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Cystic tumors of the pancreas

Giovanni Morana and Alessandro Guarise

Department of Radiology, Hospital Ca’ Foncello, Treviso, Italy

Corresponding address: Giovanni Morana, Department of Radiology, Hospital Ca’ Foncello, Piazza Ospedale 1, 31100, Treviso, Italy. E-mail: gmorana@ulss.tv.it

Dedication: In memory of Carlo Procacci (1950–2004), MD, whose brilliant studies, enthusiasm and hard work made the comprehension of pancreatic pathology easier for radiologists.

Date accepted for publication 20 March 2006

Abstract

Cystic tumors of the pancreas are less frequent than solid lesions and are often detected incidentally, as many of these lesions are small and asymptomatic. However, they may be associated with pancreatitis or have malignant potential. With advancements in diagnostic imaging, cystic lesions of the pancreas are being detected with increasing frequency. Many lesions can cause a pancreatic cyst, most being non-neoplastic while approximately 10% are cystic tumors, ranging from benign to highly malignant tumors. With increasing experience it is becoming clear that the prevalence of pseudocyst among cystic lesions of the pancreas is lower than usually presumed. A presumptive diagnosis of pseudocyst based on imaging appearance alone can cause a diagnostic error, and neoplastic cysts of the pancreas are particularly susceptible to this misdiagnosis, which can result in inappropriate treatment. Cystic tumors of the pancreas are formed by serous or mucinous structures showing all stages of cellular differentiation. According to the WHO classification, they can be subdivided on the basis of their histological type and biological behavior into benign tumors, borderline tumors, and malignant tumors. Cystic pancreatic tumors can be subdivided into peripheral (serous cystadenomas, mucinous cystic tumors, solid and papillary epithelial neoplasms, cystic islet cell tumors), which do not communicate with the main pancreatic duct, and ductal tumors (mucinous tumor), according to their site of origin. On the basis of imaging criteria alone, it can be very difficult to differentiate non-tumoral cystic lesions from neoplastic ones. The management of these patients is complex, and it is important to correlate imaging findings with knowledge of the patient’s symptoms and of the natural history and predictors of malignancy in pancreatic cysts.

Keywords: Pancreas; pancreatic neoplasms, diagnosis; cystadenoma, diagnosis; pancreas, pathology, radiography; neoplasms, cystic, mucinous; serous, diagnosis, pathology, radiography.

Introduction

Cystic tumors of the pancreas occur with less frequency than solid lesions, and are often detected incidentally, as many of these lesions are small and asymptomatic. They may, however, be associated with pancreatitis or have malignant potential. With advancements in diagnostic imaging, cystic lesions of the pancreas are increasingly being detected; in some reference centers up to 30% of pancreatic resections are performed for cystic tumor[1]. Accurate differentiation between cystic tumors is important because different treatments are required depending on the tumor’s histological type and grade. Due to frequent lack of specific clinical and laboratory signs and the overlap of imaging findings between different cystic tumors and between non-neoplastic and neoplastic cystic lesions of the pancreas[2], the management of these patients is complex. Knowledge of the patient’s symptoms and of the natural history and predictors of malignancy in pancreatic cysts is important.

When dealing with pancreatic cysts, the aim of imaging is to differentiate cystic tumors from tumor-like lesions and to characterize the cystic tumor, distinguishing

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benign tumor, which does not usually require surgical excision, from borderline or malignant tumor, which must be resected whenever possible. It can be very difficult to differentiate non-tumoral cystic lesions from neoplastic lesions on the basis of imaging criteria alone; in order to achieve a correct diagnosis it is important to correlate the imaging findings with the clinical history of the patient and the presence or absence of symptoms.

Many lesions can cause a pancreatic cyst[3]. Most of these are non-neoplastic[4,5]; approximately 10% are cystic tumors, ranging from benign to highly malignant[6]. Although all pancreatic tumors, including ductal adenocarcinoma, may appear as a cystic lesion as a result of degenerative changes[7], the classical cystic neoplasms of the pancreas are lined by different epithelium whose morphology constitutes the main diagnostic criterion and provides prognostic value, whereas their macroscopic appearance (shape, volume, etc.) has no importance[8].

