Review

Cystic pancreatic neoplasms

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Summary
Cystic pancreatic neoplasms comprise a heterogeneous group of pathologic entities. Mucinous cystic tumors and serous cystadenomas account for more than 75% of reported cases. While serous cystadenomas are almost uniformly benign, mucinous cystic tumors all have malignant potential and must be treated as such. While both clinical and biochemical features can distinguish among the various cystic pancreatic lesions, surgical resection is often required for both definitive diagnosis and treatment. When surgery is performed, benign lesions should be treated with pancreatic parenchymal sparing procedures if anatomy permits. Standard surgical oncologic principles should be employed when treating indeterminate or malignant lesions.

Key words: cystadenoma, cystic neoplasms, pancreatic cancer, mucinous cystadenoma, mucinous cystadenocarcinoma, pancreatic pseudocyst, serous cystadenoma

Introduction
Cystic pancreatic neoplasms have drawn increasing interest in recent years because of their high cure rate and potential confusion with pancreatic pseudocysts. Furthermore, the widespread use of CT scans and ultrasound in asymptomatic or minimally symptomatic patients has uncovered unsuspected cystic pancreatic lesions with increasing frequency. Consequently, accurate pre-operative diagnosis of these lesions has become a priority in developing treatment recommendations for such patients. This brief article will discuss the evaluation and treatment of the most common types of cystic pancreatic neoplasms.

Cystic pancreatic neoplasms
Cystic pancreatic neoplasms comprise a heterogeneous group of pathologic entities which share only a predilection for female gender and a gross morphologic feature i.e. cystic appearance. The most common cystic pancreatic neoplasms are mucinous cystic neoplasms and serous cystadenomas. These two entities account for more than 75% of the cystic pancreatic neoplasms reported in most series. Other less common cystic pancreatic neoplasms include papillary cystic tumors (also known as solid and papillary tumor), cystic neuroendocrine tumors, acinar cystadenocarcinoma, cystic teratoma, lymphangioma, hemangioma, and paraganglioma (Table 1). Intraductal papillary mucin producing tumors which appear to be part of a pathologic continuum with mucinous cystic neoplasms will be discussed in a subsequent article.

Mucinous cystic tumors
Mucinous cystic tumors (MCT) are the most common cystic pancreatic neoplasms [1,2] Eighty percent of MCT occur in females with a mean age at presentation of 54 years.

Abdominal pain is the most common symptom with weight loss, early satiety, nausea and vomiting also frequently reported. Most MCT are consist of large locules (macro cystic) filled with thick mucoid material. The walls are dense and fibrous and may even be calcified CT findings suggestive of a MCT include multilocular cystic lesions without surrounding inflammation, and cystic lesions with irregularity of the wall such as papillary projections. A recent report suggests diffusion-weighted echo-planar MRI can distinguish mucin producing tumors from pseudocysts[3]. Histologic evaluation reveals mucin producing epithelial cells lining the cyst, but denudation of large areas of epithelium is common.

All MCTs should be considered to be potentially malignant. One of the prominent features of mucinous cystadenocarcinoma is histologic heterogeneity with the coexistence of benign and malignant epithelia seen in nearly all tumors. Not only does this imply that mucinous cystadenocarcinomas develops from a premalignant lesion i.e. mucinous cystadenomas, it also indicates the need for extensive sampling of purportedly benign lesions (which can only be achieved if the lesion is excised) in order to be certain a lesion is benign. A cystadenocarcinoma may have a solitary focus of malignant cells arising in an otherwise bland appearing epithelial lining. Because the thoroughness of histologic sampling may be difficult to ascertain in many cases, it is best to assume that mucinous cystic tumors will

