

Solid pseudopapillary neoplasm of pancreas

Two case reports

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Abstract

Rationale: About 8384 cases of solid pseudopapillary neoplasms (SPN) of pancreas have been published in English literature, from 1933 to 2018. This is a low-grade tumor that usually occurs in children but is rare in adults and, in exceptional cases, can show extrapancreatic localization. In this paper we present 2 unusual cases of SPNs, 1 with retroperitoneal location (case 1) and 1 that was firstly diagnosed as a G1 neuroendocrine tumor (NET) and showed hepatic metastases after 13 years (case 2).

Patient concerns: No symptoms in first case. The tumor was incidentally diagnosed, during ultrasound examination. In the second case, the metastasis was observed during regular follow-up.

Diagnoses: The diagnosis was established based on the histological features and immunohistochemical profile that showed positivity for vimentin, nuclear β -catenin, cyclin D1, CD10, and SRY-related high-mobility group box 11 and negativity for maspin.

Interventions: Surgical excision, in both cases.

Outcomes: No recurrences in first case, at 5 months after diagnosis. Hepatic metastases in the second case, at 13 years after diagnosis, with portal invasion after another 15 months.

Lessons: Without a complex immunoprofile, SPN can be misdiagnosed as NET. SPN can be a low-grade tumor but long-time follow-up is mandatory to detect delayed metastases. A correct diagnosis is necessary for a proper therapeutic management.

Abbreviations: DOG-1 = gastrointestinal stromal tumor 1, IHC = immunohistochemical, MCN = mucinous cystic neoplasm of the pancreas, NET = neuroendocrine tumor, NSE = neuron-specific enolase, PDGFR = platelet-derived growth factor receptor, SOX-11 = SRY-related high-mobility group box 11, SPN = solid pseudopapillary neoplasm, WHO = World Health Organization.

Keywords: β -catenin, maspin, metastasis, retropancreatic, retroperitoneal, solid pseudopapillary neoplasm, SRY-related high-mobility group box 11

1. Introduction

First papillary cystadenocarcinoma of the pancreas was described in 1933 and published in 1934 by Lichtenstein.^[1] In 1959, Frantz^[2] described a particular type of papillary neoplasm in 2 women and 1 man, which was then nominated as Frantz tumor. Till 1996, Frantz tumor is recognized by World Health Organization (WHO) as a

tumor with uncertain differentiation or solid pseudopapillary neoplasm (SPN) of the pancreas.^[3–5] Other used synonyms are solid/papillary cystic tumor, papillary epithelial neoplasia, solid/papillary epithelial neoplasia, papillary epithelial tumor, solid and papillary/cystic tumor or epithelial neoplasm, benign or malignant papillary tumor of the pancreas, etc.^[5,6]

SPN represents 0.17% to 2.7% of all pancreatic tumors and usually affects women below their 40 years (range 2–85 years), with a M:F report of 7 to 11:1.^[3–6] As regarding pediatric cases, 8% to 12.5% of all pancreatic tumors are SPNs.^[6] It usually develops in the pancreatic body and tail (55–60%) but head/neck can also be involved (35–40%).^[6] In 1% to 1.8% of the cases, the SPN was found to be located in the extrapancreatic sites such colon, mesenterium, testis, or retroperitoneum.^[3,6] Although the number of reported SPN increased after 2003, the proportion of extrapancreatic localization decreased from 1% to 1.8% in the period 1933 to 2003 to 0.62% from 2004 to 2018.

Although 95% of the patients showed good evolution, with long-time tumor-free survival and 95% 5 and 10 year disease-specific survival, without any postoperative therapy, metastases can occur in 5% to 10% of the cases, although the histological aspect suggests a low-grade tumor.^[3,5,7] Liver and lymph nodes are the commonest sites of distant metastases but mesentery, omentum, peritoneum, and lungs can also be involved.^[5,6]

As tumor cells architecture suggests a G1 neuroendocrine tumor (NET), another challenging issue is establishing of the correct diagnosis under microscope. The main differential

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Table 1
Immunoprofile of retropancreatic solid pseudopapillary neoplasm.

