Premalignant Cystic Neoplasms of the Pancreas

Vikas Dudeja and Peter J. Allen

Due to increasing utilization of cross-sectional imaging, asymptomatic pancreatic cysts are frequently being diagnosed. Many of these cysts have premalignant potential and offer a unique opportunity for cancer prevention. Mucinous cystic neoplasm and intraductal papillary mucinous neoplasm are the major premalignant cystic neoplasms of pancreas. The prediction of the risk of malignancy (incidental and future risk of malignant transformation) and balancing the risks of watchful waiting with that of operative management with associated mortality and morbidity is the key to the management of these lesions. We review the literature that has contributed to the development of our approach to the management of these cystic neoplasms. We provide an overview of the key features used in diagnosis and in predicting malignancy. Particular attention is given to the natural history and management decision making.
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The diagnosis and management of cystic lesions of the pancreas are two of the most controversial and rapidly evolving areas in the field of pancreatology, if not surgery. Clinicians taking care of patients with pancreatic cysts are faced with a unique management challenge, and must balance the morbidity and mortality of pancreatic resection with the risk of missing a malignancy if the cyst is managed non-operatively. Uncertain natural history and malignant potential of some cystic lesions can pose additional dilemmas, especially in young patients. The fact that the preoperative ability to determine the histologic subtype of these lesions is far from perfect further compounds the problem.

Pancreatic cysts are being diagnosed with increasing frequency due to the widespread use of cross-sectional imaging. Studies evaluating computed tomography examinations have reported cystic lesions of the pancreas in 2.6% of the patients examined.[1] Similarly, studies evaluating magnetic resonance imaging suggest that 2.4% of patients[2] may have incidental cystic lesions of the pancreas. These lesions may represent benign, premalignant, or invasive entities, with recent studies suggesting that the majority likely represent the precancerous entity known as intraductal papillary mucinous neoplasms of the pancreas.[3] The current review will focus only on the cystic neoplasms with malignant potential, and will only mention the non-neoplastic and neoplastic cystic entities as a means to differentiate them from the former.

CLASSIFICATION OF PANCREATIC CYSTS

Pancreatic cysts can be classified into inflammatory and neoplastic subtypes. Historically, the majority of all pancreatic cysts were thought to represent non-neoplastic inflammatory pseudocysts that develop as a complication of acute pancreatitis. The primary histologic feature distinguishing pancreatic pseudocysts from other neoplastic cysts is the absence of an epithelial lining. Though reports differ in the overall contribution of pseudocysts to the total incidence of pancreatic cysts, it can be safely assumed that over 50% of pancreatic cysts represent pseudocysts.[4] Given their association with acute pancreatitis, pseudocysts are further enriched in symptomatic patients.

Cystic neoplasms, which are said to represent 10%–15% of cystic lesions of the pancreas, are a heterogeneous group of neoplasms that span the neoplastic spectrum from benign to malignant. Kloppel has described 15 different histologic lesions that can present as a cystic lesion of the pancreas.[4] Although multiple entities like lymphoma, islet cell tumors, teratoma, and vascular tumors can present as pancreatic cysts, the most commonly encountered cystic neoplasms include serous cystadenoma

Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY.
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Address correspondence to Peter J Allen, MD, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021. E-mail: allenp@mskcc.org
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(SCA), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasms (MCN, either cystadenoma or cystadenocarcinoma). In a study by the French Surgical Association of 372 resected cystic neoplasms of the pancreas these three histologic entities (SCA, IPMN, MCN) represented 87% of all resected cystic lesions of the pancreas.[5]

Overall cysts can be classified as mucinous or non-mucinous based on the type of fluid they produce. This classification is of clinical significance as the cyst contents can predict biology. Mucinous lesions have potential for malignant progression and/or may harbor a malignancy at the time of diagnosis. The non-mucinous lesions (if not cystic degenerations of other solid lesions like pancreatic neuroendocrine tumor and solid pseudopapillary tumor) primarily have no malignant potential. This review will focus only on premalignant cystic neoplasms, ie, IPMN and MCN. We will first discuss the epidemiology, pathogenesis, and natural history of these cystic neoplasms separately and then discuss the diagnostic approach together, thus outlining the approach to a patient with a cystic lesion of the pancreas.