According to various authors, the majority (up to 90%) of cystic lesions of the pancreas seen in clinical practice are represented by post-inflammatory pseudocysts[4]; however, in a series of 212 consecutive patients with pancreatic cystic lesions observed in a reference center for pancreatic disease, pseudocysts represented only 13.6% of the lesions; referral bias cannot explain such a big difference[9]. With increasing experience it is becoming clear that the prevalence of pseudocyst in cystic lesions of the pancreas is lower than previously thought[9,10].

Figure 1  A 55-year-old woman with no history of pancreatitis. Mucinous cystic tumor. (a) At CT a diagnosis of ‘pseudocyst’ was made, and it was treated with cysto-entero anastomosis. Thirteen years later a solid mass (b) with a liver metastasis (c) can be appreciated.
A 59-year-old woman with a serous cystic tumor. At US (a) a small hypoechoic lesion with no posterior acoustic enhancement is appreciable in the body of the pancreas. The lesion shows ‘honeycomb’ architecture. At CT in the unenhanced phase (b) the lesion appears hypodense with focal bulging of the pancreatic borders. After injection of iodinated contrast agent the lesion appears hypovascular in the arterial (c) and pancreatic (d) phase, showing enhancement of thin septa in the center of the lesion during the distribution phase (e). At MR the lesion is markedly hyperintense on T2 HASTE images, with microcystic appearance (f); in this sequence a branching of the main pancreatic duct in the tail can be observed (arrowheads). On T1w fat sat (g) the lesion appears hypointense with thin central septa which show enhancement after injection of paramagnetic contrast agent (h). MRCP (i) confirms the microcystic appearance; the close relationship between the cystic lesion and the m.p.d. does not allow exclusion of the presence of a communication. However, the microcystic appearance and the normal m.p.d. allow a correct diagnosis of serous cystic tumor. A presumptive diagnosis of pseudocyst based on imaging appearance alone can lead to a diagnostic error in up to 50% of cases\cite{10,11,12}, and neoplastic cysts of the pancreas are particularly susceptible to this misdiagnosis\cite{13}, resulting in inappropriate treatment\cite{14,15} (Fig. 1). In a comparison of incidental pancreatic cystic lesions\cite{9}, the incidence of pseudocyst was significantly higher in the group of symptomatic patients with a previous history of pancreatitis (26/29: 89.6%) than in the asymptomatic group (3/29: 10.4%). Thus, to make a confident diagnosis of pseudocyst it is necessary to correlate with the clinical history of the patient; previous chronic or severe acute pancreatitis is a useful predictor for the diagnosis of pseudocyst. However, in the same study, 25/42 (52%) of the patients with a history of pancreatitis had a cystic tumor of the pancreas\cite{9}; thus previous pancreatitis cannot exclude the presence of a cystic tumor. From an imaging point of view, it is important to confirm or exclude a communication between the cystic lesion and the main pancreatic duct (m.p.d.). Cystic pancreatic tumors can be subdivided into peripheral (serous cystadenomas, mucinous cystic tumors, solid and papillary epithelial neoplasms, cystic islet cell tumors), which do not communicate with the m.p.d., and ductal tumors (mucinous tumor), according to their site of origin, although in a multi-institutional retrospective
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Figure 4  A 47-year-old man with a serous cystic tumor. At MRCP (a) the lesion shows microcystic appearance with unclear communication with the m.p.d. The ERCP (b) shows an impression in the m.p.d., but no communication, thus allowing a correct diagnosis of serous cystic tumor.

Cystic tumors of the pancreas are formed by serous or mucinous structures showing all stages of cellular differentiation. According to the WHO classification [8], they can be subdivided on the basis of their histological type and biological behavior into benign tumors, borderline tumors, and malignant tumors [16].

Serous cystadenoma

Serous cystadenoma (SCA) occurs primarily in female patients in their fifties. It involves mainly the head of the pancreas, although it can be found in every part of the gland [17]. Histologically, it is composed of multiple cysts formed by glycogen-rich, PAS-positive epithelial cells. It is a benign lesion, and no more than 10 cases of serous cystadenocarcinoma have been published [18,19].

