



ORIGINAL ARTICLE

SOLID PSEUDOPAPILLARY TUMOR OF THE PANCREAS: ANALYSIS OF CLINICOPATHOLOGICAL FEATURES AND SURGICAL OUTCOMES

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Abstract

Background: Solid-pseudopapillary tumor (SPT) of the pancreas is an uncommon pancreatic neoplasm with a low-grade malignancy that occurs mainly in young women. This study was undertaken to analyze the clinicopathological characteristics of the disease and to evaluate the outcome of surgical intervention in a tertiary referral cancer centre.

Methods: A prospectively maintained database of the characteristics of 14 patients (13 females and 1 male), with a mean age of 21.6 years (range 17-34 years) who underwent surgical resection in our institution with a definitive histological and immunohistochemical diagnosis of SPT between 2002 and 2012 was developed and analyzed. **Results:**

5 cases (37%) presented with dull aching pain, palpable mass in 3 cases (21%), with incidental detection in 3 cases (21%). The tumor was located in the body/tail in 12 cases and in the head in 2 patients. Mean tumor diameter was 10.7cm (range 5-21). Tumors of the head were smaller (average 6.3 cm) but more symptomatic than those in the body-tail (average 13 cm). None of the patients had metastases at presentation. 2 cases underwent pancreaticoduodenectomy, 2 enucleations, while 10 patients had left pancreatectomy. All cases were positive for nuclear β -catenin, and negative for membranous E-cadherin immunoreactivity. Overall morbidity rate was 22% with no mortality. At a median follow-up of 62 months (range 15-110), all patients are alive without evidence of local recurrence, metastasis, but one case of diabetes developed.

Conclusion: SPT is an indolent neoplasm with characteristic macroscopic, microscopic, and immunohistochemical features. The low grade biological aggressiveness makes surgical resection possible despite its large size and patients can survive a long period after the operation.

Keywords: Pancreatic neoplasm, Solid pseudopapillary tumor, Diagnosis; Treatment, Prognosis.

INTRODUCTION

Solid pseudopapillary tumor (SPT) of the pancreas, first reported by Frantz in 1959,⁽¹⁾ is an uncommon pancreatic neoplasm with a low malignancy, accounting for 1%-2% of all pancreatic tumors.⁽²⁾ It is a particular

neoplasm with an unknown origin and this obscure nature was reflected in many descriptive names in the past including papillary cystic tumor, solid and cystic tumor, solid and papillary tumor, and Frantz tumor.⁽³⁻⁵⁾

In 1996 World Health Organization (WHO) defined and

named this tumor as a "solid pseudopapillary tumor" of the pancreas.⁽⁶⁾

It is almost exclusively seen in females and occurs in the second or third decades of life.^(7,8) It is an indolent malignant neoplasm with a protracted clinical course for which complete resection is curative in most cases. Metastases are found in only 15% of cases usually to liver or peritoneum.^(4,5) In spite of few reports on some highly aggressive varieties,⁽⁹⁾ death as a result of this tumor is rare, even patients with metastases. Due to the limited number of reports in the literature, the natural history of the disease is not fully understood. There has been a steady increase in the number of diagnosed cases of SPT recently, with more than two-thirds of the total cases described in the last decade.⁽²⁾

This study was undertaken to report the clinicopathological characteristics of patients with solid pseudopapillary tumors (SPT) and to evaluate the outcome of surgical intervention in a tertiary referral cancer centre.

PATIENTS AND METHODS

A prospectively maintained database of the characteristics of 14 patients, histologically diagnosed of SPT submitted to surgical resection in our Institution between 2002 and 2012 was developed. The data analyzed included age, gender, clinical presentation, tumor location and size (from radiological investigations, surgical record and as confirmed by pathology), pathological and immunohistochemical features, complications, metastasis or invasion of adjacent tissues (from radiological investigations or surgical exploration, and as confirmed by pathology), treatment (including the types of surgery), and follow-up.

Patients demographics included; 13 females and 1 male, with a mean age of 21.6 years (range 17-34 years). All patients underwent routine tests for blood sugar, liver function and tumor markers (AFP, CEA, CA19-9 and CA125), an ultrasound and CT scan of the abdomen. All cases of SPT underwent surgical resection. The procedures included local tumor resection (2/14), distal pancreatectomy with splenectomy (9/14), pancreaticoduodenectomy (2/14) and distal pancreatectomy without splenectomy (1/14). All the patients who underwent resection were followed up every 6 months.

