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Solid pseudopapillary tumor of the pancreas: A case series of 9 patients

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Background/aims: *Solid pseudopapillary tumor is a rare exocrine tumor of the pancreas. There is no clear consensus on its etiology, origin and treatment. In this study, the clinical, pathological and immunohistochemical features of nine patients with solid pseudopapillary tumor were re-evaluated in view of the current literature findings.* ***Materials and Methods:*** *We studied nine cases diagnosed with solid pseudopapillary tumor between 2005 and 2010. The clinical, pathological and laboratory data were analyzed.* ***Results:*** *On microscopy, all tumors had well-defined borders and were separated from surrounding pancreatic tissue by a thick fibrous capsule. The tumor consisted mainly of pseudopapillary structures with focal solid areas accompanied by wide hemorrhagic and cystic regions. The typical morphological features were present to varying degrees. Of the nine cases, one relapsed approximately two years after the diagnosis, and our laboratory also evaluated the surgical specimen of local recurrence.* ***Conclusions:*** *While some new light has been shed on the clinicopathological features of solid pseudopapillary tumor concerning its etiology, origin and treatment methods, there is much to be understood. Further studies focusing on genetics, pathogenesis and prognosis are needed for a better understanding of this entity.*

Key words: Solid pseudopapillary tumor, pancreatic tumors, Frantz's tumor

Pankreasın solid psödopapiller tümörü: 9 vakalık olgu serisi

Giriş ve Amaç: *Solid psödopapiller tümör pankreasın nadir ekzokrin primer tümörlerindendir. Etyolojisi, orijini ve tedavi yaklaşımına ait bilgiler halen tartışılmaktadır. Bu çalışmada 9 solid psödopapiller tümör olgusunun klinik, patolojik ve immunohistokimyasal özellikleri güncel literatür bilgilerine göre yeniden değerlendirilmiştir.* ***Gereç ve Yöntem:*** *Laboratuvarımızda 2005-2010 yılları arasında kayıtlı olup, solid psödopapiller tümör tanısı alan 9 olgu klinik, laboratuar ve histopatolojik yönleri ile değerlendirilmiş ve sunulmuştur.* ***Bulgular:*** *Mikroskopik olarak tüm olgularda tümör iyi sınırlı olup, genellikle kalın fibröz kapsül ile çevre pankreas dokusundan ayrılmaktadır. Tümör geniş hemoraji ve kistik açıklıkların eşlik ettiği, arada fokal solid alanlar dışında, genellikle psödopapiller yapılardan oluşmaktadır. Bu tümör için tanımlanan tipik morfolojik özellikler değişen oranlarda olgularımızda bulunmaktadır. Bu olgulardan biri ilk operasyondan yaklaşık 2 sene sonra nüks etmiş ve lokal nükse ait cerrahi spesmen de tarafımızdan değerlendirilmiştir.* ***Sonuç:*** *Solid psödopapiller tümörlerin son zamanlarda bildirilen olgularla birlikte klinikopatolojik özellikleri daha iyi anlaşılmaya başlanmasına rağmen, etiyolojisi, orijini ve tedavi yaklaşımı ile ilgili bilinmeyeni hala çoktur. Bu çalışmada 9 solid psödopapiller tümör olgusunun klinikopatolojik karakteristik özellikleri gözden geçirilmiştir.*

Anahtar kelimeler: Solid psödopapiller tümör, pankreas tümörleri, Frant'z tümör

INTRODUCTION

Solid pseudopapillary tumor (SPT) is one of the rare primary tumors of the pancreas. It was first described by Frantz in 1959 (1). It mainly affects young females in the second and third decades and has a low malignant potential. Despite being defined as an epithelial tumor of the pancreas, it does

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not exhibit the typical immunohistochemical staining profile as do the other epithelial tumors. The cell of origin is still the subject of debate. Although it is rarely encountered, the recent increase in the number of cases has drawn much attention. In the study conducted in our hospital (between 2005 and 2010), the clinical, pathological and immunohistochemical features of nine SPT patients were revaluated in the light of current literature findings.

