CASE REPORT

Solid Pseudopapillary Neoplasm of the Pancreas - A Report of Two Cases and a Short Review of the Current Literature

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ABSTRACT

Context Solid pseudopapillary neoplasms of the pancreas are mainly found in females and account for <2% of pancreatic tumors. They have nonspecific clinical presentation with vague radiologic features and are often histologically benign. Despite the uncertain histogenesis and the low grade of malignancy, these neoplasms present a select panel of immunostains which advantage pathologists to differentiate from other tumors of the pancreas. The current study aims to present the treatment of 2 cases of solid-pseudopapillary neoplasm of the pancreas in our hospital and a literature review on the topic. **Case report** Both patients were females with a mean tumor size of 5 cm. Preoperative diagnosis was based on distinctive features of the neoplasm in fine needle aspiration cytology in one patient. The two procedures performed were enucleation of the tumor and a distal pancreaticosplenectomy. Both patients are on a regular follow up and no recurrence has been detected 2 years after surgery. **Conclusions** It is important to differentiate solid pseudopapillary neoplasms from other pancreatic neoplasms because of the low potential for malignancy and a favorable prognosis. Fine needle aspiration cytology is the most valuable tool for diagnosis and surgical planning. Surgery is the primary therapeutic modality and in patients with distant metastasis or adjacent organ invasion aggressive approach should be considered. Local resection or enucleation can be performed for small tumors in selected cases. There are limited data about chemotherapy and radiotherapy modalities due to the availability of limited case series or reports only. Despite the excellent prognosis, the inability to predict malignant behavior mandates a long-term follow-up post-surgery.

INTRODUCTION

Solid pseudopapillary neoplasm of the pancreas (SPNP) is one of the unusual histopathological variants accounting for <2% of pancreatic neoplasms, which predominantly affect young females. It was first termed by Dr. Virginia Franz in 1959 as a "papillary tumor of the pancreas with solid and cystic components" in the Armed Forces Institute of Pathology, questioning its nature to be either benign or malignant. The patient was a 2-year-old boy who died during an attempted pancreaticoduodenectomy [1, 2]. In 1970, Hamoudi described the ultrastructural features of the tumor, which led to its acceptance as a separate clinic pathological entity [3]. Next, the tumor has been named using different terminologies until the World Health Organization (WHO) adopted the term "solid pseudopapillary tumor or neoplasm" in 1996 [4]. It was finally defined as a "low-grade malignant neoplasm of the exocrine pancreas" in the current WHO classification in 2010 [5]. Nevertheless, the term SPNP gained wide acceptance and nowadays is the commonly used name for this entity.

The typical patient is a female in the third decade of life presenting with pain and/or palpable mass in about 90% of cases [6, 7]. About 15% of the patients are asymptomatic before clinical detection; however, with the increased use of cross-sectional imaging an increasing number of cases are being detected incidentally in asymptomatic patients. Pancreatic body and tail are the most common sites of presentation but also can be found in head and uncinate process in 36% of cases [8]. Classic imaging characteristics include large size, mixed solid and cystic nature, encapsulation, hemorrhage and occasional

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calcification without ductal dilatation or atrophy of pancreatic parenchyma [2, 8]. When these features are encountered in a young female patient, SPNP should be included in differential diagnosis. Considered to be a low-grade malignant tumor, with an incidence of malignant transformation of around 15%, surgical resection is the treatment of choice. Nevertheless, since SPNP may exhibit features such as local invasion, metastases or recurrence in up to 20% of cases, an intensive follow-up is highly recommended [7].

Herein we present the management of two patients diagnosed with SPNP in our hospital and a short review of the current literature regarding this rare disease.

Case #1

A fifty-three-year-old female patient presented for routine follow up after breast-conserving surgery due to DCIS 4 years prior. Abdominal CT revealed a 5.5 × 3.7 × 5.3 cm pancreatic tail solid and cystic tumor in contact with left renal vein and splenic vein. An enhancement of the solid component and mass capsule along with a small calcification was noted on tumor imaging **(Figure 1)**. The patient underwent distal pancreatectomy and splenectomy. Histological examination showed solid pseudopapilary pancreatic tumor **(Figure 2a)**. On microscopy some of the tumor cells appear with a foamy cytoplasm and others characterized as "bizarre degenerated nuclei" with plenty eosinofilic cytoplasm **(Figure 2b)**. Evaluation of the tumor immunohistochemical expression status revealed alpha-1-antitrypsin and a-1-antichymotrypsin (moderate), b-catenin with nuclear and cytoplasmic positivity, and CD10, CD56, NSE, E-cadherin positive reactive **(Figure 3)**. The Ki-67 index was ≈2%. There was no lymph node infiltration. Postoperative course was uneventful and the patient was discharged from the hospital on the 5th postoperative day. The patient is on a regular follow up and has no recurrence 4 years after surgery.

