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TOPIC HIGHLIGHT

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Diagnosis and management of relapsing pancreatitis associated with cystic neoplasms of the pancreas

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Abstract

One of the most important causes of relapsing pancreatitis is a cystic neoplasm of the pancreas. These low grade malignancies may cause pancreatitis by obstructing or communicating with a pancreatic duct. Patients with relapsing pancreatitis and a focal fluid fluid collection should be investigated for the possibility of a mucinous cystic neoplasm. Cross sectional imaging can provide a diagnosis with the imaging findings of a low attenuation cystic lesion containing mural calcification (CT scanning) or a lobular T2 enhancing lesion (MRCP). Endoscopic ultrasound can provide more detailed imaging with the ability to guide fine needle aspiration of the cyst fluid. Cyst fluid analysis can provide a diagnosis of a mucinous cystic lesion with the combination of cytology (mucinous epithelium), elevated carcinoembryonic antigen (CEA), and the presence of DNA mutations. Management of these patients consists of surgical resection and monitoring in patients not able to withstand surgery.

Key words: Pancreatitis; Relapsing pancreatitis; Endoscopic ultrasound; Cystic neoplasms; Intraductal papillary mucinous neoplasms; Fine needle aspiration

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INTRODUCTION

Acute and chronic relapsing pancreatitis may be caused by a number of structural abnormalities of the pancreas. Of the malignant and pre-malignant lesions of the pancreas associated with pancreatitis, cystic and intraductal tumors are the most common. Patients with these lesions may experience pancreatitis at the time of diagnosis or suffer from relapsing pancreatitis throughout their medical illness. Approximately 9% of patients with recurrent pancreatitis will have an associated pancreatic malignancy[1]. The most likely cause of malignancy-associated pancreatitis is ductal obstruction. Since intraductal papillary mucinous tumors commonly involve the main pancreatic duct and its side branches, recurrent pancreatitis is particularly common in these patients[2].

CLINICAL PRESENTATION

Patients with relapsing pancreatitis present with discrete episodes of abdominal pain often accompanied by nausea and vomiting[3]. After the initial clinical evaluation with laboratory testing, cross sectional imaging is obtained in order to confirm the diagnosis and to determine the extent and severity of the pancreatic inflammation.

The most common abnormality encountered on cross sectional imaging in patients with relapsing pancreatitis is a cystic lesion or a focal fluid collection[4]. In this context, the chief differential is a pseudocyst versus a cystadenoma of the pancreas[5]. Pseudocysts represent a focal collection of inflammatory fluid, leaking from the pancreas. Pseudocysts may persist after resolution of pancreatic necrosis, and the presence of a ductal stricture may contribute to persistence[6]. In contrast, a cystadenoma of the pancreas represents a benign, pre-malignant, or malignant cyst and may also be responsible for the episode of pancreatitis[7]. It is often difficult to determine if a focal fluid lesion is responsible for the episode of pancreatitis or is a consequence of the pancreatitis (pseudocyst). In general, focal fluid collections that are surrounded by a well-defined, thin-walled rim of tissue are more likely to be a form of malignancy, in contrast to thick-walled pseudocysts containing inflammatory debris.

Clinically, there are few clues to differentiate between focal inflammatory fluid collections and cystic neoplasms. However, the findings of jaundice and the recent onset of diabetes should raise the possibility of occult malignancy[8]. Pseudocysts may become apparent with complications

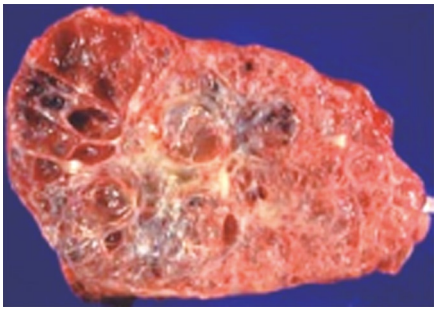

Figure 1 Gross surgical pathology specimen of a serous cystadenoma. Note the presence of a honeycomb appearance of the lesion.

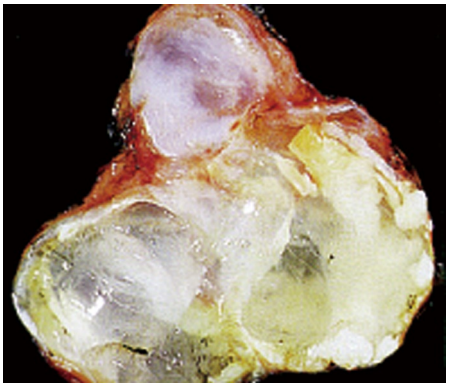

Figure 2 Gross surgical pathology specimen of a mucinous cystadenoma. The cyst cavities are filled with a clear viscous fluid.

such as hemorrhage or infection. In general, small cystic lesions are rarely responsible for chronic abdominal symptoms.