MATERIALS AND METHODS

A retrospective study was carried out between 2005 and 2010 at our hospital (Haydarpasa Numune Education and Research Hospital, Pathology Lab). All patients diagnosed with SPT were re-evaluated. The clinical data of each patient were once again examined from patient files. The patients were then interviewed by telephone for confirmation of clinical information and to assess prognosis. Questions were asked as to whether any postoperative, current or new symptoms had occurred. The initial slides of each case stained with hematoxylin and eosin (H&E) were examined, and an immunohistochemical profile was used to stain paraffin blocks. The primary antibodies used were vimentin (1:100, Neomarkers), pan-cytokeratin (CK) (1:50, Neomarkers), CD10 (1:30, Novacastra), synaptophysin (1:100, Novacastra), chromogranin (1:200, Neomarkers), neuron-specific enolase (NSE) (RU, Neomarkers), P53 (1:100, Neomarkers), progesterone (1:100, Neomarkers), estrogen (1:100, Neomarkers), Ki-67 (1:100, Neomarkers), CD56 (RU, Neomarkers), S100 (1:200, Neomarkers), E-cadherin (RU, Neomarkers), beta-catenin (1:100, Genetex), and cyclin-D1 (1:100, Biocare).

RESULTS

Solid pseudopapillary tumor (SPT) was diagnosed in 9 patients (3 men, 6 women; mean age at diagnosis: 30.8 years, age range: 18-46 years) in our hospital between 2005 and 2010. Of 9 cases, 1 presented with local recurrence approximately two years after the diagnosis. Our laboratory also evaluated the local recurrence specimen. Two patients (Cases 3 and 6) were asymptomatic, and their masses were discovered incidentally. Case 2 presented with a palpable mass, Cases 1, 5, 8 and 9 with abdominal pain, Case 1 with back and abdominal pain, and Case 7 with signs of weakness, fever, vomiting, and other non-specific symptoms. Radiological data were acquired in 4 cases. For Case 1, a hypodense mass lesion with two punctate calcifications was identified in the abdominal computed tomography (CT), but the radiologic differential diagnosis was not performed. In the data of the abdominal ultrasound of Case 2, it was described that the solid mass was heterogeneous in nature, accompanied by areas of necrosis, could be retroperitoneal or pancreatic in origin, and could be interpreted for malignancy. In the abdominal CT of Case 3, a heterogeneous solid mass lesion with clear margins with cystic component was identified in the pancreas, and it was defined as cystic mucinous cystadenoma/cystadenocarcinoma in the differential diagnosis. In the upper magnetic resonance imaging (MRI) examination of Case 7, the differential diagnosis of the mass being exophytic, partly hemorrhagic, and with clear margin was considered to be consistent with SPT given the age of the patient. The preoperative values of CEA, CA19-9, CA15-3, and CA125 were examined, and 2 cases with elevated CA19-9 were identified.

Their tumor localization was also evaluated: Of the 2, 1 was located in the body of the pancreas while the other was located in the head of the pancreas. Regarding the tumors of the patients other than the above-mentioned, 2 were localized in the pancreas tail. Macroscopically, the tumors, apart from the recurring tumor of 0.6 cm, measured 2-12.5 cm, with a mean value of 6.8 cm. A summary of tumor localization and macroscopic features is given in Table 1.

On microscopy, the tumors of all patients had well-defined borders and were separated from surrounding pancreatic tissue by a thick fibrous capsule. The tumor consisted mainly of pseudopapillary structures with focal solid areas accompanied by wide hemorrhagic and cystic regions. The typical morphological features for this tumor (accompanying histiocytes, cholesterol clefts, stromal hyalinization and myxoid degeneration, calcification, spindle and clear cell variations) were also present to varying degree (Figure 1a,b,c,d). The characteristics of SPT are seen in Table 2. A maximum ratio of 1-2 mitoses was observed. Focal necrosis was present in some cases.