IHC marker	Manufacturer	Clone	Dilution	IHC expression	Subcellular expression	Positive cells (%)
Vimentin	Dako (Glostrup, Denmark)	V9	RTU	Positive	Cytoplasm	100%
β-catenin	Dako	β-catenin 1	1:150	Positive	Nucleus and cytoplasm	100%
Cyclin D1	Dako	EP12	1:100	Positive	Nucleus	~80%
SOX11	Sigma Aldrich (ST Louis, MO)	Polyclonal	1:100	Positive	Nucleus	~80%
CD56	Dako	123C3	RTU	Positive	Cytoplasm and membrane	~70%
NSE	Dako	BBS/NC/VI-H14	RTU	Positive	Cytoplasm	~70%
Progesterone receptor	Dako	PgR636	RTU	Positive	Nucleus	~80%
Synaptophysin	Dako	DAK-SYNAP	RTU	Positive	Cytoplasm	~40%
Chromogranin A	Dako	DAK-A3	1:100	Positive	Perinuclear dots	~60%
CD10	Dako	56C6	RTU	Positive	Nucleus	~20%
AE1/AE3 cytokeratin	Dako	AE1/AE3	RTU	Positive	Cytoplasm	~60%
N-cadherin	Dako	6G11	RTU	Positive	Cytoplasm	~20%
α-1 Antitrypsin	Dako	Polyclonal	1:600	Negative	–	–
E-cadherin	Leica Biosystems (Wetzlar, Germany)	NCL-E cad	1:50	Negative	–	–
Ki67	Dako	MB1	1:100	Negative	–	–
Estrogen Receptor	Dako	1D5	RTU	Negative	–	–
Maspin	Santa Cruz Biotechnology (Dallas, Texas)	Monoclonal	1:25	Negative	–	–
S100	Dako	Polyclonal	1:6000	Negative	–	–
Melan A	Dako	A103	RTU	Negative	–	–
HMB45	Cell Marque (Rockling, California)	Monoclonal	1:100	Negative	–	–

HMB45 = human melanoma black, IHC = immunohistochemical, NSE = neuron-specific enolase, RTU = ready to use, SOX-11 = SRY-related high-mobility group box 11.

diagnosis also takes into account adenocarcinomas and cystadenomas/cystadenocarcinomas with papillary features.^{16]}

The aim of this paper is to present 2 particular cases of SPN. The first one was an extrapancreatic SPN and the second SPN showed metachronous metastases at 13 years after surgical removal. An extensive review of literature regarding the total number of reported cases, differential diagnosis, immunoprofile, and therapeutic regimen in metastatic cases was also done. Signed informed consent was obtained from both patients for surgical intervention and case publication.

2. Case report

2.1. Case 1

A 36-year-old previously healthy woman presented with an incidentally discovered, during routine ultrasound examination, of a retroperitoneal tumor that was located in the retropancreatic area. The computed tomography (CT)-scan examination revealed a well-defined retroperitoneal tumor, located between the left kidney, spleen, and pancreatic tail. Blood examination did not show significant modifications.

Surgical removal of the tumor of decided. During open surgery, an encapsulated tumor was identified and resected, with free resection margins. The surgical specimen was sent to the Pathology Department.

Macroscopic examination showed an encapsulated tumor, with smooth aspect of the capsule. The tumor capsule was incomplete but it was broken during surgery. On cut section, solid white areas were predominated but multicystic hemorrhagic areas were also identified.

Under microscope, a biphasic aspect was shown. The first component consisted on proliferation of tumor nests and sheets with monotonous aspect of the nuclei that showed dispersed chromatin. No pleomorphic nuclei or mitoses were identified. The second component was multicystic, being composed by

hemorrhagic pseudocysts filled with cords and trabeculae of tumor cells with cytological features similar to the first component. In both components, arrangement of tumor cells around fibrous or hyalinized bands and/or fibrovascular septa, forming pseudopapillary aspect, was characteristic. The tumor capsule was not infiltrated, even in the broken area. In one of the sections, pancreatic parenchyma was located outside the capsule, in the resection margin. No lymph nodes were removed.