Case #2

A forty-one-year-old female patient presented with a dull epigastric pain for approximately two months. She had no significant past medical history and she was not on any medication. A C/T scan and MRI imaging revealed a 4.9 × 4 × 4.2 cm tumor mass located in the pancreatic head **(Figures 4a and 4b)**. There was no dilatation of the main pancreatic duct. During preoperative evaluation, endoscopic ultrasound-guided fine needle (EUS-FNA) aspiration biopsy and fine-needle aspiration cytology (FNAC) was performed **(Figures 4c and 4d)**. Immunohistochemical stains, confirmed the cytological impression of SPNP **(Figure 5)**. Patient underwent enucleation of the pancreatic tumor mass, which was completed uneventfully. Frozen section of the specimen revealed an ambiguous result between SPNP and neuroendocrine tumor. On permanent section

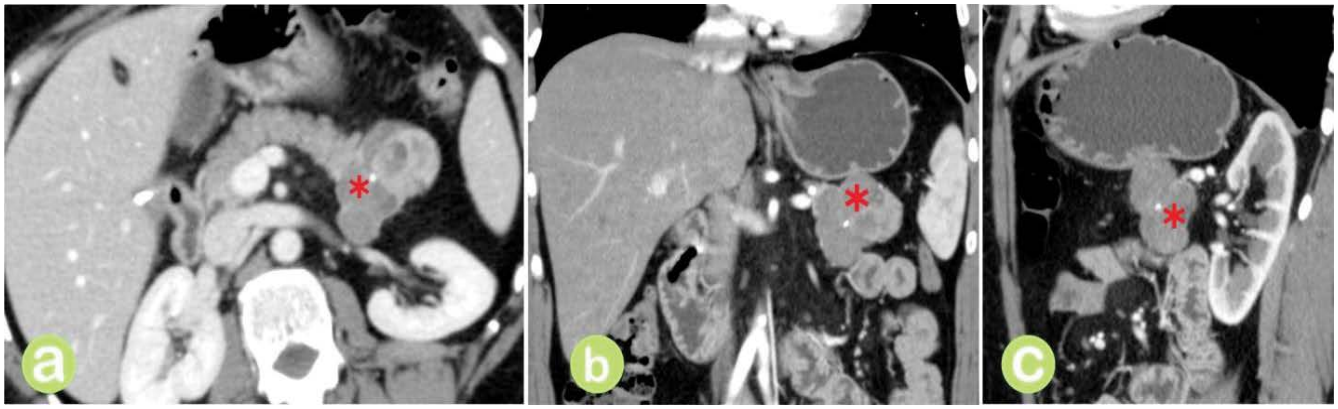

Figure 1. Contrast Enhanced Computed Tomography images. **(a).** Multiplanar reconstruction; **(b).** Coronal; **(c).** Sagittal reconstructions show a large (5.5 cm) solid and cystic mass (∗) in the pancreatic tail. Images reveal enhancement of the solid component and mass capsule. A small calcification is visible in the mass

