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Solid Pseudopapillary Tumors of the Pancreas: A Case Series, Comparison of Histopathological and Clinical Data

Solide pseudopapilläre Tumoren des Pankreas: eine Fallserie

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Schlüsselwörter
- solide pseudopapilläre Tumoren des Pankreas
- gastro-entero-pankreatische Tumoren
- Pankreas
- Immunhistochemie
- Neuroendokriner Tumor
- Azinuszellkarzinom

Key words
- solid pseudopapillary tumor
- Frantz tumor
- pancreas
- immunohistochemistry
- neuroendocrine tumor
- acinar cell carcinoma

Zusammenfassung

Solide pseudopapilläre Tumoren des Pankreas sind seltene Neoplasien dieses Organs. Sie werden zumeist zufällig diagnostiziert und treten prädominant bei Frauen auf. Die Prognose ist sehr gut. In der vorliegenden Fallserie werden der klinische Verlauf und die pathohistologischen Daten von 8 Patienten (7 weibliche, 1 männlicher Patient) beschrieben und mit den bisher publizierten Fallstudien verglichen auch im Hinblick auf klinische und pathologische Differenzialdiagnosen einer soliden Pankreasraumforderung. Pathohistologisch und immunhistochemisch zeigte sich ein vergleichbares Ergebnis in allen 8 Fällen auch unter Berücksichtigung der aktuellen Literatur. Obwohl hier einzelne Fälle mit schlechter Prognose beschrieben wurden, sind aktuell bei den vorgestellten Patienten keine Rezidive oder Metastasen bekannt.

Abstract

Solid pseudopapillary neoplasms (SPNs) are rare pancreatic tumors. They occur most frequently in young females and are often diagnosed accidentally. SPNs are characterized by an excellent clinical outcome. In our case series the clinical course, pathohistological data and clinical outcome of eight patients (7 female patients, 1 male patient) with SPN are described. Histological examination as well as immunohistochemical analysis shows similar results in all eight cases. Although in the literature a few cases of SPNs with bad prognosis have been reported, up to now none of our patients shows any signs of recurrence or metastasis. Moreover, we give in this case series a summary of SPNs in the literature, important clinical and pathological differential diagnosis, and additionally discuss relevant differential diagnosis occurring in daily routine work.

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Bibliography
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Introduction

Solid pseudopapillary neoplasms are rare pancreatic tumors, representing only 1% to 2% of all pancreatic tumors [1]. In 1959 this entity was first described by Frantz [1, 2]. She described three patients suffering from SPN, with solid and cystic components, that were previously misdiagnosed as non-functioning islet cell tumors [3]. Until the entity of solid pseudopapillary tumor was defined by the World Health Organization (WHO) in 1996 as exocrine pancreatic tumor [4], this tumor was also known as “solid cystic tumor”, “papillary cystic tumor”, “papillary epithelial neoplasia”, “papillary epithelial tumor”, “Frantz’s tumor”, “solid and papillary tumor”, “solid-cystic-papillary epithelial neoplasm”, “benign or malignant papillary tumor of the pancreas” and “adenocarcinoma of the pancreas in childhood” [5]. The actual WHO classification recommends the use of the term “solid pseudopapillary tumor” [6].

Material and Methods

We retrospectively reviewed a series of eight patients with SPN diagnosed at our institution between 2008 and 2011. Seven female patients and one male patient with an age range from 17 to 56 years were diagnosed with SPN and were followed up until now. The follow-up includes in the first year post operation abdominal computed tomography/sonography and esophagogastral endoscopy every three months, in the second year every six months then annually until now. All tumors were analyzed immunohistochemically concerning expression of α-1-