In addition to these morphologic features seen on the resection specimen of Case 2, the tumor measured 12.5 cm with well-defined borders, with no obvious capsule invasion; however, focal capsular invaginations as well as lymphatic invasion in the pancreas tissue surrounding the capsule were no-

Table 1. Tumor localization and macroscopic features

Case	Size	Macroscopic features	Localization
1	2 cm	Hemorrhagic, fragile semi-solid	Corpus
2	12.5 cm	Hemorrhagic, fragile semi-solid	Tail
3	6 cm	Hemorrhagic, cystic	Tail
4	10 cm	Hemorrhagic, microcystic	Head
5	4 cm	Hemorrhagic, fragile semi-solid	Tail
6	10 cm	Hemorrhagic, cystic	Tail
7	8.5 cm	Hemorrhagic, fragile semi-solid	Tail
8	6 cm	Hemorrhagic, fragile semi-solid	Tail
9	3 cm	Hemorrhagic, fragile semi-solid	Tail
Case 2, recurrence	0.6 cm	Solid	Tail

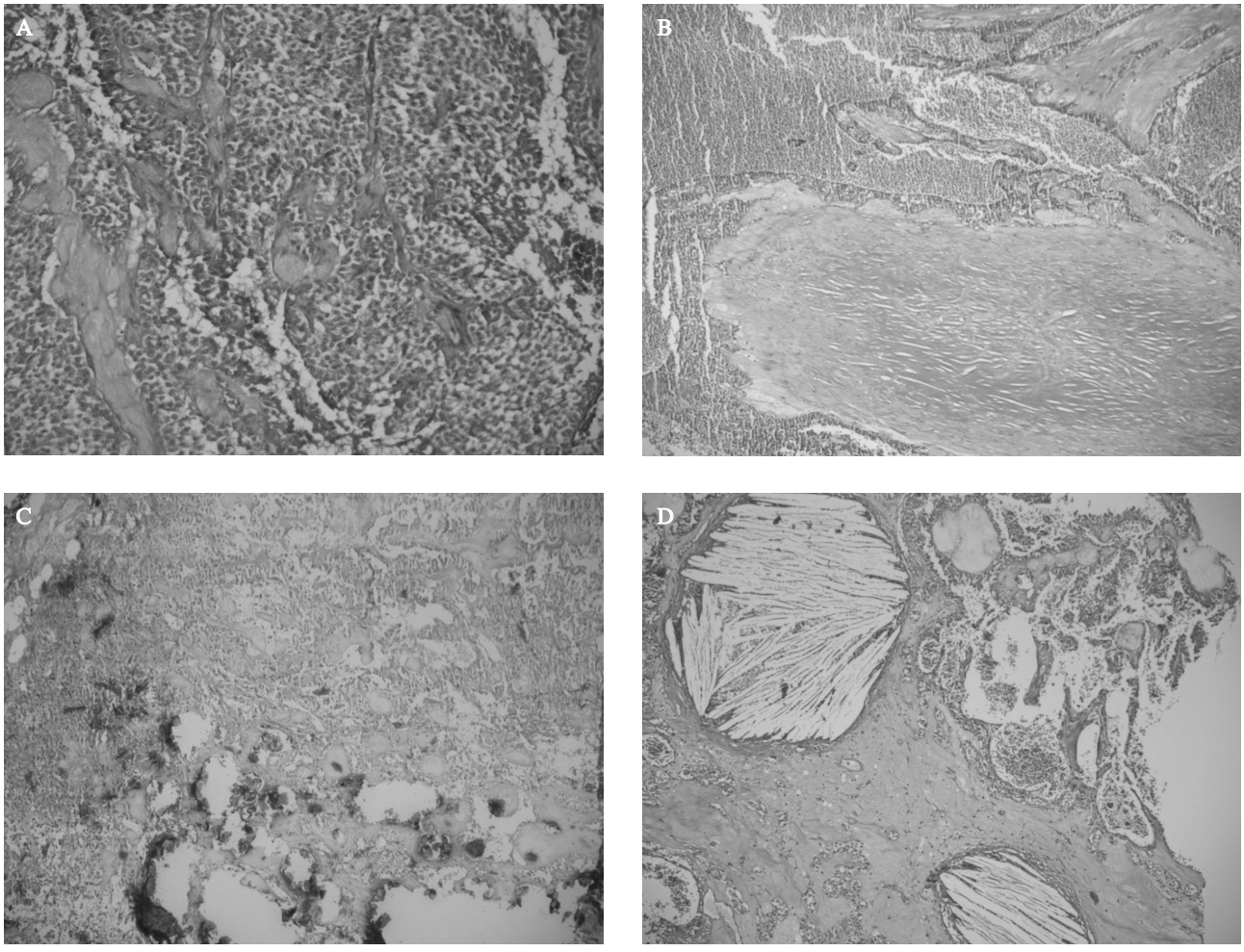

Figure 1. A monomorphous cell population is seen forming pseudopapillary patterns (**A**: H&E; 200x), stromal hyalinized fibrovascular cores (**B**: H&E; 40x), neoplastic cells with accompanying microcalcification (**C**: H&E; 100x), and cholesterol crystals (**D**: H&E; 100x).

ted. These features were highlighted in our pathology report, and we recommended strict follow-up to exclude local recurrence and/or aggressive behavior. The patient relapsed two years after the diagnosis, and our laboratory received the specimen from the distal pancreatectomy and splenectomy. The tumor of this specimen measured 0.6 cm. Case 8 exhibited a focal microscopic infiltrati-

