Cystic neoplasms of the pancreas: A diagnostic challenge

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INTRODUCTION

Pancreatic cystic neoplasms, despite increased recognition, remain rare and represent approximately 10%-15% of primary cystic masses of the pancreas[1-8]. Many pancreatic cystic masses are discovered incidentally during the work-up for abdominal pain, diarrhea, and other non-specific gastrointestinal symptoms and represent a frequent clinical referral in tertiary academic centers with pancreatic expertise. Not surprisingly, the increase in the diagnosis of a pancreatic cystic mass parallels that of the improved number and type as well as the improved overall sensitivity of cross-sectional imaging studies used in routine practice today[9]. It is important for today's practicing physician to be aware of these increasingly recognized neoplasms on radiological imaging, and more importantly, to understand the potential for the presence or development of pancreatic malignancy in a certain subset of these lesions.

CLASSIFICATION

The classification of cystic pancreatic neoplasms has its roots in the surgical, radiological, and perhaps most importantly in the clinical pathological literature, and dates from the mid to late 1970s[10]. The distinction between serous and mucinous cystic neoplasms (MCNs) was first realized at that time and despite many modifications and attempts at radiological[11], endoscopic[12], and more recently with newer laboratory-based analysis using techniques such as mass spectrometry[13], remains intact and a solid initial clinical approach to these neoplastic lesions even today. Importantly, our understanding of MCNs has evolved and since the early 1980s, the clinical entity we now recognize as intraductal papillary mucinous neoplasm (IPMN) was first described in the literature[14]. IPMN remains a very important “lesion of clinical distinction” when evaluating pancreatic cystic neoplasms and is recognized as a distinct histopathological entity as evidenced by the World Health Organization histological classification system[15] (Table 1).

Abstract

Cystic neoplasms of the pancreas are increasingly recognized due to the expanding use and improved sensitivity of cross-sectional abdominal imaging. Major advances in the last decade have led to an improved understanding of the various types of cystic lesions and their biologic behavior. Despite significant improvements in imaging technology and the advent of endoscopic-ultrasound (EUS)-guided fine-needle aspiration, the diagnosis and management of pancreatic cystic lesions remains a significant clinical challenge. The first diagnostic step is to differentiate between pancreatic pseudocyst and cystic neoplasm. If a pseudocyst has been effectively excluded, the cornerstone issue is then to determine the malignant potential of the pancreatic cystic neoplasm. In the majority of cases, the correct diagnosis and successful management is based not on a single test but on incorporating data from various sources including patient history, radiologic studies, endoscopic evaluation, and cyst fluid analysis. This review will focus on describing the various types of cystic neoplasms of the pancreas, their malignant potential, and will provide the clinician with a comprehensive diagnostic approach.

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The malignant potential of the various cystic neoplasms of the pancreas are important for the given clinician and are best understood by dividing IPMNs into main-branched vs side-branched lesions and comparing/contrasting these with the MCN. Main branch IPMN lesions carry the highest percentage of malignancy, ranging in most studies between 60% and 92%.[13-16] Invasive malignancy defined as non-carcinoma-in-situ is also more common in these lesions and approaches 60% in some studies. Side-branch IPMN lesions in comparison are less often malignant, with a range of malignancy in reported studies between 6% and 46% and are less likely to be invasive, with the highest reported percentage in the 30% range.[17,18] In comparison to IPMN lesions, MCNs have a malignant potential ranging from as low as 6% to as high as 36%.[19-21] A better understanding of the malignant potential of MCN lesions is likely to improve with further acceptance of the ovarian-type stroma as diagnostic criteria regarding these lesions.

