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Solid–pseudopapillary tumor of the pancreas: its origin revisited

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Abstract Solid–pseudopapillary tumor of the pancreas (SPT) has distinctive morphologic and biologic features but an unclear origin. It is classified among the pancreatic epithelial tumors, though many are reported to be negative for cytokeratin. Also unclear are its neuroendocrine differentiation, its capability to express alpha-1-antitrypsin (AAT) and, in view of the tumor's striking prevalence in women, its relationship with the female genital tract. To clarify these issues, the immunoprofiles of 59 SPTs were defined by applying a battery of antibodies against cytokeratin, vimentin, neuron-specific enolase (NSE), synaptophysin, chromogranin A, tyrosine hydroxylase (TH), AAT, LeuM1, Ki-M1P, smooth-muscle actin, CD34, alpha-inhibin, calretinin, placental alkaline phosphatase (PLAP), and progesterone and estrogen receptors. The most consistent markers with the strongest immunoreactivity were vimentin, AAT, NSE, and the progesterone receptor, which were each found in more than 90% of the tumors. Using immunocytochemical methods involving antigen retrieval, cytokeratin was demonstrated in almost 70% of the cases. Synaptophysin was found in 22% of the tumors, while chromogranin was absent and tyrosine hydroxylase was only present in a few tumors. None of the other markers tested were expressed by SPTs. This staining pattern fails to reveal a clear phenotypic relationship with any of the defined cell lineages of the pancreas. In view of the striking female preponderance of SPTs and the known close approximation of the genital ridges to the pancreatic anlage during embryogenesis, it is, however, hypothesized that SPTs might derive from genital ridge/ovarian anlage-related cells, which were attached to the pancreatic tissue during early embryogenesis.

Key words Solid–pseudopapillary tumor · Immunoprofile · Pancreatic origin · Genital ridge/ovarian origin

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Introduction

Solid–pseudopapillary tumor (SPT) of the pancreas is an uncommon but distinctive neoplasm occurring preferentially in women. The tumors are often asymptomatic or are associated with uncharacteristic abdominal symptoms. They are classified as papillary, cystic, solid, or epithelial neoplasms. This compilation of names reflects the purely descriptive classification of this benign or low-grade malignant tumor. Although the pathologic features of SPT have been well described in recent years, its phenotype could not be clearly related to any of the well-characterized cells of the pancreas. Some studies indicated an origin from acinar cells [2, 18, 21, 22, 23] or endocrine cells [16, 43, 46], but the results of most other studies have not been compatible with these suggestions [19, 28, 36]. The immunocytochemical phenotype is characterized by the frequent expression of vimentin, neuron-specific enolase (NSE), and alpha-1-antitrypsin (AAT) [41]. This marker pattern together with the observation that SPTs are often found to be negative for cytokeratin leads to the questions whether SPTs are mesenchymal rather than epithelial tumors, whether they show other features of macrophage differentiation apart from AAT positivity (i.e., LeuM1 [14] and Ki-M1P positivity [37, 44]), whether NSE is the only positive neuroendocrine marker, and whether there is any relationship to female genital tract cells.

The aim of our study was to clarify these issues by conducting an extensive immunocytochemical investigation on formalin-fixed paraffin-embedded material from 59 SPTs. The immunophenotypic analysis was performed using antibodies to cytokeratin (Lu5 and Cam