antitrypsin, AFP, β-catenin, Mib-1, MNF116, p53, progesterone receptor, DPC4, synaptophysin, NSE, vimentin, Her2/neu. Analysis was done according to a standardized protocol using DAKO-Autostainer and the antibodies in the following dilutions: α-1-antitrypsin: DAKO; 1:10000, AFP: DAKO; 1:200, β-catenin: DAKO; 1:400, Mib-1: DAKO, Ki-67; 1:2000, MNF116: DAKO MNF116-cytokeratin; 1:1000, p53: DAKO, Clone DO-07; 1:100, progesterone-receptor: DAKO clone PgR636; 1:1000, DPC4: Santa Cruz clone B-8; 1:100, synaptophysin: DCS, clone Snp88; 1:5000 NSE: DAKO, clone BBS/NC/VI-H14; 1:200, vimentin: DAKO, clone V9; 1:13000, Her2/neu: DAKO, c-erbB-2-oncoprotein; 1:600.

EGFR mutations was looked for in exon 18, 19 and 21 by Sanger sequencing: genomic DNA was extracted using the FFPE-DNA extraction kit (Qiagen) according the manufacturer's manual. From each patient EGFR exons 18, 19, and 21 were amplified by PCR using Pfx (Invitrogen) in a total volume of 50 µL. The PCR conditions were the same for each primer set (exon 18: forward: 5'-AGGG CTGAGGTGACCCTTGT-3', reverse: 5'GTGCCAGGGACCTTACCTATAC-3'; exon 19: forward: 5'-ACCATCTCACAATTGC CAGTTAAC-3', reverse: 5'-GAGGTTCAGAGCCATGGACC-3'; exon21: forward: 5'-TCACAGCAGGGTCTTCTCTGTTT-3', reverse: 5'-ATGCT GGCTGACCTAAAGCC-3'). Exons were amplified by PCR using the following PCR conditions: 95 °C for 5 min, and 40 cycles of 94 °C for 15 sec, 58 °C for 30 sec and 68 °C for 60 sec. Bidirectional sequencing was achieved using the GenomeLabTM Dye Terminator Cycle Sequencing kit (Beckman Coulter). Sequencing reaction products were run on a CEQ 8800 (Applied Biosystems). The sequencing chromatograms were analyzed by manual review. K-ras-mutations in exon 1 codon 12 and 13 were detected by pyrosequencing as published previously after DNA extraction as described above [7, 8].

Results

From 2008 to 2011 we diagnosed eight patients suffering from SPN at our institution, seven female patients with an age range from 17 to 56 years and one male patient, 26 years old. Four patients presented with unspecific abdominal symptoms (2 patients with unspecific abdominal pain, 1 patient with suspected Crohn's disease, 1 patient with suspected acute appendicitis) the others showed no specific symptoms. In all eight patients routine examination detected the pancreatic lesions either sonographically or radiologically. In four cases the tumor was located in the head and in one case in the tail of the organ. The other three tumors were detected in the body of the pancreas. Ultrasound (US) and computed tomography (CT) were the most common diagnostic investigations. Endoscopic retrograde cholangiopancreatography (ERCP) was used in one patient, additionally. Just in three cases the SPN was suspected preoperatively and in one case, the male patient, confined by fine needle aspiration in Russia. In the other cases a cystadenoma/cystadenocarcinoma or neuroendocrine tumors were suspected or an undefined suspicious mass was described radiologically. In one patient ductal adenocarcinoma of the pancreas was suspected.

All patients underwent therapeutic laparotomy. The technique of the operation performed was depending on tumor size and also on its localization. In five cases a partial pancreaticoduodenectomy and in two cases a pancreatic segment resection were carried out (**Fig. 1**). In one case, due to the tumor size, a distal pancreatectomy with splenectomy was performed. In one case a pancreatic fistula occurred due to fatty pancreas. Up to now, all eight patients do not show any signs of reccurence or metastasis.

Macroscopically all eight tumors were well demarcated by a fibrotic capsule without any infiltration or cutting of the capsule. Additionally four tumors presented with a solid yellow-white cut surface, and two tumors were partly solid, brown and partly cystic. Two tumors presented with a solid, grey-white and cystic cut surface. The mean tumor diameter was 4.6 cm ranging from 2 to 7.5 cm.

