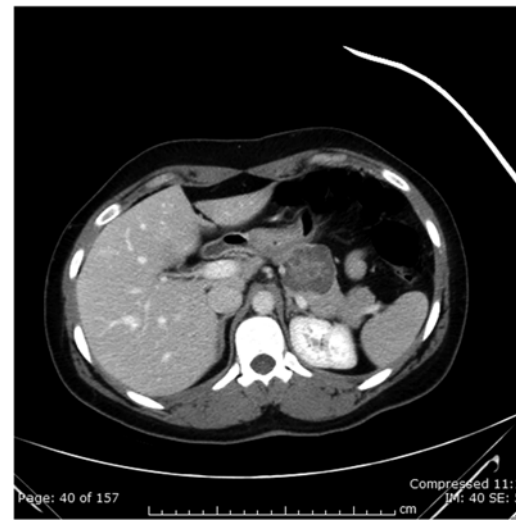

Fig. 4.8 Radiological characteristics of SCA. CT imaging in a patient with incidental lesion on the pancreas, which showed a heterogeneous, multiseptated, low-density cystic lesion in the junction of the pancreatic body and tail of the pancreas, measuring 3.7 cm in diameter, with central stellate scarring appearance

of the thin septations that radiate from a central scar may be seen on gadolinium T1W images. MRCP usually shows no communication with the pancreatic duct.

EUS Morphology

The typical SCA is a well-demarcated lesion on EUS with multiple small fluid-filled cavities, which are separated by thin septations (Fig. 4.9) [13, 44]. The honeycomb pattern is noted in most of the microcystic lesions by EUS [58]. A central calcified scar may exhibit a "sunburst" appearance (Fig. 4.9) [13, 44]. A macrocystic morphology is less commonly seen (Fig. 4.10). The solid variant of SCAs has been rarely reported but can lead to misdiagnosis as a solid tumor [44, 58, 63, 65–67]. Nevertheless, the presence of a mural nodule, wall thickening, ductal dilation, or mucin-filled cavity is atypical manifestations for SCAs and should raise the suspicion of a mucinous lesion [44, 63].

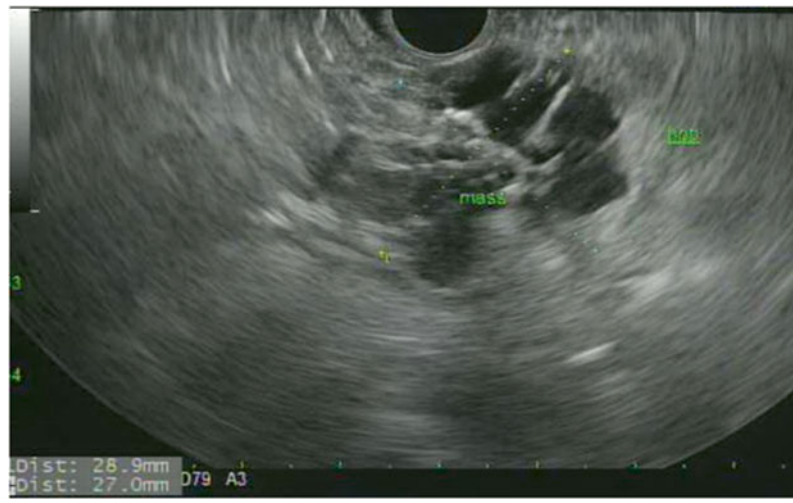

Fig. 4.9 EUS morphology of SCA. A 29-mm ×27-mm multiloculated cystic lesion was identified in the pancreatic head with central calcification, consistent with microcystic serous cystadenoma

