Cystic Pancreatic Lesions: A Simple Imaging-based Classification System for Guiding Management

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Cystic lesions of the pancreas are increasingly being recognized due to the widespread use of cross-sectional imaging. The initial evaluation of a pancreatic cyst should be directed toward exclusion of a pseudocyst. Patients with pseudocysts generally have a history of acute or chronic pancreatitis, whereas those with cystic tumors most often lack such a history. Several types of cystic lesions are encountered in the pancreas. Because of morphologic overlap at imaging, accurate characterization of these lesions can be difficult. Computed tomography and magnetic resonance imaging are excellent modalities for both initial detection and characterization of cystic pancreatic lesions. An imaging classification system for these lesions has been proposed that is based on the morphologic features of the lesion. This system can be helpful in characterizing lesions, narrowing the differential diagnosis, and making decisions regarding the treatment of affected patients. Endoscopic ultrasound–guided aspiration and biopsy is useful in cases that are indeterminate at cross-sectional imaging or that require observation.

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Abbreviations: CA = cancer antigen, CEA = carcinoembryonic antigen, IPMN = intraductal papillary mucinous neoplasm

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Introduction

Increased detection of cystic lesions of the pancreas at cross-sectional imaging has led to a rise in the number of pancreatic surgical resections (1–3). However, because many cystic lesions are known to be benign, in several instances resection may be unjustified (4). Therefore, it is important to characterize cystic neoplasms and to distinguish cystic neoplasms of the pancreas from pseudocysts. Although different histologic types of cystic pancreatic neoplasms have been reported in the literature, serous cystadenomas, mucinous cystic neoplasms, and intraductal papillary mucinous neoplasms (IPMNs) account for 90% of all primary cystic pancreatic neoplasms (5). Serous cystadenomas are benign tumors and in asymptomatic patients do not require surgical excision, whereas most mucin-producing lesions (eg, IPMNs, mucinous cystic neoplasms) have malignant potential that warrants surgery (6–9). Occasionally, solid tumors of the pancreas such as islet cell tumors and adenocarcinomas have an associated cystic component or may undergo degeneration and can mimic a cystic neoplasm at imaging. Differentiating cystic neoplasms from pancreatic adenocarcinomas is important, since the prognosis for malignant cystic neoplasms is better than that for ductal adenocarcinomas (6,8,10). Hence, accurate preoperative characterization of the lesions aids in prognostication and guides therapeutic decision making.

Imaging is indispensable in the evaluation of patients with cystic pancreatic lesions. Multi-detector row computed tomography (CT) allows thin-section scanning of the pancreas and has become the preferred imaging modality for both initial detection and characterization of pancreatic cysts (11). Magnetic resonance (MR) imaging with MR cholangiopancreatography accurately depicts the morphologic features of the cyst and has the advantage of demonstrating the relationship of the cyst to the pancreatic duct (12). Although cross-sectional imaging with CT and MR imaging can successfully characterize the cysts in a large number of patients, it can at times be confounded by a morphologic overlap (9). To a great extent, however, this problem can be overcome with endoscopic ultrasonography (US). In addition to providing high-resolution information about the morphologic features of the cyst, this technique can help further characterize the cyst by guiding cyst fluid aspiration and biopsy from suspicious areas.

The pathologic classification of cystic pancreatic lesions is outlined in the Table. Pseudocysts, serous cystadenomas, mucinous cystic neoplasms, and IPMNs are most often encountered in routine practice, accounting for more than 90% of cystic pancreatic lesions (5). We have developed a simple imaging-based classification system for cystic pancreatic lesions that is based on the morphologic features of the lesion. A systematic approach that integrates these features with the clinical presentation of the patient can serve as a practical guide for the treatment of these patients.

In this article, we discuss the clinical presentation of patients with pancreatic lesions and the morphologic classification of these lesions (unilocular cysts, microcystic lesions, macrocystic lesions, cysts with a solid component). We also review the use of endoscopic US and cyst aspiration in the evaluation of cystic lesions as well as the management of these lesions.

Clinical Presentation

A large number of pancreatic cysts are incidentally detected during imaging work-up for an unrelated medical problem. In a series of 212 consecutive patients with cystic pancreatic lesions...
encountered in a surgical practice over a 5-year period, Fernandez-del Castillo et al (1) found that more than one-third of patients were asymptomatic. The authors also reported that the majority of incidentally detected pancreatic cysts were cystic neoplasms and that asymptomatic patients were less likely to have pseudocysts. Symptomatic cysts are most likely to manifest with abdominal pain. Jaundice or recurrent pancreatitis often indicates that the lesion is either in communication with the pancreatic ductal system or obstructing the pancreatic or biliary duct. Patients with more advanced cystic malignancies may present with symptoms similar to those of pancreatic cancer (ie, pain, weight loss, jaundice) (13). Pseudocysts typically occur with acute pancreatitis or may develop insidiously in the setting of chronic pancreatitis.