The histological examination revealed in all cases a solid, pseudopapillary and cystic growth with uniform round to oval tumor cells, degenerative foci of cholesterol clefts and foamy cells (**Fig. 2**). In only one case calcification was shown. None of the patients showed infiltration of lymphatic or blood vessels or any perineural invasion.

Immunohistochemistry showed similar results in all cases: progesterone receptor was expressed in 70–95% of the nuclei of all tumors, α-1-antitrypsin was expressed in two tumors and focally detectably in four others, while two tumors did not show any detectable expression immunohistochemically (**Fig. 3**). Six tumors showed a proliferation index (MiB-1 expression) <1% and two cases showed a proliferation index (Mib-1 expression) <4%. A strong positivity in all eight cases for vimentin, NSE and p53 was detectable. β-catenin and DPC4 were expressed in the nuclei and cytoplasma of the tumor cells in all cases. In three out of eight cases synaptophysin

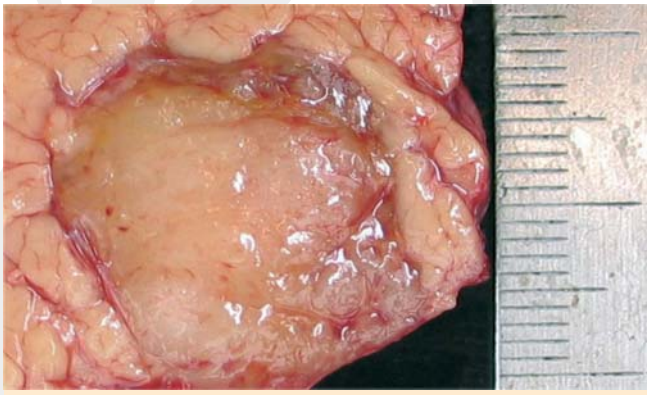

Fig. 1 Macroscopic appearance of a solid pseudopapillary tumor of the pancreas (patient 2).

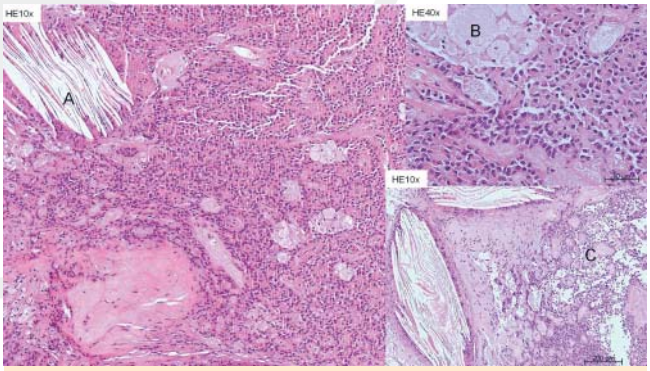

Fig. 2 Histological appearance of the tumor shown in **Fig. 1**. in the bigger picture, small pictures on the left showing examples of two other tumors (patients 3 and 4). Note the cholesterol clefts **A** and the foamy macrophages **B** as well as the pseudopapillary architecture **C**.