Based on the histological features, immunohistochemical (IHC) staining was decided to be performed, for differentiation of a G1 NET from a SPN. After a complex immunoprofile (Table 1), the diagnosis of NET was eliminated.

The final diagnosis was retropancreatic neoplasm with uncertain differentiation, possible SPN, with free resection margins. The main IHC arguments for diagnosis were diffuse positivity for vimentin, cyclin D1 and the new marker SRY-related high-mobility group box 11 (SOX-11), nuclear expression of β-catenin, and low Ki67 index (below 1%). Focal positivity for synaptophysin and perinuclear dots for chromogranin (both being performed from 2 paraffin-embedded sections) were unusual features (Fig. 1), that increased the difficulty of diagnosis.

Follow-up with “wait and see” policy was indicated. CT scan of the abdominal cavity was done at 1 month after surgery and positron emission tomography-CT was performed at 5 months after surgery. The patient has a good status at 8 months after surgery.

2.2. Case 2

A 51-year-old woman presented at routine CT examination, which was performed yearly or at every 2 years, after pancreatectomy with duodenectomy that was done 13 years before (when the patient was 38 year old), for a G1-NET of the pancreatic head, that infiltrated the duodenal serosa, with free resection margins. The tumor was then diagnosed, based on the previously used terms, carcinoid, and 6 cycles of somatostatin were administrated (Fig. 2).