PATHOGENESIS

The pathogenesis of cystic neoplasms of the pancreas is based on mutations in the epithelial cells lining the pancreatic duct[9]. Serous cystadenomas are strongly associated with mutations of the Von Hippel Lindau (VHL) gene. The VHL gene is likely to play an important role in the pathogenesis of sporadic serous cystadenomas. In one 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[10].

The pathogenesis of mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN) involves a separate set of mutations. K-ras mutations are present only in mucinous cystic neoplasms and not in serous microcystic adenomas. The frequency of K-ras mutation in mucinous cystic neoplasms is linearly related to the grades of atypia and the imposition of other mutations is thought be important in the pathogenesis of malignancy. The detection of mutations in tumor suppressor genes is the basis of a newly developed cyst fluid diagnostic test[11].

PATHOLOGY

Serous cystadenomas are benign, solitary, cystic tumors that arise from centro-acinar cells (Figure 1). Microcystic serous cystadenomas are composed of multiple small thin-walled cysts with a honeycomb-like appearance on cross section[12]. The most characteristic finding is a central fibrotic or calcified scar. Macrocystic serous cystadenomas are composed of far fewer cysts, and the diameter of each cyst varies from microcystic to large cavities[13]. The presence of discrete, large cystic cavities mimics the appearance of mucinous lesions. However, the cyst fluid from serous cystadenomas is non-viscous, contains low concentrations of tumor markers and may contain blood as a result of the vascular nature of the lesions[14].

Mucinous cystic neoplasms (MCNs) are composed of discrete individual cystic compartments that vary in diameter. The epithelium lining MCNs is a mucinous columnar epithelium (Figure 2). The World Health Organization classification catalogues MCNs into three types, based on the degree of epithelial dysplasia: benign, borderline, and malignant[15]. The degree of atypia of the tumor is classified according to the most advanced degree of dysplasia/carcinoma present.

Beneath the lining of MCNs lies a band of ovarian tissue. Many authorities have restricted the very definition of MCNs to include only those cystic mucinous tumors that contain ovarian stroma[2]. The role of the ovarian tissue in the pathogenesis is not known. However, when this definition is used, MCN's are rarely found in males.

IPMNs are similar to MCNs in that they are cystic tumors that secrete mucin into the cystic cavities. However, IPMNs are characterized by a unique papillary epithelium and arise from the ductal epithelium. The presence of a papillary neoplasm infiltrating the ductal lining causes the pancreatic duct to dilate. The presence of the tumor itself is a cause of duct dilation, as well as the obstruction induced by the papillary fronds and mucus globules. Mucin production may be so excessive that mucin may be spontaneously extruded through the pancreatic sphincter and out of 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[16]. The solid malignancies that arise from IPMN are more likely to have papillary features, as compared to typical pancreatic malignancies that arise from the main pancreatic duct.

CLINICAL PRESENTATIONS

Most patients with a pancreatic cystic lesion have non-specific symptoms[22]. The cystic lesion is usually found with CT or US imaging performed for the evaluation of another condition. When symptoms are present, the most common presentation is recurrent abdominal pain, nausea, and vomiting as result of mild pancreatitis[17]. Cystic lesions that cause duct compression or involvement of the main pancreatic duct are prone to cause pancreatitis. Chronic abdominal pain and jaundice are a rare presentation of a cystic lesion and suggests a malignancy or a pseudocyst. Patients with a cystic malignancy will present with symptoms and signs similar to pancreatic cancer, i.e. pain, weight loss, and jaundice[18]. Pseudocysts may arise after an

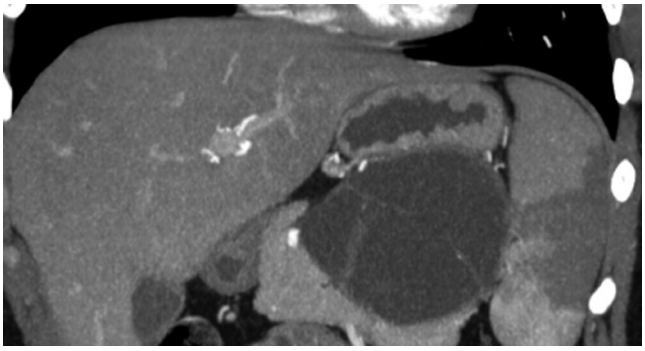

Figure 3 Reformatted CT demonstrating a mucinous cystic neoplasm indenting the stomach. Note the presence of septations.

