The use of EUS to diagnose cystic neoplasms of the pancreas

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OBJECTIVES

1. Appreciate the morphologic differences between microcystic (serous) and macrocystic (mucinous) cystic lesions.
2. Learn the origin and significance of cyst-fluid carcinoembryonic antigen and DNA mutations.
3. Critically examine the risk of malignancy in side-branch intraductal papillary mucinous neoplasms.

Pancreatic cystic lesions consist of inflammatory pseudocysts and neoplastic lesions. Mucinous cystic lesions pose a risk of malignant degeneration. Although the natural history has not been well defined, it is likely that malignant change in the epithelium takes place over years. The traditional therapy of mucinous cystic lesions has been surgical resection. Lesions in the head of the pancreas will require a Whipple resection, whereas tail lesions are managed with a distal pancreatectomy and splenectomy. In patients at high risk for surgical resection, the risk-benefit ratio may be excessively high, not supporting the use of resection therapy. Ethanol ablation therapy has been thoroughly studied in hepatic, renal, and thyroid cysts. Epithelial ablation with ethanol appears to be highly effective and relatively safe. Recently, ethanol ablation was evaluated in pancreatic-cystic neoplasms. In macrocystic lesions, between 1 to 5 cm, ethanol lavage will result in epithelial ablation and cyst resolution in about 30% of patients. Pancreatitis is rarely observed clinically and is not present in resection specimens. Low-risk intraductal papillary mucinous neoplasm lesions can be monitored with imaging and periodic FNA.

INTRODUCTION

Cystic lesions of the pancreas belong to a group of benign, premalignant, and malignant neoplasms (Table 1).[1] In the past, cystic neoplasms of the pancreas were thought to be relatively rare, but the widespread use of CT has dramatically increased the frequency of diagnosis.[2] Although most lesions are incidentally discovered, invasive lesions may come to medical attention because of jaundice, pancreatitis, or abdominal pain.[3] Cystic neoplasms are often confused or misdiagnosed as pseudocysts, collections of inflammatory fluid that mimic true cystic lesions. Furthermore, the presenting symptoms of pseudocysts may be identical to the symptoms associated with cystic neoplasms.

The classification of cystic neoplasms is based on the type of epithelium, mucinous or nonmucinous. There are 3 types of mucinous lesions: benign mucinous cystadenomas, malignant mucinous cystic lesions, and intraductal papillary mucinous neoplasms (IPMN). The nonmucinous lesions include serous cystadenomas, cystic endocrine tumors, and other rare lesions. There is a significant difference in the natural history and survival in mucinous and nonmucinous lesions.[4]

PREVALENCE

The frequency of pancreatic-cystic lesions has been determined by autopsies in elderly patients. In a series of 1374 autopsy cases, small cystic dilated lesions were found in 378 pancreata.[5] The prevalence of asymptomatic ductal neoplasia was directly related to the age of the patient. The cysts discovered at autopsy were scattered throughout the pancreatic parenchyma and were not related to chronic pancreatitis. The epithelium of the early cystic lesions displayed a full spectrum of neoplastic change, including atypical hyperplasia (16.4%) and carcinoma in situ (3.4%). Pancreatic cancer incidentally found during autopsy studies is also associated with cystic lesions of the pancreas.[6]

The prevalence of pancreatic cysts in the United States has been estimated in patients undergoing magnetic resonance imaging (MRI) for nonpancreatic diseases.[7] Nearly 20% of 1444 patients had at least 1 pancreatic cyst. Older patients are more likely to have a cyst than are younger patients. Incidental cysts in adult Americans without known pancreatic disease are seen in 0.7% of the population.[2]

PATHOGENESIS

The pathogenesis of cystic neoplasms of the pancreas is not well described. Serous cystadenomas are strongly associated with mutations of the von Hippel Lindau (VHL) gene.[8] The VHL gene product is a tumor-suppressor gene, and its mutation is associated with serous cystadenoma and neuroendocrine tumors of the pancreas. In 1 study, 70% of the sporadic serous cystadenomas studied demonstrated a mutation in the VHL gene, which probably results in hamartomatous proliferation of these centroacinar cells.[9] The vascular proliferation observed in

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TABLE 1. Characteristics of cystic neoplasms of the pancreas