Table 1 Antibodies used in SPT immunophenotyping

Antigen/antibody	Host species	Source	Working dilution	Antigen retrieval	Control tissue
LeuM1	Mouse	DAKO (Glostrup, Denmark)	1:50	Boiling	Tonsils
Ki-M1P	Mouse	Department of Pathology, University of Kiel	1:50	Protease (5 min)	Tonsils
CD34	Mouse	Immunotech (Marseille, France)	1:1500	–	GIST
Smooth muscle actin	Mouse	DAKO (Glostrup, Denmark)	1.20	–	Tonsils, duodenum
Alpha-1-antitrypsin	Rabbit	DAKO (Glostrup, Denmark)	1:50000	–	Liver
Neuron-specific enolase	Mouse	DAKO (Glostrup, Denmark)	1:500	Boiling	Pancreas
Synaptophysin	Rabbit	Biometra (Göttingen, Germany)	1:1500	–	Pancreas
Vimentin	Mouse	DAKO (Glostrup, Denmark)	1:200	Boiling	Pancreas
Lu5	Mouse	BMA (Augst, Switzerland)	1:100	Protease (10 min)	Tonsils
Cam5.2	Mouse	Bectin Dickinson (San Jose, CA, USA)	1:10	Protease (5 min)	Pancreas
Tyrosine hydroxylase	Mouse	Novo-Castra (Newcastle, England)	1:15	Boiling	Pancreas
Alpha-inhibin	Mouse	Serotec (Oxford, England)	1:10	Boiling	Ovary
Calretinin	Rabbit	Chemicon Int. (Temecula, CA, USA)	1:100	Protease (10 min)	Ovary
Chromogranin A	Mouse	Linaris (Wertheim-Bettingen, Germany)	1:2	–	Pancreas
Placental alkaline phosphatase	Mouse	Novo-Castra (Newcastle, England)	1:20	Boiling	Seminoma
Estrogen receptor	Mouse	DAKO (Glostrup, Denmark)	1:30	Boiling	Mammary
Progesterone receptor	Mouse	DAKO (Glostrup, Denmark)	1:30	Boiling	Mammary

5.2), vimentin, NSE, synaptophysin, chromogranin A, tyrosine hydroxylase (TH), AAT, LeuM1, Ki-M1P, smooth muscle actin, CD34, and estrogen and progesterone receptors, together with markers for ovarian cells, such as alpha-inhibin, calretinin, and placental alkaline phosphatase (PLAP), which stain stromal cells, luteinizing cells, hilar cells, surface epithelium, and germ cells, respectively.

Materials and methods

Patients

The study included resection specimens from 59 patients. The cases were retrieved from the surgical files and consultation archives of the Departments of Pathology and Pediatric Pathology, University of Kiel, Germany. Clinical information was obtained from the patients' records and by direct contact with the attending physician.

Histological and immunocytochemical examination

In most cases, two samples were obtained from the neoplastic lesion; many contained surrounding non-neoplastic tissue. All specimens were fixed in 10% buffered formalin and embedded in paraffin. For the study, 4-µm-thick sections were prepared and mounted on coated slides. The sections were deparaffinized in xylene for 14 min and rehydrated in graded alcohol (100%, 96%, and 70%). Immunocytochemical analysis was carried out on serial sections from one paraffin block from each case using the alkaline phosphatase-antialkaline phosphatase (APAAP) technique [7]. The primary antibodies are listed in Table 1. Endogenous phosphatase activity was blocked with 1 mM levamisole (Sigma) in the substrate solution. The slides were either directly immunostained or first pretreated by incubation with protease or boiling in citrate buffered saline for 3.5 min.