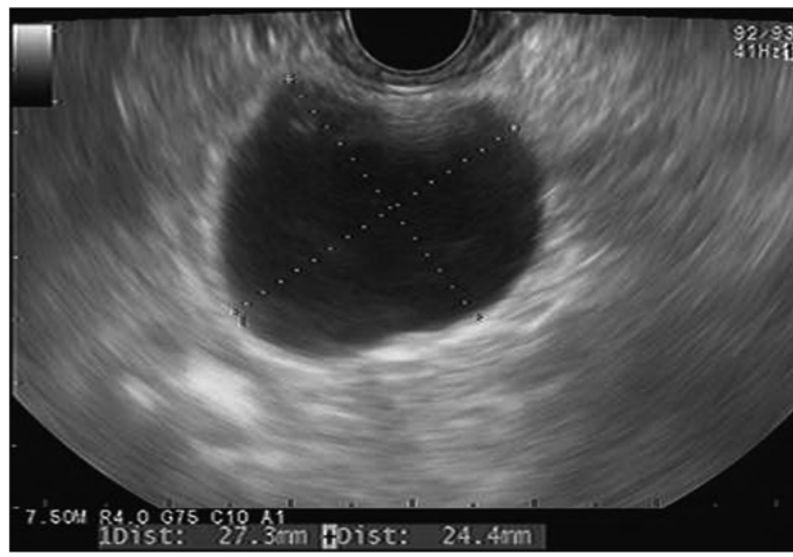

Fig. 4.10 EUS morphology of SCA. A 27-mm ×25-mm macrocystic lesion was demonstrated in the pancreatic head on EUS in this 62-year-old female patient. Cyst fluid CEA was 2.6 ng/mL, which is consistent with a serous lesion

Cystic Pancreatic Neuroendocrine Tumors

Histopathologic Features

Grossly, cystic pancreatic neuroendocrine tumors (cPNETs) are typically)comprised of a single locule, surrounded by a rim of neoplastic parenchyma, which are filled with clear to straw-colored fluid. The histopathology of solid PNETs typically shows small or medium-sized monotonous cells with granular chromatin (salt and pepper) and a plasmacystoid morphology [68]. Tumor cells may be difficult to detect in the cystic fluid [69]. However, the diagnosis can be confirmed by synaptophysin and chromogranin A staining, which is practically diagnostic of this condition [31, 69, 70]. In comparison with ductal adenocarcinomas, tumor necrosis, perineural invasion, vascular invasion, and regional lymph node metastasis are less likely to be seen in cPNETs [71, 72].

Clinical Characteristics

PNETs make up to 1–2 % of all pancreatic neoplasms, which may have a cystic component in less than 10 % of cases [1, 7, 69, 73, 74]. In a previous study of a 33-year experience at Massachusetts General Hospital, cPNETs accounted for 3 % of cystic neoplasms in the 1970s and 1980s but comprised more than 8 % of cystic tumors of the pancreas between 2005 and 2011 [1]. The majority of cases are incidentally detected on imaging studies [9]. Compared to solid neuroendocrine tumors, cPNETs tend to be larger, are more likely to be nonfunctional, and are more frequently associated with multiple endocrine neoplasia type 1 [75]. Furthermore, cPNETs have been reported in 4–15 % of patients with von Hippel–Lindau disease (VHL) [76, 77]. Similar to solid tumors, they occur nearly equally among males and females, with 50–60 years of age at diagnosis [9, 70, 71]. Patients may present with abdominal pain, pancreatitis, or symptoms related to the functioning cPNETs [69, 70, 74]. The pancreatic body and tail are the most common locations among patients with cPNETs.

Radiological Findings

CT usually demonstrates a cystic lesion with peripheral arterial enhancement (Fig. 4.11) [31, 78]. Septations or solid components are occasionally identified [79]. Compared with solid pancreatic neoplasms, cPNETs are less likely to be associated with lymph node or liver metastases [78]. MRI shows a homogeneous unilocular, thick wall lesion on T2W [54]. On gadolinium T1W, wall enhancement is seen on the arterial phase. No communication with the pancreatic ductal system is typically detected on MRCP.

EUS Morphology

By EUS, cPNETs can appear as a uni- or multilocular, anechoic, mixed solid–cystic, or hypoechoic lesion (Fig. 4.12) [69, 70, 74, 80]. Wall thickening and a nodule may be present in 60 % of cases [70]. Most of them (80 %) are thinly septated. The surrounding pancreatic parenchyma as well as the pancreatic ductal system are usually unremarkable.