	Location	Cytology	Viscosity	Cyst fluid CEA, ng/mL	Cyst fluid amylase level
Serous	Evenly distributed	Bland PAS +	Low	<0.5	Low
Mucinous	Tail	Mucinous	Increased	>200	Low
IPMN	Head	Mucinous	High	>200	High
Pseudocyst	Evenly distributed	Pigmented histiocytes	Low	<200	High

serous cystadenomas is probably similar to that observed in the related renal-cell carcinoma.[10]

The pathogenesis of mucinous cystic neoplasms (MCN) and IPMNs is most likely very different compared with serous cystadenomas. K-ras mutations are present only in MCNs but not in serous microcystic adenomas. MCNs frequently contain mutations of the K-ras oncogene and p53 tumor suppressor gene, and the frequency of these mutations increases with increasing degrees of dysplasia in the neoplasm.[11] The frequency of K-ras mutation in MCNs is linearly related to the grades of atypia.[12] Hypermethylation of the p16 tumor suppressor gene is thought to be an important genetic marker of malignant transformation.[13]

PATHOLOGY

The cellular origin of serous cystadenomas is thought to be the centroacinar cell. Microcystic serous cystadenomas are composed of multiple, small, thin-walled cysts, with a sponge-like appearance that simulate pancreatic malignancy. The most characteristic feature is the presence of vascular proliferation in and surrounding the mass. Macrocystic serous cystadenomas are composed of far fewer cysts, and the diameter of each cyst varies from microcystic to large cavities. The presence of discrete, large, cystic cavities mimics the morphology of mucinous lesions. However, the cyst fluid from serous cystadenomas is nonmucoid and may contain hemosiderin macrophages as a result of the vascular nature of the lesions.[14]

MCNs are discrete cystic lesions lined by a mucinous epithelium and surrounded by an ovarian stroma. The World Health Organization classification catalogs MCNs into 3 types based on the degree of epithelial dysplasia: benign, borderline, and malignant. The degree of atypia of the tumor is classified according to the most advanced degree of carcinoma present. Surrounding the epithelium of MCNs is a unique ovarian stroma that contains estrogen and progesterone receptors. Many authorities have restricted the very definition of MCNs to include only those cystic mucinous tumors that contain ovarian stroma. The cyst fluid from MCNs is highly viscous, probably as a result of the high DNA and glycoprotein content.

IPMNs are mucinous cystic lesions lined by a papillary epithelium. The presence of a papillary neoplasm and secreted mucin causes the pancreatic duct to dilate. Mucin production may be so excessive that mucin will be spontaneously extruded from the ampulla. The degree of dysplasia exhibited by the epithelium may range from mild to moderate to severe (carcinoma in situ), and the foci of early malignancy may be evident by the presence of mural nodules.[15] The solid malignancies that arise from IPMN are more likely to have papillary features compared with typical pancreatic malignancies that arise from the main pancreatic duct.

IMAGING OF CYSTIC LESIONS

CT is an excellent test for cystic lesions of the pancreas because of its widespread availability and ability to detect cysts.[16] MRI is increasingly used because of its ability to determine whether there is involvement of the main pancreatic duct. Both imaging modalities offer diagnostic strengths.

CT is often the initial modality with which a cystic lesion is suspected or diagnosed, although clinical and imaging findings of chronic pancreatitis may obscure the correct diagnosis. The most common findings are a diffusely dilated pancreatic duct, cystic lesions, and parenchymal changes. The finding of a solitary septated cystic lesion in the tail of the pancreas is highly diagnostic of a MCN. A grape-like cluster of involved side-branch ducts is the most common finding and represents IPMN. Thin-section contrast-enhanced CT and multiplanar reconstruction may reveal communications between cystic dilated segments and the main pancreatic ducts, common findings of IPMN. Septa and excrescent nodules seen along the dilated duct have been described as features of the main pancreatic duct type in IPMN. CT is relatively poor in the diagnosis of malignant transformation. The most specific signs of malignancy with CT are a solid mass, main pancreatic duct dilatation more than 10 mm, diffuse or multifocal involvement, and attenuating or calcified intraluminal content. Serial CT imaging is often used to detect the recurrence of IPMT after resection.

MRI AND MRCP

T2-weighted MRCP images provide a detailed set of images of the main pancreatic duct and associated cystic