

SOLID PSEUDOPAPILLARY TUMOR OF THE PANCREAS: CLINICAL-PATHOLOGICAL FEATURES AND MANAGEMENT OF 13 CASES

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Abstract

Background and aim. *Solid pseudopapillary tumor (SPT) of the pancreas is a rare pathological condition, representing less than 3% of all exocrine pancreatic tumors. SPT usually occurs in young females, without notable symptoms, with a low malignant potential and excellent prognosis.*

Method. *We conducted a retrospective study during the period January 2005 - January 2015. SPT patients admitted in our institution were reviewed by describing demographic data, clinico-pathologic and radiological features, therapeutic management and prognosis records.*

Results. *Thirteen patients with SPT were identified (10 females), with a median age of 30 years. The main clinical presentation was abdominal pain (92.3%). The tumor was mostly located in the body or tail of the pancreas (77%), and the mean size was 8.2 cm. Regarding the surgical approach there were 5 distal pancreatectomies with splenectomy, 3 body and tail pancreatectomies, 2 body and tail pancreatectomies with splenectomy, 2 pancreato-duodenectomy, 1 partial enucleation and of all only 2 partial resections. Postoperative hematoxylin-eosin staining and immunohistochemistry confirmed the diagnosis in all cases. None of the patients had lymph nodes metastases. Only one local invasion. There was one case of death due to postoperative complications. Four cases followed adjuvant systemic chemotherapy. The mean follow-up was 18 months, without evidence of recurrence during this period.*

Conclusion. *SPT should always be considered in the differential diagnosis in young women with a pancreatic tumor. Complete surgical excision is the treatment of*

choice, and is usually curative. The decision to administer systemic therapy must be individualized. Malignant behavior and late recurrences mandates long-term follow-up for patients with SPT.

Keywords: solid pseudopapillary tumor, pancreas, SPT, treatment

Introduction

Solid pseudopapillary tumor (SPT) of the pancreas is a very rare pathological condition of the pancreas, which represents less than 3% of all exocrine pancreatic tumors [1,2]. More than 90% occur in young women, with a median age of 20-30 years [2-4]. Less than 10% of cases involve men and usually they are 10 years older than affected women [5,6]. A constant apparent growth of the incidence of this tumor has been noted in the past 2 decades, but this is probably due to improved imaging techniques and better recognition of the entity [7,8].

Solid pseudopapillary tumor of the pancreas was first described by Franz in 1959 as a papillary tumor of the pancreas [9]. Historically, SPT has been defined using terms such as papillary epithelial neoplasm, solid and cystic tumor, solid and papillary epithelial neoplasm, papillary and cystic neoplasm, and Franz tumor [9-12]. In 1996 the World Health Organization (WHO) formally named it as SPT and reclassified it to be a kind of boundary malignant tumor with unclear biological behavior. In 2010, the WHO [13] classified SPT as an epithelial low-grade malignant neoplasm.

It usually behaves in a benign manner, and total resection of the tumor is curative in more than 85% of patients. However, recurrence may occur in some cases, and a small percentage (less than 15%) of patients may develop metastases. Most commonly they occur in the peritoneum and liver [2,4,14], but they have been reported to affect also lymph nodes and the spleen. Carcinomatosis was also reported [6,15]. The overall survival rate at 10 years from surgical resection was over 90% [2,16]. Even in the presence of disseminated disease, long-term survival can be achieved with aggressive treatment, where not just complete resection but also metastasectomy is required [17].

These tumors are often large but the majority of patients show few or no symptoms, a lot of SPT being incidentally discovered. The clinical presentation of these patients is not specific, with symptoms such as abdominal pain, weight loss, vomiting or abdominal mass [6,8].

The exact pathogenesis of this tumor remains unclear, some authors postulated that it may arise from centroacinar cells located between pancreatic acini and ducts, while others say that it has an endocrine origin

[5,18,19]. However, almost all SPTs show nuclear staining for β catenin and point mutations in exon 3 of catenin (cadherin-associated protein), beta 1, the gene encoding β catenin, suggesting that the int/wingless family signaling pathway may play an important role in their tumorigenesis [15,20].

The aim of this study was to review our institution's experience and provide an update on current diagnosis and management of this pathology. To the best of our knowledge, we report the largest case series of Romanian patients with SPT.