Results

Clinical data

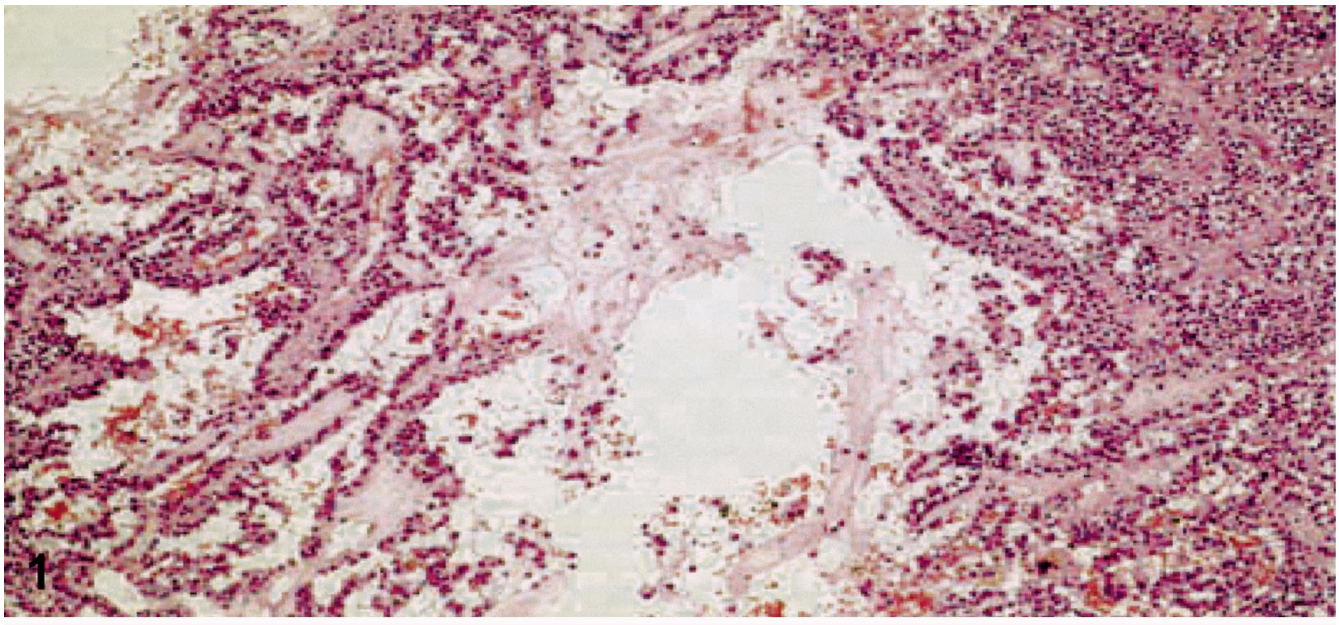
Our series of 59 patients included 52 females (88%) and 7 males (12%). The youngest female patient was 11 years, the oldest 63 years old. The mean age for females was 26 years. In males, the ages ranged from 12 years to 43 years, with a mean of 23 years. The mean age for females and males together was 25.6 years. Data on the clinical presentation were available in approximately one-third of the cases. Three patients presented with an abdominal mass. In six patients, the tumor was found incidentally. Ten patients had abdominal pain or discomfort. In one case, the tumor was detected during a gynecological operation. One tumor was diagnosed as a pancreatic pseudocyst, another as a cystic adenoma. One patient had anemia, and, in another, there was bleeding from the tumor.

