

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

P. Demetter, L. Verset

Department of Pathology, Erasme University Hospital, Université Libre de Bruxelles

### 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

Correspondence to : Pieter Demetter, Department of Pathology, Erasme University Hospital, Route de Lennik 808, 1070 Brussels, Belgium  
E-mail: pieter.demetter@erasme.ulb.ac.be

Submission date : 10/10/2016

Acceptance date : 14/12/2016

Table 1. — Classification of pancreatic cysts according to the lining epithelium.

Mucinous epithelium
Intraductal papillary mucinous neoplasm Mucinous cystic neoplasm Mucinous nonneoplastic cyst
Serous epithelium
Serous cystic neoplasm
Acinar epithelium
Acinar cell cystadenoma Acinar cell cystadenocarcinoma
Pancreatobiliary epithelium
Choledochal cyst Retention cyst
Squamous epithelium
Lymphoepithelial cyst

be used. Branch duct IPMNs, while possessing malignant potential, have been suggested to be indolent compared to their main duct counterparts (11-13).

IPMNs are classified into four histological subtypes: gastric, intestinal, oncocytic and pancreatobiliary, depending on epithelial morphology and mucin expression patterns (14). Historically, pancreatobiliary-type IPMNs have been reported to carry the worst prognosis. This finding is secondary to the fact that they are often associated with invasive cancers (50-60%) (15). Some IPMNs show fundic gland differentiation in at least part of the tumour, but currently they are not classified separately (16). The gastric type (Fig. 1) is frequently multifocal and occurs predominantly in the branch ducts whereas the other types predominantly occur in the main duct. Likewise, invasive carcinoma arising in association with IPMN is cytologically heterogeneous, and can exhibit colloid, tubular or oncocytic patterns (17,18). Intestinal-type IPMN typically progresses to invasive cancer with a colloid pattern (19-22). Colloid and oncocytic patterns have markedly improved biology, whereas the tubular pattern has a course that resembles pancreatic ductal adenocarcinoma (23). The diagnostic evaluation of IPMNs is challenging, as diagnostic imaging and cytological sampling do not provide sufficiently accurate information on lesion classification, the grade of dysplasia or the presence of invasion. Next-generation sequencing of cystic fluid samples can identify the majority of mutations arising in IPMNs, potentially improving the diagnostic and prognostic stratification of these lesions (24).

The rare variant of IPMN without overt production of mucin is called intraductal tubulopapillary neoplasm (ITPN). If there is a component of invasive carcinoma, the lesion is designated ITPN with an associated invasive carcinoma. Despite recent progress, more studies are necessary to assess the biology and genetics of such lesions (25).

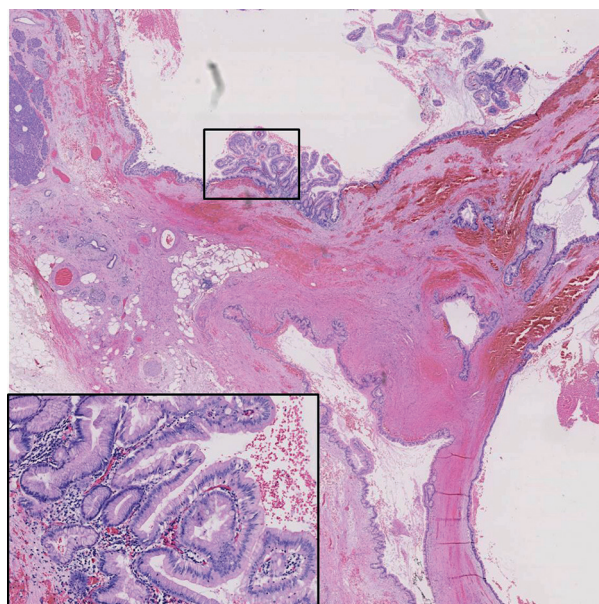


Fig. 1. — Gastric type of IPMN with intraductal papillary structures covered with low-grade dysplastic epithelium.