It is important to obtain a certain diagnosis of SCA in a non-invasive way, as if the lesion is asymptomatic, it is possible to leave it unresected and to follow it up [17]. A large lesion can be responsible for obstructive chronic pancreatitis, thus indicating a need for surgical resection (Fig. 2) [20].

SCA is generally asymptomatic and is discovered incidentally during imaging studies performed for signs and symptoms not related to the pancreas. Symptomatic patients may complain of discomfort, while more serious symptoms due to larger lesions, such as jaundice, palpable mass and upper GI tract obstruction, are rare. In 15%–30% of cases, SCA is associated with von Hippel–Lindau (VHL) disease [21].

Imaging findings of SCAs are markedly dependent on their macroscopic appearance. Typically SCA has a microcystic appearance and presents as a well-circumscribed mass with multilobulate sharp margins and an internal sponge-like architecture due to the presence of innumerable microcysts (1–5 mm), seldom with rare larger cysts (>2 cm) peripherally located. A central stellate scar is typically visible, which can be calcified due to calcium deposits [22]. These findings are recognized in about two-thirds of cases [16]. Less frequently SCAs appear as a macrocystic or oligocystic mass, characterized by a small number of cysts > 2 cm which lack a central scar and are often indistinguishable from other cystic masses of the pancreas, especially mucinous cystic tumors [22–24]. In microcystic form, at ultrasound SCAs appear as a mass with no posterior acoustic enhancement and a ‘honeycomb’ architecture (Fig. 3(a)). Due to the presence of thin-walled small cysts and a thick fibrous stroma, SCAs can be homogeneously hyperechoic at US, thus simulating a solid mass. At CT on unenhanced images SCA is hypodense (Figs 2(a) and 3(b)) or isodense to normal parenchyma, with a bulge in the contour of the gland; calcifications are well recognized, located in the center of the lesion. After contrast media administration, internal septa appear hyperdense due to contrast uptake, with the central fibrous scar visible (Figs 2(b), (e) and 3(c)–(e)). When SCA is small it can be difficult to characterize with CT, as it can appear as a solid mass (Fig. 3(b)–(d)); in this case, the great sensitivity of MR to static fluids with highly T2-weighted sequences permits demonstration of its fluid content (Fig. 3(e)), thus allowing accurate characterization. In fact, MR is assuming a preeminent role in the evaluation of cystic tumors of the pancreas, giving accurate information on the structure of the lesion (Figs 2(c)–(e) and 3(f)–(i)). Magnetic resonance cholangiopancreatography (MRCP) depicts the relationship of the lesion with the m.p.d. (Fig. 2(h)), thus permitting the differentiation between peripheral and intraductal cystic tumors. However, in some cases the close relationship between the cystic lesion and the m.p.d. does not exclude the presence of a communication (Figs 3(i) and 4); in these cases endoscopic retrograde cholangiopancreatography (ERCP) is still fundamental in the differential diagnosis (Fig. 4(b)). Contrast-enhanced MR gives the same information as CT, with clear demonstration of the enhancement of both the septa and the walls (Figs 2(e) and 3(h)). The main limitation of MR is its insensitivity to calcifications, which are better recognized with US or CT [25]. When associated with VHL disease, cystic lesions are multifocal and can involve the pancreatic gland diffusely (Fig. 5).
Oligo- or macrocystic forms of SCA, on the other hand, have a nonspecific appearance which makes them indistinguishable from other cystic lesions of the pancreas in all imaging modalities (Figs 6 and 7).

**Mucinous cystic neoplasms**

Mucinous cystic neoplasms (MCNs) are found almost exclusively in women. Histologically MCNs are formed by mucin-producing epithelial cells supported by an ovarian-type stroma\[26\]. According to the grade of epithelial dysplasia, they can be classified into adenoma, border-line tumor or carcinoma, invasive or non-invasive\[16\]. The peak age is the fifth decade, but a wide range of ages is affected. With advancing age the grade of the tumor worsens; this suggests an evolution from benign to malignant\[26\], as confirmed by the presence of the different degrees of differentiation, from benign to overtly malignant, in the same lesion\[27\].
Figure 8  A 66-year-old woman with a mucinous cystic adenocarcinoma. At US (a) a large multilocular cyst with thick septa is appreciable in the body-tail of the pancreas. After injection of second-generation ultrasound contrast agent (Sonovue, Bracco, Italy) (b) the wall and septa show significant enhancement, with infiltration of the splenic artery (arrow). (Courtesy of Mirko D’Onofrio, MD.)