**PRESENTATION/EPIEMIOLOGY**

The exact prevalence of pancreatic cysts is difficult to measure because many patients will be entirely asymptomatic, but it has been estimated to be approximately 20% in patients undergoing radiological imaging for non-pancreatic diseases/indications.[22] The asymptomatic nature of these cystic lesions (estimated at 40%-75%) in some studies[23] make further epidemiological studies a clinically difficult task. An autopsy series from Japan estimated the prevalence of pancreatic cysts to be 25%, with an increasing prevalence paralleling advanced patient age.[24] Regardless, the proportion of pancreatic cysts felt to be primary cystic neoplasms is well documented and in the range of 10%-15% with the remaining majority of cysts found to be pseudocysts.[25] This percentage draws attention to the importance of ruling out the presence of a pancreatic pseudocyst using a combination of historical questioning, and in many cases of cystic sampling, usually done via EUS.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PANCREATIC CYSTIC LESIONS**

Once the presence of a pancreatic cyst has been established by an imaging modality, the cornerstone of management is to differentiate between a pseudocyst and a cystic neoplasm. If a pseudocyst has been effectively excluded, a prudent clinical strategy regarding pancreatic cysts is the division into serous vs mucinous neoplasms. During the evaluation of a pancreatic cyst, it is important for the clinician to have an understanding of the different cyst types, their typical location in the pancreas, and their biological behavior. Serous cystic neoplasms (SCNs) represent approximately 30% of primary cystic neoplasms of the pancreas,[26] with the largest subset being SCAs. The mucinous neoplasms
Table 2  Typical characteristics of pancreatic cystic lesions

| Cyst type | Pseudocyst | SCA | MCN | IPMN | SPN |
|-----------|------------|-----|-----|------|-----|
| Age       | Variable   | Middle-aged | Middle-aged | Elderly | Young |
| Sex       | M > F      | F > M       | Female       | M > F    | Female |
| Pancreatitis history | Yes | No | No | Yes | No |
| Location  | Evenly     | Evenly     | Body/tail    | Head     | Evenly |
| Malignant potential | None | Rarely | Moderate to high | Low to high | Low |
| Biliary obstruction | Yes | Uncommon | No | No | Yes, Uncommon |

SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; SPN: Solid pseudopapillary neoplasm. A history of pancreatitis episodes and pancreatic risk factors including alcohol abuse, gallstones and complications, or family history of pancreatitis is often given; Pancreatitis due to IPMN is predominately of the main pancreatic duct subtype.

are primarily subdivided into MCNs which represent approximately 45%-50% of primary cystic neoplasms of the pancreas[26], and IPMNs which make up approximately 25% of primary cystic neoplasms[27].

It is of great clinical importance at this point of the work-up to consider the clinical background of the patient with a newly discovered pancreatic cystic neoplasm. Remembering that a large proportion of pancreatic cysts are found to be pseudocystic in nature, a thorough review of the history for episodes of definable pancreatitis in conjunction with risk factors for pancreatitis, such as chronic alcohol ingestion, family history of “pancreatic diseases” as often described by patients and their families, and autoimmune disease is always a good clinical starting point. A clear history of a well documented episode of pancreatitis strongly suggests that the cystic pancreatic lesion is a pseudocyst, but occasionally an attack of pancreatitis will be the clinical presentation of a neoplastic cystic lesion particularly an IPMN[29]. Patient demographics including age, sex, and presence or absence of symptoms and the location of the cyst are important considerations while a diagnosis is being sought. For example, MCNs tend to be a middle-age, female-predominant disease with most, but not all, lesions located in the pancreatic body or tail[29]. Serous cystic adenomas (SCAs) in contrast, while present most often in middle-aged females are evenly distributed throughout the pancreatic gland, while IPMNs have an elderly male predominance and are usually located, but not confined to the pancreatic head region[29,30]. Solid pseudopapillary tumors of the pancreas (SPNs) remain a pathologically distinct, rare clinical entity occurring predominately in young females[31]. A comparative index involving the different pancreatic cystic neoplasms as well as the pancreatic pseudocysts is shown in Table 2, and the usual location of pancreatic cystic lesions in Figure 1[29].

The discovery of a lesion thought to represent a possible pancreatic cystic neoplasm is often made incidentally by computed tomography (CT) scanning performed for other clinical reasons. With this in mind, a thorough understanding of the different imaging modalities, both radiological and if available endoscopic, is needed to best construct a diagnostic algorithm for optimum care for these patients. The availability of endoscopic retrograde cholangiopancreatography (ERCP) and perhaps most importantly, EUS plus/minus fine-needle aspirate (FNA) and cystic fluid analysis, has led to a much improved understanding and characterization of these lesions.