on into adjacent pancreatic tissue and an area of lymphovascular and perineural invasion. For this reason, in the subsequent pathology report, we pointed out that such cases had malignant potential. However, no signs of recurrence or metastases were found in the evaluation performed in the 16 postoperative months during the follow-up. There was no capsular or lymphatic invasion in our other patients. The results of our immunohistochemical analysis are summarized in Tables 3 and 4.

All patients underwent surgical treatment (2 Whipple procedure, 2 distal pancreatectomy, and distal pancreatectomy and splenectomy in the remaining patients).

Table 2. The outstanding characteristics of SPT

Case	Pseudopapillary structures	Histiocytes	Cholesterol crystals	Stromal hyalinization	Clear cell changes	Spindle cell changes	Myxoid changes	Microcalcification
1	+	+	-	+	-	-	-	+
2	+	-	+	-	+	-	-	+
3	+	+	+	+	+	-	-	-
4	+	-	+	-	-	-	+	+
5	+	+	-	-	-	-	-	-
6	+	-	-	-	-	-	-	-
7	+	+	+	+	-	-	-	+
8	+	-	-	+	-	-	-	-
9	+	-	+	+	-	-	-	+
Case 2, recurrence	+	-	-	-	-	-	-	-

Table 3. The results of immunohistochemical analysis-1

Case	Vimentin	Pan-Cytokeratin	CD10	Synaptophysin	Chromogranin	NSE	P53	PR	ER	Ki-67 %	Cd56	S100
1	+	Focal, weak +	Focal, weak +	Focal, weak +	-	2+	-	+	-	1-2	+	-
2	+	-	Focal, weak +	-	-	3+	-	+	-	1-2	+	-
3	+	-	-	Focal, weak +	-	2+	-	+	-	1-2	+	-
4	+	-	Focal, weak +	-	-	+	-	3+	-	1-2	+	-
5	+	-	-	-	-	2+	-	3+	-	<1	+	-
6	+	-	-	-	-	+	-	2+	-	<1	+	-
7	+	-	-	-	-	+	-	+	-	<1	+	-
8	+	-	-	-	-	+	-	+	-	<1	+	-
9	+	-	-	-	-	+	-	2+	-	<1	+	-
Case 2, recurrence	+	-	-	-	-	+	-	+	-	<1	+	-