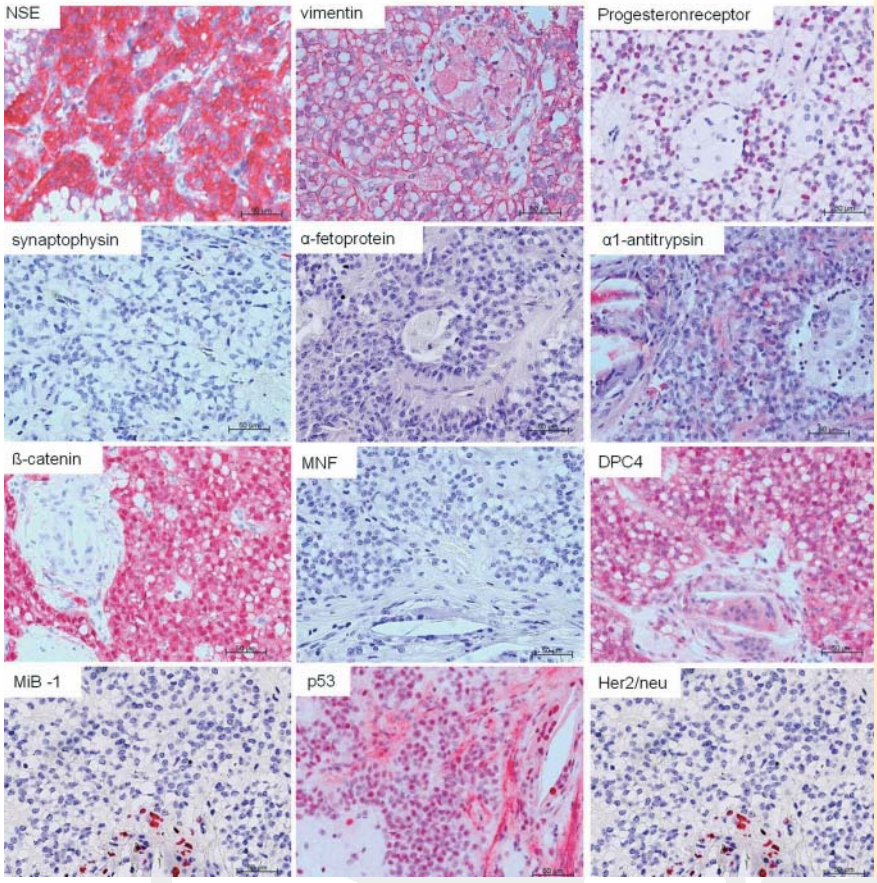

Fig. 3 Immunohistochemical expression of α-1-antitrypsin, α-fetoprotein (AFP), β-catenin, Mib-1, MNF116, p53, progesterone receptor, DPC4, synaptophysin, NSE, vimentin, Her2/neu.

patient	age/ sex	localization	tumor size	clinical diagnosis	surgical methods	symptoms
Pat 1	17/♀	head	6.7 cm	suspicious pancreatic mass	pancreaticoduodenectomy	abdominal pain
Pat 2	26/♂	corpus	2.0 cm	SPN (suspected in FNA)	segment resection	none
Pat 3	56/♀	tail	3.2 cm	cystadenoma/ cystadenocarcinoma	distal pancreatectomy with spleen	abdominal pain
Pat 4	51/♀	head	2.4 cm	neuroendocrine carcinoma	pancreaticoduodenectomy	Crohn's disease was suspected
Pat 5	33/♀	head	5 cm	suspicious pancreatic mass	pancreaticoduodenectomy	none
Pat 6	20/♀	corpus	4.2 cm	SPN-tumor possible	segment resection	none
Pat 7	22/♀	head	7.5 cm	SPN-tumor possible	pancreaticoduodenectomy	acute appendicitis was suspected
Pat 8	40/♀	corpus	5.5 cm	suspicious pancreatic mass, pancreatic ductal adenocarcinoma suspected	pancreaticoduodenectomy	none

Table 1 Clinico-pathological data of the analyzed patients, indicating age and sex of the eight different patients as well as the preoperative diagnosis, clinical symptoms, and the surgical methods used.

showed a modest positivity, while no expression was detectable in the other tumors. MNF116 and AFP were not expressed in any SPN analyzed. All tumors showed k-ras as well as EGFR wild-type status. None of the tumors showed any membranous expression of Her2/neu. ▶ **Table 1** summarises the clinicopathological data and in ▶ **Table 2** the results of the immunohistochemistry of the tumors analyzed in this study are shown.