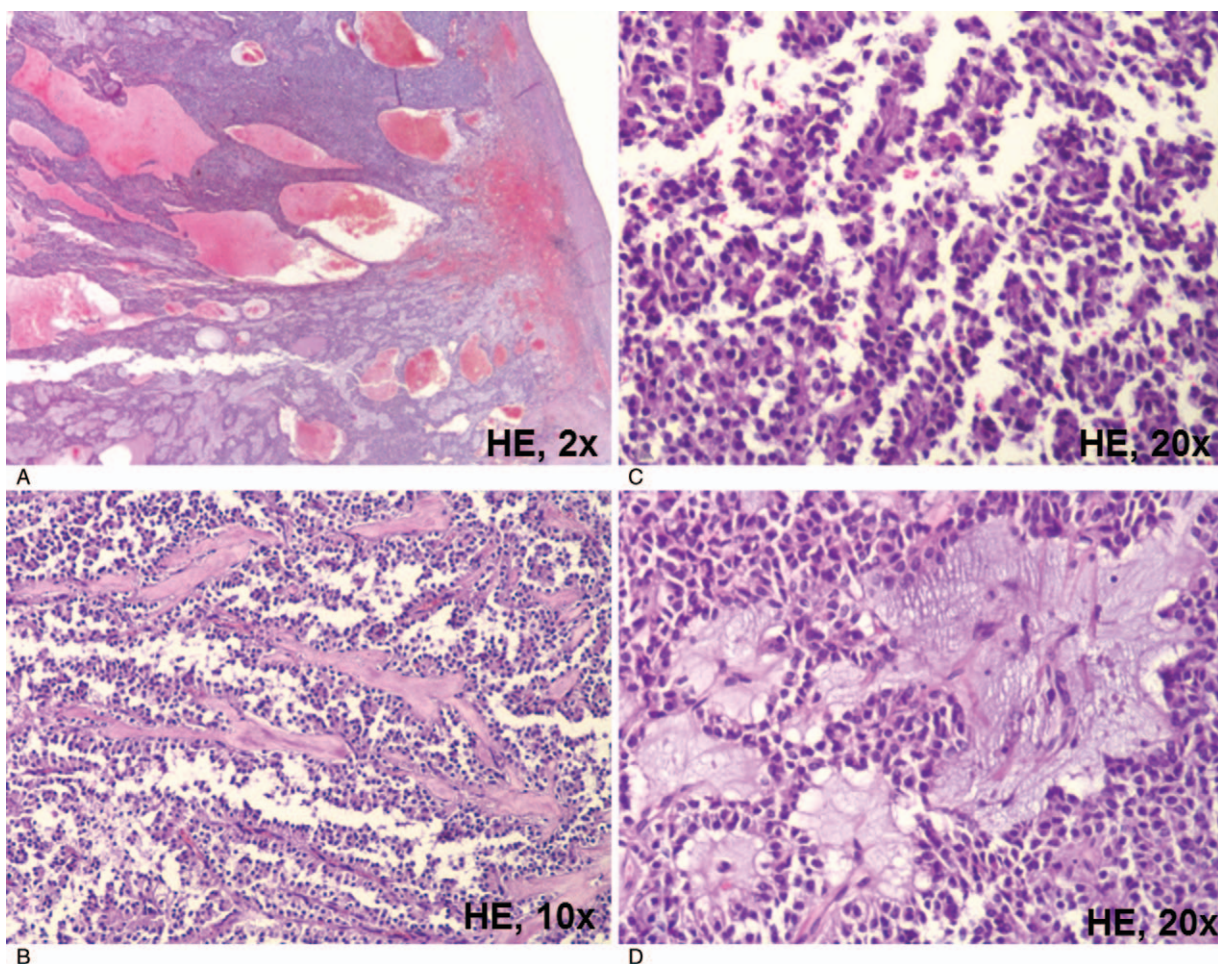


Figure 1. Solid pseudopapillary neoplasm is characterized by large hemorrhagic areas (A), papillary architecture (B) surrounding collagen bands (C), and presence of foamy cells (D).

At the present admission (13 years after first diagnosis), a hepatic nodule with suspicion of malignancy was identified and hepatic enucleation was performed. The tumor cells showed diffuse and intense positivity for CD56 (in more than 80% of tumor cells) and synaptophysin (in about 40% of tumor cells), perinuclear weak positivity for chromogranin, and negativity for Ki67. Based on the diagnosis of the primary tumor, the present diagnosis was “hepatic metastases from a G1-NET of the pancreas.” Oncologic therapy with somatostatin was performed for the second time (Fig. 2).

At 12 months after first metastasectomy (14 years after first diagnosis), the patient presented with acute abdomen and emergent open laparotomy was decided. As transmural intestinal necroses were observed, the surgical intervention consisted on right colectomy and partial resection of the small intestine. Metastatic spread in mesenterium was suspected. As a hepatic whitish nodule was also identified, it was surgically removed.

The histopathological examination revealed segmental necrosis of the intestine, without tumor cells. The hepatic parenchyma was replaced by nests tumor cells with similar aspect as in the first 2 specimens, arranged in a sclerotic stroma.

Based on the atypical evolution of the case and lack of therapeutic answer at somatostatin, we have decided

re-examination of the previous specimens and performing a complex immunoprofile of the cells in the primary tumor and metachronous metastases (Table 2).

The IHC stains showed an atypical immunoprofile for a NET, with vimentin, cyclin D1, and nuclear β -catenin positivity. Although all of the neuroendocrine markers (synaptophysin, CD56, neuron-specific enolase, and chromogranin) were weakly positive, the diagnosis was “hepatic metastases from a hybrid tumor of the pancreas, with uncertain differentiation, possible SPN with neuroendocrine component.”

The patient showed invasion of the portal vein at 7 months after last surgical intervention (14.5 years after first diagnosis).

3. Discussion

SPN is rarely reported in Europe but the recent publications revealed increasing number of cases, after the year 2004, 3 to 4 cases of such neoplasms being reported to occur every year in the references tumor centers.^[3] In Chinese literature, 533 patients were reported to be diagnosed with SPN between January 1996 and January 2009.^[5] In English literature, 718 well-documented cases from the United States, Europe, and Japan were reported from 1933/1934 till 2003, with an average number of 10 cases per year.^[6]