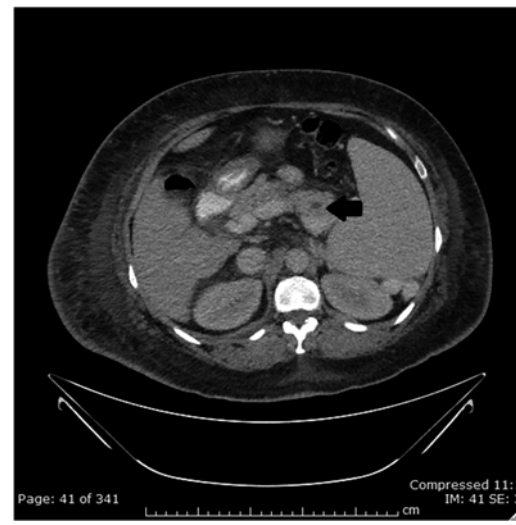

Fig. 4.11 Radiological characteristics of cystic pancreatic neuroendocrine tumor (CPNET). CT showed a low-density lesion measuring 1.0 cm with a thick wall at the junction of the pancreatic body and tail (*black arrow*)

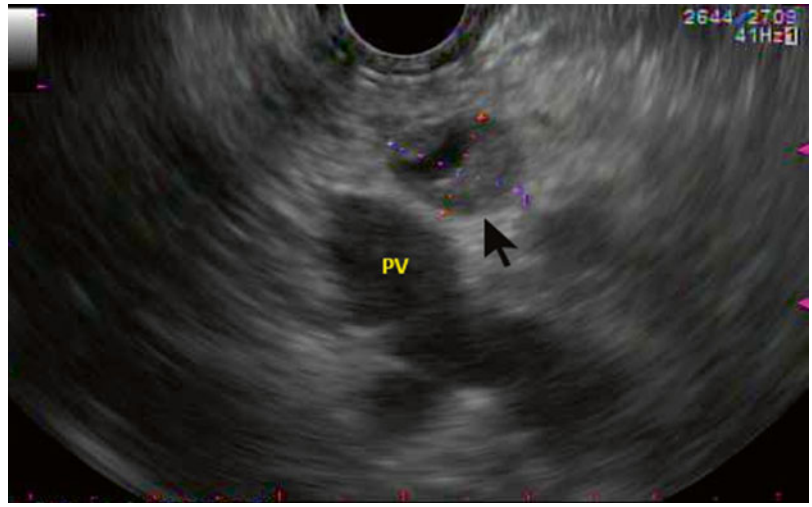

Fig. 4.12 EUS morphology of CPNET. A 12-mm ×8-mm mixed cystic–solid lesion was seen in the pancreatic neck with a thick wall (*black arrow*). Cyst fluid cytology confirmed this diagnosis after immunocytochemical stains

Solid Pseudopapillary Tumors of the Pancreas

Histopathologic Features

SPTPs are uncommon neoplasms, composed of monomorphic cells forming solid and pseudopapillary structures, frequently undergoing hemorrhagic-cystic changes [7]. Macroscopically, larger tumors are more likely to contain cystic areas of hemorrhage and necrosis but usually have a well-defined fibrous pseudocapsule [81]. Microscopically, SPTPs are composed of solid nests of uniform neuroendocrine-looking epithelial cells around delicate fibrovascular stalks [81]. Larger counterparts show pesudopapillary structures composed of tumor cells surrounding small central vessels.

Clinical Characteristics

SPTPs predominantly affect young women in their third decade of life [9, 12]. Patients may be asymptomatic, with such a lesion presenting incidentally on imaging studies. Abdominal pain is the most common presenting symptom, followed by abdominal mass, pancreatitis, and weight loss [81–83]. The tumors can occur throughout the pancreas. SPTPs are usually of low-grade pathology, but high-grade carcinomas have been rarely reported [82, 84–87].

Radiological Findings

SPTPs are typically of mixed-density on imaging, with a solid part in the periphery and a cystic component in the center on CT scan (Fig. 4.13) [81]. Large tumors are well demarcated by the capsule from the surrounding normal parenchyma. These tumors often demonstrate peripheral or central calcifications [82]. MRI usually shows areas of high and low signal intensity, corresponding to cystic and solid components, respectively, with a thick fibrous capsule [54, 81]. Heterogeneous peripheral capsule enhancement is seen on T1W postgadolinium. MRCP does not show communication with the pancreatic duct, and pancreatic duct dilation, vessel encasement, and metastasis may be used to differentiate solid pseudopapillary carcinomas from benign SPTPs [87].

