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Review Article

Role of endosonography in the management of incidental pancreatic cystic lesions

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A B S T R A C T

The management of incidental pancreatic cystic lesion (PCL) can be challenging. With a better understanding of the natural course of PCL, we recommend surveillance of PCL without high-risk stigmata for at least 5 years. The importance of interventional endoscopic ultrasound (EUS) in establishing a specific diagnosis and treatment cannot be over-emphasized. This review aims to give an overview on the latest developments in EUS-guided fine needle aspiration and EUS-guided pancreatic cyst ablation.

Keywords: Ablation, Endoscopic ultrasound, Pancreatic cyst

Introduction

Incidental pancreatic cysts are diagnosed with increasing frequency because of widespread utilization of cross-sectional imaging. With advances in imaging techniques, asymptomatic (incidental) pancreatic cystic lesions (PCL) can be detected with increased sensitivity. Two consecutive retrospective case series from the same tertiary surgical centers reflect this trend.[1,2] The initial case series reviewed 212 patients who were diagnosed with PCL (mean size = 33 mm) from 1997 to 2002, with 36% of them being incidentally detected. From 2004 to 2007, 401 patients were detected with PCL (mean size = 27 mm), with 71% of them asymptomatic.

Epidemiology and natural course

In the general population, the prevalence of pancreatic cyst is estimated to be 2.6%.[3] In the previous retrospective study, contrast-enhanced multidetector computed tomography (CT) scans of the abdomen were reviewed from 2832 consecutive examinations to identify pancreatic cysts. Patients with a history of pancreatic lesions, with predisposing factors for pancreatic disease, or who were referred for CT of the pancreas were excluded. Mean cyst size on detection was 8.9 mm (range 2–38 mm), and 85% of the cysts were solitary. Cyst occurrence was strongly correlated with increasing age and Asian ethnicity. Approximately 10% of patients older than 80 years were diagnosed with pancreatic cysts, whereas cyst presence was rare in patients younger than 40 years. No gender preponderance was observed.

With increasing data from clinical studies, we have a better understanding of the natural history of PCL. In an earlier retrospective cohort study, 112 patients who had PCL but who were not indicated for surgery were followed-up to assess malignant progression, growth of cysts, need for surgery, and mortality.[4] Exclusion criteria were evidence of pancreatitis or a history of von Hippel–Lindau disease, polycystic disease of the kidney or liver, or cystic fibrosis. During follow-up for the median period of 72.3 months, the size of the PCL increased in 18 patients (16.1%). Six of these patients experienced growth of their PCL after 5 years of follow-up. Twenty-six patients underwent surgery during follow-up, and four malignant cysts were detected. The overall rate of malignant progression during follow-up was 3.6%. The presence of mural nodules or solid components was independently associated with the presence of malignant PCL. The authors concluded that most PCL show favorable prognosis, but long-term surveillance for > 5 years was recommended. In another study, Lee et al investigated natural history of PCL with 182 patients who have incidental PCL. The mean follow-up period was 35.4 months. The results of this study showed that cyst size increased in 54 patients, did not change in 107, and decreased in 21 during follow-up period, and three cases were found to have developed a malignancy. The authors also recommended long-term regular follow-ups of PCL.[5]

A clear understanding of the long-term natural behavior of PCL is essential for investigators to establish a follow-up plan and to

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design clinical guidelines. Thus, accumulation of more long-term data is needed.

Diagnosis and investigations

Documentation of demographic data and detailed history taking are the first important steps for diagnosis. If the patient is male, mucinous cystic neoplasm (MCN) is less likely because it mainly occurs in women. If the patient is young and female, solid pseudopapillary neoplasm should be suspected. MCN tends to occur in middle-aged patients, serous cystadenoma (SCA) can occur in middle-aged to elderly people, and intraductal papillary mucinous neoplasm (IPMN) mostly occurs in the elderly. Pseudocysts are unlikely if there is no history of pancreatitis or trauma. Neuroendocrine tumor and SCA should be considered if there is a history of multiple endocrine neoplasia or von Hippel-Lindau syndrome.

Invasive carcinoma is uncommon in patients with an asymptomatic cyst of 1 cm.[6] Thus, follow-up without further investigation is generally acceptable.

For cysts $>$ 1 cm or for symptomatic cysts, further evaluation with gadolinium-enhanced magnetic resonance imaging (MRI) plus MR cholangiopancreatography or pancreatic protocol multidetector CT is recommended. MRI is the imaging procedure of choice for evaluating a pancreatic cyst due to its better visualization of pancreatic ductal communication (sensitivity 91–100%, specificity 90%), cyst septation, and solid component.[7]

CT and MRI are valuable tools to detect pancreatic cysts. However, the accuracy of MRI and CT to make a specific diagnosis is suboptimal, with reports of 39–50% and 40–44% respectively.[8,9] In predicting benign or malignant disease, CT has a sensitivity and specificity of 36–71% and 64–100%, respectively, whereas MRI has a sensitivity and specificity of 65–77% and 58–89%, respectively.