#### *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 progesterone (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

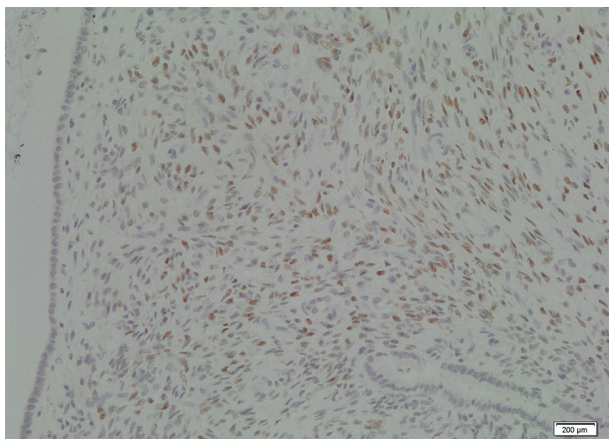


Fig. 2. — Ovarian type stroma of a mucinous cystic neoplasm expressing progesterone receptors as detected by immunohistochemistry.

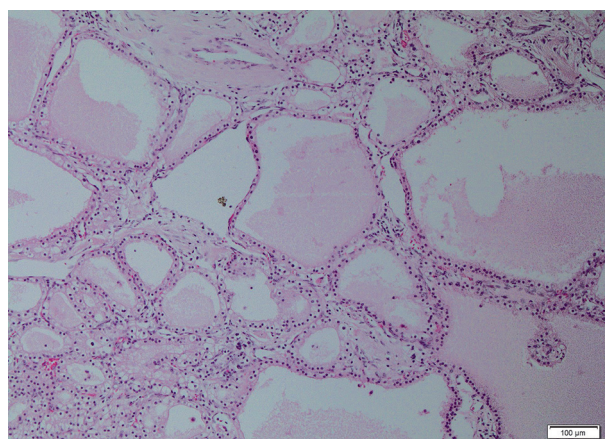


Fig. 3. — Characteristic microcystic pattern of the majority of cases of serous cystic neoplasms. Cysts are lined by glycogen-rich epithelial cells with uniform nuclei.

cysts from MCNs and IPMNs since the former is not a precursor lesion of invasive cancer.

### Serous cystic neoplasm

*Serous cystic neoplasms probably never give rise to metastatic malignancies*

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 (33). The fine needle-aspiration diagnosis of serous neoplasms has proven to be unexpectedly challenging because of the very low aspirate cellularity (34). 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) (Fig. 3). However, macrocystic and solid variants have been recognised (35). Solid variants, defined uniform small units with minimal or no lumen formation, are very uncommon (<2%) and are typically misread preoperatively as neuroendocrine tumours (35). Larger serous neoplasms may show localised adhesion or penetration of neighbouring organs, including lymph nodes, spleen, stomach and colon. This seems, however, not an indicator of malignant behaviour (35). Literature appraisal revealed that there are virtually no deaths that are directly attributable to dissemination/malignant behaviour of serous cystic neoplasms (35), and most cases reported as “malignant” or “cystadenocarcinomas” would no longer fulfil the more recent World Health

Organization criteria (36). 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 (35).

### 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 (37). SPNs generally occur in young women; about 70% of the lesions are located in the body and tail region of the pancreas (38). In experienced hands, FNA is diagnostic in 75% of these lesions (39). 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 (40).

Pancreatic neuroendocrine tumours usually present as solid, homogeneous mass lesions with a well-defined margin on endoscopic ultrasound (41). However, about 10% of neuroendocrine tumours are cystic (42). Cytology from the cyst fluid or the solid component shows cohesive groups of plasmacytoid cells with round to oval, mildly enlarged nuclei. Immunohistochemical staining is positive for synaptophysin and chromogranin (43).

Acinar cell cystadenoma is a benign cyst lined by patches of acinar and ductal epithelium (42). This lesion occurs more frequently in women and can be unilocular or multilocular (44). 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.

Choledochal cysts are rare congenital cystic 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 scolices, or immature heads of adult worms, develop. The outer cyst layers are composed of hyalinised, 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 neoplasm. 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

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, final diagnosis is often obtained only after histopathological analysis. At present molecular techniques cannot replace such analysis but should be used in parallel with it and with clinical findings.

