Benign, premalignant and malignant pancreatic cystic lesions: the pathology landscape

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Abstract

Pancreatic cystic lesions are being increasingly detected in last years. Pancreatic cysts can be classified grossly into pseudocysts and true cysts. In the true cysts group, it is important to distinguish mucinous from non-mucinous cysts because the former are considered being premalignant lesions. In this article the major types of pancreatic cysts are reviewed, with emphasis on the histopathological aspects. Molecular markers in the cyst fluid are being increasingly studied in recent years; the clinical utility of such biomarkers should be addressed in future studies. (Acta gastroenterol. belg., 2017, 80, 293-298).

Key words: pancreatic cyst, pancreas, cystic neoplasm

Introduction

Pancreatic cystic lesions are being increasingly detected in last years by significant improvement in imaging technologies, increased awareness of their existence and the growth of the aging population (1). These lesions are a broad group of pancreatic tumours with varying demographical, morphological, clinical and histological characteristics. Pancreatic cysts can be classified grossly into pseudocysts and true cysts. Pseudocysts develop mostly 4 weeks after the onset of acute pancreatitis, and are the natural evolution of acute fluid collections. In the true cysts group, it is important to distinguish mucinous from non-mucinous cysts because the former are considered being premalignant lesions. In this article the major types of pancreatic cysts are reviewed, with emphasis on the histopathological aspects.

Pseudocysts versus true cysts

The term “pseudocyst” refers to the fact that this cystic lesion has no epithelial lining and therefore is not a true cyst. Pancreatic pseudocysts are surrounded by fibrous and granulation tissue and are associated with acute or chronic pancreatitis (2). They predominantly develop in adult men as a complication of alcoholic, biliary or traumatic acute pancreatitis (3).

In the setting of acute pancreatitis, a focal fluid collection located in or near the pancreas occurs without a wall of granulation and/or fibrous tissue (4). The development of a well-defined wall composed of granulation or fibrous tissue distinguishes a pseudocyst from an acute fluid collection. Without an antecedent episode of acute pancreatitis, pseudocysts may arise insidiously in patients with chronic pancreatitis (5). Pancreatic pseudocysts are mostly unilocular or less likely oligolocular, and have few or no septa. Pseudocysts are mostly single but can be multiple in 10% of cases. Their size varies from 2 to 20 cm (3-5).

EUS guided fine-needle aspiration (FNA) with cyst fluid analysis will differentiate between pseudocysts and true cysts in more than 90% of patients (6). The aspirated fluid is examined cytologically for degenerative debris, inflammatory cells and histiocytes. If there is cytologic evidence of epithelial cells with the cyst fluid, this should raise the suspicion of a pseudocyst (7). Pseudocysts are usually sterile; the presence of granulocytes in the aspirated fluid is suggestive of an acute infection (1).

True cysts can be classified according to the type of epithelial lining that is mucinous or not. Non-mucinous cysts can be lined by serous, acinar, pancreatobiliary or squamous epithelium (Table 1).

Mucinous cysts

Intraductal papillary mucinous neoplasm

Intraductal papillary mucinous neoplasms and mucinous cystic neoplasms are precursor lesions of invasive malignancy.

Intraductal papillary mucinous neoplasms (IPMNs) are tumours characterised by intraductal proliferation of neoplastic mucinous cells with various degrees of atypia, which usually form papillae and lead to cystic dilatation of pancreatic ducts. They arise from the epithelial lining of the main pancreatic duct (main-duct IPMN), its side branches (branch-duct IPMN) or both (combined or mixed-type IPMN).

IPMNs may range from low-grade dysplasia to invasive malignancy and they have a clear tendency to become invasive carcinoma (8,9). With regard to the degree of dysplasia, it is recommended to use a 2-tiered classification: low-grade versus high-grade, with the term high-grade to be reserved only for the uppermost end of the spectrum (10). In case invasive growth arises from an IPMN, IPMN with an associated invasive carcinoma can...
Mucinous cystic neoplasm

Mucinous cystic neoplasms (MCNs) were formerly called mucinous cystadenomas. They are characterised as having mucin producing epithelial lining and ovarian-type stroma. This ovarian-type stroma contains a thick layer of spindle cells expressing receptors for oestrogen and progesteron (Fig. 2). Although involvement of the main pancreatic duct has been described (26), these lesions usually do not communicate with the pancreatic ductal system (27,28).

MCNs are seen almost exclusively in women; more than 90% of these lesions are located in the body or the tail of the pancreas (29). It has been hypothesised that ectopic ovarian stroma incorporated during embryogenesis in the pancreas may release hormones and growth factors, causing nearby epithelium to proliferate and form cystic tumours. Similar to IPMNs, it is recommended to use a 2-tiered classification for the degree of dysplasia (low-grade versus high-grade); in case of invasive cancer originating from these lesions, MCN with an associated invasive carcinoma can be used (10). Mesenchymal overgrowth, which is observed when the ovarian-type stroma predominates over the epithelial component, or sarcomatous differentiation of the stroma has also been described (30,31).

