

Pancreatic cystic neoplasms. Where clinics, imaging and surgery really count

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SUMMARY

Cystic pancreatic tumors form a heterogeneous group of tumors that usually present diagnostic difficulties concerning their neoplastic or inflammatory nature. What makes these tumors interesting and important is the fact that most of them once recognized can be definitely cured by surgical resection, making a sharp contrast to ductal adenocarcinoma. In classifying cystic pancreatic tumors we follow the WHO classification of 1996 which is based on the features of their epithelial wall. Main groups are: serous cystic tumors, mucinous cystic tumors and intraductal papillary mucinous neoplasms. The diagnostic workup of these tumors is based on modern imaging methods (Computed tomography with contrast injection, magnetic resonance imaging and cholangiopancreatography, endoscopic ultrasound). Surgery is an effective treatment and follow up is mandatory.

INTRODUCTION

Cystic pancreatic neoplasms are rare compared with the solid pancreatic neoplasms. They represent a heterogeneous group of tumors regarding morphology and clinical behavior. They usually present diagnostic problems concerning the differential diagnosis between neoplastic and inflammatory lesions. Even with a proper work-up, several uncertainties may remain about the nature of the cystic lesion. In these cases, surgery may play a therapeutic as well as a diagnostic role.

The interest that cystic tumors of the pancreas have received is reversely proportional to their low incidence. I think that the main reason for this is the fact that most cystic pancreatic tumors, once recognized by modern imaging methods, can be definitely cured by surgical resection, in contrast to ductal adenocarcinoma. In the recent past, there have been two main factors that have led to a better understanding of cystic neoplasms of the pancreas: first, the evolution in imaging techniques and endoscopic examination methods and, second, the increasingly successful resection rates of pancreatic lesions as a result of improvements in both surgical techniques and patient support.

The epidemiology of pancreatic cystic tumors has changed during the last few decades and this is not only a result of the universal classification imposed. In fact, intraductal papillary mucinous tumors (an important category of pancreatic cystic tumors, known earlier as mucin producing tumors or intraductal neoplasms of pancreas) are now the most common pancreatic cystic neoplasms that are brought to surgery. Furthermore, they have driven out from first place the former leaders, serous and mucinous cystadenoma and carcinoma.¹ The increasing incidence of such patient cases is very well reflected in a recent publication on 136 patients with intraductal papillary mucinous tumors that were diagnosed and operated upon during a 14-year period, were more than half of them were diagnosed during the last few years of the study.²

Histological classification

While at the end of the 70's the spectrum of cystic pancreatic tumors was consisted mainly from serous and mucinous cystic tumors, there was an important advance in knowledge during the 80's and 90's. Important revisions and broadening of the spectrum of pancreatic cystic neoplasms followed. New histological entities were in-

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Table 1. Histological classification of pancreatic cystic tumors (WHO 1996, ref. 3)

Serous cystic tumors

- Serous cystadenoma
- Serous cystadenocarcinoma

Mucinous cystic tumors

- Mucinous cystadenoma
- Mucinous cystadenoma with moderate dysplasia
- Mucinous cystadenocarcinoma (non infiltrating and infiltrating)
- Intraductal papillary mucinous adenoma (IPMA)
- Intraductal papillary mucinous tumors with moderate dysplasia
 - Intraductal papillary mucinous carcinoma (IPMC) (non infiltrating and infiltrating)

Solid pseudopapillary tumors

Table 2. Classification of cystic neoplasms of the pancreas according to reference 4

Benign

- Intraductal papillary mucinous adenoma
- Mucinous cystadenoma
- Serous microcystic adenoma
- Serous oligocystic ill-demarcated adenoma
- Von-Hippel-Lindau associated cystic neoplasm
- Cystic benign neuroendocrine tumors
- Acinar cell cystadenoma
- Cystic teratoma (dermoid cyst)
- Accessory splenic epidermoid cyst
- Cystic hamartoma

Borderline

- Intraductal papillary mucinous tumor, borderline
- Mucinous cystic neoplasm borderline
- Solid pseudopapillary neoplasm

Malignant

- Intraductal papillary mucinous carcinoma
- Mucinous cystic carcinoma
- Ductal adenocarcinoma, cystic
- Serous cystadenocarcinoma
- Pancreatoblastoma, cystic
- Cystic metastatic epithelial neoplasm
- Neuroendocrine carcinoma, cystic

Nonepithelial neoplasms

- Benign nonepithelial tumors (e.g. lymphangioma)
- Malignant nonepithelial tumors (e.g. sarcomas)

roduced and others became clear-cut, like the intraductal papillary mucinous tumors that were earlier described as mucin-producing tumors.

We generally follow the WHO Classification of Tumors, published 1996, (Table 1) for an understanding of the histological classification of pancreatic cystic neoplasms.³ This classification is based on the histopathological features of the epithelial wall of the cyst.