## References

- BRUGGE W.R. Diagnosis and management of cystic lesions of the pancreas. *J. Gastrointest. Oncol.*, 2015, **6** : 375-388.
- HOOKEY L.C., DEBROUX S., DELHAYE M., ARVANITAKIS M, LE MOINE O., DEVIÈRE J. Endoscopic drainage of pancreatic-fluid collections in 116 patients : a comparison of etiologies, drainage techniques, and outcomes. *Gastrointest. Endosc.*, 2006, **63** : 635-643.
- HABASHI S, DRAGANOV P.V. PANCREATIC PSEUDOCYST. *World J. Gastroenterol.*, 2009, **15** : 38-47.
- BRUN A., AGARWAL N., PITCHUMONI C.S. Fluid collections in and around the pancreas in acute pancreatitis. *J. Clin. Gastroenterol.*, 2011, **45** : 614-625.
- AGHDASSI A., MAYERLE J., KRAFT M., SIELENKÄMPER A.W., HEIDECHE C.D., LERCH M.M. Diagnosis and treatment of pancreatic pseudocysts in chronic pancreatitis. *Pancreas*, 2008, **36** : 105-112.
- BRUGGE W.R. Approaches to the drainage of pancreatic pseudocysts. *Curr. Opin. Gastroenterol.*, 2004, **20** : 488-492.
- PITMAN M.B., LEWANDROWSKI K., SHEN J., SAHANI D., BRUGGE W., FERNANDEZ-DEL CASTILLO C. Pancreatic cysts : preoperative diagnosis and clinical management. *Cancer Cytopathol.*, 2010, **118** : 1-13.
- KANG M.J., LEE K.B., JANG J.Y., KWON W, PARK J.W., CHANG Y.R. *et al.* Disease spectrum of intraductal papillary mucinous neoplasm with an associated invasive carcinoma invasive IPMN versus pancreatic ductal adenocarcinoma-associated IPMN. *Pancreas*, 2013, **42** : 1267-1274.
- SAKORAFAS G.H., SMYRNIOTIS V., REID-LOMBARDO K.M., SARR M.G. Primary pancreatic cystic neoplasms revisited. Part III. Intraductal papillary mucinous neoplasms. *Surg. Oncol.*, 2011, **20** : e109-e118.
- BASTURK O, HONG S.M, WOOD L.D, VOLKAN ADSAY N, ALBORES-SAAVEDRA J, BIANKIN A.V *et al.* A revised classification system and recommendations from the Baltimore consensus pap for neoplastic precursor lesions in the pancreas. *Am. J. Surg. Pathol.*, 2015, **39** : 1730-1741.
- SUGIYAMA M., IZUMISATO Y., ABE N, MASAKI T., MORI T., ATOMI Y. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. *Br. J. Surg.*, 2003, **90** : 1244-1249.
- IRIE H., YOSHIMITSU K., AIBE H., TAJIMA T., NISHIE A., NAKAYAMA T *et al.* Natural history of pancreatic intraductal papillary mucinous tumor of branch duct type : follow-up study by magnetic resonance cholangiopancreatography. *J. Comput. Assist. Tomogr.*, 2004, **28** : 117-122.
- PELAEZ-LUNA M., CHARI S.T., SMYRK T.C., TAKAHASHI N., CLAIN J.E., LEVY M.J. *et al.* Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy ? A study of 147 patients. *Am. J. Gastroenterol.*, 2007, **102** : 1759-1764.
- LUTTGES J., ZAMBONI G., LONGNECKER D., KLÖPPEL G. The immunohistochemical mucin expression pattern distinguishes different types of intraductal papillary mucinous neoplasms of the pancreas and determines their relationship to mucinous noncystic carcinoma and ductal adenocarcinoma. *Am. J. Surg. Pathol.*, 2001, **25** : 942-948.
- FURUKUWA T., HATORI T., FUJITA I., YAMAMOTO M., KOBAYASHI M., OHIKE N. *et al.* Prognostic relevance of morphologic types of intraductal papillary mucinous neoplasms of the pancreas. *Gut*, 2011, **60** : 509-516.
- MAMAT O., FUKUMURA Y., SAITO T., TAKAHASHI M., MITOMI H., SAI J.K. *et al.* Fundic gland differentiation of oncocytic/pancreatobiliary subtypes of pancreatic intraductal papillary mucinous neoplasm. *Histopathology*, 2016, **69** : 570-581.
- ADSAY N.V, PIERSON C., SARKAR F., ABRAMS J., WEAVER D, CONLON K.C. *et al.* Colloid (mucinous noncystic) carcinoma of the pancreas. *Am. J. Surg. Pathol.*, 2001, **25** : 26-42.