Patients and methods

After the approval of the institution review board, we conducted a retrospective study to identify patients with SPT admitted to the Oncology Institute Prof. Dr. Ion Chiricuta, Cluj-Napoca, from January 2005 to January 2015. Our institutional database was used to identify patients with SPT during this period; thirteen cases were identified. Demographic data, clinical characteristics, radiological features, pathology, immunohistochemistry reactivity, therapeutic management and outcomes were recorded and analyzed.

Results

Thirteen patients were identified. Ten patients (77%) were women, with a male-to-female ratio of 1:3.3. The median age at diagnosis was 30 years (range 14-63 years). The main clinical presentation was abdominal pain (92.3%) followed by abdominal discomfort (69.2%). Other symptoms included anorexia, nausea and emesis. Two tumors were found incidentally (Table I). None presented with abnormal clinical laboratory tests, preoperative tumor markers, carbohydrate antigen 19-9 and carcinoembryonic antigen were both negative.

The most common initial imaging performed was abdominal ultrasound. Some patients also had computed tomography (CT) or magnetic resonance imaging (MRI). Imaging identified a well-circumscribed, heterogeneous (cystic and solid) mass with hemorrhagic features and lack of central enhancement in most cases (Figure 1 and 2). The tumor was mostly located in the body or tail of the pancreas (77%), and the mean size was 8.2 cm (3.5-15 cm).

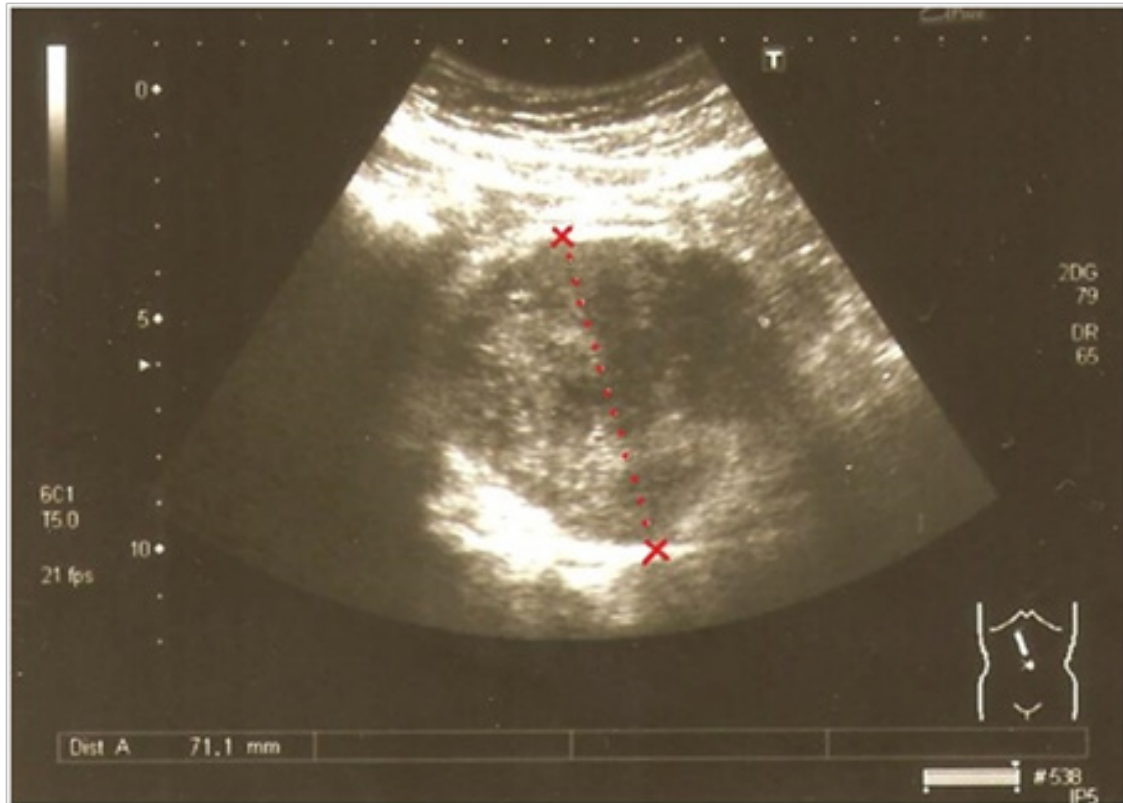


Figure 1. Abdominal ultrasound of SPT. A heterogeneous well-defined mass, apparently encapsulated, with areas of necrosis, hemorrhage, and cystic degeneration.

