Cystic Neoplasms of the Pancreas

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Physicians from a wide range of disciplines are being confronted with questions regarding the management of cystic lesions of the pancreas. Owing to recent improvements in pancreatic imaging, an increasing number of cystic lesions have been identified in asymptomatic patients as well as in patients presenting with jaundice, pancreatitis, or abdominal pain. Here we review recent developments in the understanding and management of cystic lesions of the pancreas.

Pathology

Because inflammatory pseudocysts constitute a majority of cystic lesions of the pancreas, the clinical challenge is the differential diagnosis and management of cystic neoplasms, which represent less than 10 percent of pancreatic neoplasms. In the 1990s, at our institution, the proportion of pancreatic resections that were performed for cystic neoplasms doubled, from 16 percent to 30 percent.1

With increasing experience with these lesions has come a refinement of our understanding of the pathology of pancreatic cystic neoplasms (Fig. 1) and of their natural history. These tumors encompass a spectrum of benign, malignant, and borderline neoplasms that either are primarily cystic or result from the cystic degeneration of solid tumors (Table 1). Among these neoplasms, serous cystadenomas (32 to 39 percent), mucinous cystic neoplasms (10 to 45 percent), and intraductal papillary mucinous neoplasms (21 to 33 percent) represent the majority of the cases encountered in practice.2,3 Solid pseudopapillary neoplasms represent less than 10 percent; however, these neoplasms, which occur predominantly in young women, are important, because they are characterized by a low-grade potential for the development of cancer and, when limited to the pancreas, have a high rate of cure.4

Serous cystadenomas, which are lined by a simple, glycogen-rich cuboidal epithelium, have an extremely low potential for malignant disease.5 Usually small and microcystic, they may grow to be quite large. Solid and oligocystic variants of serous adenomas have also been reported.6 Interestingly, chromosomal alterations (deletion and mutation) of the gene for von Hippel–Lindau disease located on chromosome 3p25 have been found in the DNA extracted from a majority of serous cystadenomas.7,8

The histopathological features of mucinous cystic neoplasms and intraductal papillary mucinous neoplasms are almost identical except for a dense mesenchymal ovarian-like stroma, which is a requisite feature of mucinous cystic neoplasms.9 Characteristically, mucinous cystic neoplasms lack a communication with the pancreatic ductal system, whereas a communication is a key feature of intraductal papillary mucinous neoplasms.9 The World Health Organization classification describes three stages of these neoplasms — benign (adenomatous), low-grade malignant (borderline), and malignant (carcinoma in situ and invasive cancer).10,11 In a series of 61 patients with mucinous cystic neoplasms, 44 percent of the neoplasms were classified as adenoma-
tous, 8 percent as borderline, and 15 percent as carcinoma in situ. Invasive adenocarcinomas accounted for the remaining 33 percent of these tumors. Other series have shown that approximately 8 percent of mucinous cystic neoplasms contain invasive carcinoma; this discrepancy among the series is likely to be due to differences in the pathological sampling. Carcinoma in situ is found in 5 to 27 percent of intraductal papillary mucinous neoplasms and invasive carcinoma in 15 to 40 percent. The common occurrence of genetic alterations with ductal adenocarcinomas has also been noted, with point mutations of the K-RAS gene reported in parallel with the degree of cytologic atypia.

An understanding of the natural history of these neoplasms, especially with regard to the risk of malignant degeneration, is important for management. Mucinous cystic neoplasms with evidence of changes from benign status to carcinoma in situ are routinely curable by means of complete surgical resection. Intraductal papillary mucinous neoplasms with evidence of changes to an adenomatous or borderline stage also have an excellent prognosis, although the presence of carcinoma in situ may worsen this prognosis. In the resection of intraductal papillary mucinous neoplasms, it is important to achieve a negative surgical margin at the duct, even in the absence of an invasive adenocarcinoma, in order to prevent a recurrence of the tumor. Some studies have suggested that the branch-duct variant of intraductal papillary mucinous neoplasms, when such tumors can be clearly distinguished, constitutes a distinctive group with a somewhat lower potential for malignant disease that may not require the aggressive surgical management that other papillary mucinous neoplasms require.