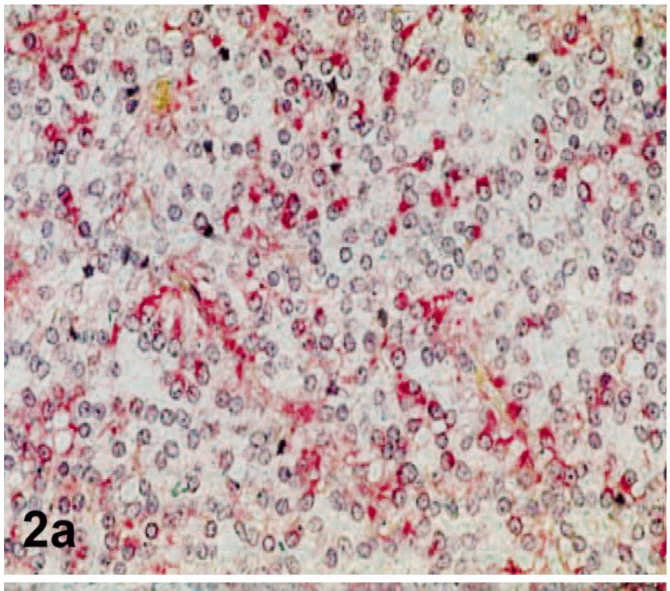
Macroscopic findings

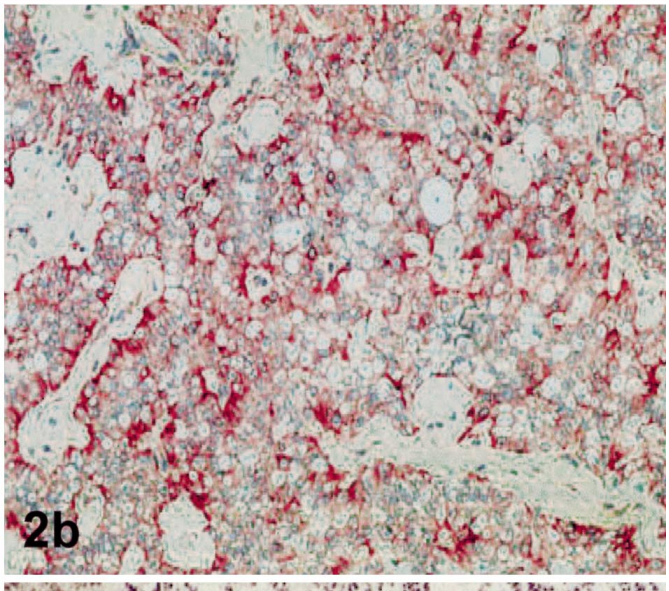
The tumor was located in the pancreas tail in 18 cases, in the head in 13 cases and in the body in 11 cases. An extrapancreatic location was seen in six cases. The size of the tumors ranged from 2 cm to 17 cm (mean size 7.5 cm). The vast majority of cases were well demarcated and did not show any distant metastases, with five exceptions: one had liver metastases; another peritoneal metastases; two cases showed invasive tumor growth into the spleen; and a fifth invasion of the duodenum.

Fig. 1 High magnification showing cells with eosinophilic cytoplasm and cells with clear cytoplasm ▶

Fig. 2 Set of four figures (a–d) (color) with cytokeratin, vimentin, neuron-specific enolase (NSE), and progesterone positivity


1


2a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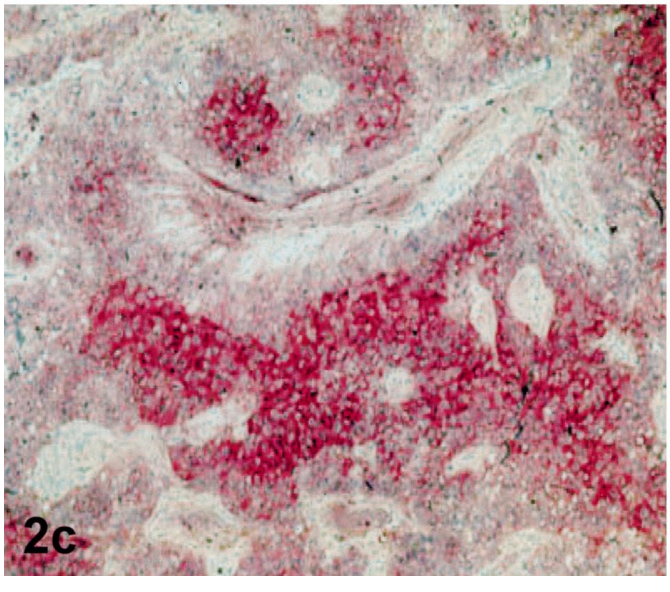
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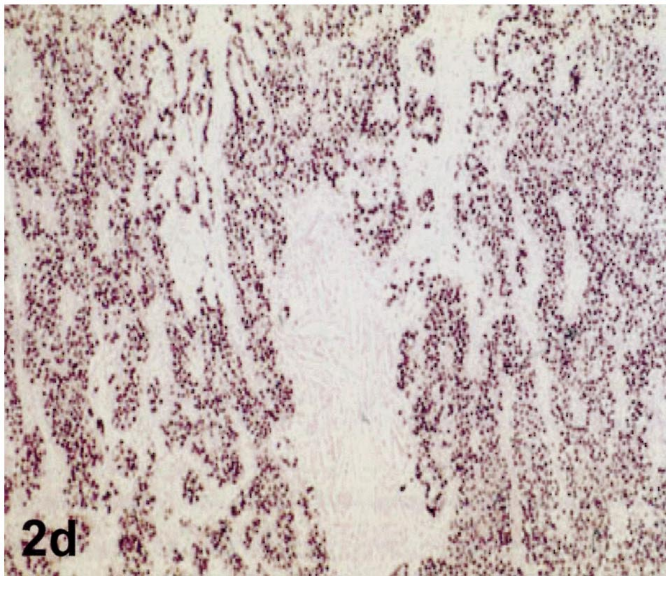
2d