Morphologic Classification of Cystic Pancreatic Lesions

Bosniak's classification scheme for renal cysts based on morphologic criteria is well established and has proved to be a reasonably accurate method for assessing the risk of malignancy in renal cysts (14). Using a similar approach, we suggest a classification scheme for pancreatic cysts that is based on the imaging morphologic features of the cyst. Pancreatic cysts can be classified into four subtypes: (a) unilocular cysts, (b) microcystic lesions, (c) macrocystic lesions, and (d) cysts with a solid component (Fig 1).
Unilocular Cysts

Unilocular cysts include pancreatic cysts without internal septa, a solid component, or central–cyst wall calcification. Pseudocyst is the most common and the most frequently encountered cystic lesion in this group (Figs 2, 3) (15). Other less commonly encountered unilocular cysts include IPMNs (Fig 4), unilocular serous cystadenomas, and lymphoepithelial cysts. These lesions can be differentiated from pseudocysts on the basis of lack of clinical, laboratory, and imaging evidence of pancreatitis.

A unilocular cyst in a patient with a clinical history of pancreatitis is almost always a pseudocyst. The diagnosis is further supported by imaging findings that include pancreatic inflammation, atrophy or calcification of the pancreatic parenchyma, and dilatation of and calculi in a typically thin-walled pancreatic duct. Communication of the pseudocyst with the pancreatic duct may be seen at MR cholangiopancreatography or CT, especially on curved reformatted images. Cyst communication with the pancreatic duct can also be seen in IPMNs (16,17); in our experience, however, IPMNs demonstrate a narrow neck at the cyst-duct junction on CT scans or MR cholangiopancreatograms. Precise characterization of a unilocular cyst on the basis of imaging findings alone can be difficult in the absence of pancreatitis or obvious cyst communication with the pancreatic duct. When there is a unilocular cyst with a lobulated contour located in the head of the pancreas, one should consider a unilocular macrocystic serous cystadenoma (18). The presence of irregular wall thickening in a unilocular cyst is suggestive of a more aggressive biologic nature. When differentiation is not possible at imaging, symptomatic patients can be further treated with endoscopic US–guided cyst aspiration or surgical resection. Asymptomatic thin-walled unilocular cysts can be monitored with CT or MR imaging, especially when they are small.

Figure 2. Pseudocyst. (a) Contrast material–enhanced CT scan shows a well-defined unilocular cyst (arrow) in the head of the pancreas. (b) Endoscopic US image helps confirm the unilocular nature of the cyst. PV = portal vein, SPL V = splenic vein. (c) Photograph of the gross specimen shows a unilocular chronic pseudocyst (arrow).
Figure 3. Pseudocyst in a patient with a recent history of pancreatitis. (a, b) Axial CT scan (a) and coronal contrast-enhanced T1-weighted MR image (b) depict a well-defined unilocular cyst (arrow) in the tail of the pancreas. (c) T2-weighted MR image shows the cyst (arrow) with homogeneously bright signal intensity, a finding that confirms the unilocular nature of the cyst.

Figure 4. Side-branch IPMN manifesting as a unilocular cyst. (a) Contrast-enhanced CT scan demonstrates a small cyst (arrow) in the head of the pancreas. (b) Coronal oblique single-shot fast spin-echo MR cholangiopancreatogram shows communication of the cyst (arrow) with the main pancreatic duct (arrowheads), a finding that helped establish the diagnosis.
Recent unpublished data from our institution suggest that small (<3-cm) unilocular cysts are almost always benign (19). This observation suggests that treating affected patients surgically may be overly aggressive; instead, a conservative approach using imaging follow-up is appropriate. Recent publications also support these recommendations (1,4,20). Although there is no consensus on what constitutes the optimal follow-up schedule, current recommendations include serial imaging at 6-month intervals for the 1st year, followed by annual imaging for a period of 3 years. If cyst stability has been established at this point and the patient remains symptom free, no further work-up may be needed.