Recently, a new classification of morphological and biological relevance has been proposed which is mainly based both on a better immunohistochemical characterization of already known tumors and the description of several new ones (cystic hamartomas, mucinous non-neoplastic cysts and acinar cell cystadenomas). In Table 2, this new classification of cystic neoplasms of the pancreas is presented.⁴

Serous cystic tumors

The group most commonly affected by serous cystic tumors women in their sixth decade of life comprises. The most frequently involved part of the pancreas is the pancreatic head. Serous cystic tumors appear histologically as multiple cysts lined with cubic flat epithelium that produces serous fluid.

Most of serous cystic adenomas are asymptomatic and detected incidentally. When symptomatic, the commonest complaint is abdominal discomfort. When the lesion has reached an extensive size, a palpable abdominal mass or signs of upper GI tract obstruction may prevail. Usually, it is in US that a sponge-like mass with multilobulated borders is seen with an internal honeycomb structure. In some cases there can be calcifications between the lobes. Computed tomography and magnetic resonance imaging may give some more information e.g. punctuated or globular calcifications, when present, as opposed to lamellar calcifications that are seen in mucinous cystic tumors, better recognition of peripheral macrocysts and the honeycomb pattern, enhancement around microcysts after contrast injection (CT), better demonstration of even small fluid content within the septa of a sponge-like mass (MRI), better evaluation of the spatial relationship between the tumor and the pancreatic ducts helping in discriminating with intraductal papillary mucinous tumors. In endoscopic ultrasound (EUS), serous cyst adenomas may show diverse features as well as the typical honeycomb appearance as described above.⁵ Serous cystic adenomas are benign tumors and their treatment is conservative, whenever possible. Von Hippel-Lindau syndrome, a genetic conditioned syndrome, is associated in 15-30% of cases with serous cystic adenomas.⁶

Serous cystic adenocarcinomas are extremely rare tumors that usually produce no symptoms and have similar findings in the imaging methods.

The incidental finding in an imaging method of a mass in the pancreatic head with the above mentioned features in a woman with no dilatation of the pancreatic duct, normal pancreatic parenchyma and calcifications should suggest the diagnosis of a serous cystic tumor. It is important to demonstrate the relationship between mass and main pancreatic duct.⁴ Most patients with serous cystic tumors undergo pancreatic resection when symptoms are present or when the nature of the cystic lesion cannot be definitively established. Conservative management by yearly US monitoring is warranted for asymptomatic and well-documented serous cystic tumors, although this strategy has not been fully evaluated. The risk of incorrect treatment of a serous cystadenocarcinoma with this approach is very low as the latter represents an extremely rare malignant form of a serous cystic tumor.

Mucinous cystic tumors

They occur almost exclusively in women. They are located in the body and tail of pancreas and, characteristically, they do not communicate with the pancreatic duct system. Mucinous cystic tumors are encapsulated and lined by mucin-producing cells that overlie a stroma of ovarian type. The latter explains their exclusive incidence in females. Patients with a malignant mucinous cystic tumor tend to be older than patients with a benign one. The evidence of an adenoma-carcinoma sequence in mucinous cystic tumors is very strong. Once the malignant transformation occurs, the prognosis is similar to ductal adenocarcinoma. Therefore it is important for these tumors to be early diagnosed.

Symptoms in mucinous cystadenomas most frequently appear as abdominal discomfort or mild pain and they are non-specific, as in serous cystic tumors. Almost all patients with mucinous cystadenocarcinomas are symptomatic: obstructive jaundice, bleeding related to gastric involvement, symptoms and signs of portal hypertension are the most common symptoms.

The lack of communication between cyst and pancreatic ducts can be shown in MRCP images. The density of the content of the cystic mass on imaging techniques depends on the amount of mucin or blood in the cyst. Thickening of the cystic wall, the presence of papillary proliferations arising from the wall or septa, peripheral calcifications, and invasion of the surrounding vascular structure are regarded as signs of malignancy. CT is the primary imaging technique for these patients as it can

detect calcifications easier than MRI. Features and distribution of internal septa are better seen in T-2 weighted MRI images due to the mainly fluid content of mucinous cystic tumors, which renders them brighter in these images.

In EUS mucinous cystadenocarcinomas are characterized by hypoechoic cystic or solid mass or a complex cyst. They are usually associated with a dilated main pancreatic duct. Benign mucinous duct ectasia is characterized by a dilated main pancreatic duct in conjunction with hyperechoic thickening of the pancreatic duct wall.⁷

The differential diagnosis between mucinous cystic tumors and pseudocysts may be difficult and the clinical history of pancreatitis attacks is relevant in these cases. If there is uncertainty, examination of the cyst fluid may discriminate between a pseudocyst and a cystic tumor. Aspirates in mucous cystic adenomas show high levels of CEA and mucin-containing cells on cytology. In neuroendocrine tumors with cystic component due to necrosis and bleeding, the clinical syndrome may help in differential diagnosis. Oligocystic serous cystic tumors are almost never differentiated before surgery from benign mucinous cystic tumors. The presence of a communication between cystic tumor and pancreatic duct, a rarity in mucinous cystic tumors, raises the question of a possible intraductal papillary mucinous tumor.⁸