Table 2 Immunoprofile of solid-pseudopapillary tumors of the pancreas (–: no tumor cells were positive, 1+: less than one-third of tumor cells were positive, 2+: one-third to two-thirds of tumor cells were positive, 3+: more than two-thirds of tumor cells were positive)

Antigen/antibody	Total no.	Negative	1+	2+	3+	Total positive (%)
Lu5	59	19	20	12	7	39 (66)
Cam5.2	59	20	30	8	1	39 (66)
Vimentin	59	5	15	16	23	54 (92)
Alpha-1-antitrypsin	58	2	34	16	6	56 (97)
Neuron-specific enolase	59	4	22	16	17	55 (93)
Synaptophysin	59	40	11	2	–	13 (22)
CD34	59	59	–	–	–	0
LeuM1	59	59	–	–	–	0
Smooth muscle actin	59	59	–	–	–	0
Ki-M1P	59	59	–	–	–	0
Alpha-inhibin	58	58	–	–	–	0
Calretinin	58	56	2	–	–	2 (3)
Tyrosine hydroxylase	57	52	5	–	–	5 (9)
Placental alkaline phosphatase	53	53	–	–	–	0
Chromogranin A	53	53	–	–	–	0
Estrogen receptor	57	57	–	–	–	0
Progesterone receptor	57	–	13	35	9	57 (100)

Microscopic findings

The growth pattern of the tumors was heterogeneous, with a combination of solid, pseudopapillary, and/or hemorrhagic pseudocystic structures in various proportions. Admixed with the epithelial elements there was hyalinized to myxoid connective tissue forming small strands or large areas along or around thin-walled blood vessels. These changes were severe in 10 cases, moderate in 18, and mild in the remaining cases. Cholesterol crystals were found together with foreign body giant cells in 22 of the 59 SPTs. Small calcifications were detected in 8 of 59 cases. Hemorrhagic necrosis was found in 16 cases. Pseudopapillary structures forming pseudorosettes were almost uniformly present. The pseudocystic cavities were filled with a homogeneous eosinophilic material, which showed a scalloping pattern at the edges in two cases. A microcystic pattern was seen in seven cases. The solid and pseudopapillary structures were composed of monomorphous rounded cells with minimal atypia (Fig. 1). The cytoplasm was faintly eosinophilic. In addition, 34 of 59 SPTs contained cells with clear cytoplasm, the percentage of which varied from tumor to tumor. In all cases, eosinophilic Periodic acid–Schiff (PAS)-positive hyaline globules of varying size were found. In the vast majority of cases, the nuclei were ovoid with slight indentations and no mitoses. Five SPTs, however, had cells with large grooved or spindle-shaped nuclei together with occasional giant nuclei. Most tumors were separated from the adjacent pancreatic tissue by a fibrous capsule. Infiltration into the pancreatic tissue was found in 14 SPTs, including all malignant cases.