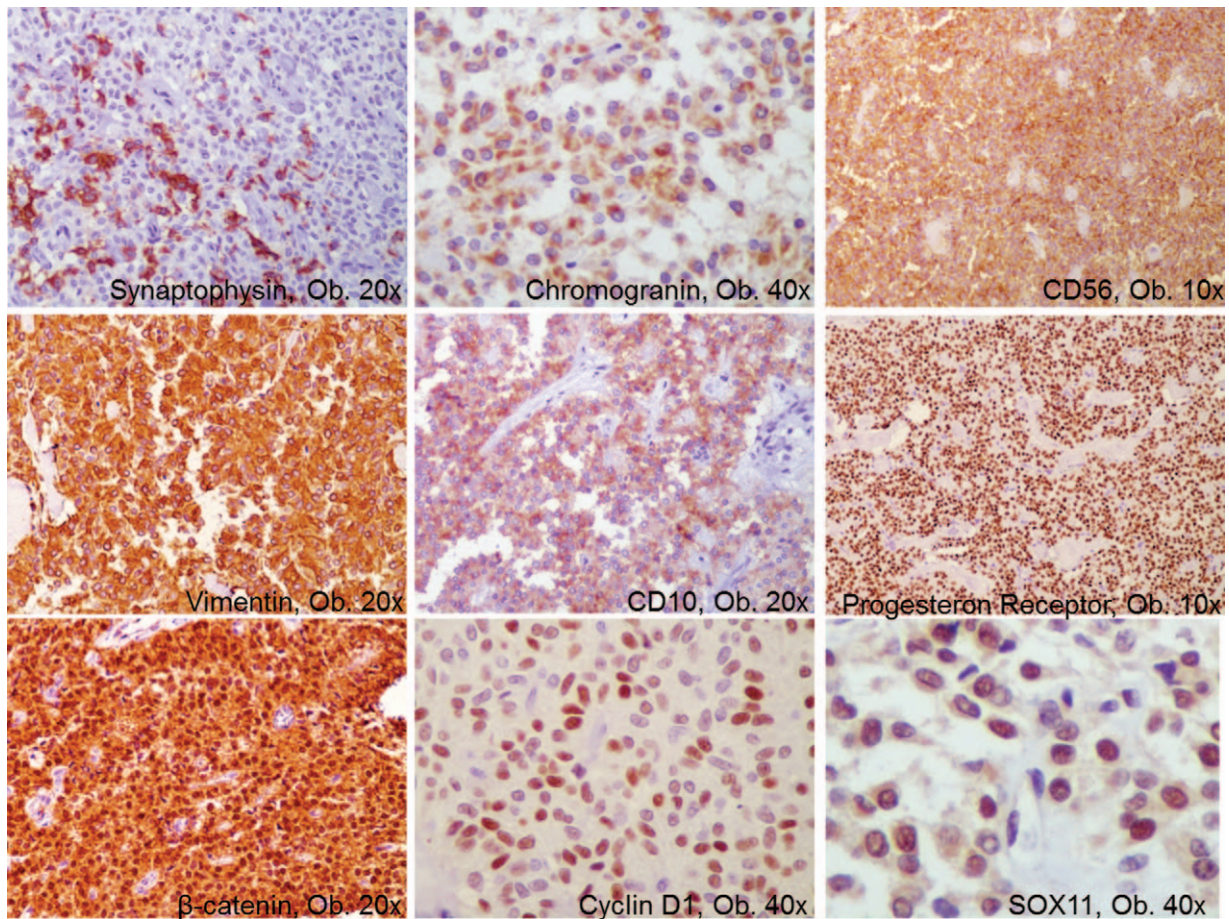


Figure 2. Immunoprofile of solid pseudopapillary neoplasm: weak positivity for synaptophysin, perinuclear dots-like chromogranin, diffuse cytoplasmic positivity for CD56, vimentin, CD10, and nuclear expression of Progesterone, β -catenin, cyclin D1, and SOX-11. SOX-11 = SRY-related high-mobility group box 11.

Table 2
Immunoprofile of pancreatic solid pseudopapillary neoplasm and its hepatic metastases.