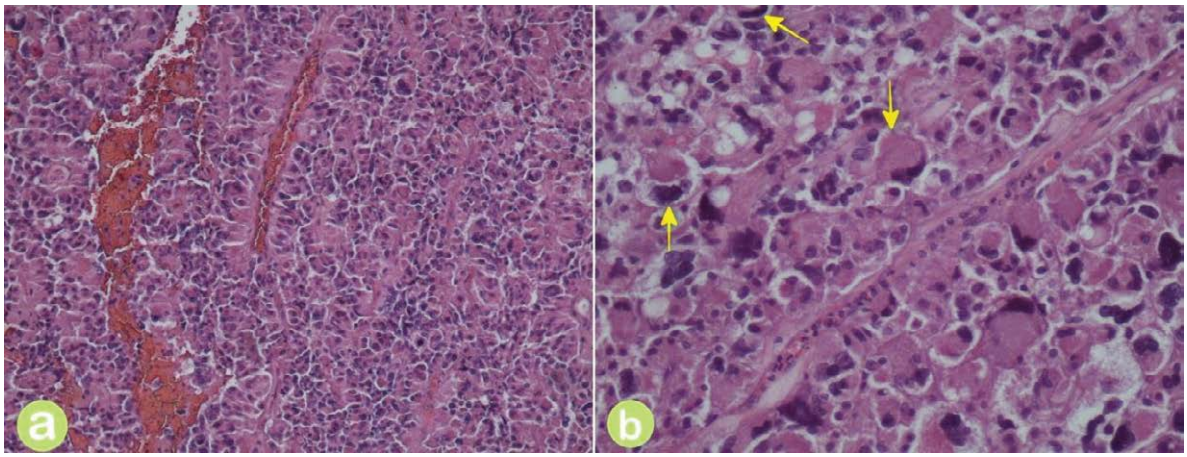

Figure 2. Solid pseudopapillary neoplasm of the pancreas. **(a).** Solid area composed of closely packed sheets of pseudopapillae, (H-E X200); **(b).** Presence of rare bizarre degenerated nuclei (arrows), (H-E X400)

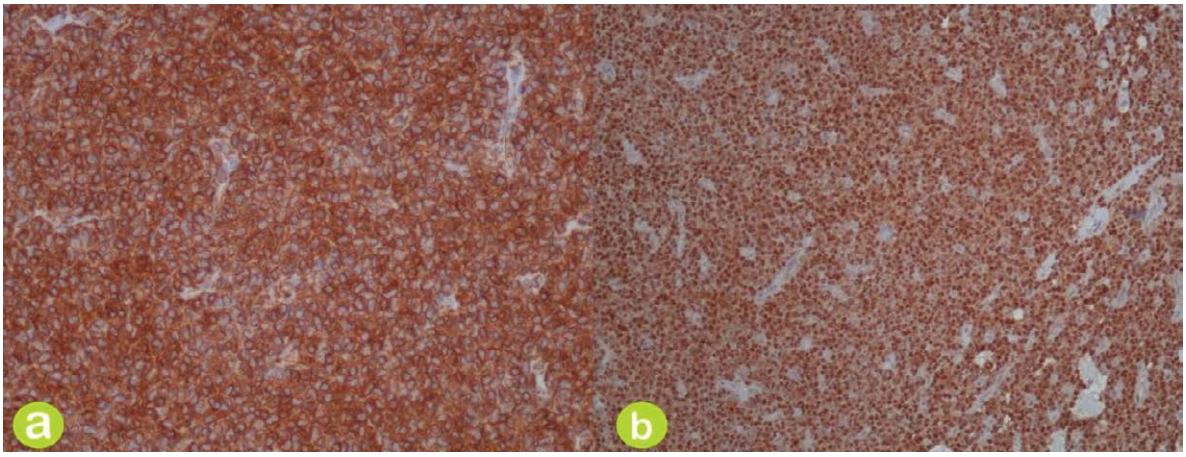

Figure 3. Solid pseudopapillary neoplasm of the pancreas. **(a).** Positive cytoplasmic immunohistochemical staining for CD 56; **(b).** Positive nuclear immunohistochemical staining for β-catenin in the majority of tumor cells (X200)