episode of acute pancreatitis or insidiously in the setting of chronic pancreatitis and are associated with chronic abdominal pain. It is common for cystic lesions associated with pancreatitis to be diagnosed as pseudocysts and be confused with cystic neoplasms that also cause pancreatitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a cystic lesion of pancreas is very wide and often causes confusion. Since the treatment of a pseudocyst and cystic neoplasm are so different, it is incumbent on the clinician to first differentiate between these major categories of lesions. Although it is unusual for a patient with a pseudocyst to present without preceding symptoms, it may occur in mild chronic pancreatitis. Evidence of inflammatory changes or calcifications in the pancreas is suggestive of a pancreatic pseudocyst. However, in the initial setting of mild pancreatitis it may be difficult to differentiate between a cystic neoplasm that has caused pancreatitis and a small pseudocyst that has formed as a result of pancreatitis. If a cystic lesion has been present for many years, it is highly likely that the lesion represents a cystic neoplasm. Congenital cysts of the pancreas are rare[19].

DIAGNOSIS WITH CROSS SECTIONAL IMAGING

CT is an excellent test for cystic lesions of the pancreas because of its widespread availability and ability to detect cysts[4]. MR imaging is used increasingly because of its ability to determine if there is involvement of the main pancreatic duct[20]. 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 finings 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 mucinous cystic neoplasm (Figure 3). A grapelike 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 IPMT. 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 greater than 10 mm, diffuse or multifocal involvement, and attenuating or calcified intraluminal content[21]. Serial CT imaging is often used to detect recurrence of IPMT after resection[22].

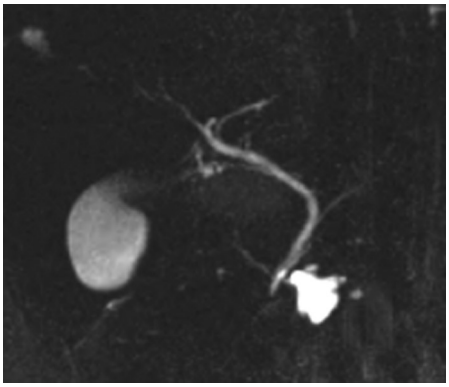

Figure 4 MRCP of side branch IPMN.

MR AND MR CHOLANGIOPANCREATOGRAPHY (MRCP)

T2-weighted MRCP images provide a detailed set of images of the main pancreatic duct and associated cystic lesions. A diffusely dilated main pancreatic duct containing mucinous filling defects is highly diagnostic of main duct IPMN. Side branch IPMN lesions appear as grape-like clusters associated with the pancreatic ductal system (Figure 4). The diagnostic accuracy using MRCP is 80% for the main duct-type and 100% for branch duct type tumors. Because of increased spatial and contrast resolution, increased sensitivity of fluid and mucin on MRCP as well as the increased sensitivity of MRI to gadolinium, the internal architecture of IPMT should be better defined with MRI and MRCP when compared to ERCP. MRCP is more sensitive than endoscopic retrograde cholangio-pancreatography (ERCP) in detecting mural nodules and wall thickening, which are of decreased signal on heavily T2 weighted MRCP sequences and are associated with malignancy.

MR imaging can reveal the full extent of ductal involvement, particularly when obstructing mucus prevents diagnostic opacification of the entire duct and is much less invasive than ERCP. MRCP findings suggestive of malignancy include: (1) filling defects/mural nodules (64% of tumors with mural nodules show invasion), (2) diffuse main pancreatic duct dilatation greater than 15 mm in main duct type. In contrast to ERCP, MRCP images the extraductal structures, and therefore is more accurate in preoperative assessment of disease. The sensitivity in the diagnosis of IPMN was highest by MRCP (88%), followed by endoscopic retrograde cholangiopancreatography (ERCP) (68%), and computed tomography scan (CT scan) (42%) and sonography (10%)[23]. Other reports

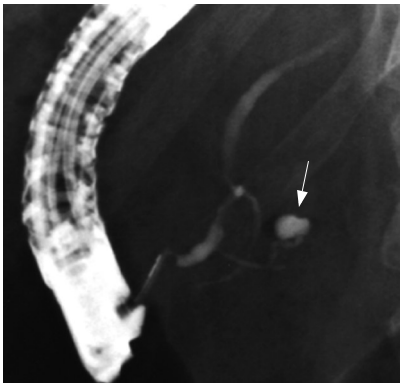

Figure 5 Pancreatogram during ERCP demonstrating a small side branch IPMN.

