

Pancreatic Solid Pseudopapillary Neoplasm

Key Pathologic and Genetic Features

Stefano La Rosa, MD; Massimo Bongiovanni, MD

• **Context.**—Solid pseudopapillary neoplasm of the pancreas is a low-grade malignant tumor generally associated with a good prognosis. Solid pseudopapillary neoplasms show peculiar morphologic features, but sometimes the differential diagnosis with other pancreatic neoplasms (ie, pancreatic neuroendocrine tumors) can be a challenging task, especially in cytologic or biopsy specimens. In these cases immunohistochemistry is a useful tool, but the diagnostic utility of several proposed immunohistochemical markers is questionable. In recent years, despite several attempts to characterize the pathogenetic, molecular, and prognostic features of solid pseudopapillary neoplasms, they still remain unclear.

Objective.—To give the reader a comprehensive update on this entity.

Data Sources.—The PubMed database (US National

Library of Medicine) was searched using the following string: pseudopapillary tumor [AND/OR] neoplasm [AND/OR] pancreas. All articles written in English were included. In addition, because a heterogeneous terminology has been used in the past to define solid pseudopapillary neoplasms, the reference lists of each paper selected in the PubMed database were also reviewed.

Conclusions.—This review gives a comprehensive update on the pathologic, clinical, and molecular features of solid pseudopapillary neoplasms, particularly addressing issues and challenges related to diagnosis. In addition, we have tried to correlate the molecular alterations with the morphologic and clinical features.

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Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade malignant tumor composed of poorly cohesive epithelial cells, forming solid and pseudopapillary structures and lacking a specific line of pancreatic epithelial differentiation.¹ Since the first description in 1959 by Frantz,² several cases have been reported in the literature but using different terms, including Frantz's Tumor, Hamoudi's tumor, solid-pseudopapillary tumor, papillary epithelial neoplasm, papillary and solid neoplasm, papillary-cystic carcinoma, solid-cystic tumor, and papillary-cystic tumor.³ For several years, it has been considered a "benign" or "borderline" tumor, but recent molecular evidence demonstrating alterations in cancer-associated genes and the ability to metastasize have confirmed the true malignant nature of this disease, although it is generally associated with a good prognosis.

In recent years, several attempts have been made to better characterize the morphologic, immunohistochemical, pathogenetic, molecular, and prognostic features of SPNs. Considerable data are now available. However, the diagnostic and prognostic uses of these data are not always clear. This review considers this new knowledge with the aim of giving the reader a comprehensive and modern vision of this fascinating entity.

EPIDEMIOLOGY

Solid pseudopapillary neoplasm is rare, accounting for about 0.9% to 2.7% of all exocrine pancreatic neoplasms in adults but representing about 5% of all cystic pancreatic neoplasms.¹ Interestingly, the number of cases reported in the English literature has increased 7-fold since 2000, although this probably reflects better awareness of this pathology among clinicians rather than a true increase in incidence.⁴ No apparent ethnic predilection has been observed. Young women (mean age 28 years) are more frequently affected, and SPN represents about 30% of pancreatic neoplasms in women younger than 40 years. Solid pseudopapillary neoplasm can also be observed in men, albeit more rarely, and in general these patients are 5 to 10 years older than women.³ It is worth noting that SPN can also affect children, where it represents 6% to 17% of all pancreatic neoplasms.^{5,6}

CLINICAL PRESENTATION

Most SPNs are asymptomatic and incidentally found by imaging. In some cases, patients may present nonspecific

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From the Institute of Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland (Dr La Rosa); Synlab Swiss SA, Pathology, Lausanne, Switzerland (Dr Bongiovanni).

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Corresponding author: Stefano La Rosa, MD, Institute of Pathology, University Hospital, 25 Rue du Bugnon, 1011 Lausanne, Switzerland (email: stefano.larosa@chuv.ch).

