Research Letter

Pancreatic Cystic Neoplasms

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Abstract

Background: Cystic neoplasms of the pancreas are rare and constitute approximately 0.5% of all pancreatic neoplasms. **Aims:** The study was to describe clinicopathological features of pancreatic cystic tumors. **Patients and Methods:** In our retrospective study, we reviewed 10 cases of pancreatic cystic neoplasms that were diagnosed at the pathology department of Mongi Slim hospital over a 14-year period (2000-2013). We adopted the latest World Health Organization (WHO) classification (2010) in grouping all tumors. **Results:** There were one male and nine female patients (sex ratio M/F = 1:9) aged between 21 and 68 years (mean = 37.5 years). The most common clinical presentation was epigastric and abdominal pain (n = 6) followed by vomiting (n = 3). Abdominal computed tomography (CT) scan disclosed a cystic lesion of the pancreas ranging in size between 2 and 10 cm (mean = 6.75 cm). All patients underwent surgical treatment. Histopathological examination of the surgical specimen established the diagnosis of solid pseudopapillary neoplasm (n = 2), serous cystic neoplasm (n = 2), mucinous cystadenoma (n = 4), mucinous cystadenocarcinoma (n = 1), and intraductal papillary mucinous neoplasm with invasive carcinoma (n = 1). **Conclusion:** Better understanding of pancreatic cystic neoplasms is essential for clinicians to make accurate diagnosis and to provide the best management for patients.

Keywords: Immunohistochemistry, Mucinous cystic neoplasms, Pancreas, Serous cystic neoplasms, Solid pseudopapillary neoplasm

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Introduction

Cystic neoplasms of the pancreas are rare andconstitute approximately 0.5% of all pancreaticneoplasms.[1,2] They form a heterogeneous group of tumors and are more increasingly encountered with the widespread of abdominal screening and improved imaging techniques. While some show benign behavior, others are precancerous or have an unequivocal malignant potential. Only 5-15% of pancreatic cysts are neoplastic.[3] For clinicians, a reliable diagnosis and the subsequent management of pancreatic cystic neoplasms are critical. The aim of the present study was to describe the histological features and the natural history of cystic tumors of the pancreas, the modalities of diagnostic imaging, and amanagement approach adapted to the specific diagnosis.

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Patients and Methods

We undertook a retrospective study of 10 patients who were operated on for cystic tumors of the pancreas at the surgery department of Mongi Slim hospital of Tunis between February 2000 and August 2013. The cases were retrieved from the files of the registry of surgery of the same hospital. Clinical records and microscopic slides of each patient were available for review in all cases. Clinical data, radiological investigations, treatment, and outcome were retrospectively analyzed. All patients underwent imaging evaluation during the preoperative period. All specimens were surgically obtained. Tissues were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin and sections were prepared for routine light microscopy after staining with hematoxylin and eosin. In two cases of solid pseudopapillary neoplasm (SPPN), we carried out an immunohistochemical study on serial paraffin sections encompassing both tumor and adjacent normal pancreatic tissue from each patient. The sections were

deparaffinized with xylene, rehydrated through a graded alcohol series, and microwaved at 500 W for 2-5 minute in 10 mM citrate buffer (pH 6.0). After rinsing in Tris-buffered saline (pH 7.6), sections were treated with 3% hydrogen peroxide in methanol and then incubated overnight at 4°C with monoclonal primary antibodies diluted in 1% bovine serum albumin. After washing, the primary antibody was detected with appropriate secondary antibody for 30 minute at 37°C. Following washes, slides were incubated in avidin-biotin complex for 20 minute at 37°C and visualized using Digital Audio Broadcasting (DAB). Counterstaining was performed with hematoxylin. The antibodies used were: Chromogranin A, synaptophysin, CD10, cytokeratin, beta-catenin, vimentin, and progesterone receptors (mouse monoclonal, 1:100 dilution, DAKO). Patient confidentiality was maintained.