Pathological examination: All specimens were examined histopathologically by the same pathologist. Description of the gross morphology, and histopathologic features on H&E stained sections was done. Immunohistochemical stains of all cases for β -catenin and E-cadherin were performed using an avidin-biotinylated immunoperoxidase methodology. Both primary antibodies were mouse monoclonal. For β -catenin clone 14/b-catenin (Biocare Medical, LCC, USA) at a dilution of 1:100 was used, while for E-

cadherin clone 36B5 (Neomarkers, Lab Vision Corporation, Thermo Fisher Scientific Inc., USA) at a dilution of 1:20 was used. The bound antibodies were detected by the UltraVision Detection System Anti-Polyvalent, HRP/DAB (Ready-To-Use) (Neomarkers, Labvision, USA). Positive and negative control was included in all runs.

Evaluation of immunostaining: Overexpression of nuclear β -catenin was defined as a reactivity of >50% of the tumor cell nuclei. For E-cadherin scoring of positive tumor cells was done semiquantitatively using a cut off of 50% to classify tumors as high or low expressors. Cases were classified as negative when no single tumor cell showed membranous E-cadherin immunostaining in the presence of positive controls.

RESULTS

In three patients (21%), the diagnosis of pseudopapillary tumor of the pancreas was incidental, with the tumor found at routine physical or radiological examination. In 11 patients (79%), the presenting symptoms were vague and non-specific, and coexistence of two or more symptoms was usually found (Table 1). The prevailing symptoms were dull aching and non-specific abdominal pain in 5 cases (37%) and the presence of palpable mass located in the upper left abdominal quadrant in 3 cases (21%). The most common sites of the tumor were the body and tail (65%), pancreatic head (14%), tail only (7%), body only (7%), and neck (7%).

Table 1. Presenting symptoms for the studied population with Solid pseudopapillary tumor of the pancreas.

Symptoms	Patients (n)	Percentage (%)
Abdominal mass	3	21%
Abdominal pain	5	37%
Back pain	2	14%
Asymptomatic	3	21%
Jaundice	1	7%

The laboratory tests were within the normal values with the exception of one patient with jaundice. All 14 patients underwent abdominal ultrasound and CT scan with additional abdominal MRI was used in two patients and MRCP in one patient. The level of tumor markers, including α -fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), and CA125, was slightly increased in 2 patients, but only one was diagnosed as malignant SPT. The masses were shown on cross-sectional imaging as heterogeneous (n=11,79%), cystic (n=1,7%), or solid (2,14%).

Macroscopically all the cases were well-circumscribed single masses. The tumor diameter ranged from 5 to 21 cm with a mean of 10.7 cm. Tumors located at the head of the pancreas had a mean size of 6.3 cm in contrast to

13 cm for those located in the body/tail of the gland. Well defined capsule was present in 57% (8/14), with internal necrotic-hemorrhagic areas in 29% (4/14) of patients. The aspect was solid in 79% of cases (11/14) as illustrated in (Figs. 1-3). The cut surface revealed a solid tumor in 58%, solid-cystic tumor in 35%, with foci of hemorrhage and necrosis and a cystic tumor in 7%.

Microscopically all cases showed tumor cells arranged in the form of solid sheets and microcysts with pseudopapillary areas. The pseudo-papillae featured fibrovascular cores surrounded by several layers of polygonal cells that had moderate eosinophilic to vacuolated cytoplasm. The nuclei were ovoid and folded with indistinct nucleoli and few mitoses. Regional cystic degeneration, hemorrhage, necrosis, aggregates of foamy histiocytes, and cholesterol clefts were common. Despite being macroscopically well circumscribed, there was microscopic coalescence between the tumor and the surrounding normal pancreatic tissue. Enlarged lymph nodes and lymph node metastasis were detected in 3 and 2 patients; respectively. None of the cases had vascular infiltration or fixation to mesenteric, portal or splenic vessels. Distant metastases were not detected in any case and all the lesions were potentially resectable at the end of the diagnostic work-up.