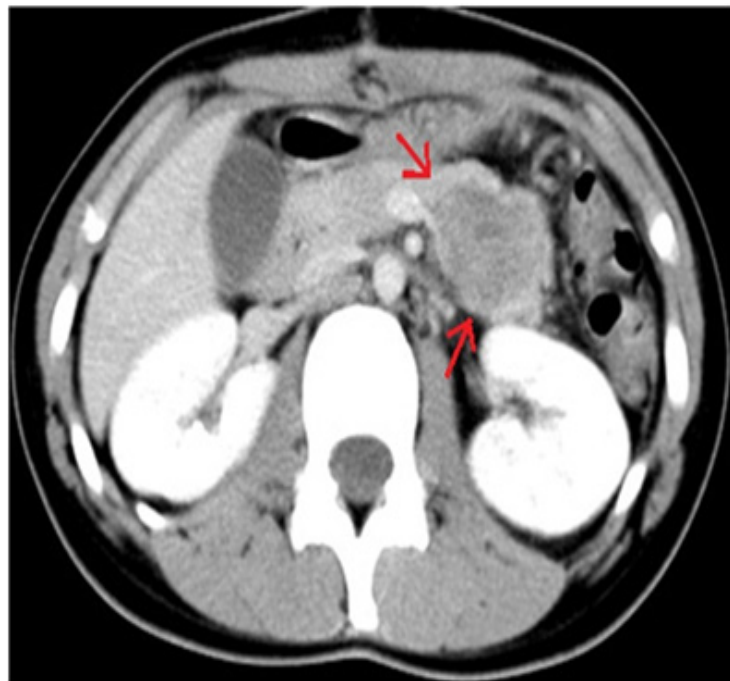


Figure 2. Computed tomography of SPT. The solid portion of SPT was moderately or obviously enhanced whereas the cystic part remained unenhanced.

Regarding the surgical approach, the majority of patients had a distal pancreatectomy with splenectomy (Table II), and of all 13 cases there were 2 partial resections. Most tumors were encapsulated or had a fibrous pseudocapsule, and all specimens demonstrated characteristic areas of hemorrhage and necrosis (Figure 1). Postoperative hematoxylin- eosin staining and immunohistochemistry confirmed the diagnosis in all cases. Most tumors had low or no mitotic activity and no perineural or lymphovascular invasion. None of the patients had lymph nodes metastases. We identified only one local invasion. There was one case of death due to postoperative complications. Four cases followed adjuvant systemic chemotherapy. The preferred protocol was Gemcitabine 1000mg/mp on days 1, 8, 15, for 6 cycles. The mean follow-up was 18 months, without any evidence of recurrence during this period.

Table I. Clinical presentation.

Symptom	%
Abdominal pain	92.3
Abdominal discomfort	69.2
Anorexia	23
Emesis	23
Bowel obstruction	7.7
Incidentally found	15.3

Table II. Surgical approach.

Type of surgery	No.
distal pancreatectomy with splenectomy	5
body and tail pancreatectomy	3
body and tail pancreatectomy with splenectomy	2
pancreato-duodenectomy	2
partial enucleation	1

Pathological findings

Microscopically, SPT is composed of poorly cohesive, monomorphic cells forming solid and pseudopapillary structures with fibrovascular cores lined by neoplastic cells and cystic spaces containing blood and necrotic debris. All 13 cases showed the characteristic feature of pseudopapillae, which are formed as a result of the cleavage of poorly cohesive neoplastic cells (Figure 3 and 4). Immunohistochemical stains are helpful in making the diagnosis of SPT. The cells are characteristically strongly positive for vimentin, a1-antitrypsin, a1-antichymotrypsin, CD10, progesteron receptor, neuron-specific enolase, CD56 and cyclin D1 [21,22]. In our cases, on immunohistochemistry (IHC), the tumor cells were consistently positive for vimentin (Figure 5) and CD10. We found positivity for neuron-specific enolase (NSE) (Figure 6) and progesterone receptors in all cases where IHC was performed (see Table III).