When present, multiple unilocular cysts are most often pseudocysts resulting from prior pancreatitis. Other causes of multiple cysts include von Hippel–Lindau disease (Fig 5) and, rarely, IPMN. In von Hippel–Lindau disease, the pancreas is otherwise healthy and cysts may also be present in the kidneys or liver (21).

**Microcystic Lesions**

The only cystic lesion included in the category of microcystic lesions is serous cystadenoma. In 70% of cases, these benign tumors demonstrate a polycystic or microcystic pattern consisting of a collection of cysts (usually more than six) that range from a few millimeters up to 2 cm in size (22). Fine, external lobulations are a common feature (Figs 6, 7), and enhancement of septa and the cyst wall may be seen. A fibrous central scar with or without a characteristic stellate pattern of calcification is seen in 30% of cases and, when demonstrated at CT or MR imaging (Figs 1b, 6a), is highly specific and is considered to be virtually pathognomonic for serous cystadenoma (11,23,24). Pancreatic ductal dilatation is an uncommon finding in these patients. In 20% of cases, these tumors are composed of microcysts in a honeycomb pattern and appear as well-marginated, “spongy” lesions with soft-tissue or mixed attenuation and a sharp interface with the vascular structures at CT (22). In patients with indeterminate CT findings, further characterization with MR imaging or endoscopic US may be possible. At MR imaging, the microcysts may be seen as numerous discrete foci with bright signal intensity on T2-weighted images (Fig 7b) (25). Likewise, endoscopic US can help accurately depict these small microcysts as discrete small anechoic areas (26). The macrocystic or oligocystic variant of these tumors is very uncommon and is seen in less than 10% of cases. Either of these variants can take the form of a single dominant macrocavity, in which case it will appear as a unilocular cyst (Fig 8), or may contain fewer large (>2-cm) cysts. The latter variant is classified as a macrocystic lesion and may be difficult to differentiate from a mucinous cystic tumor (11,27,28). Because of the benign nature of serous cystadenomas, some surgeons recommend imaging surveillance of microcystic tumors as being sufficient in asymptomatic patients (29). Although the rate of growth for serous cystadenomas is unknown, preliminary data obtained at our institution over a 3-year follow-up period indicate that the average growth rate is about 4 mm per year.
Figure 6. Serous cystadenoma. (a) Contrast-enhanced CT scan shows a classic serous cystadenoma (arrow) in the head and neck of the pancreas. The lesion has the appearance of a solid mass with numerous small cysts ("honeycomb" effect). The lobulated outlines and the calcified central scar (arrowhead) are typical findings in these tumors. (b) Photograph of the gross specimen clearly demonstrates the microcystic nature of the tumor (arrow).

Figure 7. Serous cystadenoma. (a) CT scan shows a serous cystadenoma (arrow) of the pancreatic head, with the classic findings of lobulated outlines, lack of vascular encasement, and a central scar (arrowhead). (b) T2-weighted MR image shows the internal morphologic features of the cyst, with high-signal-intensity microcysts (arrows) being clearly distinguished from the dark central scar (arrowhead).

Figure 8. Serous cystadenoma (macrocystic variant). Contrast-enhanced CT scan demonstrates a variant of a serous cystadenoma in the pancreatic body. The mass appears as a septated lesion that contains a few macrocysts (arrow). Note the lobulated outlines of the lesion, a feature that is often seen in microcystic tumors (cf Figs 6, 7). Serous cystadenoma was confirmed at surgery and histopathologic analysis.
Macrocystic Lesions

Macrocystic lesions include multilocular cysts with fewer compartments (Figs 1c, 9). In addition, the individual compartments (>2 cm) are larger than in serous cystadenomas. The cystic tumors in this category include mucinous cystic neoplasms and IPMNs. Mucinous cystic neoplasms (mucinous cystadenomas) predominantly involve the body and tail of the pancreas (29), and, although they do not communicate with the pancreatic duct, they can cause partial pancreatic ductal obstruction. At cross-sectional imaging, these neoplasms appear as multilocular macrocystic lesions (Figs 10, 11) (30). The cysts may occasionally contain debris or hemorrhage. The complex internal architecture of the cyst, including septa and an internal wall, is best appreciated at MR imaging and endoscopic US, allowing differentiation from serous cystadenomas (Fig 9) (22,31). Although peripheral eggshell calcification is not frequently seen at CT, such a finding is specific for a mucinous cystic neoplasm and is highly predictive of malignancy (Fig 12) (32). These tumors can be asymptomatic in up to 75% of cases (22). When present, symptoms are caused by the mass effect of these often large neoplasms. Because mucinous cystic neoplasms have a high potential for malignancy, surgical resection is usually advocated (15,33). Prognosis is good for benign or borderline malignant tumors (>95% 5-year survival rate), and long-term survival can also be expected for 50%–75% of patients with fully resected malignant tumors (15).