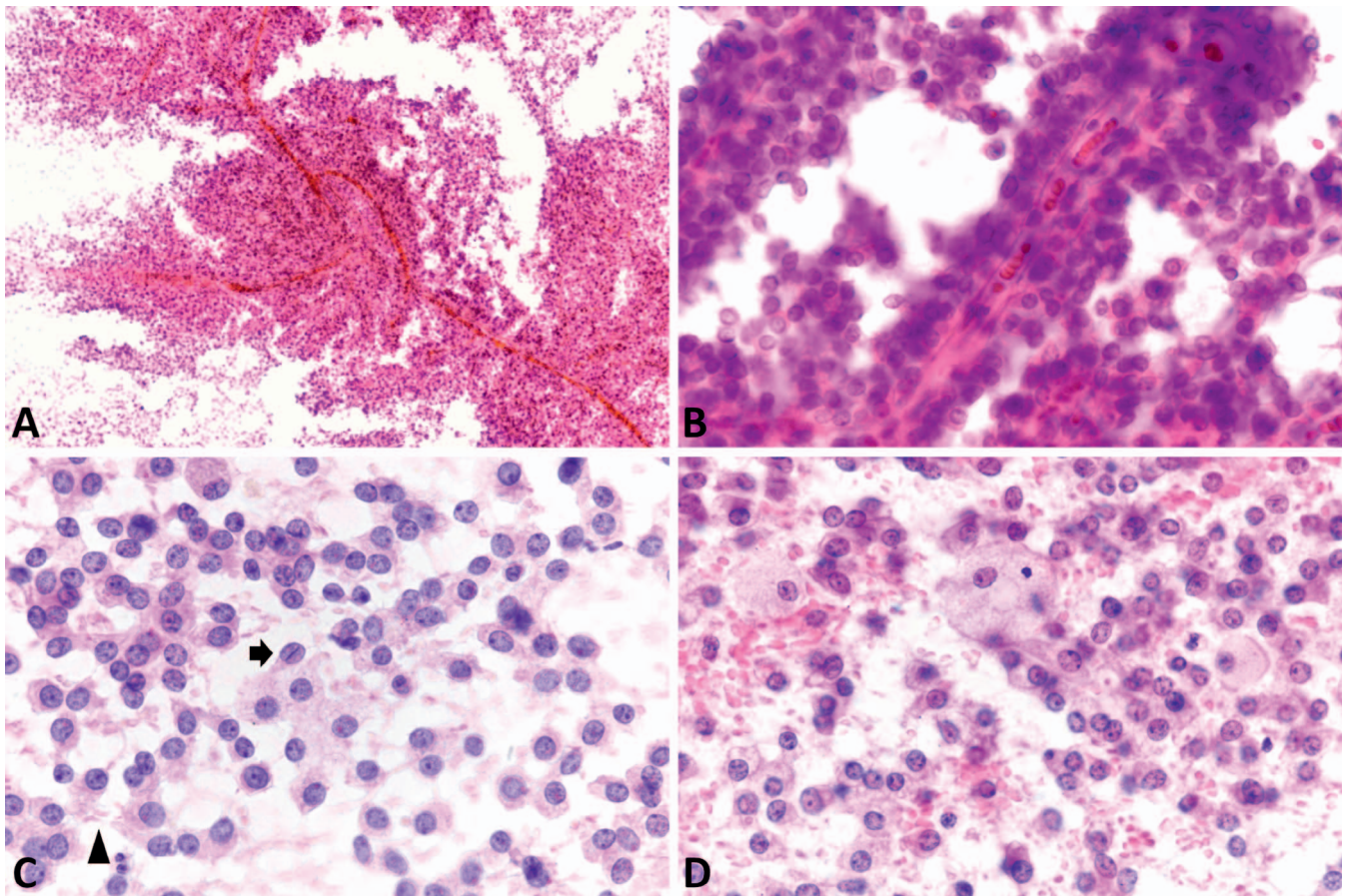


Figure 1. *A*, At low-power magnification, solid pseudopapillary neoplasm shows papillary structures of branching capillaries surrounded by discohesive neoplastic cells. *B*, Tumor cells are small and monomorphic and show a tendency to detach from the papillae. *C*, They show slight nuclear atypia, nuclear grooves (arrow), and cytoplasm with a delicate elongation (some indicated by the arrowhead), the so-called cercariform cells. *D*, In addition to the monotonous cell population, another characteristic is the presence of a hemorrhagic background containing macrophages and/or giant cells (Papanicolaou staining, original magnifications $\times 100$ [*A*], $\times 200$ [*B*], and $\times 400$ [*C* and *D*]).

symptoms, including abdominal discomfort, nausea, vomiting, asthenia, or pain.⁷ In patients with large neoplasms, acute abdomen resulting from traumatic intratumoral hemorrhage has been described.³ Tumor markers' serum levels are within normal range, so they are not useful in the diagnostic workup. Rare SPNs have been found to be associated with familial adenomatous polyposis.^{8,9}