IHC marker	Primary tumor (pancreas)	Hepatic metastasis (13 years after primary tumor)	Hepatic metastasis (14 years after primary tumor)
Vimentin	Positive	Positive	Positive
β -catenin	Nucleus and cytoplasm positivity	Nucleus and cytoplasm positivity	Nucleus and cytoplasm positivity
Cyclin D1	Positive	Positive	Positive
SOX11	Positive	Positive	Positive
CD56	Positive	Positive	Positive
Neuron-specific enolase	Positive	Positive	Positive
Progesterone receptor	Negative	Positive	Positive
Synaptophysin	Positive	Positive	Positive
Chromogranin A	Positive	Positive	Positive
CD10	Positive	Positive	Positive
AE1/AE3 cytokeratin	Positive	Positive	Positive
N-cadherin	Negative	Negative	Negative
α -1 antitrypsin	Negative	Negative	Negative
E-cadherin	Negative	Negative	Negative
Ki67	Negative	Negative	Negative
Estrogen receptor	Negative	Negative	Negative
Maspin	Negative	Negative	Negative
S100	Negative	Negative	Negative
Melan A	—	—	—
HMB45	—	—	—

HMB45 = human melanoma black, IHC = immunohistochemical, SOX-11 = SRY-related high-mobility group box 11.

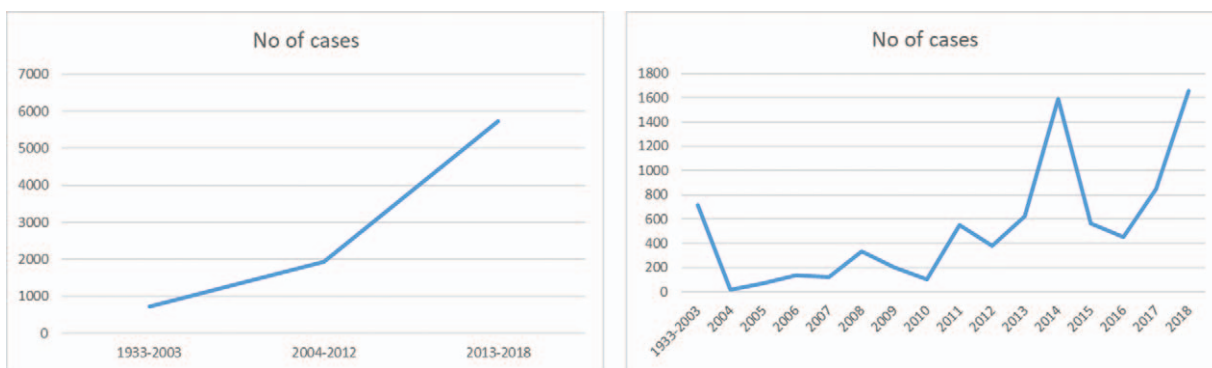


Figure 3. Time-related incidence of solid pseudopapillary neoplasm, in decades (left) and years (rights).

We have counted the number of cases reported in English literature, after December 2003, using the keywords “pseudopapillary neoplasm” and “Frantz tumor,” and found a significant progressive increasing number of cases, probably based on development of IHC methods and increasing number of used antibodies (Fig. 3).

The total reported cases, in PubMed-indexed English literature, was 1924 from 2004 to 2012 (median number is 240 cases per year, ranging from 20 in 2004 till 381 in 2012), respectively, 5742 from 2013 till November 25, 2018 (median number increased to 1148 cases per year, ranging from 452 in 2016 till 1660 in 2018). Till now, over 8384 cases of SPNs were reported in English literature (1933–2018).

As regarding the extrapancreatic MPN, we have identified 48 cases reported between 2004 and 2018 (0.62% of all reported SPNs), mostly in testis/paratesticular area (over 20 cases) and ovary (10 cases) but localization in adrenal gland, mesenterium, omentum, and retroperitoneum, such in our first case, was also shown. In testis, this tumor is called pancreatic analogue SPN or SPN of the testis, but the IHC studies proved similar immunoprofile and behavior with primary pancreatic SPN.^[8] In testis, a signet ring cell component can be associated.^[8]

Association with B or C hepatitis virus was reported from 5%^[3] to 62.5% of cases^[4] but the role of viral infection in tumorigenesis was not proved yet.^[3,5] As most of the cases express progesteron receptor (PR) and occur in females, the role of hormonal influence was supposed but not proved for tumorigenesis.^[6] Based on PR positivity in the tumor cells of SPN, same as in the stroma of the mucinous cystic neoplasm of the pancreas (MCN), it can be supposed that the 2 tumors (SPN and MCN) originate from primitive germ cells/genital ridge/ovarian anlage-related cells that have migrated to the pancreas during early embryogenesis.^[9,10]