Results

Clinical findings

Clinical data of the 10 cases of our series are summarized in Table 1.

Our study group comprised one male and nine female patients (sex ratio M/F = 0:11) between 21 and 68 years of age (mean = 37.5 years). The delay from onset of symptoms to diagnosis ranged between 2 weeks and 3 months. Past medical history of the patients included hypertension ($n = 1$), diabetes ($n = 1$), and diaphragmatic hernia ($n = 1$). Seven patients had no past medical history.

Biological tests

Serum tumor markers namely carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were performed in 4 cases (two cases of SPPN, one case of intraductal papillary mucinous neoplasm (IPMN) with invasive carcinoma and one case of mucinous cystadenocarcinoma). They were within normal range in 3 cases and elevated in the case of mucinous cystadenocarcinoma (CEA = 80 ng/ml; CA 19-9 = 69 u/ml).

Radiological findings and localization of cystic tumors of the pancreas

Diagnostic imaging techniques included ultrasonography in 10 cases, computed tomography (CT) scan in 10 cases and magnetic resonance imaging (MRI) in 2 cases. Based on imaging findings, three cases (two cases solid pseudopapillary neoplasms, SPPN, and mucinous cystadenocarcinoma) were misdiagnosed preoperatively as having respectively stromal tumor,

Table 1: Clinical presentation and imaging findings in our series

Cases	Age	Sex	Symptoms	Treatment	Size (cm)	Location (pancreas)	Diagnosis	Evolution follow-up
1	46	F	Incidental finding	Tumor enucleation	2	Tail	SC	Favorable evolution
2	24	F	Epigastric pain and vomiting	CDP	7.5	Head	SC	Digestive hemorrhage 18 months post-operatively
3	26	F	Epigastric pain	Distal pancreatectomy	4.5	Tail	MC	No recurrence 2 years post-operatively then was lost to follow-up
4	37	F	Epigastric pain, vomiting Altered general health	Tumor enucleation	10	Tail	MC	No recurrence 1 year post-operatively then was lost to follow-up
5	68	F	Epigastric pain	Tumor enucleation	2	Head	MC	No recurrence 5 years post-operatively then was lost to follow-up
6	24	F	Painless abdominal mass	Distal pancreatectomy and splenectomy	10	Tail	MC	No recurrence 9 years post-operatively then was lost to follow-up
7	31	F	Dyspnea	Tumor enucleation	6.5	Head	SPPN	Favorable evolution
8	21	F	Abdominal pain, vomiting, fever	CDP	9	Head	SPPN	Favorable evolution
9	56	M	Abdominal pain, jaundice, fever	CDP	4,5	Head	IPMN + invasive ductal ADC	Peritoneal carcinomatosis 1 year post-operatively
10	42	F	Incidental Finding	CDP	10	Head	MCC	Died 18 months post-operatively ovarian and colonic metastases

ADC: Adenocarcinoma, CDP: Cephalic duodenopancreatectomy, MC: Mucinous cystadenoma, MCC: Mucinous cystadenocarcinoma, SC: Serous cystadenoma

mucinous cystadenoma, and serous cystic neoplasm. On CT scan, serous, and mucinous cystadenomas [Figure 1a] presented as well-delineated non-enhancing hypodensemasses. Solid pseudopapillary neoplasms appeared as heterogeneous, mixed solid-cystic enhancingmasses [Figure 2a]. Intraductal papillary mucinous neoplasm with invasive carcinoma presented as a well-delineated heterogeneous hyperdense cystic mass [Figure 3a]. Mucinous cystadenocarcinoma presented as a well-delineated multilocular hyperdense heterogeneous mass with peripheral calcifications. On MRI, one case of SPPN presented as a heterogeneous pancreatic mass hyperintense on T2 and hypointense on T1. On MRI, mucinous cystadenocarcinoma presented as a heterogeneous cystic and solid enhancing mass.