Mucinous cystic tumors should be resected because of the risk of malignant progression. A large unilocular cyst, in the absence of any history of pancreatitis is probably a mucinous cystic neoplasm and should be resected. The management of mucinous cystadenoma involves complete resection, as enucleation in most cases is an inadequate oncologic approach with high rates of pancreatic fistulas. The management of mucinous adenocarcinoma should be an aggressive one. Curative resection is possible in 65-74% of cases.⁶

Lymph node involvement is less common for mucinous adenocarcinoma than for ductal adenocarcinomas. For the above-mentioned reasons survival after pancreatic resection is better for mucinous cystadenocarcinomas than for ductal adenocarcinomas. The 5-year survival rate exceeds 50% whereas prognosis for the unresected tumor is as poor as for unresected pancreatic ductal adenocarcinoma.

Intraductal papillary mucinous neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) were originally described in the 1980s. They are characterized by mucin production, cystic dilation of the pan-

creatic ducts, and intraductal papillary growth. They may exhibit a spectrum of dysplasia ranging from minimal mucinous hyperplasia to invasive carcinoma. A male preponderance has been found or no difference in sex. The average age of a patient with IPMN is 65-70 years.⁹

Like the well-described adenoma-carcinoma sequence in colorectal cancer, IPMNs seem to follow a similar pattern progressing from IPMN adenoma to borderline IPMN with dysplasia, further to IPMN with carcinoma in situ, and finally to invasive carcinoma. In several surgery studies half of the resected IPMN specimens were found to contain atypia or carcinoma in situ. Besides, tumors with invasive components all occurred within areas of carcinoma in situ.⁹ This fact brings strong evidence in favor of IPMNs progressing slowly along the adenoma-carcinoma sequence. The clinical behavior of IPMNs is in stark contrast to that of ductal pancreatic adenocarcinomas, which are usually diagnosed in an advanced state.¹⁰

IPMNs are symptomatic in most cases, with a history of relapsing pancreatitis for 2-4 years. Clinical presentation includes epigastric or back pain, weight loss, diabetes, and a picture of pancreatic exocrine insufficiency. Jaundice is an uncommon presentation unlike adenocarcinoma of the pancreas. The characteristic pain is a result of duct obstruction and dilatation caused by excessive mucus production from a dysplastic or malignant adenomatous epithelium. The disease is more frequently localized in the pancreatic head. Typical findings of IPMNs with imaging methods include a distinct cystic mass and/or markedly dilated pancreatic duct. Noninvasive IPMNs are often identifiable in CT and MRI years before an invasive cancer develops. In favor of a malignant lesion are a history of alcohol abuse, jaundice and involvement of both main pancreatic and side branch ducts.¹⁰

The therapeutic aim in treating patients with both invasive and noninvasive IPMNs is complete surgical resection of the tumor. Total pancreatectomy is only indicated for extensive but resectable tumors involving the whole pancreas. Most importantly, early diagnosis and effective, aggressive management of IPMNs is a feasible goal due to the rather long interval between recognizable precursors and invasive cancer.

Forty to fifty per cent of resected IPMN specimens contain invasive carcinoma while the rest of them contain atypia or carcinoma in situ. The 5-year survival rate for patients with resected infiltrating intraductal mucinous carcinoma was reported to be 40-50% and is better

than the one reported for resected invasive ductal adenocarcinoma of the pancreas.¹¹ Patients with advanced stage disease, i.e. with positive lymph nodes and vascular invasion, have a poor survival, which is similar to that of patients with invasive ductal adenocarcinoma. The overall 5-year survival time for patients with IPMN was found to be 75%.²

It should be emphasized that IPMN of the pancreas is a tumor with a significant malignant potential that warrants surgical resection and careful follow-up. Unlike those patients with completely resected noninvasive mucinous cystic neoplasms of the pancreas, who are definitely cured, all patients with completely resected noninvasive IPMNs should undergo careful follow-up and surveillance for the early diagnosis of recurrent disease after partial pancreatectomy. Recurrence of invasive IPMN after intended curative resection occurs mainly in liver and lymph nodes. (12) Surveillance is better carried out with magnetic resonance cholangiopancreatography and EUS performed yearly.

Conclusions

Pancreatic cystic tumors are uncommon lesions, but, unlike ductal tumors, most of them can be radically resected. New classifications are useful for a better comprehension of treatment indications and prognosis. Every effort should be made to identify patients who may only have mild symptoms early. Diagnostic workup is mainly based on modern imaging methods. Surgery plays the main role in the treatment of these tumors. Several of the patients with these tumors have to be followed up either because they have a benign lesion or a doubtful one or because they had been surgically treated.

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