Mucinous nonneoplastic cyst

This entity is defined as a cystic lesion lined by mucinous epithelium, supported by hypocellular stroma and not communicating with the pancreatic ductal system (32). Clonality assay revealed that these cysts are of polyclonal origin; they also differ from IPMNs with regard to their mucin immunophenotype (32). It is important to distinguish mucinous nonneoplastic cysts from the other types of pancreatic cysts.
Serous cystic neoplasm

Serous cystic neoplasms (serous cystadenomas) of the pancreas are benign tumours whose unique cytomorphology is specific to the pancreas (and perhaps the liver). These lesions are characterised by distinctive glycogen-rich epithelial cells with uniform round nuclei, dense, homogenous chromatin, and a prominent epithelium-associated microvascular network. The fine needle-aspiration diagnosis of serous neoplasms has proven to be unexpectedly challenging because of the very low aspirate cellularity. This is probably due to the cohesiveness and adhesion of the cells to the tissue but not due to low tumour cellularity because serous neoplasms are often not as paucicellular as mucinous neoplasms.

The majority of cases have a very distinctive macroscopic morphology with innumerable back-to-back tubules of variable size and shape, creating a characteristic microcystic pattern (microcystic serous neoplasm). However, macrocystic and solid variants have been recognised. Solid variants, defined uniform small units with minimal or no lumen formation, are very uncommon (<2%) and are typically misread preoperatively as neuroendocrine tumours. Larger serous neoplasms may show localised adhesion or penetration of neighbouring organs, including lymph nodes, spleen, stomach and colon. This seems, however, not and indicator of malignant behaviour. Literature appraisal revealed that there are virtually no deaths that are directly attributable to dissemination/malignant behaviour of serous cystic neoplasms, and most cases reported as “malignant” or “cystadenocarcinomas” would no longer fulfill the more recent World Health Organization criteria. For cases with liver involvement, the possibility of “multifocal” disease rather than metastasis should be considered since hepatic serous cystic neoplasms can probably occur independently.

Rare pancreatic cysts

Some pancreatic neoplasms like solid pseudopapillary neoplasms (SPNs) or pancreatic neuroendocrine tumours can undergo secondary cystic changes. SPNs are low-grade malignant neoplasms composed of monomorphic epithelial cells that form solid and pseudopapillary structures. Microscopically, there is a combination of solid pseudopapillary components and haemorrhagic-necrotic pseudocystic components. Mucin is absent, and glycogen is not conspicuous. Even SPNs without histologic criteria of malignant behaviour such as perineural invasion, angioinvasion or infiltration of the surrounding parenchyma may metastasise; therefore, all SPNs are now classified as low-grade malignant neoplasms. SPNs generally occur in young women; about 70% of the lesions are located in the body and tail region of the pancreas. In experienced hands, FNA is diagnostic in 75% of these lesions. FNA typically shows cohesive groups of small uniform cells in branching and papillary structures. Immunohistochemical staining on tumour cells is positive for vimentin and CD10.

Pancreatic neuroendocrine tumours usually present as solid, homogeneous mass lesions with a well-defined margin on endoscopic ultrasound. Cytology from the cyst fluid or the solid component shows cohesive groups of plasmacytoid cells with rount to oval, mildly enlarged nuclei. Immunohistochemical staining is positive for synaptophysin and chromogranin.

Acinar cell cystadenoma is a benign cyst lined by patches of acinar and ductal epithelium. This lesion occurs more frequently in women and can be unilocular or multilocular. This entity was initially...
called acinar cystic transformation (45). Acinar cell cystadenocarcinoma is a rare variant of acinar cell carcinoma presenting cystic architecture. The clinical behaviour of this subtype is similar to that of the classical type of acinar cell carcinoma (46). Acinar cell cystadenoma presents at a younger median age (49.5 years) than acinar cell cystadenocarcinoma (60 years) (46) and acinar cell carcinoma (60 years) (47). This age difference is similar to that observed between certain premalignant lesions of the pancreas and their malignant counterparts such as the progression of IPMN to invasive carcinoma (48). These observations suggest that acinar cell cystadenoma may harbour a malignant potential.

Cholecystic cysts are rare congenital cyst dilations of the biliary tract generally involving the common bile duct. These benign cysts can be associated with serious complications such as malignant transformation, cholangitis, pancreatitis, and cholelithiasis (49).

Retention cysts result from obstructed pancreatic ducts. They are also called true or simple cysts and are usually found incidentally during an imaging study and have no clinical significance. They are usually small and their wall is covered by normal epithelium with ductal and centroacinar cells. They are observed in 25% of patients with cystic fibrosis (50).