Table 4. The results of immunohistochemical analysis-2

Case	E-Cadherin	β-Catenin		Cyclin-D1
		Cytoplasmic Staining	Membranous Staining	Nuclear Staining	
1	-	2+	1+	1+	-
2	-	2+	2+	-	+
3	-	-	3+	-	2+
4	-	2+	-	2+	3+
5	-	2+	1+	3+	+
6	-	2+	-	3+	3+
7	-	-	2+	2+	-
8	-	1+	-	3+	+
9	-	1+	-	2+	+
Case 2, recurrence	-	1+	-	2+	+

DISCUSSION

Solid pseudopapillary tumor (SPT) was first observed in a 19-year-old girl in 1927. However, Frantz first described it in 1959, and he proposed that four cases with non-functional island cell tumors were actually a new entity called 'papillary pancreas tumor' (1). SPT accounts for 1-2% of exocrine pancreas neoplasms (2,6,11). It accounts for 1% of all pancreas tumors and 3% of all cystic pancreas neoplasms (3).

There are 750 cases reported in the English literature, and 553 cases were reported in Chinese literature studies (4,5). The increasing frequency of SPT in the last 10 years has caught much attention. The broadest series of reported cases came from China, comprising 26, 20 and 14 cases, respectively (4,6-10). SPT can be observed in patients of all ages, with the mean age of 30 years. The male to female ratio is 1:8-1:9 (2,5). In our series, two-thirds were female (6 female/3 male), and the mean age was 30.8 (15-46) years. As patients present with no specific symptoms, tumors are usually identified incidentally on routine radiological examination, and consequently, the tumors reach large proportions at the time of identification. The mean size is 9.5 cm; however, tumors measuring 30 cm in size have been described (7,11). In our series, the largest tumor was 12.5 cm, the smallest was 2 cm, and the mean tumor size was 6.8 cm. These tumors do not have definite localization (4,7). However, there is a predilection for the body and tail of the pancreas (64%) (11). In our series, all except two of the tumors were located in the tail of the pancreas: one tumor was located in the head and one tumor was located in the body of the pancreas. While most patients are asymptomatic on presentation, patients may also frequently present with the following symptoms: stomachache, weight loss, loss of appetite, and bloating. These symptoms appear when the tumor size reaches 6 cm and beyond (12). Rare cases presenting with spontaneous rupture, intraabdominal bleeding and gastric outlet obstruction have also been reported (13). In SPT patients, tumor markers are generally within normal limits. In a Chinese study of 553 cases, elevated alpha fetoprotein (AFP), CEA, CA19-9, CA125 and CA242 were found in 11 cases. Of these, only two were found to be malignant SPT. We studied the values of CEA, CA19-9, CA15-3, and CA125 in our patients. Elevated CA19-9 was found in two patients, one minimally, the other significantly higher. The levels rapidly normalized, especially in the postoperative period. The other laboratory values were normal, consistent with the literature (8). The prognosis of SPT is favorable with adequate surgical resection (14-16). Therefore, it is important to establish the correct diagnosis and determine the surgical margins preoperatively (17). Intraoperative consultation is recommended. Frozen section specimens were sent for intraoperative diagnosis in five of our cases. In three cases, our findings suggested a diagnosis of low-grade neuroendocrine neoplasm, whereas two cases were diagnosed with SPT due to the presence of pseudopapillary projections. In one case, frozen section was applied to confirm clear surgical margins.