Figure 9  Mucinous cystic adenocarcinoma, two different cases at CT. After injection of CM the thick wall (a) and the solid component (∗ in b) show significant enhancement.

Figure 10  ((a), (b)) Pseudocyst in a 70-year-old woman with a previous history of severe acute pancreatitis. A large unilocular cyst is appreciable in the tail of the pancreas with a solid component which does not show significant enhancement after injection of CM (arrowhead in (b)). (c) Coronal MPR.

MCN is located predominantly in the body-tail of the pancreas; when located in the head of the pancreas, mucinous cystadenocarcinoma is more prevalent[26]. It is important to recognize this entity in an early phase of development, as prognosis of in situ carcinoma is much better than that of infiltrative carcinoma, which has a prognosis similar to that of ductal adenocarcinoma[26].

As for SCAs, symptoms for MCNs are nonspecific, with some degree of abdominal pain or discomfort, seldom referred to the pancreatic region. For advanced malignant lesions, clinical signs, such as dyspepsia, pain, weight loss and jaundice, may be more evident[28].

Imaging characteristics are again dependent on the macroscopic appearance. MCNs appear as a round mass with sharp margins with two main patterns, uni- or multilocular macrocysts[29]. A macrocystic multilocular pattern is the most typical[30], while a unicystic appearance is similar to many other cystic lesions. In the absence of a history of pancreatitis, the correct diagnosis of a unicystic lesion with a thin wall is possible only after resection (Fig. 7)[31–33]. At US
multicystic MCN appears as a deeply hypoechoic mass with sharp margins; the wall has various thickness\cite{30}, with mural vegetation or parietal calcifications\cite{32}. Thick septa and/or papillary proliferations are suggestive of the malignant degeneration of MCN (Fig. 8(a))\cite{32}. With contrast-enhanced US (CEUS), the wall and septa show variable degrees of enhancement (Fig. 8(b)). At unenhanced CT calcifications are clearly recognizable. The density of MCNs can vary from hypodense to hyperdense due to hemorrhage or mucin content\cite{34}. After CM injection either the wall (Fig. 9(a)) and the septa or solid component (Fig. 9(b)) show variable enhancement, although less than normal parenchyma\cite{35}. However, pseudocysts with necrotic debris, which can simulate parietal nodules, do not show significant enhancement after CM injection (Fig. 10(a)–(c)). The imaging triad of calcifications, thick walls, and mural vegetation is predictive of malignant degeneration in 95% of cases\cite{24}. MR with heavily T2-weighted sequences allows better identification of the thin septa than CT but has less sensitivity in identifying the calcifications. With MRCP the lack of communication between the MCN and the m.p.d. can be easily demonstrated, thus excluding an intraductal origin of neoplasia\cite{36–38}.

As a differential diagnosis for the macrocystic pattern of SCA (Figs 6 and 7), the cystic variant of solid pseudopapillary tumor (Fig. 11), the cystic endocrine tumor (Fig. 12) should be considered\cite{30}. Clinical history (MEN syndrome) or the evidence of hemorrhage inside the lesion (pseudopapillary tumor) can help in the diagnosis.

**Intraductal papillary mucinous tumor**

Intraductal papillary mucinous tumor (IPMT) was first described in 1982\cite{39}. In the last 10 years it has been increasingly described\cite{40–42}, thanks to the evolution of imaging modalities, especially MR, and to more widespread knowledge of this entity. In the past, many IPMTs were misdiagnosed as chronic pancreatitis. It has been classically described as a mucin-secreting tumor with dilation of the m.p.d. and a protruding papilla\cite{39}. IPMT can affect the m.p.d. and/or a branch-side duct. The tumor originates from the ductal epithelium and can evolve from slight dysplasia to infiltrating carcinoma over time with different aspects seen in the same lesion\cite{43–45}.