Lymphoepithelial cysts are rare, benign pancreatic cysts lined by squamous epithelium and surrounded by mature lymphoid tissue (51). These lesions are more common in men and evenly distributed throughout the pancreas. The cyst fluid is milky in colour and cytology shows squamous cells, keratinaceous debris and lymphoid cells (52). While cystic fluid analysis allow to assess the CEA level and identify mucinous cystic lesions, CEA levels can be elevated in lymphoepithelial cysts representing a potential pitfall (53).

Schwannomas or neurilemmomas are rare, well-defined, benign, encapsulated, slow growing tumours arising from Schwann cells that encase the peripheral nerves. Schwannoma of the pancreas is particularly rare; half of these lesions are cystic (54). Although CT and MRI may aid in the differential diagnosis, a definitive diagnosis of pancreatic schwannoma requires histopathological examination. Immunohistochemically, schwannomas are strongly positive for S-100 protein, vimentin and CD56.

Pancreatic or parapancreatic tuberculosis is an extremely rare clinical entity even in endemic regions. It can present as a cystic or solid pancreatic mass mimicking malignancy. Therefore, most cases are diagnosed after surgical exploration for presumed pancreatic neoplasia. The presence of granulomas in a pancreatic fine-needle aspiration specimen is highly suspicious of tuberculosis; the diagnosis needs to be confirmed either by Ziehl-Neelsen staining or a positive culture (55).

Hydatid (Echinococcal) cyst of the pancreas is rare but should always be considered in the differential diagnosis of cystic pancreatic lesions in patients from endemic regions. Pancreatic hydatid cysts are solitary in 90% of cases and more frequent in the head than in the body and the tail of the pancreas (56). Grossly, the cysts are large and unilocular. The cyst fluid is strikingly antigenic and may lead to anaphylaxis on spillage. The inner layer of the cysts consists of epithelial cells that give rise to the brood capsules from which scoleces, or immature heads of adult worms, develop. The outer cyst layers are composed of hyaliniased, acellular, PAS-positive material.

### Cyst fluid analysis as a tool in preoperative diagnosis

The sensitivity of cytology varies depending on the expertise of the endoscopist and the pathologist. Cytology may be false negative because of sampling error. In a single center study of 141 cysts, cytology was diagnostic in 58% of subjects (57). Diagnostic accuracy can increase up to 80-90% if cytology is complemented with measurements of CEA, amylase levels and mucin staining (58). CEA measurement in the fluid is particularly helpful to separate serous from mucinous lesions. The accuracy may vary among different laboratories and approximately 0.2 to 1.0 mL of cyst fluid is required to run the test. A cut-off of 192 ng/mL is typically referenced as the standard although not insignificant differences can be seen between studies and levels can vary from laboratory to laboratory (59). It should be noted that cyst fluid CEA is not accurate enough for differentiating malignant from non-malignant mucinous cysts (60). Amylase levels are commonly used as an indicator of pancreatic duct communication. Cyst fluid amylase of less than 250 U/L virtually excludes pseudocyst (61). However, high levels of amylase cannot confirm the diagnosis of pseudocyst or exclude mucinous cystic neoplasia. High levels of cyst fluid amylase are also seen in patients with IPMN as the cyst has communication with the pancreatic ductal system.

Molecular markers in the cyst fluid are being increasingly studied in recent years. Molecular tests of the aspirated cystic fluid seem particularly useful for detecting the accumulation of genetic mutations associated with lesion progression from early dysplasia to carcinoma (24,62). A recent meta-analysis revealed that KRAS mutations can confirm diagnoses of mucinous and malignant pancreatic cysts but should not be used to exclude such diagnoses because of the low sensitivity value (62). Loss of heterozygosity tests had a low level of accuracy for differentiating mucinous cysts but were able to differentiate malignant from benign cysts accurately (50). Variants in TP53, SMAD4, CDKN2A and NOTCH1 support the diagnosis of a high-risk cyst requiring surgery or additional sampling (63). Taken together, molecular analyses cannot replace more conventional tests but should be used in parallel with them and clinical findings.

### Prospects for future research

Among all the cyst fluid diagnostic parameters, CEA concentration alone is the most accurate test for the
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Diagnosis of cystic mucinous neoplasms. EUS-derived cytology and CEA analysis have, however, diagnostic limitations (64,65). A recent study identified glucose and kynurenine to be differentially expressed between mucinous and non-mucinous pancreatic cysts (66). Metabolic abundances for both were significantly lower in mucinous cysts compared with non-mucinous cysts. The clinical utility of such biomarkers should be addressed in future studies. Similarly, the use of next-generation sequencing of cystic fluid samples for diagnostic and prognostic stratification needs further investigation.

Conclusions

Different types of benign, premalignant and malignant cystic lesions can be observed in the pancreas. Distinguishing between the various types of lesions has important prognostic and therapeutic implications. Although cyst fluid analysis is a tool in preoperative diagnosis and clinical management, it has important prognostic and therapeutic implications.

References