Correct preoperatively diagnosis for SPT was reached in only three patients (21%), while an incorrect diagnosis was made in 4 patients (29%): non-functioning neuroendocrine tumor in two patients, mucinous cystic neoplasm in one case, and pancreatic carcinoma in one case. Indeterminate diagnosis of a focal pancreatic neoplasm was made in the remaining cases (50%). In four cases, a CT guided fine-needle biopsy was performed with a correct diagnosis achieved in only two of them. One case was not diagnostic, and the other was misdiagnosed as neuroendocrine tumor.

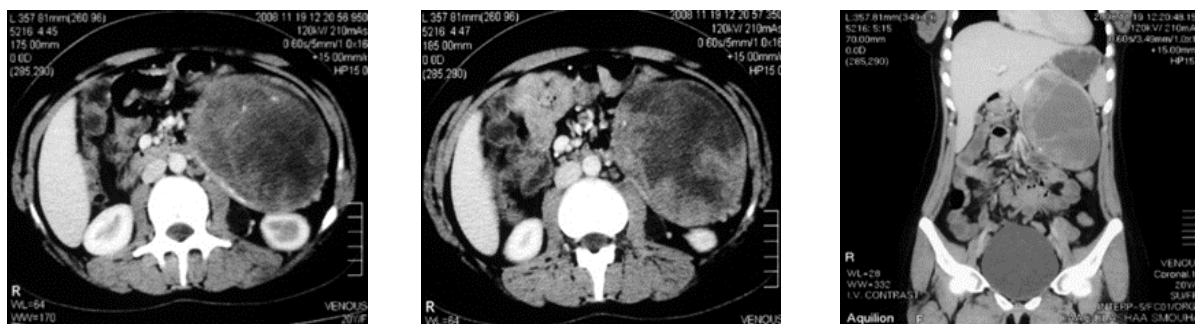
Surgery performed included two

pancreaticoduodenectomy procedures (one Whipple procedures and one pylorus-preserving), 10 distal pancreatectomy operation (9 with splenectomy and one with spleen preservation) while two patients underwent atypical local resections (enucleation) as illustrated in Table 2. The latter was performed in two cases for relatively small tumors; one exophytic from pancreatic neck and the other in the body of the pancreas. Intra-operative frozen section was of help to ascertain the adequate resection of margins especially in local resections. Blood transfusion was needed in five patients during surgery. During the perioperative period, there was no mortality and the morbidity was 22%. The most common complication after operation was pancreatic fistula which occurred in three cases (Grade A), all fistulas settled shortly after conservative treatment. Other complications included wound infection and delayed gastric emptying, were observed in 2 and 1 patient, respectively. The mean hospital stay was 7 days (range 4– 16 days).

Table 2. Types of surgical procedures performed in 14 patients with solid pseudopapillary tumor of the pancreas.

Operative procedure	Patients (n)	Percentage (%)
Distal pancreatectomy with splenectomy	9	65%
Pancreaticoduodenectomy	2	14%
Local tumor resection	2	14%
Distal pancreatectomy Without splenectomy	1	7%

After a median follow-up of 62 months (range 15– 110m), all patients are disease free with no local or distance recurrences observed. At present, no patient is under pancreatic enzyme therapy while two cases of diabetes were observed.

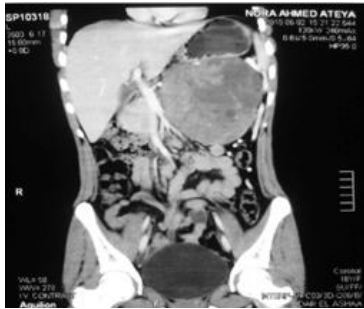


(a) CT of a SPT of the body and tail of pancreas.



b) Operative pictures of distal pancreatectomy with splenectomy.

Fig 1. Solid Pseudopapillary tumor of the body and tail of pancreas.



a



b



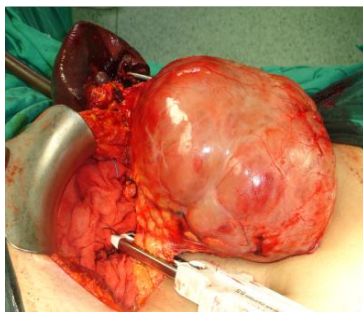
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CT (a) and operative pictures (b&c) of SPT of the pancreas with cystic-solid components treated with distal pancreatectomy with splenectomy.