Discussion

Solid pseudopapillary neoplasms are uncommon pancreatic tumors, accounting for less than 1% of pancreatic tumors [3]. They have a strong tendency to appear in young woman, although a few cases in children [3, 9], men and elder persons have been reported [10]. In a cumulative review of the literature, Mao et al. found that 90% of the patients were females

Table 2 Immunohistochemical data: Expression of NSE, vimentin, progesteronreceptor (nuclear expression), synaptophysin, α-fetoprotein (AFP), α-1-antitrypsin, β-catenin (nuclear and cytoplasmatic expression, MNF116 (membranous expression), DPC4 (nuclear and cytoplasmatic expression), p53 (nuclear expression, Mib-1 (nuclear expression), Her2/neu (membranous staining), k-ras (pyrosequencing-analysis of exon 1 codon 12, 13), EGFR (Sanger sequencing of exons 18, 19 and 21).

	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8
NSE	+	+	+	+	+	++	+	++
Vimentin	++	+++	++	+++	++	++	++	+
Progesterone receptor	80%	90%	80%	95%	70%	90%	90%	90%
Synaptophysin	focally +	focally +	–	–	–	–	focally +	–
α-fetoprotein (AFP)	–	–	–	–	–	–	–	–
α-1-antitrypsin	focally +	–	+	focally +	–	focally +	+	focally +
β-catenin	+	+	+	+	+	+	+	+
MNF116	–	–	–	–	–	–	–	–
DPC4	+	+	+	+	+	+	+	+
P53	80%	80%	85%	95%	50%	95%	90%	90%
Mib1	<1%	<1%	<4%	<4%	<1%	<1%	<1%	<1%
Her2/neu	–	–	–	–	–	–	–	–
EGFR	wt	wt	wt	wt	wt	wt	wt	wt
K-ras	wt	wt	wt	wt	wt	wt	wt	wt

with a mean age of 23.9 years (female:male ratio 1:9.5). It tends to be a benign lesion in young females but appears to be more aggressive in older and male patients [11].

One hypothesis assumes that during embryogenesis the pancreas anlage and the left genital ridge are close to each other, therefore cells from the genital ridge might migrate to the pancreas and as a consequence a solid pseudopapillary neoplasm may develop later. The immunoprofile with a positivity of progesterone receptor would be also convenient to this thesis [12]. Accordingly three tumors of the same morphology and immunoprofile were described in the ovary up to now resembling those of the pancreas further supporting this hypothesis [13].

A recently published mouse model by Heiser et al. gives further hints concerning pathogenesis [14] and contradicts the hypothesis of embryonal migration errors. In a mouse model with activated β-catenin they found tumors which corresponded to the morphology to human SPN. Most of the tumors were located in the ventral anlage of the pancreas. Whereas the precursor cell still has to be elucidated, they hypothesized a subgroup of ductal epithelial cells as precursor cells.

Usually β-catenin is important for the embryonal development of the pancreas, and is down-regulated in adults [15]. β-Catenin mutations are implicated in the development of many different malignant tumors by exerting tumor-promotive effects via increased Cyclin D1-expression among others. Interestingly the mutations described above do not increase proliferation rate in SPN, which is addressed in another study by Tiemann et al. [16]. The authors hypothesize herein that the cyclin-dependent kinase inhibitors p21 and p27 might play a role in stopping activated Wnt signalling. Other studies described an overexpression of CD117 in SPN leading to the discussion whether these tumors might be related to gastrointestinal stromal tumors [17] but no KIT/PDGFRA mutations could be detected in these tumors. The most recent publication showed a similar expression of DOG-1 in SPN and in pancreatic centroacinar cells hypothesizing that these cells might be another potential cell of origin [18]. At last gene expression profiling does also enhance the hypothesis of a pancreatic tumor with a distinct intrapancreatic precursor cell. Cavard et al. revealed by gene expression profiling the up-regulation of proteins involved in Wnt- and Notch-signalling, as well as neural differentiation markers (SOX10 and TuJ-1), indicating a closer association to neuroendocrine tumors than to adenocarcinomas [19].