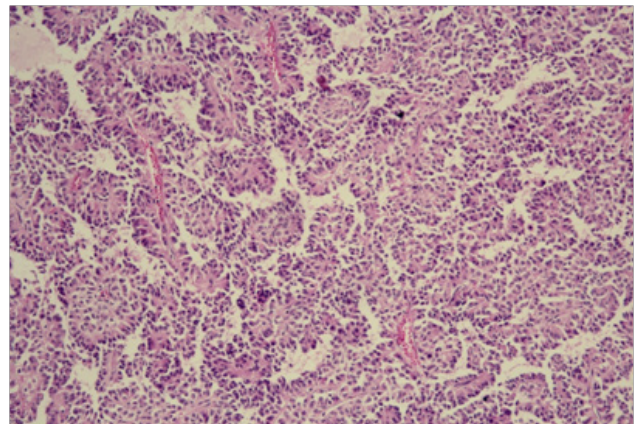


Figure 3. Pseudopapillary pattern with thin-walled blood vessels surrounded by poorly cohesive monomorphic cells. HE staining, ×200.

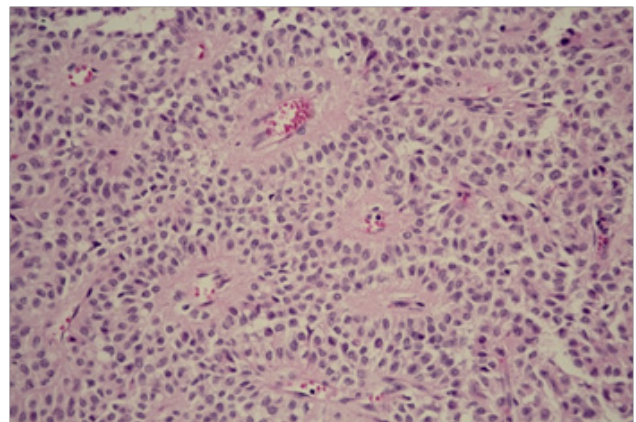


Figure 4. Neoplastic cells have round to oval nuclei, often grooved or indented, with a finely dispersed chromatin and small nucleoli. Very rare mitoses. HE staining, ×400.

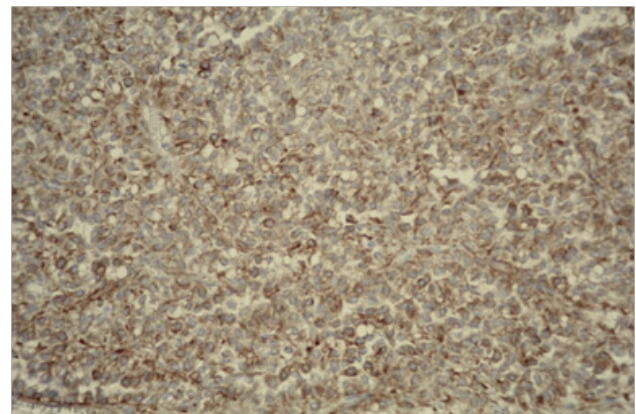


Figure 5. The neoplastic cells membrane has mild positivity for vimentin, with strong positivity of the basal pole. Vimentin immunohistochemistry, ×200.

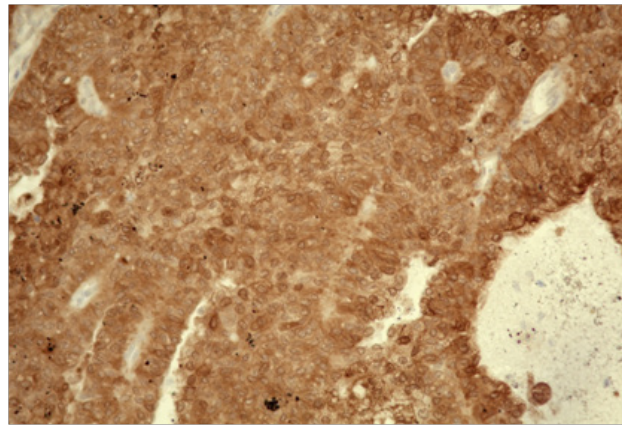


Figure 6. Neoplastic cells have strong and diffuse positivity for neuron-specific enolase. NSE immunohistochemistry, $\times 200$.