Fig 2. Solid Pseudopapillary tumor of the body and tail of pancreas.



a) CT pictures of SPT of the body of pancreas



b) Operative pictures of distal pancreatectomy with splenectomy.

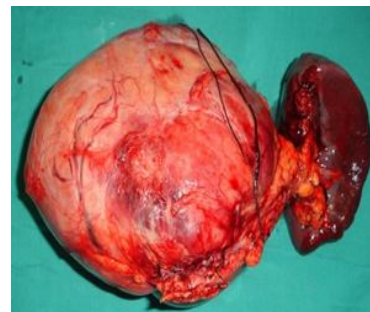


Fig 3. Solid Pseudopapillary tumor of the body of the pancreas.

DISCUSSION

Solid pseudopapillary tumor (SPT) is a rare tumor with a protracted clinical course. Its pathogenesis still remains unknown, although its tendency to affect young women was attributed to the involvement of sex hormones. However, no difference has been found in immunohistochemical staining for sex hormone-receptor proteins or in clinicopathologic characteristics attributable to gender alone.⁽¹⁰⁾ In our series, all the patients except one were females with a median age of 21 years. Our experience confirms that SPT prevalently affects women in the second and third decade of life. The immunoprofile of SPT in our male patient didn't differ from the female profile with a remarkable high expression of progesterone receptors.

While some of its morphological and immunohistochemical features support the idea that it originates from multipotent cells that have not differentiated into either endocrine or exocrine cells.⁽¹¹⁻¹³⁾

The immunohistochemical pattern of SPTs is characterized by the frequent expression of NSE, a common neuroendocrine marker. However, the absence of chromogranin A and the low-expression of other endocrine markers suggests that SPTs cannot be regarded as "pure" endocrine neoplasms. Furthermore, the production of hormones or neuropeptides by SPTs has never been demonstrated.^(4,5,11,12) The complex immunoprofile of SPTs fails to reveal a clear phenotypic relationship with any of the defined cell lineages of the pancreas.

Histopathologically, it is known that both SPT and pancreatic endocrine tumors (PET) could be arranged as solid areas and the size and shape of the tumor cells are relatively uniform with round or oval nuclei and vacuolated or eosinophilic cytoplasm. It is sometimes difficult to distinguish these two tumors if only such histological pattern was used as the diagnostic basis. Also, the immunohistochemical findings reported in early literature were of variation with absence of a specific immunoprofile. There was overlap of positive expression on immunostaining using such markers as α 1-antitrypsin, α 1- antichymotrypsin, NSE, Syn, progesterone receptor, carcinoembryonic antigen, pan CK, vimentin, CD10, CD56, and cyclin D1, so that immunohistochemistry was incapable of giving much helpful additional information for the differential diagnosis of SPT.⁽¹⁴⁾

However, in the current study, the detection of pseudopapillary structures indicating evidence of cellular dyscohesion, cholesterol clefts, and aggregation of foamy histiocytes, helped to settle the H&E based diagnosis of SPT from PET. Further confirmation was achieved via the characteristic immunohistochemical profile of SPT being positive for nuclear β -catenin expression, and negative for membranous E-cadherin immunostaining. Thus our findings go in accordance with literature reports.⁽¹⁵⁻¹⁸⁾ that showed that nuclear

expression of β -catenin and loss of E-cadherin were seen in nearly all cases of SPT. Thus, the application of E-cadherin and β -catenin possess highly sensitivity and specificity in diagnosis.

Sun et al⁽¹⁹⁾ reported that 62.5% of SPT patients are infected with hepatitis B virus (HBV), which can induce over-expression of β -catenin in tumor cells, indicating that HBV infection may be involved in the pathogenesis of SPT, which, however, has not been confirmed. In our experience and in spite of Egypt being one of the countries with high predominance of hepatitis C and to a lesser extent hepatitis B infection, none of our patients tested positive for either of them.