Immunocytochemical results

The detailed results are listed in Table 2. Thirty-nine of 59 (66%) SPTs stained for both broad-spectrum cytokeratin antibodies (Lu5 and Cam5.2) (Fig. 2a). The staining was weak and focal in most cases (20 of 39 and 29 of 39, respectively). Vimentin was found to be positive in 54 of 59 (92%) cases (Fig. 2b); in 32 SPTs, the vimentin staining intensity was inversely proportional to that of cytokeratin staining. AAT was strongly positive in 56 of 58 (97%) SPTs; the staining pattern was patchy with scattered clusters of strongly positive tumor cells. NSE was diffusely and strongly expressed in 55 of 59 cases (93%) (Fig. 2c). Synaptophysin, in contrast, was only positive in 13 of 59 (22%) SPTs, with faint and focal staining in most cases. TH was negative in the majority of SPTs. Only 5 of 57 (9%) cases showed focal reactivity in the tumor cells. TH was positive in small nerves at the tumor periphery and in individual islet cells. Chromogranin A was absent in all tumors. Exceptions were small islet cell clusters entrapped in peripheral tumor tissue. In separate staining reactions it was shown that these islet cell clusters were composed of insulin, glucagon, and somatostatin cells and an occasional PP cell (data not shown).

In all SPTs, the tumor cells were negative for CD34, while endothelial cells were positive. Ki-M1P was found to be positive in single cells scattered within the tumor tissue. These positive cells corresponded histologically to macrophages. The strongest staining of macrophages was observed around cholesterol granulomas. Ki-M1P-positive cells also stained for LeuM1. In areas with cholesterol granulomas and necrosis, the LeuM1 positivity was stronger than in other areas. Smooth muscle actin was only positive in smooth muscle cells of the walls of blood vessels. Alpha-inhibin and PLAP were absent in all SPTs. Calretinin was positive in small nerves between the tumor cells. Only two of the 58 SPTs showed focal reactivity. All examined SPTs were strongly positive for progesterone receptors (Fig. 2d), but lacked estrogen receptors.

To test fetal pancreatic tissue and adult ovarian tissue for the expression of cytokeratin, vimentin, AAT, NSE,

synaptophysin, and alpha-inhibin, we examined pancreatic specimens from three 9- to 11-week-old fetuses and ovarian specimens from two premenopausal women. The pancreatic tissue showed extensive staining for cytokeratin in all epithelial structures. NSE and synaptophysin stained cells in ductular structures and in small islet-like cell aggregates. Vimentin and alpha-inhibin were not expressed in either ductular cells or islet-like cells of the fetal pancreas. Hilar and luteinizing stromal cells in the ovarian tissue stained for alpha-inhibin.

Discussion

The SPT of the pancreas is characterized by monomorphic tumor cells that look like endocrine cells and form solid tissue, which undergoes a process of degeneration with cellular disintegration resulting in pseudopapillary structures, hemorrhage, and tissue degeneration. The patients are usually young women and the prognosis is excellent. In contrast to the tumors' clearly delineated biological and histological features, their cellular origin and phenotypic relationship to the pancreas have remained enigmatic. Our results do not clarify these issues further, but in discussing the data we will attempt to introduce a new view on the derivation of the SPT.

SPTs are generally held to be epithelial neoplasms [20, 41]. However, cytokeratin expression, which is usually, but not exclusively, associated with epithelial differentiation, is rare (<30%) or even absent in most SPTs [3, 19, 24, 35, 36]. Only a few series have reported cytokeratin expression rates of around 60% [39, 42, 47, 48]. Applying the antibodies CAM5.2 and Lu5, which recognize broad-spectrum cytokeratin profiles, and using an antigen retrieval method we found immunoreactivity in almost 70% of the cases. Why about one-third of the tumors remained negative is unclear, but it is likely that, as has previously been shown [48], enhancing the stringency of the antigen retrieval method would have resulted in an increase in the number of cytokeratin-positive cases. These results suggest that most, if not all, SPTs express cytokeratin, but at a very low level, as is also indicated by the usually weak and focal immunostaining for cytokeratin.