- ADSAY N.V., ADAIR C.F., HEFFESS C.S., KLIMSTRA D.S. Intraductal oncocytic papillary neoplasms of the pancreas. *Am. J. Surg. Pathol.*, 1996, **20** : 980-994.
- BAN S., NAITOH Y., MINO-KENUDSON M., SAKURAI T., KURODA M., KOYAMA I. *et al.* Intraductal papillary mucinous neoplasm (IPMN) of the pancreas : its histopathologic difference between 2 major types. *Am. J. Surg. Pathol.*, 2006, **30** : 1561-1569.
- ADSAY N.V., MERATI K., BASTURK O., IACOBUIZIO-DONAHUE C., LEVI E, CHENG J.D. *et al.* Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms : delineation of an "intestinal" pathway of carcinogenesis in the pancreas. *Am. J. Surg. Pathol.*, 2004, **28** : 839-848.
- LUTTGES J., BEYSER K., PUST S., PAULUS A., RÜSCHOFF J., KLÖPPEL G. Pancreatic mucinous noncystic (colloid) carcinomas and intraductal papillary mucinous carcinomas are usually microsatellite stable. *Mod. Pathol.*, 2003, **16** : 537-542.
- NAKAMURA A., HORINOUCHE M., GOTO M., NAGATA K., SAKODA K., TAKAO S. *et al.* New classification of pancreatic intraductal papillary-mucinous tumour by mucin expression : its relationship with potential for malignancy. *J. Pathol.*, 2002, **197** : 201-210.
- MINO-KENUDSON M., FERNANDEZ-DEL CASTILLO C., BABA Y, VALSANGKAR N.P., LISS A.S., HSU M. *et al.* Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. *Gut*, 2011, **60** : 1712-1720.
- AMATO E., DAL MOLIN M., MAFFICINI A., YU J., MALLEO G., RUSEV B. *et al.* Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. *J. Pathol.*, 2014, **233** : 217-227.
- ROONEY S.L., SHI J. Intraductal tubulopapillary neoplasm of the pancreas : an update from a pathologist's perspective. *Arch. Pathol. Lab. Med.*, 2016, **140** : 1068-1073.
- Masia R., Mino-Kenudson M., Warshaw A.L., Pitman M.B., Misraji J. Pancreatic mucinous cystic neoplasm of the main pancreatic duct. *Arch. Pathol. Lab. Med.*, 2011, **135** : 264-267.
- YOON W.J., BRUGGE W.R. Pancreatic cystic neoplasms : diagnosis and management. *Gastroenterol. Clin. North Am.*, 2012, **41** : 103-118.
- GOH B.K., TAN Y.M., CHUNG Y.F., CHOW P.K., CHEOW P.C., WONG W.K. *et al.* A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma : clinicopathological features of 344 patients. *World J. Surg.*, 2006, **30** : 2236-2245.
- REDDY R.P., SMYRK T.C., ZAPIACH M., LEVY M.J., PEARSON R.K., CLAIN J.E. *et al.* Pancreatic mucinous cystic neoplasms defined by ovarian stroma : demographics, clinical features, and prevalence of cancer. *Clin. Gastroenterol. Hepatol.*, 2004, **2** : 1026-1031.
- HANDRA-LUCA A., COUVELARD A., SAUVANET A., FLÉJOU J.F., DEGOTT C. Mucinous cystadenoma with mesenchymal over-growth : a new variant among pancreatic mucinous cystadenomas? *Virchows Arch.*, 2004, **445** : 203-205.
- WAYNE M., GUR D., ASCUNCE G., ABODESSA B., GHALI V. Pancreatic mucinous cystic neoplasm with sarcomatous stroma metastasizing to liver : a case report and review of literature. *World J. Surg. Oncol.*, 2013, **11** : 100.
- CAO W., ADLEY B.P., LIAO J., LIN X., TALAMONTI M., BENTREM D.J. *et al.* Mucinous nonneoplastic cyst of the pancreas : apomucin phenotype distinguishes this entity from intraductal papillary mucinous neoplasm. *Hum. Pathol.*, 2010, **41** : 513-521.
- THIRABANJASAK D., BASTURK O., ALTINEL D., CHENG J.D., ADSAY N.V. Is serous cystadenoma of the pancreas a model of clear-cell-associated angiogenesis and tumorigenesis? *Pancreatol.*, 2009, **9** : 182-188.
- COLLINS B.T. Serous cystadenoma of the pancreas with endoscopic ultrasound fine needle aspiration biopsy and surgical correlation. *Acta Cytol.*, 2013, **57** : 241-251.