Related to our study, SPN are often found incidentally in routine examinations. The patients usually have vague abdominal symptoms, which are generally not specific [20]. Patients may present with abdominal pain or palpable mass [21]. Physical examination is often normal, except for the presence of a mass in the pancreas [10]. Usually there are no elevated pancreatic enzymes or a pancreatic insufficiency, abnormal liver function tests, cholestasis, or an endocrine syndrome. Tumor markers are also unremarkable [22].

Abdominal US and CT usually show a well demarcated, encapsulated mass with solid and cystic components, sometimes with calcifications and maybe a displacement of nearby structures [9, 22]. In addition for preoperative diagnosis fine needle aspiration can be recommended. In a study of 150 cases SPN were successfully confirmed preoperatively as SPN based on a radiologically guided fine-needle aspiration [23].

The histological differential diagnosis of SPN without immunohistochemistry especially intraoperatively on frozen sections can be difficult. **Table 3** summarizes the gross, cytological, histopathological, and immunohistochemical features of SPN and its differential diagnosis. Pancreatic neuroendocrine neoplasms can mimic SPNs especially when they are solid or cystic as they show similar cytologic features and growth patterns. Both neoplasms are composed of clusters of uniform, homogeneous, round to oval cells. Solid pseudopapillary neoplasms usually show a positivity of NSE, vimentin and a nuclear positivity of β-catenin. In contrast, neuroendocrine tumors show usually a positivity for synaptophysin or chromogranin A [24]. Further two other pancreatic neoplasms are very important for differential diagnosis: pancreatoblastoma and acinar cell carcinoma. Pancreatoblastomas are very rare; they often affect children younger than 10 years. Histologically they show nests of polygonal cells with areas of acinar differentiation in addition to the characteristic squamoid corpuscles, which are not detectable in SPN. Immunohistochemically pancreatoblastoma expresses markers of acinar differentiation (trypsin, chymotrypsin and lipase) and markers of endocrine differentiation (chromogranin A or synaptophysin) and displays a nuclear staining of β-catenin. Acinar cell carcinomas grow in acinar, trabecular or solid patterns with granular cyto-

Table 3 Summary of the main clinical and pathohistological characteristics of the most important differential diagnosis [14, 18 – 20].

	patients	prognosis	histology	immunohistochemistry
SPN	young female patients	5 year survival 95 %	solid, pseudopapillary, cholesterol clefts	vimentin, NSE, progesteronreceptor, β-catenin; negative for cytokeratins
acinar carcinoma	50 – 70 years of age, predominant male	mean survival 36 months	acinar and solid	trypsin, chymotrypsin, amylase, lipase, β-catenin (< 50 %)
neuroendocrine tumor	20 – 70 years of age,	mean survival 4 years	trabecular, solid, glandular	NSE, synaptophysin chromogranin
pancreatoblastoma	children (≤ 10 years)	5 year survival 50 %	acinar and solid structure, squamoid corpuscles	trypsin, chymotrypsin, amylase, lipase, β-catenin

plasm and immunhistochemiacl expression of pancreatic enzymes, a nuclear staining of β-catenin is less frequent (< 50 %). Also pseudocysts can be an important differential diagnosis [25].

Pancreatic adenocarcinomas and SPNs differ in between their genetic profile. SPNs do not harbour a k-ras gene mutation or exhibit silencing of DPC4 gene but Frantz tumors are characterized by the presence of activating β-catenin gene mutations [26]. In 83 – 90 % these tumors show an activation of the Wnt signalling pathway due to the mutation of β-catenin in exon 3 [16, 27]. The nuclear expression of β-catenin is proven to be a good immunohistochemical marker for diagnosing SPNs [28].

Generally SPNs are well-circumscribed tumors and are usually demarcated by a pseudocapsule [9]. The cut surface shows large spongy areas of hemorrhage alternating with solid and cystic degeneration [9]. Chakhachiro et al. reported that smaller lesions seem to be more solid but less circumscribed in comparison to larger lesions [25].