IPMNs can be classified as main duct, branch duct (side-branch), or mixed IPMNs, depending on the site and extent of involvement. Main duct IPMN is a morphologically distinct entity and cannot be included in the discussion of pancreatic cysts. However, a side-branch IPMN or a mixed IPMN (in which a side-branch tumor extends to the main pancreatic duct) can have the morphologic features of a complex pancreatic cyst, making clear-cut distinction from a mucinous cystic neoplasm difficult. Identification of a septated cyst that communicates with the main pancreatic duct is highly suggestive of a side-branch or mixed IPMN (Fig 4) (16,17). However, it is important to be aware that lack of communication with the main pancreatic duct at imaging does not exclude an IPMN. Currently, MR cholangiopancreatography is considered the modality of choice for demonstrating the morphologic features of the
Figure 10. Mucinous cystadenocarcinoma. Contrast-enhanced CT scans (a obtained at a lower level than b) show a large cystic mass (arrows) with internal septa in the head of the pancreas. The peripheral and septal calcifications (arrowheads) indicate the malignant nature of the lesion.

Figure 11. Mucinous cystic tumor. (a) Endoscopic US image shows a complex pancreatic cyst with internal septa. (b) Photograph of the gross specimen shows large cysts and septa.

Figure 12. Mucinous cystadenoma. Contrast-enhanced CT scan shows a cystic mass (arrow) with rim calcification (arrowhead) in the tail of the pancreas.
cyst (including septa and mural nodules), establishing the presence of communication between the cystic lesion and the pancreatic duct, and evaluating the extent of pancreatic ductal dilatation. Endoscopic retrograde cholangiopancreatography is now rarely needed for diagnosis of an IPMN. Advances in CT technology such as thin-section high-resolution multi-detector row CT have enhanced the capacity of CT to help define the morphologic features of the cyst. As with MR cholangiopancreatography, cyst communication with the main pancreatic duct can be reliably demonstrated with multi-detector row CT (34,35). Because these lesions are considered premalignant, surgical resection has been recommended (36). The occurrence of malignancy is significantly higher in main duct and mixed IPMNs than in side-branch IPMNs (16,35). Therefore, in cases of side-branch IPMN, the treatment decision should be based on the risk-benefit ratio, taking into account the patient’s clinical presentation, age, and surgical risk and the size and imaging morphologic features of the cyst. Our unpublished data on small cysts show that septated pancreatic cysts less than 3 cm in diameter have a low malignant potential, so that aggressive pancreatic surgery may not be appropriate for these patients (19). Cyst location may also be a factor in decision making, since a small lesion located in the tail of the pancreas may require a relatively less aggressive distal pancreatectomy, whereas a lesion located in the pancreatic head requires the far more complex Whipple procedure.

Other uncommon tumors in this category (macrocytic lesions) include nonfunctioning neuroendocrine tumors and rare congenital malformations such as lymphangiomas. Currently, surgery is the treatment of choice for these tumors (37).

Cysts with a Solid Component

Cysts with a solid component may be either unilocular or multilocular. True cystic tumors (eg, mucinous cystic neoplasms, IPMNs) as well as solid pancreatic neoplasms associated with a cystic component or cystic degeneration are included in this category. Solid tumors associated with a cystic component include islet cell tumor (Fig 13), solid pseudopapillary tumor (Fig 14), adenocarcinoma of the pancreas, and metastasis (Fig 15a). Because all of the tumors in this
**Figure 14.** Solid pseudopapillary tumor manifesting as a cyst with a solid component. (a) Contrast-enhanced CT scan shows a lesion in the body of the pancreas with cystic areas and a solid component or mural nodule (arrow). (b) T1-weighted MR image more clearly demonstrates the solid component (arrow).

**Figure 15.** Metastases manifesting as cysts with solid components. (a) CT scan obtained in a patient with pancreatic adenocarcinoma demonstrates a solid tumor with cystic degeneration (arrow). (b) CT scan obtained in a patient with malignant IPMN shows a multiseptated cyst with solid components (arrow). (c) Photograph of the gross specimen obtained in a different patient with malignant IPMN shows a complex cyst with a large solid component (arrow).
category are either malignant or have a high-malignant potential, surgical resection is the accepted method of management (38). MR imaging with MR cholangiopancreatography is considered superior to single-section helical CT for the detection of small mural nodules (12,35). A mural nodule is seen as an area of low signal intensity on T2-weighted MR images, and contrast material enhancement following the injection of gadopentetate dimeglumine is diagnostic for its presence. Insipissated mucin or calcification in the cyst may mimic a mural nodule at MR cholangiopancreatography (12). Although small mural nodules may go undetected at both thin-section CT and MR imaging, high-resolution endoscopic US is extremely sensitive in their detection.