For extrapancreatic location, development on background of ectopic pancreas was supposed. K-RAS and p63 gene mutations were not proved to be involved in SPN genesis.^[6]

Nuclear expression of β -catenin and vimentin positivity, associated with negativity for E-cadherin and infrequent positivity for N-cadherin, firstly reported in 1 of our cases, suggest that Wnt/ β -catenin pathway alteration is implicated in SPN tumorigenesis.^[6,7,9,11] Nuclear β -catenin reflects mutation in exon 3 of the *CTNNB1* (β -catenin) gene.^[8,12]

The clinical symptoms of pancreatic SPN are non-specific and incidental identification during routine examination, such in our first case, was reported in 1 quarter of the patients.^[3] Although

serum markers (e.g., alfa fetoprotein, carcinoembryonic antigen, CA199, CA125, and CA242) can be elevated, they are not specific for SPN and the serum level value is not an indicator of malignancy.^[3,5]

The imagistic investigations (CT, magnetic rezonance imaging) can show a heterogenous tumor, with solid and cystic areas, usually well-defined and encapsulated.^[3,5]

SPN is considered as a low-grade slowly growing tumor, with a doubling time of about 765 days.^[6,12,13] There are some criteria of malignancy proposed in some papers, which include diffuse growth, capsular involvement, extrapancreatic invasion, angiolymphatic or perineural invasion, lymph node or distant metastases, nuclear pleomorphism, Ki67 positivity, necrosis, dedifferentiation, DNA aneuploidy, double loss of X chromosomes, trisomy for chromosome 3, unbalanced translocation between chromosomes 13 and 17, etc.^[3,5] From them, only incomplete capsule was proved to be a significant predictor of malignant behavior.^[3]

In our metastatic case (case 2), no criteria of malignancy were identified in the primary tumor. Despite of this, liver metastases occurred at 13 years after diagnosis. The pathologists should be also aware for capsule rupture during surgery, such in our first case. In these patients, the tumor is diagnosed with R0 margins but the rupture should be analyzed under microscope, to eliminate the suspicion of capsular invasion.

The differential diagnosis between SPN and an islet cell tumor or acinar cell carcinoma is difficult to be done, especially in cases with Ki67 <5%. It is mainly based on the tumor cells immunoprofile (Table 3). Although positivity for PR is considered to be specific for SPN, it is also expressed in normal pancreatic islets and can also mark the NETs or other cystic tumors of the pancreas, such MCNs with/without neuroendocrine features.^[9,14] On the other hand, the neuroendocrine markers can be expressed simultaneously with cytokeratin, proving a possible double (exo and endocrine) differentiation.^[6,14] Moreover, in our cases, chromogranin was expressed perinuclear only and showed a granular positivity, in contrast with NETs, that mostly show diffuse cytoplasmic positivity. The main IHC markers, which are not expressed in NETs, are vimentin (usually diffuse in SPN) and nuclear expression for β -catenin (Table 3). We performed β -catenin stain in more than 20 NETs and did not observe β -catenin positivity (data not shown, unpublished personal observation). However, β -catenin nuclear expression was also reported in pancreatoblastoma (100%), acinar cell carcinoma (12%), and

Table 3
Immunoprofile of solid pseudopapillary neoplasm, in the 2 cases and literature.