Table 1. Spectrum of cystic neoplasms of the pancreas

<table>
<thead>
<tr>
<th>Mucinous Cystadenoma</th>
<th>Mucinous Cystadenocarcinoma</th>
<th>Serous Cystadenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary Cystic Tumor</td>
<td>Cystic Neuroendocrine Tumor</td>
<td>Adenocarcinoma of the pancreas with cystic degeneration</td>
</tr>
<tr>
<td>Acinar cystadenocarcinoma</td>
<td>Cystic Teratoma</td>
<td>Lymphangioma</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Paraganglioma</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Cyst fluid characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Viscosity</th>
<th>Amylase</th>
<th>CEA</th>
<th>CA 15-3</th>
<th>CA72-4</th>
<th>Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>low</td>
<td>high</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>inflammatory</td>
</tr>
<tr>
<td>SCA</td>
<td>low</td>
<td>variable</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>25% positive</td>
</tr>
<tr>
<td>MCT-benign</td>
<td>high</td>
<td>variable</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>40% positive</td>
</tr>
<tr>
<td>MCT-Malignant</td>
<td>high</td>
<td>variable</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>67% positive</td>
</tr>
</tbody>
</table>

behave as malignant lesions if left untreated. There are documented cases of MCT managed expectantly for many years which then developed malignant features leading to death[4,5].

MCT should be resected according to standard oncologic principles. There is no role for enucleation of these lesions. Furthermore, if metastases are present and resectable, they should be excised as long term cures have been reported in this situation[5]. The prognosis for completely resected MCT is excellent with five year survival over 50% reported in malignant lesions [1,6,7]. However, unresectable MCT behave similar to unresectable pancreatic adenocarcinoma and pursue a rapid downhill course.

Serous cystadenoma

Serous cystadenoma (SCA) is the second most common cystic pancreatic neoplasm. Like MCT, nearly four fifths of these tumors occur in women although the mean age at diagnosis is a decade older (63 years vs. 54 years). As many as 50% of SCA are discovered incidentally during a laparotomy or radiologic evaluation for unrelated problems. Symptomatic patients present with upper abdominal pain, weight loss or an abdominal mass. These tumors can be quite large at the time of presentation with a mean diameter of 7 cm in the MGH series[1]. SCA occur commonly in patients with von Hippel-Lindau syndrome [8].

The appearance of SCA is that of a well circumscribed nodular tumor which on cut section reveals a honeycomb appearance due to the presence of multiple small cysts. The lesion may contain a central focus of calcification with radiating septa of connective tissue which leads to the pathognomonic CT "sunburst" appearance. In the absence of this pathognomonic CT finding, endoscopic ultrasound (EUS) may better identify the delicate septae and microcysts which characterize these lesions. Only rarely are SCA unilocular or macrocystic [9]. The microscopic appearance consists of cystic spaces lined by glycogen rich cells with no mitotic activity seen.

Since malignancy is extremely rare in SCA, (less than 1% of reported SCA) these tumors can be managed as benign lesions. For symptomatic patients, surgical resection is the best treatment. Controversy exists over the optimal procedure for these lesions, but there is a clear trend towards preservation of pancreatic parenchyma. Talamini et al reported ten patients undergoing enucleation of cystic lesions with no recurrence at an average follow up of 43 months [10]. However the fistula rate in this series was 50%. Our group has preferred to employ middle pancreatectomy when feasible for tumors in the neck or body of the pancreas [11]. Likewise for lesions in the tail of the pancreas, a distal pancreatectomy with splenic preservation should be considered. In asymptomatic patients the management depends in part on the degree of certainty that the lesion is an SCA and not another type of cystic pancreatic neoplasm.

Lesions with a pathognomonic appearance on imaging studies and appropriate cyst fluid characteristics (see below) can be managed with observation alone. If there is any doubt as to the nature of the lesion, however, it should be resected because of the potential for malignancy. Given the low morbidity and mortality rate associated with pancreatic resection in specialized centers, the threshold to err on the side of resection should be low unless the general condition of the patient precludes it.

Uncommon cystic pancreatic neoplasms

Like most other pancreatic cystic neoplasms, papillary cystic tumors (also referred to as solid and papillary tumors) occur predominantly in females. However these tumors usually present in the second and third decade of life. These tumors usually do not produce symptoms until they are large and often present as an abdominal mass. The correct preoperative diagnosis is made less than half the time. The majority of tumors are benign, but malignant papillary cystic tumors do occur especially in older females suggesting that these tumors in young women should be regarded as pre-malignant. Unless there are extenuating circumstances these lesions should be treated with a formal pancreatic resection. Papillary cystic tumors can be multicentric so a careful intraoperative evaluation of the entire pancreas is necessary.