Pathologic findings

Macroscopic findings

Based on macroscopic findings, cystic tumors of the pancreas ranged in size from 2 to 10 cm (mean = 6.75cm). On cut section, serous cystic neoplasms presented as well-circumscribed round, sponge-like lesions composed of numerous tiny cysts filled with serous fluid. Mucinous cystadenomas were unilocular in two cases and multilocular in two cases filled with either thick mucin (n = 3) [Figure 1b] or a mixture of hemorrhagic-necrotic material with no papillary projections in the internal surface. Solid pseudopapillary neoplasms presented as large round solitary mixed solid-cystic masses with brown to yellow solid areas and zones of hemorrhage, necrosis and cystic degeneration [Figure 2b]. Intraductal papillary mucinous neoplasm with invasive carcinoma presented as an irregular dilated mucin-filled main pancreatic duct with foci of hemorrhage and thickening of the surrounding pancreas [Figure 3b]. Mucinous cystadenocarcinoma was grossly multilocular and the locules contained mural nodules.

Microscopic findings

Histopathological examination of the surgical specimen established the diagnosis of mucinous cystadenoma (n = 4) [Figure 1c], SPPN (n = 2) [Figure 2c], serous cystic neoplasm (n = 2), mucinous cystadenocarcinoma (n = 1) and intraductal papillary mucinous neoplasms (IPMN) with invasive carcinoma (n = 1) [Figures 3c and d]. Immunohistochemical study was performed in two cases of SPPN and revealed thatthe tumor cells were positive for CD10, cytokeratin, βeta-catenin [Figure 2d], vimentin, and progesterone receptors but they were negative for chromogranin A and synaptophysin.

Discussion

Although cystic tumors of the pancreas are relatively rare, they constitute an increasingly important category. Advances in imaging and interventional techniques and the sharp drop in the mortality rate of pancreatic surgery have rendered pancreatic biopsies and resections commonplace specimens. Consequently, in the past two decades, the nature of many cystic tumors in this organ has been better characterized.[4-6] As the spectrum of diseases classified as cystic neoplasms can range from benign to frank malignancy and most of the patients

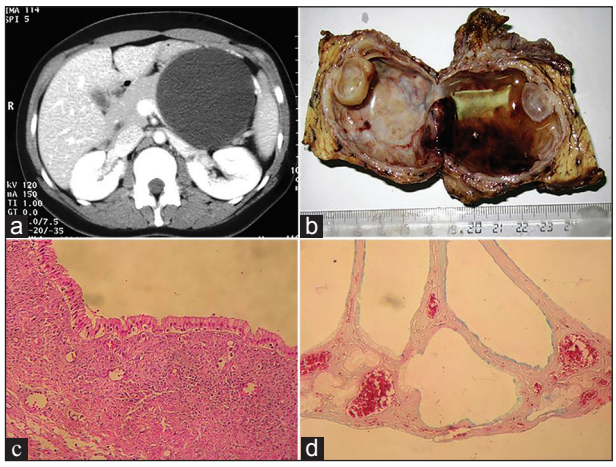

Figure 1: Mucinous cystadenoma: Radiological and pathological findings (a) Computed tomography scan demonstrating a well-delineated non-enhancing hypodense mass (b) Macroscopic findings: A well-circumscribed, multilocular cystic tumor with a fibrous capsule of variable thickness and a smooth internal surface (c) The cyst was lined by columnar mucin-containing epithelium with sub-epithelial stroma (hematoylin and eosin × 400). (d) The epithelial lining of the cyst stained with alcian blue (alcian blue × 100)