From the imaging point of view it is important not only to correctly differentiate IPMT from chronic pancreatitis,
Figure 13  An 83-year-old man with a history of abdominal pain and the onset of jaundice. Diffuse IPMT. On T2w images (a) a diffuse dilation of the main pancreatic duct is appreciable. With coronal MRCP (b) the dilation of the main pancreatic duct as well as of the biliary system can be depicted as a whole. A bulging of both major and minor papillae in the duodenal lumen can be appreciated (arrows), but is better depicted on coronal HASTE (c). At the uncinate process level a small defect in a dilated secondary duct can be seen (d), which shows significant enhancement after paramagnetic CM injection (arrow in (e)).

Figure 14  A 75-year-old man with chance detection of pancreatic cyst at US performed as part of a routine check-up. Branch duct IPMT. With MRCP (a) a large plurilobular cyst in the head of the pancreas can be appreciated with normal m.p.d. (b), (c) Coronal HASTE: the lesion presents thin septa, no solid component, and a small communication with the m.p.d. can be appreciated (arrow in (c)).

but also to suggest the histological grading of the tumor. In fact the only valid therapeutic option for IPMT is partial or total pancreatectomy, which in the case of a benign IPMT would amount to overtreatment, especially in branch-duct type\cite{46,47}. Thus, in order to achieve the correct management of these lesions, it is important to obtain all the clinical information and to correlate with imaging findings. IPMT affects patients in theirs 60s to 70s, with an equal distribution between men and women, while chronic pancreatitis is more frequent during the 40s\cite{48}. When located in the m.p.d. it is clinically characterized by recurrent abdominal pain simulating chronic pancreatitis\cite{49,50}, secondary to the obstruction of the pancreatic duct as a result of the hypersecretion of mucin\cite{51}. In a small percentage (<2%) of cases, IMPT can provoke an acute severe pancreatitis\cite{51}. In about 50% of cases patients complain of weight loss; in the early phase this is secondary to the pain evoked by food consumption while in the advanced phase it is secondary to the malignant degeneration of IPMT\cite{50}. About 10% of the patients suffer from diabetes, and the rapid onset of diabetes is highly suggestive of a malignant degeneration
of IPMT. In a similar way, the onset of jaundice is suggestive of IPMT in an advanced stage. When IPMT is limited to side branch ducts it is almost always asymptomatic and becomes clinically evident when there is involvement of the m.p.d., with the same symptoms as an IPMT of the m.p.d.

There is common agreement that the only valid therapeutic option for IPMT of the m.p.d. as well as for side branch IPMT with involvement of the m.p.d., is surgical resection, as they are malignant at the time of the diagnosis in most of the cases. However, branch-duct type IPMT with a diameter < 3 cm, thin walls, and with no solid component or involvement of the m.p.d. can be followed-up, as most are asymptomatic, benign (hyperplasia-adenoma), and exhibit very slow growth.