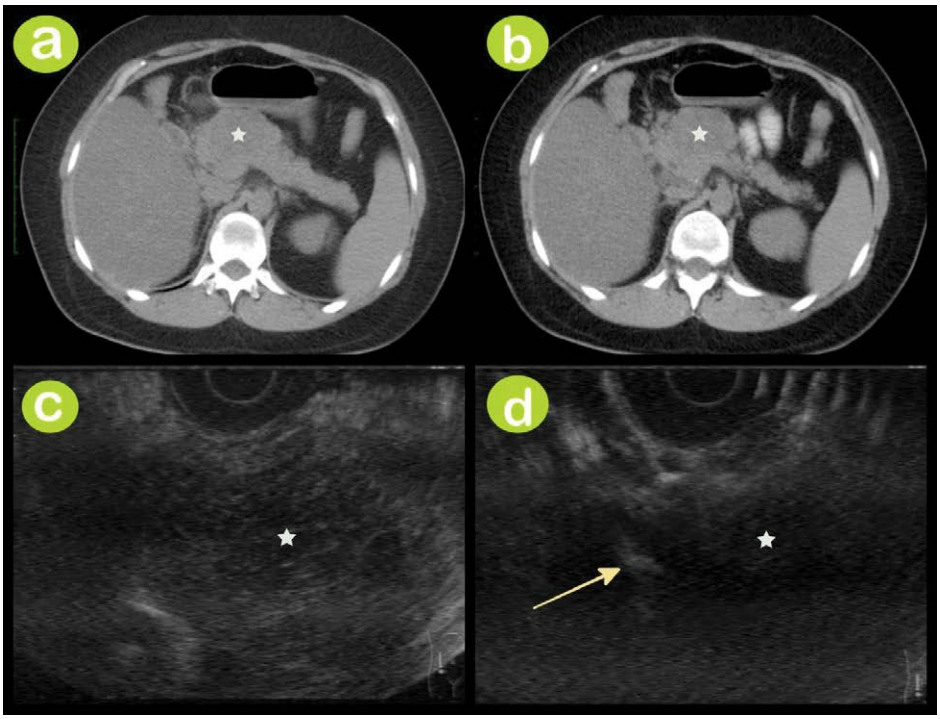

Figure 4. (a, b). Axial CT slices show a hypodense pancreatic mass (white star); **(c, d).** Endoscopic ultrasound images. The mass (white star) is hypoechoic. Yellow arrow: Biopsy needle

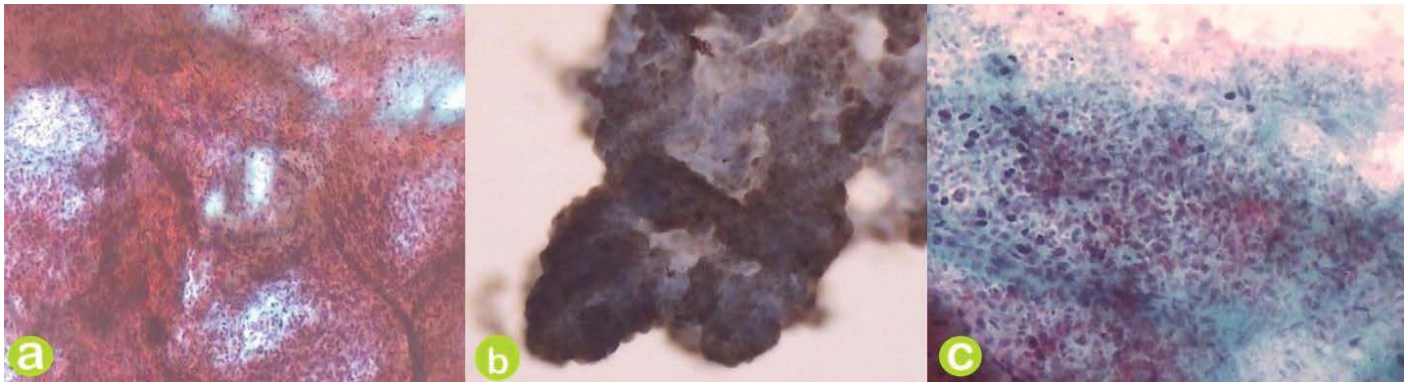

Figure 5. Solid pseudopapillary neoplasm of the pancreas, (EUS-FNAC direct smear). **(a).** Cellular smear composed of small, uniform cells, lying in a meshwork of blood vessels, (Papanicolaou stain X 100); **(b).** Neoplastic cells showing positive nuclear staining for b-catenin, (peroxidase anti-peroxidase X200); **(c).** Area of cystic degeneration, (Papanicolaou stain X 200)

pathology, the tumor was well defined with solid and cystic areas without any mitotic activity with cystic degeneration and vacuolization. Immunohistochemical examination was positive for b-catenin (nuclear staining), progesterone receptors (PgR), CD56, Vimentin and focal positive for Synaptophysine **(Figure 6)**. The final pathology report revealed a SPNP. She is doing well afterwards and the patient's 2-year follow up is currently expected.