SPT may be discovered by chance during routine clinical or imaging procedures or may be suspected in the presence of an asymptomatic palpable mass in young women. In our series, 21% were accidentally discovered, five patients presented with dull aching abdominal pain, while three patients presented with an abdominal mass. The clinical presentation of SPT is usually unspecific. Most patients have unclear clinical features including abdominal pain or discomfort, poor appetite and nausea, which are related to tumor compression on adjacent organs.

In our study, 80% of cases, the neoplasm was located in the body-tail of the pancreas, in contrast that reported in the WHO classification.⁽²⁰⁾ The tumors located in the head was smaller (average of 6.3 cm) but more symptomatic than those in the body-tail (average 13 cm) and none of them was incidentally discovered. Solid pseudopapillary tumors (SPTs) have not been associated with specific tumor serum markers,⁽²¹⁾ which was confirmed by the present study.

In our series, we relied on CT imaging for the preoperative work-up. The SPTs are well-encapsulated complex mass with both solid and cystic components. Dynamic contrast-enhanced CT can show less enhanced tumor, typical cystic spaces in the center, and enhanced solid areas at its surroundings.⁽²²⁾ Calcifications and septa are characteristic features of SPTs. MRI didn't add further diagnostic data in our study, but MRCP was used only in jaundiced patients with pancreatic head SPT compressing the common bile duct. However, while imaging may be highly suggestive of a diagnosis, it is not specific.⁽²³⁻²⁵⁾ In our study a correct diagnosis preoperatively was obtained in only three (21%) of the cases.

Data concerning preoperative cytological tests are conflicting.⁽²⁶⁾ The most conclusive criterion for identification of SPT is the pseudopapillary arrangement with bland appearing tumor cells. Percutaneous or EUS-guided fine-needle aspiration (FNAC) can help to distinguish SPT from other pancreatic tumors. However, reports are also available on seeding of the needle track by neoplastic cells and complications such as bleeding, pancreatic fistula and biliary fistula during the procedure.⁽²⁶⁾ In our series, we submitted only 4 of

14 patients to pre-operative percutaneous US-guided FNAC; and in agreement with previously published series, the presence of a "solid" resectable tumor in young patients has negatively influenced our strategy about the utility of fine-needle aspiration.⁽²⁷⁻²⁹⁾ We didn't experience any complication related to biopsy taking and the diagnostic accuracy of FNAC was 50 %. The results of our study show that it was not necessary to have a tissue diagnosis pre-operatively, where CT/MRI scans combined with age and gender should be sufficient for the decision to operate, and diagnostic interventions such as FNAC should be performed when radiology fails in diagnosing it.

Despite the large size of the tumor, surgical excision was possible in all our cases. On surgical exploration, no severe adhesion or invasion of the SPT to the adjacent organs and near-by vessels was grossly noted. Lymph node enlargements were confirmed to be benign, reactive hyperplasia on pathology except in 2 patients. There was no case of perioperative mortality. Another characteristic feature of our series is the low incidence of diabetes after distal pancreatectomy (one cases) which is much less than commonly reported after distal pancreatectomy.

It has been reported that the overall 5-year survival rate of SPT patients is about 95%.⁽³⁰⁾ Due to the favorable prognosis and long survival rate of SPT patients with local recurrence or metastasis, it is difficult to identify the predictive factors for their survival time. Tang et al. have reported an overall 5-year survival rate of 97% in a series that includes seven cases of SPTs with liver metastases in an experience of 36 patients resected at the Memorial Sloan-Kettering Cancer Center.⁽⁹⁾ In our study and during a median follow-up of 62 months, neither long-term complications nor local recurrences or metastases were observed in all 14 patients.

In conclusion, SPT of the pancreas is an infrequently-encountered tumor with benign or low-grade aggressiveness, typically affects young women without significant symptoms. Macroscopically, the solid cystic or cystic cut section, and the presence of hemorrhage and necrosis, added to the pseudopapillary structures on light microscopy supports the pathologic diagnosis. Further confirmation by β -catenin and E-cadherin immunostaining is recommended when necessary. Unfortunately, at present, preoperative information does not allow a definitive diagnosis in all cases. A high index of clinical suspicion is necessary and the diagnosis should be borne in mind when young female patients present with a pancreatic mass. Despite the large tumor size, resection plays a fundamental diagnostic role and at present represents the only therapeutic choice that can achieve long term survival.

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