**Endoscopic US and Cyst Aspiration**

When cross-sectional imaging does not allow definitive diagnosis, endoscopic US can provide detailed information regarding the morphologic features of cystic lesions. However, this information is not sufficient to accurately help differentiate between benign and malignant mucinous neoplasms unless there is evidence of a solid component, invasion outside the confines of the pancreas, or pancreatic ductal obstruction. The sensitivity, specificity, and accuracy of endoscopic US for detecting malignant mucinous tumors have been reported as 40%, 100%, and 55%, respectively (39). Endoscopic US has the added advantage of allowing aspiration of the cyst contents and sampling of the cyst wall and septa or mural nodules (26,40). Consequently, endoscopic US is currently recommended as the technique of choice for the aspiration of cyst fluid and for fine-needle aspiration biopsy of cystic pancreatic lesions. Unlike percutaneous sampling, aspiration with this technique minimizes the potential for tumor seeding along the needle pathway and is extremely reliable and accurate in experienced hands. Small lesions as well as suspicious areas such as mural nodules can be sampled. The combined use of cytologic analysis, biochemical markers, and tumor markers can help establish a diagnosis and differentiate mucinous from nonmucinous lesions, thereby preventing unjustified resection of benign mucinous lesions (41). High-viscosity cyst contents or the detection of extracellular mucin is indicative of a mucinous neoplasm (42,43). Cyst fluid amylase, although not a tumor marker, is used as an indicator of cyst communication with the ductal system. Amylase-rich fluid is uniformly found in pancreatic pseudocysts and often in cysts associated with IPMNs, whereas a low concentration of amylase is found in serous tumors and in the great majority of mucinous cystadenomas. Tumor markers such as carcinoembryonic antigen (CEA), cancer antigen (CA) 72–4, CA 19–9, and C15.3 have been used to differentiate mucinous from nonmucinous lesions and to identify malignant cystic lesions; these markers demonstrate varying sensitivities and specificities (42,44). Studies have shown that CEA and CA 72–4 are useful in identifying mucinous lesions (45). A CEA level greater than 400 ng/mL is a good predictor of malignancy in mucinous neoplasms (46).

**Management**

The management of cystic neoplasms has not yet been standardized and continues to evolve. Because the long-term survival rate for patients with cystic neoplasms is far better than that for patients with pancreatic adenocarcinoma, an aggressive approach in the form of surgical resection is recommended (13). However, advocating resection for all cystic lesions would be inappropriate, since over one-third of these lesions are discovered incidentally (45). Adopting this policy would lead to resection of innocuous benign lesions along with some potentially malignant mucin-producing cystic neoplasms. In addition, patients may be unnecessarily subjected to the risk of aggressive pancreatic surgery. However, surgical resection is indicated for most symptomatic patients (45). Besides patient symptomatology, other factors that influence patient treatment include tumor histologic features, the patient’s age and surgical risk, and tumor size and location. Our unpublished data have shown that small cysts have a low malignant potential and that imaging follow-up may therefore be sufficient for the management of small, asymptomatic pancreatic cysts. The location of the cyst can also influence the treatment decision, since cysts located in the head of the pancreas require more complex and aggressive surgery than do those located in the tail. Therefore, it is imperative that the risk-benefit ratio be assessed before deciding on patient treatment. Because most investigators recommend surgery for symptomatic patients, deciding whether asymptomatic patients should undergo surgery or simple observation hinges to a large extent on accurate cyst characterization. High-resolution CT and MR imaging play a very important role in this regard and have been recommended for cyst characterization in all cases (45).
Combining the imaging classification of pancreatic cysts with the patient’s clinical presentation constitutes a systematic approach for the treatment of affected patients (Fig 16).

Conclusions

CT and MR imaging are excellent modalities for the initial detection as well as the characterization of cystic pancreatic lesions. Endoscopic US-guided aspiration and biopsy is useful in cases that are indeterminate at cross-sectional imaging or require observation. The classification of cystic pancreatic lesions on the basis of their imaging morphologic features can simplify the differential diagnosis and be of value in management.

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