35. REID M.D., CHOI H.J., MEMIS B., KRASINSKAS A.M., JANG K.T., AKKAS G. *et al.* Serous neoplasms of the pancreas : a clinicopathologic analysis of 193 cases and literature review with new insights on macrocystic and solid variants and critical reappraisal of so-called "serous cystadenocarcinoma". *Am. J. Surg. Pathol.*, 2015, **39** : 1597-1610.
36. TERRIS B., FUKUSHIMA N., HRUBAN R.H. SEROUS NEOPLASMS OF THE PANCREAS. IN : BOSMAN F.T., CARNEIRO F., HRUBAN R.H., THEISE N.D., eds. WHO classification of tumours of the digestive system. Lyon, France : IARC Press, 2010 : 296-299.
37. TIPTON S.G., SMYRK T.C., SARR M.G., THOMPSON G.B. Malignant potential of solid pseudopapillary neoplasm of the pancreas. *Br. J. Surg.*, 2006, **93** : 733-737.
38. VALSANGKAR N.P., MORALES-OYARVIDE V., THAYER S.P., APPALANENI V., WARGO J.A., WARSHAW A.L. *et al.* 851 resected cystic tumors of the pancreas : a 33-year experience at the Massachusetts General Hospital. *Surgery*, 2012, **152** (3 suppl 1) : S4-S12.
39. JANI N., DEWITT J., ELOUBEIDI M., VARADARAJULU S., APPALANENI V., HOFFMAN B. *et al.* Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas : a multicenter experience. *Endoscopy*, 2008, **40** : 200-203.
40. SONG J.S., YOO C.W., KWON Y., HONG E.K. Endoscopic ultrasound-guided fine needle aspiration cytology diagnosis of solid pseudopapillary neoplasm : three case reports with review of the literature. *Korean J. Pathol.*, 2012, **46** : 399-406.
41. PAIS S.A., AL-HADDAD M., MOHAMADNEJAD M., LEBLANC J.K., SHERMAN S., MCHENRY L. *et al.* EUS for pancreatic neuroendocrine tumors : a single-center, 11-year experience. *Gastrointest. Endosc.*, 2010, **71** : 1185-1193.
42. KONGKAM P., AL-HADDAD M., ATTASARANYA S., O'NEIL J., PAIS S., SHERMAN S. *et al.* EUS and clinical characteristics of cystic pancreatic neuroendocrine tumors. *Endoscopy*, 2008, **40** : 602-605.
43. MOHAMADNEJAD M., EMERSON R., DEWITT J. Photoclinic. Pancreatic neuroendocrine tumor. *Arch. Iran. Med.*, 2010, **13** : 445-446.
44. SINGHI A.D., NORWOOD S., LIU T.C., SHARMA R., WOLFGANG C.L., SCHULICK R.D. *et al.* Acinar cell cystadenoma of the pancreas : a benign neoplasm or non-neoplastic ballooning of acinar and ductal epithelium? *Am. J. Surg. Pathol.*, 2013, **37** : 1329-1335.
45. KLÖPPEL G. Pseudocysts and other non-neoplastic cysts of the pancreas. *Semin. Diagn. Pathol.*, 2000, **17** : 7-15.
46. COLOMBO P., ARIZZI C., RONCALLI M. Acinar cell cystadenocarcinoma of the pancreas : report of rare case and review of the literature. *Hum. Pathol.*, 2004, **35** : 1568-1571.
47. HOLDEN K.D., KLIMSTRA D.S., HUMMER A., GONEN M., CONLON K., BRENNAN M., SALTZ L.B. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. *J. Clin. Oncol.*, 2002, **20** : 4673-4678.
48. SOHN T.A., YEO C.J., CAMERON J.L., HRUBAN R.H., FUKUSHIMA N., CAMPBELL K.A., LILLEMÖE K.D. Intraductal papillary mucinous neoplasms of the pancreas : an updated experience. *Ann. Surg.*, 2004, **239** : 788-797.
49. SOARES K.C., ARNAOUTAKIS D.J., KAMEL I., RASTEGAR N., ANDERS R., MAITHEL S. *et al.* Choledochal cysts : presentation, clinical differentiation, and management. *J. Am. Coll. Surg.*, 2014, **219** : 1167-1180.
50. DIETRICH C.F., CHICHAKLI M., HIRCHE T.O., BARGON J., LEITZMANN P., WAGNER T.O. *et al.* Sonographic findings of the hepatobiliary-pancreatic system in adult patients with cystic fibrosis. *J. Ultrasound Med.*, 2002, **21** : 409-416.