As for the cytokeratin profile expressed by SPTs, it has already been shown that the tumors may express CK7, 8, 18, and 19 [13, 42]. This CK profile characterizes the duct and ductular cells of the pancreas. As there may also be ultrastructural features, such as primitive cell junctions, small bundles of tonofilaments, and intermediate microfilaments reminiscent of ductal/ductular differentiation or myoepithelial differentiation [1, 23, 27], an origin from the duct cell compartment of the pancreas has been suggested [12, 23, 25, 30]. However, there are two findings that argue against this assumption. First, myoepithelial differentiation was excluded in all cases by a negative immunoreaction to alpha-smooth muscle antigen. Second, in confirmation of previous studies [19, 27], we found that more than 90% of the SPTs expressed vimentin, usually at high levels. Vimentin expression, however, is not an in vivo feature of duct cells or any other epithelial cell type of the adult pancreas. This also holds true for the fetal pancreas, as shown in this study. It is therefore difficult to relate the SPT cells to any of the epithelial components of the pancreas, even if a multipotent stem cell origin is considered. Another point that speaks against the latter assumption is the well-developed cytological features of the SPTs, and their low proliferative activity and malignancy rate, which are more consistent with a terminally differentiated than with a protodifferentiated cell.

NSE, synaptophysin, chromogranin A, and TH are considered neuroendocrine markers [8]. While NSE was strongly positive in more than 90% of SPTs, synaptophysin showed patchy immunoreactivity in 22% of the tumors, TH stained only a few tumors, and chromogranin A was not detected. This indistinct staining pattern for neuroendocrine markers, which confirms and partly extends the results of other studies [4, 27], suggests that the SPTs cannot be regarded as pure neuroendocrine neoplasms. In line with this assumption is the fact that SPTs have never been convincingly shown to produce pancreatic hormones or other neuropeptides, nor have they been found to be associated with any clinical endocrine dysfunction. Some pancreatic hormones, such as insulin, somatostatin, and glucagon, were immunocytochemically demonstrated in single tumor cells or small clusters in some studies [27, 29, 43, 46], but most investigators failed to confirm these data [19, 21, 22, 23, 28, 32, 42]. Clusters of cells positive for pancreatic hormones, which we found in the periphery of a few SPTs (usually when they were ill demarcated), were identified as entrapped islets and could therefore be excluded as an integral component of the SPT. Ultrastructurally, membrane-bound dense core granules have occasionally been described [1, 18, 22, 27, 47], but have never been proven to contain a neurosecretory product. Taken together, the incomplete neuroendocrine differentiation in SPTs must therefore be regarded as a special feature of this neoplasm, which distinguishes it from true neuroendocrine tumors. In this context, it is interesting that expression of synaptophysin and/or NSE in the absence of chromogranin A has also been noted in adrenal cortex tumors that were considered to be non-neuroendocrine neoplasms [26, 40] and some other non-neuroendocrine neoplasms as well as non-neoplastic tissues, such as renal tubular cells and spermatogonia [11, 34].

AAT inhibits proteases and is considered a marker of lysosomes. Cells with phagocytic properties may therefore be positive for AAT. In SPT, the positivity for AAT is most likely not related to macrophage differentiation, since the other macrophage markers that we tested, i.e., Ki-M1P [37, 44] and LeuM1 [14], failed to label AAT-positive tumor cells and were only positive in macrophages scattered in the tumor tissue or surrounding cholesterol granulomas. AAT has also been found to be posi-