Clinical Presentation

Many patients with a pancreatic cystic lesion present with no relevant signs or symptoms. Often the lesion is serendipitously detected by abdominal ultrasonography or cross-sectional imaging studies performed for the evaluation of another condition. When the lesion is symptomatic, the patient may present with recurrent pancreatitis, chronic abdominal pain, or jaundice. These symptoms often indicate a lesion obstructing a pancreatic biliary duct or a communication between a cystic lesion and the pancreatic ductal system. Patients with an advanced cystic neoplasm present with symptoms similar to those of pancreatic ductal carcinoma, including pain, weight loss, and jaundice.

True cystic lesions of the pancreas may be confused with pseudocysts owing to similarities in the clinical presentations and in the characteristics visualized in imaging studies. Pseudocysts may arise after an episode of acute pancreatitis or insidiously in the setting of chronic pancreatitis, and they are frequently, but not invariably, associated with pain. Large pseudocysts can compress the stomach, duodenum, or bile duct, resulting in early satiety, vomiting, or jaundice.

Diagnosis

Cystic lesions in the pancreas are increasingly being discovered because of the wide use of transabdominal ultrasonography, computed tomogra-
CT is an excellent test for cystic lesions in the pancreas, not only for the initial detection of a lesion but also for the characterization of such lesions by visualization of the calcification of the cyst wall, septa, mural nodules, and findings suggestive of pancreatitis (Fig. 2). MRI has the added advantage of providing better characterization of the morphologic features of a cyst and possibly of showing a communication between the cyst and the pancreatic duct. Transabdominal ultrasonography may aid in the differentiation of solid and cystic lesions, but a complete evaluation of the pancreas is often difficult owing to the presence of overlying bowel gas.

The presence of a central scar visualized with the use of CT or MRI is a highly diagnostic feature that is found in about 20 percent of serous cystadenomas. Serous cystadenomas are typically composed of honeycomb-like microcysts, but on CT they may appear solid or show a single dominant macrocavity — features that can result in the confusion of these tumors with mucinous cystadenomas. Mucinous cystic neoplasms, in contrast, are typically unilocular or multilocular, with a small number of discrete compartments.

The uncommon finding of peripheral eggshell calcification on CT is specific to a mucinous cystic neoplasm and highly predictive of cancer. Intraductal papillary mucinous neoplasms may involve the main pancreatic duct exclusively, a side branch of the main duct, or both. Magnetic resonance cholangiopancreatography can adequately indicate the extent of dilatation of the pancreatic duct, the size of mural nodules, and the presence of a communication between the duct and the cystic lesion. Newer developments in CT — for example, high-resolution multislice helical imaging — in combination with postprocessing techniques such as curved reformations can provide details in imaging studies of intraductal papillary mucinous neoplasms, including the presence of a ductal communication, similar to the findings on magnetic resonance cholangiopancreatography. The presence of mural nodules and a segmental or diffuse dilatation of the main pancreatic duct greater than 15 mm in diameter has been reported as indicative of the development of malignant disease. The role of positron-emission tomography with 18F-fluorodeoxyglucose in the evaluation of cystic neoplasms has not been established. Although these features are visible on imaging, there is a substantial overlap in the morphologic features of

Table 1. Epidemiologic and Biologic Characteristics of Pancreatic Cystic Neoplasms.