Imaging techniques are of great importance for the diagnosis of SPT. Ultrasonography and CT reveal a sharply demarcated mass with solid and cystic areas together with pressure effect on the surrounding tissue. Procacci et al. (18) found that CT was 60% accurate in the diagnosis of cystic pancreatic tumors. MRI is superior to CT in distinguishing cystic from solid lesions. Encapsulated cystic tumors that are hemorrhagic and lack an internal septum strongly point to the diagnosis of SPT (5). Macroscopically, these tumors are solitary, well- circumscribed, and encapsulated. Multiple tumors are exceptional. These tumors undergo cystic degeneration during their growth process; these cystic spaces then fill with necrotic debris. On cross-section, the tumor is yellow-brown in color with hemorrhagic areas. These hemorrhagic and cystic changes occasionally encompass the entire lesion and thus can easily be mistaken for a pseudocyst (as seen in Cases 3 and 7).

Morphologically, this neoplasm is characterized by large areas of necrosis with preserved tissue situated peripherally beneath the fibrous capsule. The tumor cells are arranged around delicate, often hyalinized fibrovascular stalks with small vessels. The neoplastic cells distant from the blood vessels become degenerated and the cells adjacent to the blood vessels create a 'viable' cuff that forms the pseudopapillary structures. These structures have no luminal spaces (2). Solid areas consist of nests of neoplastic cells with accompanying foamy histiocytes and cholesterol crystals. Varying degrees of stromal hyalinization may be present. In a number of cylindrical pattern cases, stromal groups can be noted in the nest of tumor cells (2). "Clear" and "spindle" cell changes can be encountered (19-21). Eosinophilic periodic acid Schiff (PAS)-positi-

ve and diastase-resistant hyaline globules are found within the cells cytoplasm or outside the cell itself. The signs of stromal degeneration such as myxoid changes and microcalcification may exist (4). Mitoses are rare.

The cell of origin of SPT remains a matter of controversy. While some researches believe that the tumor cell line originates from ductal epithelium, acinar or endocrine cells, others have shown that naming a pancreatic or extrapancreatic cell of origin is impossible (12,22,23). The latter is supported by the immunohistochemical profile that does not correlate with any pancreatic cell staining. Likewise, markers supporting the theory of an epithelial neoplasm have a low percentage of positive findings. CK expression is less than 30% or negative. Alpha-smooth muscle actin (SMA) negativity rules out myoepithelial differentiation. No association was found between alpha-1 anti-trypsin (AAT) positivity and macrophage differentiation in SPT, because positive staining was detected in macrophages surrounding cholesterol granulomas or in those found dispersed in the tumor, while other macrophage markers such as Ki-MP and LeuM1 were negative. Thus, although SPT is thought to be of multipotent stem cell origin, it has no relation to pancreatic epithelium. The researches have described the rare extrapancreatic tumors that would support the theory that the tumor is not derived from pancreatic cells (25). Another hypothesis is that the tumor originates from pluripotent embryonic cells of the pancreas. In contrast to ductal pancreas cancer, mucinous cystic neoplasms, microcystic serous adenoma and SPT are primarily reported in young females. Consequently, these tumors are thought to be influenced by sex hormones and their receptors. The theory proposed here is that the pancreas and the genital tubercle/ridge (especially on the left side) are closely related, and in the 7th gestational week, primitive ovarian cells attach to and fuse with pancreatic tissue (12,25,26).

Immunohistochemically, SPT stains strongly positive with vimentin (80%) (7). All our cases showed powerful positive staining for vimentin. Similarly, our cases were negative for CK except one having weak focal positivity. CD10 has been known to have 80-83% positivity in SPTs (27). The staining pattern is generally cytoplasmic, and to a lesser extent "dot-like" or membranous. This staining pattern is found to be insignificant. Of our cases, three displayed cytoplasmic staining, and the others were negative. Progesterone receptor (PR) is positive in 60% of pancreatic island cells and also stains positive in pancreatic neuroendocrine tumors (NETs). In our study, varying degree of PR positivity was present, and estrogen receptor (ER) was negative. Although the reason for ER staining negative while PR is positive is not clear, it has been ascribed to the Wnt pathway abnormalities, in particular β-catenin (28). Chromogranin was negative in our cases, consistent with the literature. CD56 is reported to have 55-100% staining in SPTs (23). In our cases, positive staining was shown. NSE is positive in most SPTs. However, as it has a low specificity, its diagnostic value is limited. All our cases were positive with varying degree of staining. S100 was negative in all our cases, consistent with the literature (29). Cytoplasmic c-kit staining has been positive, whereas KIT/PDGFRA mutation/translocation has not been seen (11,30). C-kit non-mutation-mediated activation has been reported to be positive in 50% (23). In our cases, C-kit was negative.