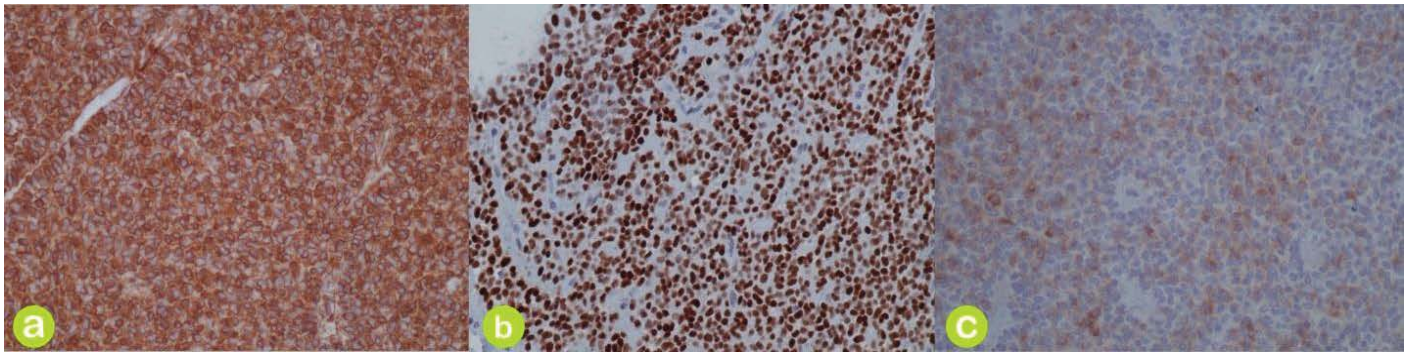

Figure 6. Solid pseudopapillary neoplasm of the pancreas. **(a).** Strong immunohistochemical expression for vimentin (X400); **(b).** Strong nuclear immunohistochemical expression for progesterone receptors (X400). **(c).** Rare tumor cells expressing synaptophysin (X200)

DISCUSSION

Mostly found incidentally on radiologic examination, SPNP is extremely rare disease presented in young women within the second or third decade of life [2, 7, 8]. They account for 1-2% of all exocrine pancreatic tumors, but 52-71% of pancreatic tumors in children and adolescents [6]. Few cases have been reported in men [9]. Choi *et al*. found that children with SPNP with a median age of 13 years old presented as adolescents and were mostly female in 78% [10]. More recent studies suggest a lower female predominance of SPNP in children, with male-to-female ratios that can approach, 1:1.75, instead of the 1:9.78 reported for all age groups [11, 12]. The most commonly reported complaint patient present is the diffuse nonspecific abdominal pain and discomfort later in the course of the disease due to the tumor enlargement causing a mass effect [2, 13]. Lee *et al* compared the clinical features of adults and children with SPNP. In the adult group, the diagnosis was usually made incidentally during screening with detection of a mass. By contrast, all of the children were symptomatic [14]. Leraas *et al*. evaluate a national combined cohort of pediatric and adult patients with SPNP. They found that children with SPNP have similar disease severity at presentation, receive similar treatments, and demonstrate equivalent postoperative outcomes compared with their adult counterparts [15].

The initial diagnosis of SPNP relies mostly on imaging, as there are no specific tumor markers for this entity. However, diagnosis with imaging alone is technically challenging in small tumors and in those without cystic component. Other major pancreatic cystic neoplasms should be taken into considerations, such as a pancreatic cyst, cystadenocarcinoma, islet cell tumor or neuroendocrine tumor. The presence of SPNP is highly suggested when certain pathognomonic features are identified on CT scan: well-defined, encapsulated mass with cystic and solid component, areas of central calcification, necrosis or hemorrhage. Tumors are encapsulated and usually well demarcated. Tumor capsule as well as the solid part enhance after intravenous contrast administration to a degree similar to normal pancreatic tissue during both arterial and venous phases. Calcification found approximately in one third of cases, usually peripheral and less common at the central part of the mass as in our case [16]. Occasionally, intra tumor hemorrhage or a fluid-debris level is depicted [17]. On magnetic resonance imaging (MRI) these tumors have characteristic properties, such as heterogeneous high signal intensity on T2-weighted images and an early peripheral heterogeneous enhancement on dynamic contrast enhanced imaging [2]. The role of positron emission tomography has not been established yet in the diagnostic algorithm of SPNP, as these tumors are usually benign [18].