IHC marker	Case 1	Case 2	Literature data—rate of positive cases
Vimentin	Positive	Positive	88.1–93.1%
β-catenin	Positive	Nucleus ± cytoplasm positivity	93.3–100%
Cyclin D1	Positive	Positive	100%
SOX-11	Positive	Positive	100%
CD56	Positive	Positive	67.4%
NSE			70–81%
Progesterone receptor	Positive	Negative	56.70–95.45%
Synaptophysin	Positive	Positive	42.30–72.73%
Chromogranin A	Positive	Positive	23.30%
CD10	Positive	Positive	64.70–86.36%
AE1/AE3 cytokeratin	Positive	Positive	31%
N-cadherin	Positive	Negative	No data for SPN
α-1 antitrypsin	Negative	Negative	82.50–94.60%
E-cadherin	Negative	Negative	Negative
Ki67	Negative	Negative	5%
Estrogen receptor	Negative	Negative	11.30%
Maspin	Negative	Negative	No data for SPN (it is reported as positive in ductal adenocarcinoma and negative in NET and acinar cell carcinoma)
S100	Negative	–	14%
Melan A	Negative	–	No data for SPN
HMB45	Negative	–	No data for SPN
α-1 antichymotrypsin	–	–	90.70–95.70%
Transcription factor E3	–	–	70%
CD117 (C-KIT)	–	–	40–50%
DOG-1	–	–	53%
Glypican 3	–	–	95.45%
Calretinin	–	–	Negative
Inhibin	–	–	Negative
GFAP	–	–	Negative
EPCAM	–	–	Negative
Amylase	–	–	Negative
CA19.9	–	–	Negative
CEA	–	–	Negative
Pancreatic development transcription factors (PDX1, SOX9, NKX2.2, PTF1A)	–	–	Negative

CEA = carcinoembryonic antigen, DOG-1 = gastrointestinal stromal tumor 1, EPCAM = epithelial cells adhesion molecule, GFAP = glial fibrillar acid protein, HMB45 = human melanoma black, IHC = immunohistochemical, NET = neuroendocrine tumor, NKX2 = NK homebox protein, NSE = neuron-specific enolase, PDX1 = pancreatic and duodenal homeobox1, PTF1A = pancreas associated transcription factor, SOX = SRY-related high-mobility group box, SPN = solid pseudopapillary neoplasms, Adapted with permission from^[3,5,7,8,10,12,14,16].

rarely in NETs (8%).^[7] Other newly proposed markers, which were reported to be negative in NETs, and positive in both of our cases, in line to literature data, are CD10, cyclin D1, and SOX-11.^[7,14] Triple positivity for vimentin, nuclear β-catenin, and SOX-11 is considered specific for SPN.^[7] Other non-specific markers such discovered on gastrointestinal stromal tumor 1 (DOG-1) and c-KIT (CD117), common markers of gastrointestinal stromal tumors,^[15] can mark both SPN (especially the spindle cell variant) and acinar carcinoma cells.^[10,16] In contrast with gastrointestinal stromal tumors, SPN does not display KIT/platelet-derived growth factor receptor (PDGFR) mutations.^[10,15,16]

As regarding the extrapancreatic SPN, the newest studies suggest a common origin for SPN and signet ring cell carcinoma of testis or ovary, both variants showing nuclear β-catenin.^[8] It was then suggested, for ovary and testis, to consider that, the family of β-catenin tumors includes SPN, primary signet ring stromal tumor, and microcystic stromal tumor of the ovary or testis.^[8] Microcystic stromal tumor shows similar immunoprofile with SPN (nuclear β-catenin and positivity for CD10, with

negativity for inhibin and calretinin, but is usually negative for CD56).^[8] Although microcystic stromal tumor of the ovary and signet ring cell carcinoma of the testis are now considered as a sex cord stromal tumors, reclassification as SPN was suggested.^[8]

The therapy of SPN consists in surgical resection of tumor, with free resection margins, and long-term follow-up.^[17] Bypass procedure is indicated for inoperable tumors.^[17] It is important mentioning that, for pancreatic SPN, vascular invasion (usually portal vein or superior mesenteric artery) is not considered a criterion for nonresectability.^[6,17] Extensive lymphadenectomy is not indicated.^[6,17]

In metastatic cases, chemotherapy or intra-arterial chemo-embolization (for hepatic metastases) is indicated.^[6] The ideal chemotherapeutic regimen is not known yet. SPN also proved to be radiosensitive.^[6] Although SPN can express c-KIT, absence of KIT/PDGFR mutations indicates that SPNs are not candidates for imatinib mesylate.^[15]

As the origin of SPN remains controversial (exo versus dual exo–endocrine or acinar), the best chemotherapeutic regimen should be more extensively explored.

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