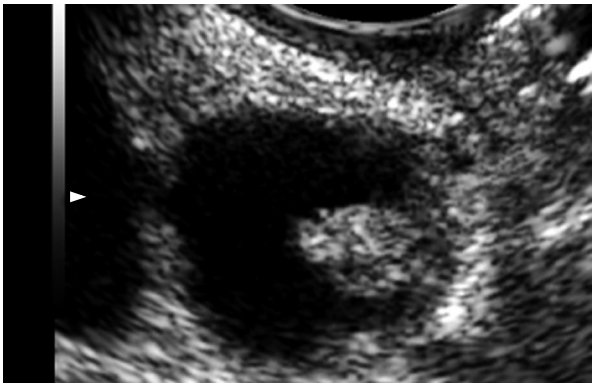

Figure 6 Linear EUS Imaging of a mucinous cystic neoplasm containing a mural nodule.

have suggested that preoperative assessment of extent using pancreatoscopy and MRCP may reduce the rate of operative positive margins and decrease postoperative recurrence. As MRCP can be performed quite rapidly without instrumentation and avoids the complications associated with ERCP, some have suggested that MRCP is superior to ERCP because it can consistently demonstrate the extent and internal architecture.

Although seen in less than 20 percent of lesions, demonstration of a central area of fibrosis by CT or MR is a highly diagnostic feature of a serous cystadenoma. The honey-combed or microcystic appearance of the lesion is commonly used to provide a diagnosis. Mucinous cystic neoplasms, in contrast, are commonly diagnosed with CT based on the unilocular or macrocystic characteristics. Although not frequently seen, the finding of peripheral calcification of the wall is specific for a mucinous cystic neoplasm. Intraductal papillary mucinous neoplasms (IPMN) may involve the main pancreatic duct exclusively, a side-branch or both. MRCP can demonstrate the diagnostic findings of pancreatic duct dilation, mural nodules, and ductal connection better than ERCP.

Despite these imaging features, the ability to accurately diagnose a specific cystic lesion and to determine whether malignancy is present by CT and MR remains uncertain. The diagnosis of a pancreatic pseudocyst is more dependent upon the clinical history and the associated findings of chronic pancreatitis. Pancreatic pseudocysts appear as unilocular fluid-filled cavities associated with parenchymal changes such as calcifications and atrophy.

THE ROLE OF ENDOSCOPY

An endoscopic evaluation may be obtained when cross sectional imaging has detected a cystic lesion, but no diagnostic features are apparent[24]. In selected patients, endoscopy is used to provide the cause of recurrent pancreatitis[3]. ERCP and EUS are powerful tools in the diagnosis of cystic and intraductal neoplasms. ERCP excels at the detection of main duct IPMNs and can provide cytologic material from strictures, nodules, or intraductal masses (Figure 5). Side branch IPMN lesions appear as fluid-filled dilated ductal branches filled with mucin (Figure 6). The finding of a focal pancreatic duct stricture in the setting of a cystic lesion is highly suggestive of a malignant process[25].

Pancreatography and pancreatoscopy are very sensitive techniques for the diagnosis of IPMNs[26]. The diagnostic features of IPMN include frond-like epithelial protuberances that are active in the secretion of intraductal mucin[26]. During ERCP, diagnostic tissue can be obtained from the ductal epithelium and analyzed using cytology as well as molecular markers[27]. Intraductal pancreatoscopy can be supplemented with the use of intraductal ultrasound to detect early malignancies arising from IPMN lesions[28]. 88% of fish-egg- like villous masses protruding more than 4 mm were found to be malignant.

The disadvantages of ERCP for the evaluation of patients with relapsing pancreatitis and suspected cystic neoplasm include the risk pancreatitis, poor quality of epithelial samples, and the technical difficulties of placement of a small probe through the pancreatic duct and sphincter. Many of the challenges will be overcome in the near future when small diameter high resolution digital probes are released for use.