The uncertain histogenesis and the low grade of malignancy make these neoplasms strongly interesting for medical research. Despite numerous investigations, the cellular origin of the tumors is unclear but they possibly originate from the multipotent primordial cells and lack certain endocrine and exocrine differentiation [19]. Other common theories suggest the origin to be from the ductal epithelium, neuroendocrine cells, or possibly extrapancreatic genital ridge angle. Regardless the association of the disease with young women, there are no reports suggesting connection with endocrine disturbances although progesterone receptor positivity is seen in almost all cases of SPN irrespective of sex [20]. Distinctive molecular alterations such as the presence of somatic-catenin coding gene (CTNNB1) mutations, the gene encoding b-catenin in Wnt signaling pathway, are demonstrated in almost all cases [7]. These changes will be detected by strong nuclear staining of b-catenin. Recent investigations on cellular signaling have successfully demonstrated that activation of the Wnt/b-catenin pathway in these tumors is associated with the up regulation of genes required in Notch, Hedgehog, and androgen receptor signaling pathways [21]. Guo *et al*. detected that CTNNB1 mutations were presented throughout all of their patients studied (100%), and a higher count of single nucleotide polymorphisms (SNPs) was particularly detected in patients with older age, larger tumor, and metastatic disease [22]. No other genetic alterations, such as KRAS, TP53, and SMAD4, which are established in ductal adenocarcinoma, are involved in SPNP, demonstrating its different nature from other pancreatic neoplasms.

The cells of SPNP demonstrate strong positive staining for CD10, vimentin, a-1-antitrypsin, a-1-antichymotrypsin, neuron-specific enolase, and cyclin D1. Some cases of SPNP present neuroendocrine immunostaining by consistent staining with CD56 and focal reactivity for synaptophysin,

as in our patients' immune profiles. Due to these staining characteristics, fine-needle aspiration cytology (FNAC) is helpful for making a diagnosis preoperatively to perform the appropriate surgery [6, 23]. EUS-FNAC demonstrates improved sensitivity for diagnosing SPNP of the pancreas in adults, correctly identifying over 80% of patients with SPNP [24, 25].

Although the malignant potential is low, up to 15% of SPNP patients develop metastasis. According to WHO, perineural, pancreatic paranchymal or lymphovascular invasions are predictive factors for aggressive behavior [5, 13]. In addition, factors such as male gender, younger age, large tumor size (>5 cm), capsule invasion, and elevated mitotic rate are suggestive in the literature to result in increased malignant behavior [26, 27]. The most common metastatic sites of the SPNP are the liver, regional lymph nodes, mesocolon, omentum and peritoneum [28]. The lung is a very rare metastatic site and was found in only three cases in the literature [7, 29].

First choice of treatment remains complete surgical resection since SPNP is limited to the pancreas in over 95% of its patients and can be radically resected. However, it should be noted that SPNP is clearly a malignant neoplasm with local and metastatic potential. Thus, there is debate about the optimum extent and type of surgical operation for SPNP [30]. In the majority of cases aggressive resection offers an excellent prognosis and a long survival. In case of patients with suspected lymph nodes, lymphadenectomies must be performed in order to avoid relapses [13, 31, 32]. Since these are low-grade tumors and especially surrounded by a fibrous capsule, some surgeons advocate simple enucleation of the lesion. Although still relatively rare, the number of pancreatic parenchyma-sparing operations performed for SPNP has doubled over the last years and account for almost 15% of all pancreatic resections [30]. Because it is a low-grade malignant tumor, usually occurring in young and healthy patients with a long life expectancy, parenchyma-preserving procedures are worthwhile especially to avoid exocrine and endocrine insufficiency. Pancreatic enucleations and central pancreatectomies compared to standard resections have comparable short-term outcomes regarding morbidity and mortality [33, 34]. One of the critical questions when considering parenchymal-sparing surgery in patients with SPNP is the risk of lymph node metastases. Overall, lymph node involvement was reported to be almost 2.0% in a review study by Law *et al*. ranging from 0.5 to 2.2% [30]. The number of lymph nodes examined at surgery has been shown to influence the staging in patients with pancreatic ductal adenocarcinoma, where patients with fewer than 12 lymph nodes found to be understaged [35]. Thus, local resection or enucleation can be performed for small tumors in selected cases of SPNP. When considering enucleation to avoid extensive procedures, the size of the tumor, well-defined margin and distance to the main pancreatic duct and/or common bile duct should be carefully assessed [33, 36]. A recent study by Wang *et al*. comparing enucleation of the SPNP with conventional pancreatic resection revealed that enucleation was associated with a low rate of severe postoperative morbidity and no increased risk of tumor recurrence. Moreover, enucleation had a lower rate of postoperative long-term exocrine insufficiency compared with conventional resection of the pancreas, although the difference was non-significant [36].