Studies on 18-fluorodeoxyglucose positron emission tomography (PET) scan studies have produced varying results. Three studies investigated the ability of PET-CT to differentiate between benign and malignant lesions.[10–12] Definitive histology was available in all patients. The reported sensitivity and specificity ranged from 57–94% and 65–97%, respectively. A recent study comparing PET-CT with CT to predict malignancy showed a sensitivity and specificity of 100% and 87% respectively.[13] Further evaluation of PET-CT in multicenter controlled trials is warranted.

Role of endoscopic ultrasonography in diagnosis and risk stratification

Endoscopic ultrasonography (EUS) has become an important tool in the diagnosis and risk stratification of pancreatic cysts. It can accurately visualize the cyst morphology, assess vascular pattern by contrast harmonic scan, and perform fine-needle aspiration (FNA) for evaluation of cytology and molecular markers.

Morphology

Many PCL have typical features. In order to make a presumptive diagnosis by EUS examination, cyst size, number, and shape, state of cyst wall, internal cyst features, presence of calcification or scarring, communication with pancreatic duct, presence of mural nodules, and lymphadenopathy should be carefully inspected (Fig. 1 and 2). However, a number of studies showed low accuracy of EUS alone to determine benign versus malignant disease.[14] In addition, interobserver agreement among endosonographers to morphologically differentiate between mucinous and non-mucinous cysts was shown to be only fair ($\kappa = 0.24$).[15] Thus, EUS alone does not appear to be very reliable to establish a specific diagnosis or to differentiate between benign and malignant disease (Table 1).[16]

EUS-FNA with cyst fluid cytology

Cystic fluid aspirate is acellular or with minimal cellularity in up to 72% of aspirated cysts.[17] Analysis of cystic fluid aspirate can be used to differentiate mucinous from nonmucinous cysts with a sensitivity, specificity, and accuracy of 12.5–27%, 90–100%, and 55%, respectively.[18,19] In another report, cytology was shown to have an accuracy of 50% in differentiating benign from malignant disease.[20] Aspiration may be difficult in SCA because of its microcystic structure. However, the presence of glycogen-rich cells is highly specific to SCA.[21]

Cystic fluid analysis and molecular markers

Carcinoembryonic antigen (CEA) in cyst fluid is one of the most studied tumor markers. It is a useful marker to predict the presence of mucinous cysts but not of malignancy.[21] However, the reported cut-off values vary. In a large prospective study in 2004, the utility of CEA, CA19-9, CA72-4, CA15-3, and CA125 to differentiate mucinous and nonmucinous cysts was evaluated in 341 patients who underwent EUS-FNA of pancreatic cysts.[22] That study suggested that an intracystic CEA level of $\geq$ 192 ng/mL could predict the presence of mucinous cysts with a diagnostic accuracy of 79%, which was superior to either EUS morphology alone (51%) or cytology (59%). However, with this cut-off, about one-fifth of the cases with genuine mucinous cysts would be missed as false negatives. Another study performed a pooled analysis of 12 trials and demonstrated that when CEA levels were $\geq$ 800 ng/mL, the specificity for differentiating mucinous cysts was 98%, whereas the sensitivity dropped to 48%.[23] By contrast, a CEA level $\leq$ 6 ng/mL has been shown to be highly specific for serous/non-mucinous cysts. Hence, we can only conclusively determine the nature of the cysts when the intracystic fluid CEA is $\leq$ 6 ng/mL or $\geq$ 800 ng/mL.

As an enzymatic marker, cyst fluid amylase is useful in the differentiation of pseudocysts from cystic neoplasm. An amylase level $<$ 250 U/L essentially excludes pseudocysts. Another enzymatic marker, serine peptidase inhibitor Kazal type 1 (SPINK1), is a polypeptide synthesized by several types of tumors and cell lines.[24] A previous study evaluated cyst fluid SPINK1 levels in resected pancreatic cystic lesions and found that the levels were significantly higher in main-duct/mixed type IPMN and MCN patients, than in SCN and branch-duct (BD) IPMN patients.[25] Furthermore, SPINK1 may be a predictive marker of the need for surgery in PCL.

Identification of genetic mutations may represent the next frontier for research. The oncogene *GNAS* was recently detected in IPMN tissue as well as in duodenal juice.[26] Some reports have suggested that *GNAS* mutations are prevalent in IPMN, especially in the intestinal form and in invasive IPMN.[27] K-*ras*, *p*16, and *p*53 mutations have also been reported to be associated with progression of pancreatic cysts from nondysplastic to dysplastic cysts.[28]

Treatment strategy

Surgery

Surgery remains the mainstay treatment for pancreatic cystic neoplasms, either to relieve symptoms in nonmucinous benign disease, or to prevent or eliminate malignant neoplasms.

Early resection of premalignant lesions is associated with survival benefit. For example, the prognosis of a resected benign IPMN is excellent with a 10-year survival rate of $>$ 95% or both main-duct