On electron microscopy, SPT imaging is seen to have non-specific cell junctions, although typical desmosome-like junctions are absent. The mitochondria-rich cytoplasm contains dense granules of different sizes. Some of these granules contain AAT. Nuclear indentation and cleft are seen (4).

In conclusion, electron microscopy and immunohistochemical studies remain inadequate in specifying tumor histogenesis. However, recent studies focus on β-catenin mutation in the Wnt pathway (4). Activation of the Wnt pathway causing β-catenin mutation on exon 3 has been found in 83-90% of SPTs (31,32). This mutation enables β-catenin to escape intracytoplasmic phosphorylation leading to degradation and binding to t-cell transcription factor (tcf)/lymphoid enhancer binding factor (lef). β-catenin-tcf/lef complexes translocate to the cell nucleus leading to strong nuclear and cytoplasmic staining (27,33-35). At the same time, this complex activates oncogenic gene transcription, the pathways of which contain cyclin-D. This leads to overexpression of cyclin-D (70-100% of SPN) (23). While K-ras mutation is seen in most ductal adenocarcinomas, it is absent in SPN (27). β-catenin forms the main component of the cadherin-catenin epithelial adhesion complex (30,36). E-cadherin and β-catenin are the key components of the Wnt transduction pathway that influence differentiation and growth of the exocrine pancreas. The E-cadherin gene (CDH 1) is a 120 kDa pro-

tein located on the 16g22.1 locus. E-cadherin binds to the actin skeleton. They interact with catenins and affect homotypic cell adhesion. E-cadherin plays a key role in the integrity and polarization of the epithelium. Structurally, it is made up of a molecular cytoplasmic domain, a single-pass transmembrane domain and an extracytoplasmic domain that consists of five repetitive cadherin motifs and is considered to be a calcium-binding region. The cytoplasmic domain interacts with catenin and binds to the actin skeleton. A decrease in the expression of E-cadherin is related to the invasive behavior of epithelial cells, dedifferentiation and metastatic potential. There are a number of views supporting the theory of this protein as an "invasion suppressor molecule" (33). The loss or decrease in the expression of E-cadherin can be seen in many malignancies, such as diffuse-type gastric adenocarcinomas or lobular carcinoma of the breast. Cytoplasmic-nuclear β-catenin expression together with loss of E-cadherin is rare. It is seen in some endometrial adenocarcinomas, endometrioid cancers of the ovary and hepatocellular carcinomas. Studies showing this union in SPN are reported (27,33). E-cadherin has been shown to have a different staining pattern in SPT. In immunohistochemical studies, if the E-cadherin molecule used recognizes the extracellular domain, membranous staining is seen in all cases, with varying degree of dot-like staining. The importance of this pattern of staining, also seen in some gastric cancers, is unknown. If the antibody recognizes the cytoplasmic domain, nuclear staining is positive (33,37). Nuclear E-cadherin immunoreactivity is positive in SPT, 30% of pancreatic NETs, Merkel cell carcinoma, and 50% of renal cell carcinomas.

The β-catenin staining pattern in our cases is summarized in Table 4. Two of our cases (Cases 2 and 3) were negative for nuclear β-catenin staining; the rest displayed varying degree of positive staining. Case 3 displayed powerful (3+) membranous staining, whereas Case 2 displayed average intensity (2+) cytoplasmic and membranous staining. All our cases were negative for E-cadherin staining. In accordance with the literature, all our cases stained positive for cyclin-D, other than Cases 1 and 7.