RADIOLOGICAL IMAGING STUDIES

Traditionally, three imaging modalities have been used to evaluate pancreatic lesions: trans-abdominal ultrasound (US), CT scanning, and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP). Trans-abdominal US, while having the advantage of being inexpensive and readily available, is very operator-dependent, and is limited in its ability to visualize the entire pancreas. Furthermore, the presence of significant bowel gas limits the sensitivity of US for characterization of pancreatic cystic processes.

CT scanning, particularly with intravenous contrast enhancement, is a widely available, relatively inexpensive imaging modality and is often the first imaging procedure ordered when a diagnosis of a pancreatic cystic neoplasm is considered. A review of the diagnostic accuracy of CT scanning has recently been performed[32] with a reported range between 20% and 90%. Differences in study design, characterization of lesions, especially those with atypical features[33,34], and the ultimate study goal, i.e. specific cyst type[35-37] vs differentiation of benign vs malignant cyst types[38] all were felt to contribute to the wide range in diagnostic accuracy.

The typical appearance of a given cystic neoplasm is reported in many ways via CT. Size (i.e. microcystic (< 2 cm) vs macrocystic (> 2 cm), unilocular vs multilocularity, pancreatic duct communication and/or dilation, and the presence of a mass or mural nodule remain the most important imaging characteristics seen on routine CT. SCAs are characteristically microcystic with many small cysts within the larger cyst creating a “honeycomb” type pattern. A central stellate scar is often seen at the center of an SCA and is considered pathognomonic. Pancreatic duct communication is rarely seen and dilation of the pancreatic duct also remains uncommon. MCNs are in comparison, most often macrocystic, although...
microcystic lesions do occur and characteristically are multilocular with an “orange fruit” type appearance. Dilation of the pancreatic duct is uncommon as is communication with the main pancreatic duct. IPMN lesions in contrast, are often described as a “bag of grapes” and contain numerous smaller cysts. Pancreatic duct communication is common, and in main branch IPMN lesions, pancreatic duct dilation is seen and predictive of an invasive nature. Associated mural nodules and/or masses are most often observed in IPMN lesions and to a lesser extent in MCNs. The presence of a mural nodule is significant, as this is often predictive of an invasive cystic neoplasm.

MRI of the abdomen when combined with MRCP is a rapidly emerging imaging modality with widespread availability, and has great potential to add to our understanding of pancreatic cystic lesions. MRI/MRCP comparatively, in relation to other imaging modalities, is rivaled only by EUS in its ability to obtain quality images of not only the pancreatic parenchyma, but also of the pancreatic and biliary ductal structures. MRCP does remain inferior to ERCP in terms of diagnostic accuracy, but the gap is narrowing and MRCP offers a non-invasive means of diagnosis compared with ERCP and its complications, most notably post-ERCP pancreatitis.

ENDOSCOPIC STUDIES

The role of endoscopy, specifically ERCP and EUS, in the evaluation and diagnosis of pancreatic cystic neoplasms is a study in evolution that continues today. ERCP remains the most sensitive diagnostic modality for detecting communication between the main pancreatic duct and a given cystic lesion. Additionally, in a minority of cases an endoscopic diagnosis of an IPMN can be established if a patulous papilla with mucin extrusion, also sometimes referred to as the “fish-eye” ampulla is visualized. The use of ERCP as a primary diagnostic tool in pancreatic cystic neoplasms is not routinely recommended. In most cases, the correct diagnosis can be achieved with a higher yield, less invasive test.