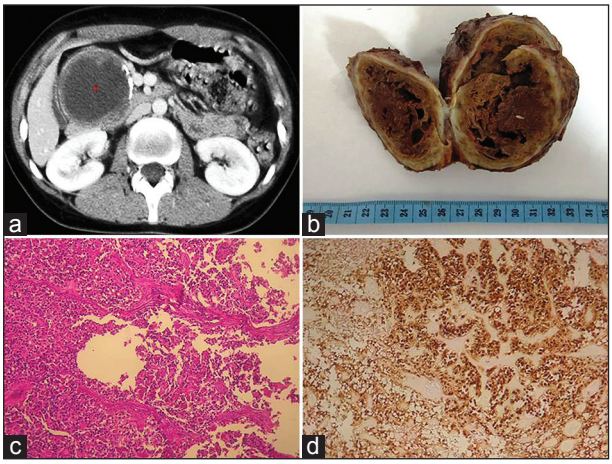

Figure 2: Solid pseudopapillary neoplasm: Radiological, pathological, and immunohistochemical findings (a) Computed tomography scan displaying a heterogeneous, mixed solid-cystic-enhancing masses (b) Macroscopic findings: Large round solitary mixed solid-cystic mass with brown to yellow solid areas and foci of hemorrhage, necrosis, and cystic degeneration (c) Heterogeneous growth pattern with a combination of solid and pseudopapillary structures (hematoylin and eosin × 100) (d) Tumor cells showing positive immunostaining with beta-catenin, (immunohistochemistry × 100)

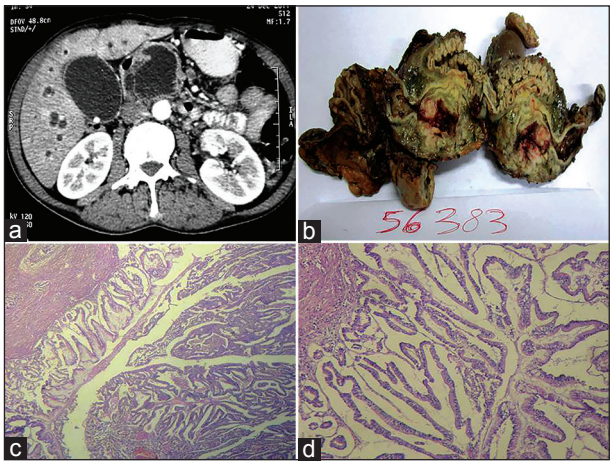

Figure 3: Intraductal papillary mucinous neoplasm: Radiological and pathological findings (a) Computed tomography scan showing a well-delineated heterogeneous hyperdense cystic mass (b) Macroscopic findings: Irregular dilated mucin-filled main pancreatic duct with foci of hemorrhage and thickening of the surrounding pancreas (c) Intraductal proliferation of columnar mucin-producing cells arranged in a papillary pattern (hematoylin and eosin × 40) (d) Intraductal papillary mucinous neoplasm: Papillae lined by columnar cells with pseudo-stratified cigar-shaped nuclei and basophilic cytoplasm (hematoylin and eosin × 200)

are detected asymptomatically, the condition presents a particular dilemma for the managing clinician. This difficult situation is further compounded by the frequent inability in establishing a definitive diagnosis preoperatively.[7] Imaging modalities range from the basic ultrasonography for screening and detection, to higher definition cross-sectional imaging methods such as CT and MRI, to invasive methods such as endoscopic ultrasound (EUS) and radionuclear imaging such as positron-emission tomography (PET) scanning.[7] EUS is widely used to perform fine needle aspiration in order to provide fluid for cytological analysis and tumor markers or amylase testing, which plays an important role in diagnosis of pancreatic cystic neoplasm.[5,6] It can also be used to analyze morphological features of pancreatic cystic neoplasm. Until today, surgery is considered the best management option for pancreatic cystic neoplasms. It has a number of benefits, including long-term survival of patients, relief of symptoms, and diagnostic certainty based on histopathological examination. The World Health Organisation (WHO) classifies cystic neoplasms of the pancreas into 3 main categories: benign, premalignant, and malignant.[8] The major histologic subtypes include (a) serous cystic neoplasms (SCN), (b) mucinous cystic neoplasms (MCN), (c) IPMN), and (d) SPPN).[8-11] Rarer types include cystic pancreatic endocrine neoplasms (PEN), cystic ductal adenocarcinomas, and acinar cell cystadenomas.