<table>
<thead>
<tr>
<th>Type</th>
<th>Sex Predilection</th>
<th>Peak Decade of Life</th>
<th>% of Cystic Neoplasms</th>
<th>Malignant Potential and Natural History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma</td>
<td>Female</td>
<td>7th</td>
<td>32–39</td>
<td>Resection curative; serous cystadenocarcinoma extremely rare</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>Female</td>
<td>5th</td>
<td>10–45</td>
<td>Resection curative, regardless of degree of epithelial dysplasia; poor prognosis when invasive adenocarcinoma present</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>Equal distribution</td>
<td>6th–7th</td>
<td>21–33</td>
<td>Excellent prognosis for lesions showing only adenomatous and borderline cytologic atypia; poor prognosis when invasive carcinoma present</td>
</tr>
<tr>
<td>Solid pseudopapillary neoplasm</td>
<td>Female</td>
<td>4th</td>
<td>&lt;10</td>
<td>Indolent neoplasm with rare nodal and extranodal metastases; excellent prognosis when completely resected</td>
</tr>
<tr>
<td>Cystic endocrine neoplasm</td>
<td>Equal distribution</td>
<td>5th–6th</td>
<td>&lt;10</td>
<td>Similar to solid neuroendocrine neoplasm</td>
</tr>
<tr>
<td>Ductal adenocarcinoma with cystic degeneration</td>
<td>Slight male predominance</td>
<td>6th–7th</td>
<td>&lt;1</td>
<td>Dismal prognosis, similar to solid adenocarcinoma</td>
</tr>
<tr>
<td>Acinar-cell cystadenocarcinoma</td>
<td>Male</td>
<td>6th–7th</td>
<td>&lt;1</td>
<td>Similar to solid type; aggressive neoplasm with slightly better prognosis than ductal adenocarcinoma</td>
</tr>
</tbody>
</table>
cystic neoplasms. The ability of CT and MRI to diagnose a specific cystic lesion accurately and to determine whether malignant disease is present remains uncertain.\textsuperscript{25,35}

The diagnosis of a pancreatic pseudocyst depends on the clinical history and the associated findings within the pancreas, such as gland atrophy, duct dilatation, calcification of the parenchyma, and calculi in the pancreatic duct. On CT, the appearance of a pseudocyst is that of a low-attenuation, unilocular cyst with accompanying signs of acute or chronic pancreatitis.\textsuperscript{36} The density of the fluid in a complex pseudocyst may be higher than that in an uncomplicated pseudocyst, owing to the presence of hemorrhage or gas that develops as a result of bacterial infection. In categorizing unilocular cystic lesions, noninvasive imaging methods have limitations when there are no obvious clinical and morphologic hallmarks of pancreatitis and no communication with the pancreatic duct.\textsuperscript{25}

When cross-sectional imaging does not provide a definitive diagnosis, additional information may be sought by means of aspiration of the contents of a cyst.\textsuperscript{37} Cytologic examination of cyst fluid and the analysis of a variety of biochemical and tumor markers may aid in establishing a diagnosis. However, cytologic analysis of cyst fluid has identified cells that indicate the presence of malignant disease or a benign mucinous cystic lesion in perhaps only half the aspirates obtained.\textsuperscript{38} Only inflammatory cells should be present in fluid aspirated from pseudocysts.\textsuperscript{39}

A variety of tumor markers present in the fluid in a cyst have been proposed for use in the differentiation among the major types of cystic lesions (Table 3).\textsuperscript{40} Although cancer antigen (CA) 19-9 is associated with pancreatic adenocarcinoma, its concentration in cyst fluid has not been established as a useful indicator for discriminating between mucinous and nonmucinous cystic lesions.\textsuperscript{41} Studies conducted in the past decade have suggested that carcinoembryonic antigen and CA 72-4 are useful for identifying mucinous lesions.\textsuperscript{42} The presence of a mucin-like antigen that reflects the presence of a mucinous epithelium has also been used to diagnose mucinous lesions and cancers.\textsuperscript{43} The findings in a recent series called into question the use of carcinoembryonic antigen as a marker for mucinous lesions, and other studies have reported the superiority of extracellular mucin in the cyst fluid to carcinoembryonic antigen as a means to identification.\textsuperscript{44,45} Although amylase is not a tu-