Table III. Immunohistochemistry reactivity.

Antigen	Marker	Positive	Negative	Not available
Positive staining				
Vimentin	Mesenchyme	13	0	0
CD10	Neuroendocrine	9	1	3
CD56	Neuroendocrine	6	0	7
Neuron-specific enolase	Neuroendocrine	7	0	6
Progesteron receptor	Hormone-proliferation	5	0	8
Variable staining				
Chromogranin	Neuroendocrine	3	9	1
Synaptophysin	Neuroendocrine	3	4	6
Cytokeratine	Epithelium	6	4	3

Benign vs. malignant SPT

Pathologically, SPT is considered malignant if it manifests pancreatic parenchymal infiltration, perineural invasion, angio-invasion, increased mitotic rate, peripancreatic soft tissue invasion, capsular invasion, lymph node involvement, adjacent organ invasion or distant metastases [23,24]. In our series we identified only 1 case with malignant features (peripancreatic soft tissue invasion). However, recurrence and metastasis cannot be excluded even in the absence of these findings, and, therefore, aggressive behavior is sometimes unpredictable and a rigorous follow-up after surgical resection is required [25,26].

Discussion

Solid pseudopapillary tumor of the pancreas is an uncommon condition, which was first reported by Frantz in 1959 and described as a new entity with solid and cystic components [9]. The last WHO classification from 2010 classified SPT as an epithelial low-grade malignant

neoplasm [13]. Worldwide SPT comprises less than 3% of all exocrine pancreatic tumors [1,2] and in Romania only few cases were reported in several studies [8].

These tumors show clear female predilection (male to female ratio 1:10) [2,5,6], however, in our series, we found a greater proportion of male patients (male to female ratio 1:3.3). Also we did not identify a more aggressive behavior in male patients or a difference in onset, compared to other studies [27].

The clinical picture is not relevant. Although, the majority of patients present large tumors located in the epigastrium or left hypochondrium, frequently they are asymptomatic or may present chronic abdominal pain. Rarely, the patients can experience acute abdominal pain due to the rupture of a cyst [28]. Exocrine or endocrine pancreatic insufficiencies have not been described and there are no specific tumor markers known [16]. In our series, the main clinical presentations were abdominal pain (92.3%) and abdominal discomfort (69.2%), without abnormal clinical laboratory tests or pancreatic insufficiencies.

Taking into account the fact that the symptoms are non-specific, imaging investigations, such as abdominal ultrasound, CT or MRI are mandatory. SPT presents as heterogeneous mass, apparently encapsulated, with areas of necrosis, hemorrhage, and cystic degeneration, which leads to the differential diagnosis with other similar tumors, such as: pancreatic pseudocyst, pancreatic adenocarcinoma, mucinous cystic tumors, mucus secreting tumors, microcystic adenoma, islet cell tumor, cystadenocarcinoma, pancreaticoblastoma and vascular tumors [6].

Several studies have confirmed that EUS–fine-needle aspiration is a reliable tool that significantly increases diagnostic accuracy by characterizing the cytopathological features [29,30]. To ensure a better surgical approach, a clear preoperative diagnosis of SPT is preferable.

Similar to the results of Lee et al. [17] who reported 80.9% of SPTs to be located in the body or tail of the pancreas, our series describes the involvement of the body or tail of the pancreas as the most frequent, being noted in 77% of cases. The most common surgical procedures were distal pancreatectomy with splenectomy, followed by simple body or tail pancreatectomy.

The pathogenesis and origin of SPT of the pancreas remain uncertain, the inconsistent immune profile of SPTs fails to reveal a clear phenotypic relationship with any of the defined pancreatic cell lineages [4,28,31,32]. Although it has been suggested to be associated with a mutation of beta-catenin, identified in almost all tumor cells, which results in diffuse cytoplasmic and aberrant nuclear expression of β -catenin and is accompanied by a lack of membranous E-cadherin [15,33,34]. Unfortunately our case series lacks these tests. It was also suggested that because of the strong predilection for females and the common expression of progesterone receptors in tumor cells, SPTs might be hormone-dependent tumors [35-37]. Also, some cases of SPT exhibit neuroendocrine differentiation by consistent staining with CD56, CD10, neuron-specific enolase and occasionally focal reactivity for synaptophysin [21,22]. Our patients' immune profiles confirm data published in several studies, in which SPTs cells present progesterone receptors and neuroendocrine immunostaining profiles [2,11,32,34].