The size of the tumors at presentation is variable, in the literature the mean diameter ranges from 0.3 cm [1] to 19.3 cm [3]. In our case series the mean diameter ranges from 2 cm to 7.5 cm. Herein the tumors were predominantly localized in the head of the pancreas (four in the head, three in the corpus/body and one in the tail of pancreas).

For tumors of the head of the pancreas a partial pancreaticoduodenectomy according to Whipple should be performed, for tumors of the tail and the body a distal pancreatectomy or even a segment resection can be considered [25]. In our case series five partial pancreaticoduodenectomies, one distal and two segment resections were performed. Although the postoperative outcome of SPN is really good, in the literature the most common complication is the development of pancreatic fistula in 6.2 % of the patients, a delayed gastric emptying (10 %) or pancreatitis (10 %) [1].

Curative surgical resection may be performed safely to rule out malignancy. After complete resection of the tumor the prognosis is excellent, 95 % of patients can be cured. Even in cases of metastasic disease the long-term prognosis is excellent [29]. In more than 85 % of patients, SPN is restricted to the pancreas. 10 – 15 % of the tumors described in the literature have already metastasized. The most common sites are liver, regional lymph nodes, mesentery and omentum majus [22]. It has been reported that the overall 5-year survival rate of SPN is about 95 % [4]. Deep extrapancreatic invasion, vascular or perineural invasion, significant cellular pleomorphism and nuclear atypia, as well as increased mitotic activity indicate SPNs with metastatic and recurrent potential [30]. Nevertheless surgical treatment of SPN should be curative, there are some fatal cases reported in the literature. Rebhandl et al. report about a 12-year-old girl with peritoneal dissemination of SPN two years after primary surgery [9]. Adamthwaite et al. reported the case of a 34-year-old female patient, who presented with a tumor in the pancreatic head measuring 11 × 9.5 × 6.5 cm with lymphovascular tumor permeation and metastatic spread to 7 out of 28 lymph nodes [21]. The patient refused adjuvant treatment and died two months later with gross liver metastasis.

In conclusion, SPN is a rare neoplasm, which typically occurs in young females. The diagnosis depends on histological confirmation. In a high percentage radiologically guided fine-needle aspiration can ensure diagnoses before operation. SPN has a good prognosis with a really good clinical outcome and an overall 5-year survival rate of nearly 95 %.

References

1 *Reddy S, Wolfgang CL.* Solid pseudopapillary neoplasms of the pancreas. Adv Surg 2009; 43: 269–282
2 *Casanova M, Collini P, Ferrari A et al.* Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children. Med Pediatr Oncol 2003; 41: 74–76
3 *Matos JM, Grutzmann R, Agaram NP et al.* Solid pseudopapillary neoplasms of the pancreas: a multi-institutional study of 21 patients. J Surg Res 2009; 157: e137–e142
4 *Papavramidis T, Papavramidis S.* Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. J Am Coll Surg 2005; 200: 965–972
5 *Bostanoglu S, Otan E, Akturan S et al.* Frantz's tumor (solid pseudopapillary tumor) of the pancreas. A case report. JOP 2009; 10: 209–211
6 *Bosman FT, Carneiro F, Hruban RH, eds.* WHO Classification of Tumours of the Digestive System. 4 edn. World Health Organization, 2010
7 *Ogino S, Kawasaki T, Brahmandam M et al.* Sensitive sequencing method for KRAS mutation detection by pyrosequencing. J Mol Diagn 2005; 7: 413–421
8 *Poehlmann A, Kuester D, Meyer F et al.* K-ras mutation detection in colorectal cancer using the pyrosequencing technique. Pathol Res Pract 2007; 203: 489–497
9 *Rebhandl W, Felberbauer FX, Puig S et al.* Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children: report of four cases and review of the literature. J Surg Oncol 2001; 76: 289–296
10 *Seo HE, Lee MK, Lee YD et al.* Solid-pseudopapillary tumor of the pancreas. J Clin Gastroenterol 2006; 40: 919–922
11 *Mao C, Guvendi M, Domenico DR et al.* Papillary cystic and solid tumors of the pancreas: a pancreatic embryonic tumor? Studies of three cases and cumulative review of the world's literature. Surgery 1995; 118: 821–828
12 *Salvia R, Bassi C, Festa L et al.* Clinical and biological behavior of pancreatic solid pseudopapillary tumors: report on 31 consecutive patients. J Surg Oncol 2007; 95: 304–310
13 *Deshpande V, Oliva E, Young RH.* Solid pseudopapillary neoplasm of the ovary: a report of 3 primary ovarian tumors resembling those of the pancreas. Am J Surg Pathol 2010; 34: 1514–1520
14 *Heiser PW, Cano DA, Landsman L et al.* Stabilization of beta-catenin induces pancreas tumor formation. Gastroenterology 2008; 135: 1288–1300
15 *Murtaugh LC, Law AC, Dor Y et al.* Beta-catenin is essential for pancreatic acinar but not islet development. Development 2005; 132: 4663–4674