\textbf{Table 2. Diagnostic Features of Pancreatic Cystic Lesions.*}

<table>
<thead>
<tr>
<th>Cystic Neoplasm</th>
<th>Serous Cystadenoma</th>
<th>Mucinous Cystic Neoplasm</th>
<th>Intraductal Papillary Mucinous Neoplasm</th>
<th>Solid Pseudopapillary Neoplasm</th>
<th>Cystic Endocrine Neoplasm</th>
<th>Ductal Adenocarcinoma with Cystic Degeneration</th>
<th>Acinar Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Feature</td>
<td>Microcystic or honeycomb lesion; 20 percent are macrocystic</td>
<td>Mixed features of solid mass with fluid and hemorrhage</td>
<td>Mixed features of solid mass with fluid and hemorrhage</td>
<td>Variable appearance</td>
<td>Variable appearance</td>
<td>Mass with localized fluid collection</td>
<td>Mass with localized fluid collection</td>
</tr>
<tr>
<td>Appearance of fluid</td>
<td>Viscous, clear, with mucin</td>
<td>Viscous, clear, with mucin</td>
<td>Viscous, clear, with mucin</td>
<td>Thin, clear</td>
<td>Thin, clear</td>
<td>Thin, clear</td>
<td>Thin, clear</td>
</tr>
<tr>
<td>Cytologic feature</td>
<td>Monomorphic cubic or columnar cells with variable cellularity and columnar mucin (PAS-positive)</td>
<td>Mucin-rich fluid with variable cellularity and columnar mucin (PAS-positive)</td>
<td>Mucin-rich fluid with variable cellularity and columnar mucin (PAS-positive)</td>
<td>Necrotic debris</td>
<td>Necrotic debris</td>
<td>Necrotic debris</td>
<td>Necrotic debris</td>
</tr>
</tbody>
</table>

* PAS denotes periodic acid–Schiff stain.
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mor marker, its presence in cyst fluid is often used as an indicator of a communication between a cystic lesion and the ductal system. Amylase-rich fluid is uniformly found in pancreatic pseudocysts and in cysts that are associated with intraductal papillary mucinous neoplasms, whereas low concentrations of amylase are found in the fluid of both serous cystadenomas and the great majority of mucinous cystadenomas.

Serum levels of CA 19-9 are slightly elevated in some patients who have malignant cystic lesions.

In the past several years, endoscopy and endoscopic ultrasonography have been used to diagnose cystic lesions of the pancreas and to guide fine-needle aspiration. The high-resolution imaging possible with endoscopic ultrasonography permits the identification of the morphologic features of various cystadenomas and has been used to aid in the differential diagnosis of these lesions (Fig. 3).

However, the detailed features that can be visualized with this technique do not appear to be sufficiently accurate to allow a differentiation between benign and malignant cystadenomas unless there is evidence of a solid mass or an invasive tumor outside the pancreas. The finding of obstruction of the pancreatic duct is suggestive of malignant disease arising from a cystic neoplasm.

Endoscopic ultrasonography is currently the technique of choice for guiding the aspiration of pancreatic cystic lesions because of its safety record and its capacity to obtain cyst fluid; the aspirate can be examined for tumor markers and for cytologic features.

Intraductal neoplasms can be visualized with endoscopic retrograde cholangiopancreatography and with endoscopic ultrasonography. On endoscopy, the appearance of a mucin extrusion from a widely patent ampulla is pathognomonic of an intraductal papillary mucinous neoplasm. The use of injections of contrast material in the main pancreatic duct will enhance the characteristic findings of mucinous filling defects, ductal dilatation, and cystic dilatation of side branches. The characteristic papillary projections arising from the wall of the main pancreatic duct can also be visualized directly on endoscopic pancreatoscopy.

Endoscopic ultrasonography may assist in the detection of malignant disease arising from intraductal papillary mucinous neoplasms by showing wall invasion and may be used to guide fine-needle aspiration to suspicious lesions. The staging of intraductal papillary mucinous neoplasms on the basis of endoscopic ultrasonographic examination alone may be compromised by inflammatory changes in the surrounding parenchyma that may simulate malignant disease.