tive in other pancreatic neoplasms, such as acinar cell carcinoma or endocrine tumor [28, 33, 38]. However, these neoplasms only stain faintly and do not show the strong focal ("single cell") immunoreactivity to AAT seen in SPTs, which also seems to involve the hyaline PAS-positive globules commonly seen in SPTs. Similar findings have been reported in malignant (Muellerian) mixed mesodermal tumors of the ovary, in which AAT immunoreactivity correlated at the ultrastructural level with the presence of large inclusion bodies closely resembling the zymogen-like granules in SPTs [9, 10]. The hyaline globules in hepatocellular carcinomas, which may also stain for AAT [45], seem to differ in their ultrastructural appearance from the large granules seen in SPTs and malignant mixed mesodermal tumors. Though these rare and special ovarian tumors appear to have little resemblance to SPTs, the occurrence of similar granules in these neoplasms and SPTs could be an indication that the SPTs of the pancreas might have some relationship to primitive ovarian tissue.

SPTs, together with mucinous cystic neoplasms and serous microcystic adenomas, belong to the pancreatic tumors with a strong female preponderance [5, 6, 41, 49]. This suggests that these tumors are either dependent on female hormones or are related to cells of the female genital tract, in particular the ovary and its anlage. So far, female hormone overproduction has never been demonstrated in association with SPTs. It is therefore tempting to speculate that the close approximation between the genital ridges (particularly the left one) and the pancreas anlage during the 7th week of gestation leads to attachment or even incorporation of primitive ovarian cells into pancreatic tissue. This theory has been discussed for mucinous cystic tumors and may also be valid for SPT [49]. A comparison of the immunoprofile of SPTs with that of the different cell lineages of the ovary reveals a good correlation with the immunocytochemical pattern of the surface cells derived from the coelomic epithelium and the cells in the rete ovarii but not with stromal cells, sex cord cells, hilar cells, and germ cells. Surface cells are positive for both keratin and vimentin and stain for receptors for progesterone and estrogen, but they are negative for calretinin, alpha-inhibin, PLAP, and TH, which stain stromal and hilar cells and germinal epithelium. So far unexplained is the positivity for NSE, AAT and, to a minor degree, also synaptophysin, which has been found in germ cell tumors but not in tumors deriving from the ovarian surface epithelium [31]. It is therefore not possible to identify a certain cell in the ovary that exactly corresponds to the immunoprofile of the cells in SPTs. There are also no ovarian tumors with strong similarity to SPTs.

In the light of these findings, it is therefore highly speculative to try to construct a connection between SPTs and ovarian anlage cells. However, assuming that the cells of the genital ridge are influenced in their further differentiation by the surrounding tissue, it is conceivable that genital ridge cells that become detached from their place of origin and come into contact with other tissues acquire a special phenotype. The occurrence of a few SPTs in the retroperitoneal space outside the pancreas [15, 17, 19] can easily be related to the localization of the genital ridges during embryogenesis.

The observation that SPTs are mainly detected in adolescent girls and young women could indicate that SPTs are responsive to sex hormones. Their sharp rise at the beginning of the reproductive period might stimulate the growth of these tumors. A good candidate among the sex hormones would be progesterone because of the ubiquitous expression of progesterone receptors in SPT cells [32, 48]. The continuous rise and fall of progesterone levels during the menstrual cycle could also help to explain the finding that SPTs usually display large areas of extensive hemorrhagic necrosis in addition to solid and preserved areas. What is not considered by this hypothesis, however, and remains an open question is the fact that a few of the SPTs occurred in men with no obvious sex hormone abnormalities.

In summary, our results show that SPTs are neoplasms with a complex immunoprofile, which is not consistent with that of any of the pancreatic cell types. It is therefore doubtful that they originate from the pancreas. We speculate, on the basis of some similarities between SPT and ovarian surface cells and the close vicinity between the genital ridges (particularly the left one) and the pancreas anlage during early embryogenesis, that SPTs might originate from genital ridge-related cells that were incorporated into the pancreas during organogenesis.

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