EUS Morphology

SPTPs are endosonographically well-defined, echo-poor lesions [83] and can be solid, mixed solid–cystic, or cystic in nature (Fig. 4.14). Internal or peripheral calcifications may be seen with postacoustic shadowing. EUS-ENA is useful for definitive preoperative diagnosis of SPTPs [88]. The largest series of EUS-FNA for the diagnosis of SPTPs demonstrated a preoperative diagnostic accuracy of 75 % [83].

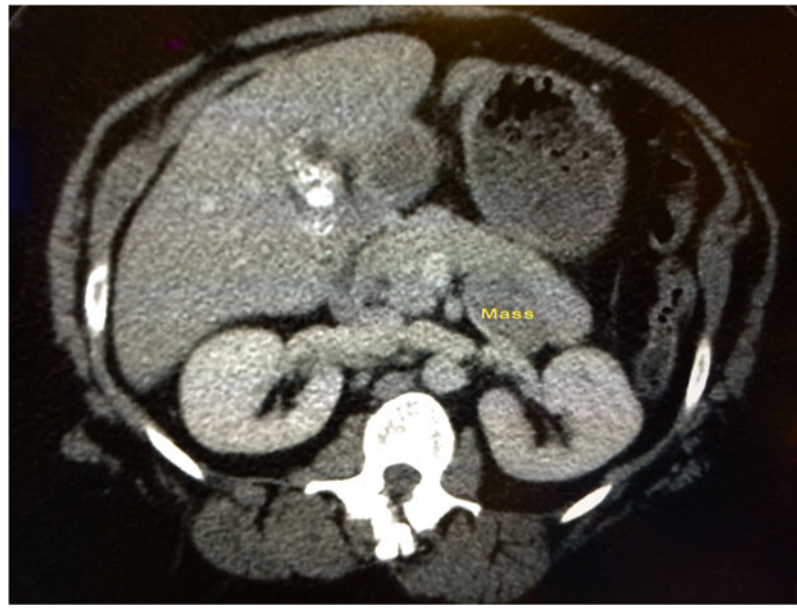

Fig. 4.13 Radiological characteristics of solid pseudopapillary tumor (PSPT) in a 28-year-old female patient. CT demonstrated an oval-shaped area of mixed-density measuring 3.5 cm in the pancreatic body, which was well demarcated by the capsule from the surrounding normal parenchyma

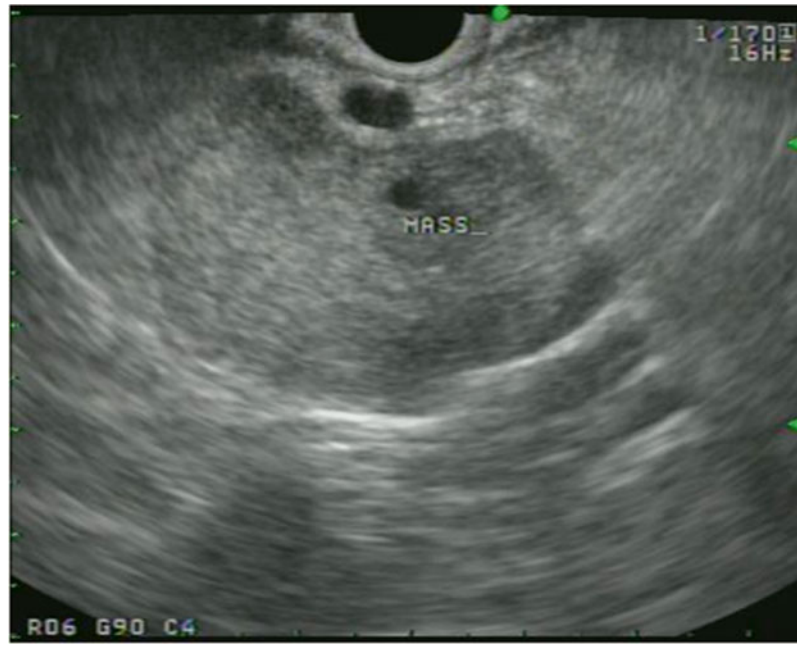

Fig. 4.14 EUS morphology of PSPT. A 3-cm lesion in the pancreatic body, with more than 90 % solid component with a small cystic space. Final cytopathology from fine-needle aspiration and core biopsy confirmed solid pseudopapillary neoplasm