The role of neoadjuvant and adjuvant therapy in the treatment of SPNP is unclear [19]. Studies have demonstrated a role for gemcitabine and radiotherapy either to downsize large tumors or to treat the rare case of unresectable disease [37, 38, 39, 40, 41, 42]. Intra-arterial chemoembolization in patients with multiple hepatic metastases, radiofrequency ablation and liver transplantation has also been used in patients with unresectable liver metastasis to extend survival [19, 43, 44]. Recurrence with peritoneal carcinomatosis in SPNP is very rare and is predominately caused by accidently rupture during surgery [32]. The treatment strategies of SPNP with peritoneal metastases reported in review articles include cytoreductive surgery (CRS), complete cytoreductive surgery (CCRS), and HIPEC [31, 32, 45]. The value of chemotherapy for patients with SPNP is not well studied and remains unknown. Since the period of recurrences ranges in years and the recurrences (local or metastatic) usually being resectable, the role of adjuvant treatment is uncertain and often redundant. There are few studies that have addressed the use of adjuvant therapy for patients with SPNP using various chemotherapy regimens based upon cisplatin, oxaliplatin, cyclophosphamide, adriamycin, 5 FU, etoposide, and gemcitabine [19]. The two most commonly used chemotherapeutic agents were 5-Fluorouracil and gemcitabine, while Kang *et al*. showed that cisplatin was the most potent drug for these tumors [46]. However, the small numbers of cases make it difficult to draw any conclusions on the role of adjuvant therapy or the optimal type of therapy for SPNP [30]. Therefore, the decision to consider any adjuvant treatment for SPNP with rare aggressive behavior in un-resectable or recurrent cases is on physician's discretion. Recently, a pyrosequencing of the SPNP antecedent to metastasis showed an uncommon EGFR mutation at L861Q in the kinase domain of exon 21 [47]. Confirmation of this finding in future studies could support preoperative testing for EGFR mutation analysis to detect aggressive SPNP and treatment response using EGFR inhibitors. Nevertheless, taking into consideration the slow progression of the tumor and the high rate of resectability, resection of recurrences and metastases can offer good long-term survival [48]. In contrast to other pancreatic tumors, aggressive surgical resection is reasonable even in the presence of recurrence or limited metastases and invasion of the portal vein or superior mesenteric artery does not indicate tumor unresectability. Thus, every effort should be made to obtain a preoperative diagnosis in these settings. Since all recurrences occurred more than 5 years after curative resection, patients should undergo > 5 year follow-up surveillance with routine imaging [49]. Because of rarity of SPNP, its indolent character and based on the literature results, the length of surveillance to at least 10

years is warranted. Nevertheless, evaluations of these patients with a C/T scan each year for the first 5 years of follow up is a reasonable option.

In conclusion, SPNP is a rare disease with atypical clinical symptoms an indolent clinical course. The characteristic imaging features though, can help to make the correct diagnosis and differentiate from other pancreatic tumors. FNAC and cytomorphological recognition of this tumor is the most valuable tool for diagnosis and surgical planning. Surgery is the primary therapeutic modality and in patients with distant metastasis or adjacent organ invasion aggressive approach should be considered. Despite the excellent prognosis, with a 5-year survival rate of ~95%, the inability to predict malignant behavior mandates a long-term follow-up post-surgery. At present, there is a definite role of both neoadjuvant chemotherapy and radiotherapy in selected cases.

Conflict of Interest

The authors declare no conflict of interest.

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