EUS, since its introduction as an endoscopic technology in the late 1970s and early 1980s, has become an increasingly available tool in the diagnosis, management, and in some cases, therapy of pancreatic cystic neoplasms. The ability to better describe/characterize pancreatic cystic neoplasms, in particular those lesions thought to be pre-malignant or frankly malignant, make the use of EUS, both with and without FNA, an attractive option in the cystic neoplastic work up. EUS criteria for mucinous/malignant neoplasms is still evolving, but include size greater than 2 cm, pancreatic duct dilation, the presence of wall calcifications, and perhaps most importantly the presence of a frank mass or mural nodule. Despite initial enthusiasm, however, numerous studies have demonstrated a wide range of diagnostic accuracy for EUS imaging alone ranging from 40%-96%. While many factors including study design, number of patients enrolled, goals of a particular study, and interobserver EUS agreement contribute to this discrepancy, it is important to note that a single, prospective study achieved a diagnostic accuracy of approximately 51%. Clearly, larger, prospective, multi-center studies are needed to better define the role of EUS in the diagnostic work up of a pancreatic cystic neoplasm.

EUS, in addition to its imaging capabilities outlined above, allows direct sampling of cystic contents and the cyst wall in an effort to better determine the type of cyst present. The performance of FNA does, however, remain limited to larger, tertiary centers with extensive experience in EUS. In addition, analysis of cystic fluid is often subject to local cytological and laboratory expertise, with a definite learning curve present for accurate analysis of cystic contents and in some cases, by a small volume of aspirate obtained at FNA.

Ideally, an aspirated pancreatic cystic neoplasm should be evaluated for both cytological diagnosis and for the presence of specific intracystic proteins such as amylase and carcinoembryonic antigen (CEA). The cytological evaluation includes specific testing for the presence of columnar epithelial cells which stain for mucin (MCNs, IPMNs), or cuboidal epithelial cells which stain for glycogen (SCAs). Several studies have appeared in the literature regarding the analysis of pancreatic cystic fluid. Several larger studies involving cystic fluid cytological analysis reflect a sensitivity of approximately 50%, a low but reproducible percentage, while a more recent study by Umpathy et al. revealed a cytological sensitivity of approximately 93% in the differentiation of mucinous and non-mucinous pancreatic neoplasms. The cytological analysis of cystic fluid continues to be an area of intense research.

Amylase level is routinely checked in the cyst fluid aspirate and may be of some diagnostic value. It is uniformly elevated in pseudocysts and IPMNs and frequently elevated in MCNs, but consistently low in SCAs. The analysis of specific intracystic, aspirated proteins continues to be an evolving process. Several proteins including CA19-9, CEA, CA-125, and CA72-4 have been studied. The best studied and currently used most often in routine practice is the level of CEA. The basic differentiation involving CEA level is between the lesions which are mucinous (usually, but not always elevated CEA levels) and those which are serous (low CEA levels). A low CEA level (i.e. < 5 ng/mL) has been shown in pooled data to have a sensitivity between 50%-100% and a specificity of 77%-95% to differentiate between mucinous and serous lesions. The CEA level required to best distinguish a mucinous from a serous lesion continues to be debated in the pancreatic literature, with CEA cutoff levels deemed diagnostically sensitive in the range 20 to 800. The wide range of reported CEA levels lends confusion to the analysis of cystic pancreatic fluid. It must be remembered, however, that by increasing the cutoff value of the CEA level considered diagnostic for mucinous lesions, the specificity of the test increases at the expense of decreased sensitivity. Currently, no standardized cutoff...
level for CEA exists, however, many centers, particularly in the US, use a CEA level of 192 ng/mL, as established by Brugge et al [49] as diagnostically sensitive (75%) and specific (84%). At present, aspirated cystic fluid should be evaluated for cytological and biochemical analysis. The biochemical tests which should be routinely ordered are CEA level and amylase. If insufficient fluid is available (e.g. small cyst or very viscous fluid), CEA level should be obtained first with cytology and amylase level ordered only if there is a sufficient amount of fluid left for analysis.

CONCLUSION

The evaluation of cystic lesions of the pancreas remains a process in evolution. Significant advances have been made in expanding our understanding of these lesions and in the refinement of our diagnostic approach. A comprehensive diagnostic strategy which incorporates data from patient history, lesion imaging, EUS, and cyst fluid analysis will provide an accurate diagnosis in most cases.

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