The management of cystic neoplasms of the pancreas has not been standardized and is evolving. Surgical resection is indicated for most such lesions in patients who are symptomatic and for whom the surgical risk is low; the proper evaluation and subsequent management of disease in patients without symptoms have not been fully de-
fined. Accurate delineation of the type of tumor and of the prognosis are particularly important, because over a third of cystic lesions are discovered incidentally. On the one hand, a blanket policy of resection for all would certainly lead to the removal of some potentially malignant mucin-producing cystic neoplasms before the patients become symptomatic and have a lower rate of cure. On the other hand, such an approach would also lead to surgery for some serous cystadenomas and other benign lesions that might never cause problems.

In addition to the presence or absence of symptoms, other factors to be considered in the management of cystic neoplasms of the pancreas include the patient’s age, the degree of surgical risk for the patient, and the location and size of the lesion (Fig. 4). High-resolution CT or MRI should be performed as part of planning in all cases. Endoscopic ultrasonography, as compared with CT and MRI, provides further detail of the morphologic features of the lesion as well as an opportunity to obtain specimens of the fluid and the cyst wall, all of which provide additional information about the nature of the lesion, particularly for the differentiation among mucinous lesions, nonmucinous lesions, and pseudocysts. However, endoscopic ultrasonography is not indicated when surgery is planned, regardless of the outcome of the study (i.e., for a patient at low risk from surgery who is symptomatic). In intermediate cases, endoscopic ultrasonography and fine-needle aspiration are useful to guide management toward observation when the lesions show minimal potential for malignant disease or toward resection when there is a substantial risk of it.

The current rate of death among patients undergoing pancreatic resection in specialized centers is less than 2 percent.55

#### Table 3. Tumor Markers in Cyst Fluid in the Differential Diagnosis of Cystic Lesions of the Pancreas

<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>Serous Cystadenoma</th>
<th>Mucinous Cystic Neoplasm</th>
<th>Intraductal Papillary Mucinous Neoplasm</th>
<th>Solid Pseudopapillary Neoplasm</th>
<th>Cystic Endocrine Neoplasm</th>
<th>Ductal Adenocarcinoma with Cystic Degeneration</th>
<th>Acinar-Cell Cystadenocarcinoma</th>
<th>Pseudocyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Low but variable</td>
</tr>
<tr>
<td>CA 72-4</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Low but variable</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Low but variable</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Low</td>
</tr>
<tr>
<td>Amylase</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>High</td>
</tr>
</tbody>
</table>

* CEA denotes carcinoembryonic antigen, and CA cancer antigen.
Intraductal papillary mucinous neoplasms are more frequently located in the head of the pancreas and therefore require a pancreatoduodenectomy. However, because they tend to grow longitudinally along ducts, rather than radially into the parenchyma, the resection margins of intraductal papillary mucinous neoplasms must be examined intraoperatively with a frozen section to confirm clearance of the tumor. As many as 19 percent of patients who have an intraductal papillary mucinous neoplasm require a total pancreatectomy because of the extensive involvement of the ductal system. Since pancreatectomy cannot be performed safely in all hospitals, the relative risk of the procedure must be considered when the physician is recommending whether and where surgical treatment should take place.

The prognosis for patients who have undergone resection of a mucinous cystic neoplasm without evidence of transmural invasion is excellent (nearly 100 percent). Even for intraductal papillary mucinous neoplasms containing carcinoma (which make up almost 60 percent of resected tumors), the five-year rate of survival is over 50 percent.21

Some aspects of the management of cystic neoplasms remain unsettled. Our recommendations for the management of this disease are limited by the difficulty of distinguishing accurately between benign and malignant or potentially malignant mucinous lesions before resection and by the incomplete understanding of the natural history of these neoplasms. Were it possible to predict the likelihood and the rate of progression to invasive cancer in a given patient, potentially we could offer continued observation or no resection for some. Likewise, very little information is available on the growth rate of serous cystadenomas and on the likelihood of these lesions’ producing symptoms.21

The development of new treatments for cystic tumors of the pancreas, such as ethanol ablation and radiofrequency ablation, or even the use of cyclooxygenase inhibitors to arrest the progression of adenomas to cancer, await further understanding of the biology of cystic neoplasms.

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