MUCINOUS CYSTIC NEOPLASM

The true prevalence of mucinous cystic neoplasm is difficult to predict but in surgical series they constitute up to 23% of all resected cystic neoplasms of the pancreas.[6] MCN present almost exclusively in females,[7,8] are almost always solitary, and more than 90% are located in the body and tail of the pancreas. Lesions may be asymptomatic or may present with abdominal symptoms, including discomfort, nausea, and dyspepsia. Thus the typical demographic and clinical profile of a female in her 40s–50s with a solitary cyst in the body or tail of the pancreas suggests the diagnosis of MCN. This contrasts with IPMN, which may present in males, is often identified in the elderly, is often multi-focal, and often disease is identified in the head of the pancreas.

Pathology

Macroscopically, MCN are thick-walled unilocular or multilocular cysts containing mucinous material (Figure 1A). Lack of communication with the pancreatic ductal system distinguishes them from IPMN and thus amylase within the cyst fluid should be low. Microscopically, the cysts are lined by a mucin-secreting, columnar epithelium (Figure 1B). The epithelial lining of the cyst may exhibit variable degrees of atypia, the extent of which is used to classify these lesions into (1) mucinous cystadenoma, (2) mucinous cystic tumor (borderline), and (3) mucinous cystadenocarcinoma. Underlying the epithelium is the pathognomonic densely cellular ovarian type stroma (Figure 1B). The ovarian type stroma of MCN shares many of the histological characteristics with the stroma of mucinous tumors of the ovary and can help distinguish MCN from branch duct IPMN, as the MCN tissue will stain variably for estrogen receptor/progesterone receptor and human chorionic gonadotrophin.[9] Even when MCN occurs in a male patient, or postmenopausal patient, ovarian-type stroma is present and is generally considered essential for the diagnosis of MCN.[7]

Genetics

The pathogenesis of MCN with respect to the underlying molecular pathways is not well understood. *Kras* mutations have been detected in benign, borderline and malignant MCN with frequency increasing with increasing dysplasia.[10] However, *p53* mutations are only detected in the presence of severe dysplasia or cancer.[10] Similarly, loss of *DPC4* in MCN with invasive but not with its benign component suggests a potential role of *DPC4* in malignant progression.[11] In fact, expression of *Kras* G12D mutation along with haploinsufficiency of *SMAD4/Dpc4* in mouse models lead to formation of MCNs with typical progression to invasive ductal adenocarcinoma.[12]

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM

IPMN are epithelial tumors that arise from the main pancreatic duct or the branch ducts causing ductal dilatation from mucin production. It is a recently described entity and was first classified into a unified diagnosis by the World Health Organization in 1996.[13] Prior to 1996, IPMN were described under a variety of names, including mucinous ductal ectasia, papillary carcinoma, and villous adenoma. This 1996 classification is important, as surgical and pathologic series describing mucinous neoplasms from the 1980s and early 1990s may misclassify branch duct IPMN as MCN. In recent surgical series up to 36% of all resected cystic lesions of the pancreas are IPMN.[3] Because of the increasing use of high-quality cross-sectional imaging, the identification of asymptomatic cystic lesions of the pancreas has increased and a significant percentage of patients with incidentally discovered cysts will have IPMN.[14]

IPMN originates from the cells of the pancreatic ductal system and may grossly or microscopically involve the pancreatic ducts in a diffuse or multifocal fashion. Most clinicians and investigators now believe that IPMN represents a field defect.[15] With respect to dysplasia, IPMN encompasses a spectrum of precursor lesions, from adenoma to intraductal

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