MCN are relatively rare, accounting for about 8% of surgically resected cystic lesions of the pancreas.[9] MCN are precancerous lesions that evolve to invasive adenocarcinoma in 30% of cases.[12] MCN are formed by mucus-producing cells and the presence of ovarian-like stroma is now considered a prerequisite for diagnosis. If an invasive carcinoma is present, the neoplasm should be classified as a mucinous cystadenocarcinoma. MCN almost always occur in females predominantly the middle-aged and often in the body or tail of the pancreas.[9,12,13] At present, all MCN are considered at least potentially malignant and all surgically-fit patients should undergo surgical resection. The prognosis of patients after resection is significantly better when compared with patients with primary ductal adenocarcinoma of the pancreas.

The second most common primary cystic neoplasmof the pancreas is serous cystic neoplasm, representing 1-2% of all pancreatic neoplasms and 30% of all cystic pancreatic neoplasms.[14] Previously termed serous cystadenoma, SCN are lined by simple glycogen-rich cuboidal epithelium. Malignant change although reported, is extremely rare and the condition is considered benign. There is a female predilection and occurrence is mostly in the sixth decade.[7,14] SCN can exhibit macroscopic variations in locule size and are now subdivided into: (a) serous microcystic and (b) serous oligocystic adenomas.[8] The definitive management of SCN is surgery. However, with asymptomatic tumors management remains controversial; although most would observe, a recent study suggests that large (> 4cm) SCN have a tendency to increase in size and cause symptoms at a later date which may support the role of "prophylactic resection" in this subgroup of patients.

Intraductal papillary mucinous neoplasm are precancerous lesions currently estimated to account for 1-3% of exocrine pancreatic neoplasms and for 20% of all cystic neoplasms of the pancreas.[15] IPMN are more common in the elderly with a median age at diagnosis of about 66 years. The mean age of patients with IPMN without an associated invasive carcinoma is 3-5 years younger than the mean age of patients with IPMN with an associated invasive carcinoma.[7,15] IPMN is now considered a distinct entity from MCN and like MCN produce mucin. A communication with the pancreatic duct is invariable and patients may present with pancreatitis from ductal obstruction. Approximately 30% of resected IPMN have an associated invasive carcinoma as it was the case in our patient. It is generally agreed that all main-duct IPMN should be surgically resected because of the significant risk of high-grade dysplasia or an invasive carcinoma. The prognosis of IPMN with an associated invasive carcinoma is significantly worse than for noninvasive IPMN. The 5-year survival rates for IPMN with an associated invasive carcinoma are reported to be between 27 and 60%.[7]

SPPN are rare low-grade malignant neoplasms, accounting for 0.9-2.7% of all exocrine pancreatic neoplasms and only 5% of cystic neoplasms.[7] They occur predominantly in adolescent girls and young women (90%) with a mean age of 28 years (range: 7-79 years). SPPN have a distinctive microscopic appearance. The growth pattern is heterogeneous, with a combination of solid, pseudopapillary, and hemorrhagic-necrotic, pseudocystic structures in various proportions. The tumor cells are poorly cohesive monomorphic admixed with hyalinized to myxoid stromal bands containing thin-walled blood vessels. Immunohistochemically, all SPPN express alpha-1-antitrypsin, alpha-1-antichymotrypsin, NSE, vimentin, progesteron receptors, CD10, CD56, claudin 5 et 7, galectin 3, cyclin D1, and nuclear/cytoplasmic β-catenin. Metastases occur in 5-15% of cases usually to the peritoneum and liver.[7]

In summary, cystic neoplasms of the pancreas are relatively rare but constitute an increasingly important category with a challenging differential diagnosis. In contrast with solid tumors of this organ, most of which are ductal adenocarcinomas with dismal outcomes, the vast majority of cystic neoplasia is either benign tumors or low-grade malignancies with indolent behavior. An appropriate differential diagnostic modality is critical for patients with pancreatic cystic neoplasms to avoid unnecessary surgery.

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