Less Frequently Encountered Cystic Lesions of the Pancreas

Lymphoepithelial cysts (LECs) of the pancreas are rare benign lesions. They are composed mainly of keratinous material and can occur throughout the pancreas. Histologically, the cysts are lined by stratified squamous epithelium and surrounded by dense epithelial lymphoid tissue containing lymphoid follicles [89]. Since the first case was reported in 1985 [90], 109 patients with LECs have been described in the literature [91]. Such lesions are predominantly seen in middle-aged

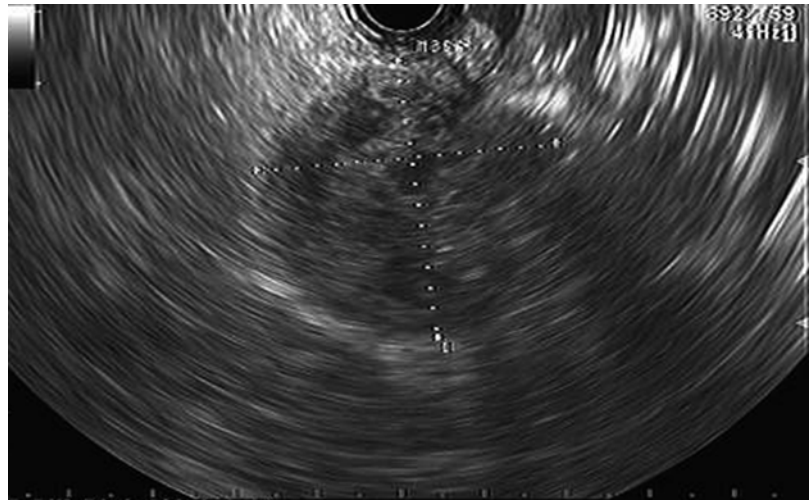

Fig. 4.15 EUS morphology of lymphoepithelial cyst. A 3.6-cm hypoechoic lesion with fine hyperechoic debris within the cyst in the body of the pancreas. Final cytology confirmed lymphoepithelial cyst

men [92]. Although the most common presentation is abdominal pain, nausea, vomiting, anorexia, and back pain may occur [89]. LECs exhibit a benign behavior and are not considered a risk factor for the development of pancreatic cancer [91]. On CT scan, LECs can appear as either a cystic or solid lesion of low attenuation, which may be uni- or multiloculated [91, 93]. The imaging characteristics of LECs on CT can be similar to that of a pseudocyst or a MCN [91]. EUS typically shows a hypoechoic, uniloculated, or multiloculated lesion with fine or coarse hyperechoic debris within the cyst (Fig. 4.15) [89, 94]. Thick milky, creamy fluid may be seen during EUS-FNA [93].

von Hippel–Lindau (VHL) is a rare autosomal dominant hereditary disorder resulting from a germline mutation in the VHL gene [95]. Pancreatic cysts can occur in approximately 70 % of VHL patients [96, 97] and include simple cysts (47 %) and SCAs (11 %), which are benign lesions [77]. In addition, cPNETs have been reported in 4–15 % of patients with VHL, which have malignant potential [76, 77]. Therefore, surgical treatment may be required in some cases. Nevertheless, unlike sporadic nonfunctioning PNETs without VHL, PNETs in VHL patients are believed to be of lower metastatic risk [98]. Most pancreatic lesions in VHL are asymptomatic; however, abdominal pain and jaundice may be present [95]. Pancreatic involvement in previous series of VHL detected by CT and MRI has varied from 20 to 80 % [99–101]. Simple cysts appear as unilocular, homogeneous, fluid-attenuation or fluid signal lesions with a thin wall and no calcification or enhancement [100]. SCAs and PNETs in this context have a similar morphology to those identified without VHL and as previously described in this chapter. EUS can be helpful to better characterize the cystic lesions and may influence clinical management [102]. Nevertheless, these pancreatic cysts often do not influence the outcome of the majority of VHL patients [101].

Conclusion

CLPs are increasingly detected by imaging studies among asymptomatic and symptomatic patients. Depending on the pathological type of the cyst, the clinical features, radiological characteristics, and EUS morphology vary significantly. In combination with minimally invasive investigations like EUS-FNA, clinical and imaging findings are essential to provide an accurate diagnosis of CLPs and improve early detection of cancer in the potentially malignant ones. Therefore, patients with CLPs should be evaluated thoroughly to determine the appropriate management, ideally in a multidisciplinary approach.

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