ROLE OF EUS

EUS is often performed in the evaluation of relapsing pancreatitis when cross sectional imaging has not provided a definitive diagnosis. In nearly 60% of patients, EUS can provide a cause of recurrent pancreatitis[29]. The most common EUS finding in patients with recurrent pancreatitis is parenchymal changes suggestive of chronic pancreatitis[30]. EUS findings were similar in those with a single episode of idiopathic pancreatitis *vs* those with recurrent episodes. There is now some evidence in the literature suggesting that these early changes detected by EUS correlate with the histological changes of chronic pancreatitis and may predict progression to more advanced disease[31]. The EUS diagnosis of chronic pancreatitis relies on quantitative parenchymal and ductal criteria. It is generally accepted that, in the absence of any criteria, chronic pancreatitis is unlikely, whereas in the presence of 5 or more criteria (out of 9-11) chronic pancreatitis is likely. Diffuse changes may also represent autoimmune pancreatitis[32].

IPMN of the pancreas is the most common malignancy associated with recurrent pancreatitis[33]. Although there is considerable overlap between the parenchymal features of IPMN and chronic pancreatitis, EUS is fairly reliable in

Table 1 Characteristics of cystic neoplasms

	Morphology	Location	Ductal communication	Associated with pancreatitis	Cyst fluid CEA (pg/mL)
Serous	Microcystic	Evenly distributed	No	Rare	< 0.5
MCN	Macrocystic	Tail	Rare	Occasionally	> 200
IPMT	Mixed	Head	Yes	Yes	> 200
Pseudocyst	Unilocular	Evenly distributed	Yes	Yes	< 200

differentiating between IPMN and CP[33]. When compared with patients with chronic pancreatitis, the EUS features of dilation of pancreatic duct, cysts, and pancreatic atrophy were the most common findings of IPMN. The majority of IPMNs at the time of diagnosis are non-invasive and benign[34]. In a small percentage of patients, EUS will demonstrate a focal malignancy[29]. Pancreatic malignancies may arise from IPMN or from remote sites within the pancreas[35].

Mucinous cystic neoplasms (MCN) are a rare cause of recurrent pancreatitis. Nevertheless, these solitary cystic lesions may be encountered during EUS (Figure 6). Morphologically, these mucinous lesions are usually thin-walled and contain a few thin septations. FNA reveals thick, translucent fluid characterized by a mucinous epithelium. Cyst fluid CEA > 200 pg/mL is the most diagnostic parameter[36] (Table 1).

Serous cystadenomas, just like MCNs, rarely communicate with the main pancreatic duct and therefore rarely cause pancreatitis. Morphologically, the EUS appearance of serous cystadenoma is unique. The multiple fine septations coursing across the cyst result in a microcystic or a honeycomb appearance. At times, the septations are so dense that the lesion appears as a solid mass. The increased vascularity of the lesion, driven by high levels of vascular endothelial growth factor (VEGF) results in bloody contamination of cyst fluid during FNA.

TREATMENT

Pre-malignant cystic lesions should be resected surgically unless the risks of surgery are excessive. The decision to resect a lesion, however, is based on the presence or absence of symptoms, the risk of malignancy, and the surgical risk of the patient. High risk patients with low grade cystic neoplasms may be monitored with periodic CT/MRI scanning or EUS-FNA. Small cystic lesions in the elderly can be safely monitored.

The increasing safety of surgical resection has encouraged the use of surgical resection for a wider range of lesions (Table 2). However, many cystadenomas do not require resection except for relief of symptoms. Furthermore, mucinous lesions are slow growing lesions and small lesions pose little risk. The risk of surgical resection, particularly of the head has raised questions about management[37]. Justification of surgery is readily obtained with high risk lesions as defined by cyst fluid analysis[38]. Since most mucinous cystic neoplasms are located in the tail of the pancreas, a distal pancreatectomy is sufficient for these pre-malignant lesions. Lesions in the body of pancreas can be selectively resected with a middle segmentectomy. The highest risk surgical approach is for lesions in the head of the pancreas.

Table 2 Traditional therapeutic approach to the management of cystic lesions

Location	Mucinous	Malignant	Serous	Pseudocyst
Head	Monitor	Resect	Monitor	Drain
Body	Resect	Resect	Monitor	Drain
Tail	Resect[1]	Resect	Resect[1]	Resect

[1]Approach varies with risk of surgery.

CONCLUSION

Patients with relapsing pancreatitis associated with a cystic lesion pose an important challenge to the clinician. A diagnosis of a cystic neoplasm is very important because this finding will provide an opportunity to resect a lesion responsible for pancreatitis and a risk of malignancy. An accurate diagnosis requires a thorough clinical evaluation combined with high resolution pancreatic imaging. Cyst fluid analysis will often complement and strengthen the diagnosis of a cystic neoplasm and provide the basis for a surgical resection.

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