The differential diagnosis of SPT includes neoplasms that are partially solid, mostly cystic with cellular features that differ from conventional ductal adenocarcinomas. Pancreatic endocrine neoplasms head the list of differential diagnoses. Endocrine tumors with cystic areas or SPT with a more solid pattern are especially hard to distinguish from one another. The presence of pseudopapillary structures, hyaline globules, foamy macrophages, and a nuclear groove with absence of fine endocrine-chromatin makes the diagnosis of SPT easy. However, immunohistochemical analysis is still necessary. Nuclear β-catenin staining, loss of E-cadherin expression, and CD10 and AAT staining positive together with chromogranin staining negative are helpful in the differential diagnosis. Pancreatoblastoma, which is a rare tumor, usually affecting children younger than 10 years of age, is also part of the differential diagnosis. Histologically, polygonal cells in the areas of acinar differentiation and characteristic squamous corpuscles are helpful in the diagnosis. The corpuscles are separated by hypercellular stroma. On immunohistochemical analysis, pancreatoblastoma shows acinar (trypsin, chymotrypsin, lipase) and endocrine differentiation. Acinar carcinoma displays an acinar, trabecular and solid pattern. On immunohistochemical analysis, pancreatic enzyme expression is present. Nuclear β-catenin expression is less common. Due to wide areas of cystic degeneration in SPT, it can be hard to distinguish from pancreatic pseudocysts; therefore, good clinical history together with extensive sampling is necessary. Case 7 had a cystic lesion with signs of previous hemorrhage, where large areas of the wall epithelium were absent together with chronic non-specific pancreatitis in the surrounding tissue. On extensive sampling, we discovered focal areas with pseudopapillary structures of the tumor. The prognosis of SPT even in the presence of local recurrence, invasion or metastases is favorable. The five-year survival rate is more than 95% (3,25,27). Local recurrence is less than 10% and usually occurs four years after surgery (3,6,8,10). Even with metastases, the survival rate is reported to be more than 10 years (38). In a series of 34 cases by Tang et al. (39), two cases of SPT with high-grade malignant transformation and aggressive courses were reported. One of our cases relapsed two years after the diagnosis. In this case, we stated in the initial report that the tumor had invaded the capsule in certain areas together with lymphatic invasion of the surrounding pancreas tissue, and we recommended strict follow-up in case local recurrence and/or aggressive transformation occurred. No additional features showing aggressive behavior, such as diffuse

growth pattern, nuclear pleomorphism, increased mitotic index, necrosis, and dedifferentiation, were present in our cases. Although criteria of malignancy have not yet been clearly established, perineural invasion, angioinvasion or deep invasion into the surrounding tissue is thought to indicate malignant behavior (40). Some studies believe a high proliferation index for Ki-67 (>25%) is an indication of malignancy (6). In our cases, including our case with local recurrence, the Ki-67 proliferation index was a maximum 1-2%. Studies proposing the theory that tumors of more than 5 cm have malignant potential were later unproven by subsequent studies (3). The follow-up of our cases ranged from 9 months to 5 years. After the second surgery for local recurrence in our relapsing case, a further two-year follow-up showed no recurrence or metastases. The clinical details of our other cases were updated and no metastases or recurrences were found.

In conclusion, the diagnosis of SPT, due to its low-grade malignant potential as well as its different treatment protocols for primary lesions and/or metastases, is of paramount importance. SPTs, clinically and histopathologically, exhibit different properties from other pancreatic tumors. While some new light has been shed on the clinicopathological features of SPT with regard to the etiology, origin and treatment methods, there is still much to be known. Further studies focusing on genetics, pathogenesis and prognosis are needed for a better understanding of this entity.

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