51. ARUMUGAM P., FLETCHER N., KYRIAKIDES C., MEARS L., KOCHER H.M. Lymphoepithelial cyst of the pancreas. *Case Rep. Gastroenterol.*, 2016, **10** : 181-192.
52. KARIM Z., WALKER B., LAM E. Lymphoepithelial cysts of the pancreas : the use of endoscopic ultrasound-guided fine-needle aspiration in diagnosis. *Can. J. Gastroenterol.*, 2010, **24** : 348-350.
53. RAVAL J.S., ZEH H.J., MOSER A.J., LEE K.K., SANDERS M.K., NAVINA S. *et al.* Pancreatic lymphoepithelial cysts express CEA and can contain mucous cells : potential pitfalls in the preoperative diagnosis. *Mod. Pathol.*, 2010, **23** : 1467-1476.
54. CILEDAG N., ARDA K., AKSOY M. Pancreatic schwannoma : a case report and review of the literature. *Oncol. Lett.*, 2014, **8** : 2741-2743.
55. VAFA H., ARVANITAKIS M., MATOS C., DEMETTER P., EISENDRATH P., TOUSSAINT E. *et al.* Pancreatic tuberculosis diagnosed by EUS : one disease, many faces. *JOP*, 2013, **14** : 256-260.
56. AKBULUT S. Hydatid cyst of the pancreas : report of an undiagnosed case of pancreatic hydatid cyst and brief literature review. *World J. Gastrointest. Surg.*, 2014, **6** : 190-200.
57. CIZGINER S., TURNER B., BILGE A.R., KARACA C., PITMAN M.B., BRÜGGE W.R. Cyst fluid carcinoembryonic antigen is an accurate diagnostic marker of pancreatic mucinous cysts. *Pancreas*, 2011, **40** : 1024-1028.
58. SAND J.A., HYOTY M.K., MATILLA J., DAGORN J.C., NORDBACK I.H. Clinical assessment compared with cyst fluid analysis in the differential diagnosis of cystic lesions in the pancreas. *Surgery*, 1996, **119** : 275-280.
59. ROCKACY M., KHALID A. Update on pancreatic cyst fluid analysis. *Ann. Gastroenterol.*, 2013, **26** : 122-127.
60. PAIS S.A., ATTASARANYA S., LEBLANC J.K., SHERMAN S., SCHMIDT C.M., DEWITT J. Role of endoscopic ultrasound in the diagnosis of intraductal papillary mucinous neoplasms : correlation with surgical histopathology. *Clin. Gastroenterol. Hepatol.*, 2007, **5** : 489-495.
61. VAN DER WAAIJ L.A., VAN DULLEMEN H.M., PORTE R.J. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions : a pooled analysis. *Gastrointest. Endosc.*, 2005, **62** : 383-389.
62. GUO X., ZHAN X., LI Z. Molecular analyses of aspirated cystic fluid for the differential diagnosis of cystic lesions of the pancreas : a systematic review and meta-analysis. *Gastroenterol. Res. Pract.*, 2016, 2016 : 3546085.
63. ROSENBAUM M.W., JONES M., DUDLEY J.C., LE L.P., IAFRATE A.J., PITMAN M.B. Next-generation sequencing adds value to the preoperative diagnosis of pancreatic cysts. *Cancer Cytopathol.*, 2016 Sep 20 (Epub ahead of print).
64. JACOBSON B.C., BARON T.H., ADLER D.G., DAVILA R.E., EGAN J., HIROTA W.K. *et al.* ASGE guideline : the role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. *Gastrointest. Endosc.*, 2005, **61** : 363-370.
65. BRÜGGE W.R., LEWANDROWSKI K., LEE-LEWANDROWSKI E., CENTENO B.A., SZYDLO T., REGAN S. *et al.* Diagnosis of pancreatic cystic neoplasms : a report of the cooperative pancreatic cyst study. *Gastroenterology*, 2004, **126** : 1330-1336.
66. PARK W.G., WU M., BOWEN R., ZHENG M., FITCH W.L., PAI R.K. *et al.* Metabolomic-derived novel cyst fluid biomarkers for pancreatic cysts : glucose and kynurenine. *Gastrointest. Endosc.*, 2013, **78** : 295-302.e2.