Pancreatic SPT is often located to the pancreas, but extrapancreatic SPT may occur in the retroperitoneum, mesentery, liver, great omentum, ovary, duodenum, stomach, or lung [38]. Usually it behaves in a benign manner, and total resection of the tumor is curative in more than 85% of patients. Even so, SPT can undergo malignant changes as it grows, these changes have been observed in 10-15% of cases [39,40]. The World Health Organization defines tumors with surrounding tissue invasion, perineural invasion, vascular invasion on microscopic pathology, and metastasis as malignant SPT [41]. Peripheral parenchymal infiltration is the most common manifestation of malignancy [42]. In our series we identified only one case with malignant characteristics, expressed by local

invasion, but without implication in patient outcomes. The regional lymph nodes, peritoneum, omentum, portal vein, spleen, duodenum, colon and lung can also be involved [2,26,43]. The liver is the most common organ affected by SPT metastases. Liver metastases can be discovered at diagnosis or even at 10-15 years postoperatively [44,45].

Despite the large tumor size at the time of diagnosis, surgical resection is usually possible and curative. Therefore, complete aggressive resection is the treatment of choice for these tumors even in the presence of metastases [6]. Resection of distant metastases should be performed at the time of primary resection and even in relapses. For liver metastases, other treatments include chemotherapy, alcohol injection, transcatheter arterial chemoembolization, radiotherapy, and liver transplantation [44]. After total resection of the tumor, most patients are cured, but there still remains a low risk of recurrence [19]. Surgical resection is the treatment of choice for SPTs even in cases of distant or local recurrences, moreover repeated surgical resection for recurrences can considerably prolong survival [46]. In children it is very important to recognize this entity because tumor resection can be performed without large safety margins. To avoid long-term complication, the preservation of pancreatic tissue and the spleen should be attempted in every child [47].

Long term complications, such as endocrine or exocrine pancreatic insufficiency are very important, but are rarely described in literature. Our study did not identify any patient with this kind of complications. Taking into account the amplitude of surgery necessary to excise these large tumors, immediate postoperative complications may occur, and some can be extremely severe, such as wound infection, pancreatic pseudocyst and pancreatic fistula [48,49]. Pancreatic fistula with secondary peritonitis was the cause of death in one patient of our cases. To avoid this complication, this type of surgical resection should be performed only by well-trained surgeons and only in specialized centers.

Despite all these possible complications, surgery is the cornerstone of SPT treatment. For inoperable cases and for malignant SPTs with aggressive features a multimodal approach has been tempted, but so far there is limited experience with chemotherapy and radiotherapy, with no reliable data for these low-grade tumors [36,50,51]. In table IV we summarized the complementary treatment modalities identified in the literature. Although only 1 patient of the present series showed malignant characteristics, the Gemcitabine-based systemic chemotherapy was administered in 4 cases. Taking into consideration that there is not sufficient data regarding the benefits of chemotherapy or radiotherapy in SPT treatment, and that in more than 85% of patients surgery is curative, the decision to administer systemic therapy must be individualized.

Table IV. Complementary treatment modalities.

Neoadjuvant	Adjuvant
Gemcitabine 1000 mg/mp, day 1,8,15 [51]	Gemcitabine [40,54]
Gemcitabine 800 mg/mp + Cisplatin 30 mg/mp weekly [52]	Gemcitabine+Capecitabine [40]
5FU+EBRT [53]	5FU+Cisplatin [27]
	Cisplatin+Etoposide+Doxorubicin [54]
	EBRT [54]

5FU (5-fluorouracil); EBRT (external beam radiation therapy)

In conclusion, the clinico-pathological features of SPT in our population are similar to those described in the literature. The tumor affected young females and followed a favorable prognosis in most cases. Complete surgical excision is the treatment of choice, and is usually curative. The decision to administer systemic therapy must be individualized. Inability to predict malignant behavior and late recurrences mandates long-term follow-up for patients with SPT.

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