16 *Tiemann K, Heitling U, Kosmahl M et al.* Solid pseudopapillary neoplasms of the pancreas show an interruption of the Wnt-signaling pathway and express gene products of 11q. Mod Pathol 2007; 20: 955–960
17 *Cao D, Antonescu C, Wong G et al.* Positive immunohistochemical staining of KIT in solid-pseudopapillary neoplasms of the pancreas is not associated with KIT/PDGFRA mutations. Mod Pathol 2006; 19: 1157–1163
18 *Bergmann F, Andrulis M, Hartwig W et al.* Discovered on gastrointestinal stromal tumor 1 (DOG1) is expressed in pancreatic centroacinar cells and in solid-pseudopapillary neoplasms – novel evidence for a histogenetic relationship. Hum Pathol 2011; 42: 817–823
19 *Cavard C, Audebourg A, Letourneur F et al.* Gene expression profiling provides insights into the pathways involved in solid pseudopapillary neoplasm of the pancreas. J Pathol 2009; 218: 201–209
20 *Ooi LL, Ho GH, Chew SP et al.* Cystic tumours of the pancreas: a diagnostic dilemma. Aust NZ J Surg 1998; 68: 844–846
21 *Adamthwaite JA, Verbeke CS, Stringer MD et al.* Solid pseudopapillary tumour of the pancreas: diverse presentation, outcome and histology. JOP 2006; 7: 635–642
22 *Huang HL, Shih SC, Chang WH et al.* Solid-pseudopapillary tumor of the pancreas: clinical experience and literature review. World J Gastroenterol 2005; 11: 1403–1409
23 *Crawford BE.* Solid and papillary epithelial neoplasm of the pancreas, diagnosis by cytology. South Med J 1998; 91: 973–977
24 *Anlauf M, Sipos B, Kloppel G.* Tumors of the endocrine pancreas. Pathologe 2005; 26: 46–51
25 *Chakhachiro ZI, Zaatari G.* Solid-pseudopapillary neoplasm: a pancreatic enigma. Arch Pathol Lab Med 2009; 133: 1989–1993
26 *Abraham SC, Klimstra DS, Wilentz RE et al.* Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 2002; 160: 1361–1369
27 *Tanaka Y, Kato K, Notohara K et al.* Frequent beta-catenin mutation and cytoplasmic/nuclear accumulation in pancreatic solid-pseudopapillary neoplasm. Cancer Res 2001; 61: 8401–8404
28 *Tanaka Y, Tran PO, Harmon J et al.* A role for glutathione peroxidase in protecting pancreatic beta cells against oxidative stress in a model of glucose toxicity. Proc Natl Acad Sci U S A 2002; 99: 12363–12368
29 *Romics Jr L, Olah A, Belagyi T et al.* Solid pseudopapillary neoplasm of the pancreas – proposed algorithms for diagnosis and surgical treatment. Langenbecks Arch Surg 2010; 395: 747–755
30 *Tang LH, Aydin H, Brennan MF et al.* Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. Am J Surg Pathol 2005; 29: 512–519