IPMT of the m.p.d. can present as segmental or diffuse. When the entire duct is involved, this tumor can be confused with chronic pancreatitis. Segmental IPMT is very difficult to diagnose as it presents as a nonspecific segmental dilation of the m.p.d. without a clear cause of obstruction or a previous pancreatitis with post-inflammatory stenosis. The affected segment tends to enlarge with dilatation of the collateral ducts. When the lesion is localized in the head of the pancreas, there is a dilatation of the m.p.d. upstream, secondary to the obstruction of the outflow of pancreatic juice, thus simulating a diffuse IPMT. ERCP is able to characterize the lesion, with a clear demonstration of endoluminal defects and the possibility of aspirating the pancreatic juice in order to demonstrate the presence of mucin. Diffuse IPMT presents as a dilatation of the entire m.p.d. (Fig. 13(a), (b)) often indistinguishable from obstructive chronic pancreatitis. In diffuse IPMT there is frequent cystic dilation of branch ducts, especially in the uncinate process and in the tail of the pancreas, moreover, in IPMT a bulging papilla into the duodenum can be observed, especially with CT or MR (Fig. 13(c)) after distension of the intestinal lumen with water or contrast agent. This latter observation is easily obtained with ERCP, which can also observe the mucin leaking into the papilla, making the diagnosis certain. However, in some cases ERCP is unable to opacify the m.p.d. owing to the reflux of contrast agent into the duodenum secondary to the patulous papilla or to the obstructive dense mucin, which can also hinder the opacification of branch ducts. MRCP can overcome the limitation of ERCP with a constant demonstration of branch ducts, thus giving an exact definition of the extent of IPMT. Both mucin and papillary growth appear hyperechoic at US; the solid component is better recognized at CT, especially after CM injection, or with MR, where it appears hypointense on T2-weighted MR sequences, showing enhancement after paramagnetic CM injection. IPMT of the branch ducts is easily visualized as a cystic dilation of branch ducts (Fig. 14) and is increasingly diagnosed by chance during imaging studies performed for other reasons than the pancreas. They are more often located in the uncinate process, less frequently in the other portions of the pancreas, especially the tail. In 30% of cases IPMT is multifocal (Fig. 15). It appears as a round or oval lesion with multilobulated margins (Fig. 14). Cystic lesions converge in a ductal branch which communicates with the m.p.d.; this communication can be easily demonstrated with multislice CT by using thin collimation and is even better demonstrated with MRCP (Fig. 14(c)). Sometimes the communication between the IPMT of the branch duct and the m.p.d. is not easily demonstrated; in such cases the administration of secretin with MRCP can facilitate the visualization of the communication, but sometimes even after secretin the communication cannot be demonstrated. In these cases ERCP can solve the diagnostic problem.

**Figure 15** A 72-year-old man with recurrent episodes of acute pancreatitis. Segmental m.p.d. and branch duct IPMT. MRCP. Branch duct dilations located at the head and tail of the pancreas (arrows). Mild segmental dilation of m.p.d. at the tail (asterisk).

### Solid pseudopapillary tumor

Solid pseudopapillary tumor (SPT) is the least frequent cystic tumor of the pancreas whose origin is still uncertain. Since its first description in 1959, it has gone under different names and it was only in 1996 that the World Health Organization (WHO) renamed this tumor as SPT. It has a low malignant potential and a favorable prognosis. It may affect any age, but most often affects young women in their 30s. Clinically it is fairly nonspecific, with abdominal pain as the main symptom, sometimes together with a palpable mass. The low malignant potential of the lesion is demonstrated by its large size at the time of the diagnosis. The tumor appears as a round, well-encapsulated mass. The content of the lesion is solid with a variable amount of necrosis or hemorrhage, responsible for its frequent cystic appearance (Fig. 11). In a series of 56 patients with SPT, calcifications were found in 29% of the cases. After contrast agent administration the solid component of the tumor appears well vascularized with all imaging techniques (Fig. 11(a), (c)). When fresh hemorrhage is

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1. [41,56,57]
2. [56,57]
3. [59]
4. [47,53,54]
5. [52,55]
6. [40,51]
7. [42]
8. [40,51]
9. [62]
10. [58,61,65]
11. [69]
12. [70]
13. [71]
present, it is well recognized by MR, with high signal intensity on T1-weighted sequences and fluid–debris level\textsuperscript{[12,13]}. When large cystic changes are present, SPT appears as a macrocystic uni- or multilocular lesion, similarly to MCN; in this situation the young age of the patient helps in the differential diagnosis.

### Conclusion

In conclusion, cystic tumors of the pancreas represent a diagnostic challenge for both radiologists and clinicians because of their overlapping clinical, radiological, and pathologic features. Although less prevalent than previously thought, pseudocysts are the most frequent cystic lesions of the pancreas, and a history of pancreatitis is an important factor in suggesting a diagnosis of pseudocyst, although it cannot exclude the coexistence of a pancreatic cystic tumor. The diagnosis of SCA can be considered certain when based on the finding of a microcystic or mixed (micro- and macrocystic) pattern; the diagnosis of either SPT (solid and fluid structure) or MCN (multilocular macrocystic pattern) is only presumptive, and all cystic tumors and tumor-like conditions may present a macrocystic uni- or multilocular pattern. Finally, even small cystic lesions of the pancreas appear to have the potential to progress to malignancy\textsuperscript{[74]}, and at least need follow-up with repeat imaging.

### References