Neuroendocrine tumors of the pancreas may undergo cystic degeneration and present as cystic pancreatic neoplasms. They tend to present in the fifth decade like MCT but they do not have a predilection for females. They may be hormonally functional or non-functional. Slightly less than half are malignant. Therefore all should be approached as though they were malignant and treated with formal pancreatic resection rather than enucleation.

Differential diagnosis of cystic pancreatic lesions

Differeniating cystic neoplasms from pseudocysts

Misdiagnosis of a cystic neoplasm as a pancreatic pseudocyst either delays appropriate resection or leads to performance of an inappropriate procedure in as many as 37% of cases [1]. Consideration of the following clinical details may minimize confusion between these entities. A pseudocyst develops either in the setting of chronic pancreatitis or following an episode of acute necrotizing pancreatitis. Neoplastic cysts, on the other hand arise de
novo. Rarely, cystic tumors can cause acute pancreatitis due to obstruction of the pancreatic duct. An elevated serum amylase strongly suggests a pseudocyst while a normal serum amylase provides no discriminative information. CT scans showing solid components of the cyst, septa and localizations, or calcification in the wall of the cyst are highly suggestive of neoplasm. Cysts whose fluid is low in amylase activity are almost always neoplastic. When facilities are available, a more rigorous cyst fluid analysis may provide additional information as described in the subsequent section of this article. Endoscopic pancreateography demonstrates communication with the cyst in 65% of pseudocysts, but almost never in cystic neoplasms.

At the time of surgery, a pseudocyst will be found to have a thick wall adherent to and composed of adjacent structures. The pancreas is usually thickened, indurated, or inflamed. Cystic pancreatic neoplasms are usually discrete lesions arising within a normal textured pancreas. Occasionally MCT may elicit a strong pericystic reaction making differentiation from pseudocysts difficult. If a frozen section biopsy of the wall demonstrates the presence of epithelium, the suspicion of a neoplastic cyst is confirmed. The converse, however, is not true since the lining of neoplastic cysts can be denuded for up to 98% of the surface area! If the nature of a cystic lesion cannot be established it is better to proceed with resection even if the lesions ultimately proves to be a pseudocyst than to internally drain a potentially malignant lesion.

Cyst fluid analysis

Differentiating between cystic lesions on the basis of CT and ultrasound imaging can be difficult, especially for solitary unicocular cysts. The diagnostic accuracy of cytology obtained by CT guided aspiration is limited by the difficulty in finding diagnostic cells, but overall the diagnostic accuracy is 67% for malignant cysts and 40% for mucinous cysts.[12] SCA are the most difficult to diagnose cytologically because glycogen rich epithelial cells are rarely seen leading to an accuracy of only 25%. To improve the diagnostic yield of cyst fluid analysis, both the physical characteristics of cyst fluid and other tumor markers in the cyst fluid have been studied. The fluid within MCT is more viscous than in SCA and this property can be measured and quantified. CEA appears to be the most useful marker for detecting MCT[13] Other tumor markers such as CA 72-4 and CA 15-3 appear better than CEA at discriminating benign from malignant lesions.[14] DNA ploidy has also been found useful in predicting the biologic behavior of cystic neoplasms[15]. K-ras oncogene mutations have also been studied and appear to be associated with malignancy.[16] See Table 2.

Conclusions

Cystic pancreatic neoplasms are being recognized with increasing frequency as we approach the new millennium. While the clinical, radiographic, and biochemical characteristics are more clearly understood than they were 10 years ago, it is still fairly common to lack a definitive diagnosis prior to resecting these lesions. Since most cystic pancreatic neoplasms have a high cure rate with surgical resection and pancreatic surgery has become safe and routine in many centers, an aggressive surgical approach is warranted.

References


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