CYTOLOGY

Cytologic examination is usually the first and most used approach in the diagnostic workup of pancreatic solid and cystic masses, so the first diagnosis of SPN is frequently cytologic. Because of its peculiar clinical and prognostic features, a definitive and quick diagnosis of SPN is mandatory to avoid aggressive surgery or chemotherapy. Endoscopic ultrasound-guided fine-needle aspiration is the most frequently used procedure, which in expert hands is a safe, cost-effective, and valuable technique.¹⁰ In our experience, endoscopic ultrasound-guided fine-needle aspiration, performed in conjunction with the cytologic rapid on-site evaluation, increases the yield of the collected material and permits the best triage of specimens. In our daily practice, we use a linear endosonographic device with a 22- or 25-gauge needle: the first pass is used to prepare a smear that is rapidly (10 seconds) stained with toluidine blue staining to assess the quality of material and the

possible diagnosis. In the case of a suspected neuroendocrine neoplasm or SPN a second, third, or even fourth pass is performed to enrich the yield to produce a cytoblock, which permits the testing of multiple immunocytochemical or even molecular markers.

Smears are generally richly cellular and characterized by branching capillaries surrounded by discohesive small and monomorphic neoplastic cells. Nuclei are monomorphic, sometimes with indented or grooved nuclear membranes. Naked nuclei are also present, and the background is clean or more frequently hemorrhagic (Figure 1; Table 1). Characteristic myxoid clear material surrounding the papillae, the presence of cercariform cells and of foamy histiocytes or multinucleated giant cells are additional important cytologic features.^{11,12} Cercariform cells are particularly useful to distinguish SPN cells from those of neuroendocrine neoplasms, that are more regular and without cytoplasmic tails, a key cytologic feature of SPNs (Figure 2). Immunohistochemistry is mandatory for the final diagnosis, and the choice of the correct diagnostic antibody panel (see below) is particularly important in this setting because the available material is not always abundant.

MACROSCOPIC FEATURES

Solid pseudopapillary neoplasm is a solitary tumor. In adults, it is slightly more frequently located in the tail,¹³

Table 1. Main Cytologic Features of Pancreatic Solid Pseudopapillary Neoplasm

| |
|--|
| Architecture |
| Cellular smear with monomorphic population |
| Clean background or hemorrhagic |
| Papillary structures and/or isolated cells |
| Cells |
| Small to medium sized |
| Uniform |
| Cercariform cells |
| Cytoplasm |
| Variable in amount |
| Delicate |
| Pale to vacuolated |
| Nuclei |
| Round to oval |
| Homogenous and finely granular chromatin |
| Sometimes distinct nucleoli |
| Presence of grooves |
| Naked nuclei in background |

whereas in children it is located in the pancreatic head.⁵ Tumors are round, well demarcated, and generally large, with an average size of 8 to 10 cm (range, 0.5–25.0 cm). The cut surface shows a variable appearance from case to case: some cases are completely cystic (Figure 3, A), whereas others show a variable combination of solid, cystic, hemorrhagic, and necrotic areas (Figure 3, B). More rarely, SPNs have a predominantly solid appearance, especially when small (Figure 3, C).^{3,13} Although generally well circumscribed, rare tumors extending into the duodenal wall or other adjacent structures have been reported.¹⁴

MORPHOLOGIC FEATURES

At low magnification, SPNs generally show a heterogeneous appearance, including various proportions of solid and pseudopapillary structures (Figure 4, A and B). Neoplastic cells are rather monomorphic, with eosinophilic or vacuolated cytoplasm often containing small diastase-resistant, periodic acid-Schiff–positive hyaline globules (Figure 4, C). The solid component is composed of uniform cells admixed with numerous delicate capillary-sized blood vessels. The pseudopapillary appearance is the result of neoplastic cells detaching from the capillary-sized blood vessels. Nuclei are round to oval, often grooved or indented, with finely dispersed chromatin without a prominent nucleolus. Bizarre nuclei may occasionally be observed. Mitoses are uncommon. Vascular and perineural invasion is rarely found. Additional features that can be observed include hemorrhage areas, pseudocystic changes, the presence of foamy macrophages (Figure 4, D), and deposits of cholesterol crystals.

In addition to these typical features, some variants have been described, including oncocytic, pigmented, and clear cells subtypes. These variants can give diagnostic difficulties, especially on cytologic preparations or small biopsies. In the oncocytic variant the cytoplasm of cells is abundantly eosinophilic and filled with mitochondria, and may simulate oncocyoma or chromophobe renal cell carcinoma.¹⁵ In pigmented SPNs the brown pigments can be due either to lipofuscin or melanin.^{16,17} In clear cell SPNs, cells present clear cytoplasm resulting from the accumulation of multiple

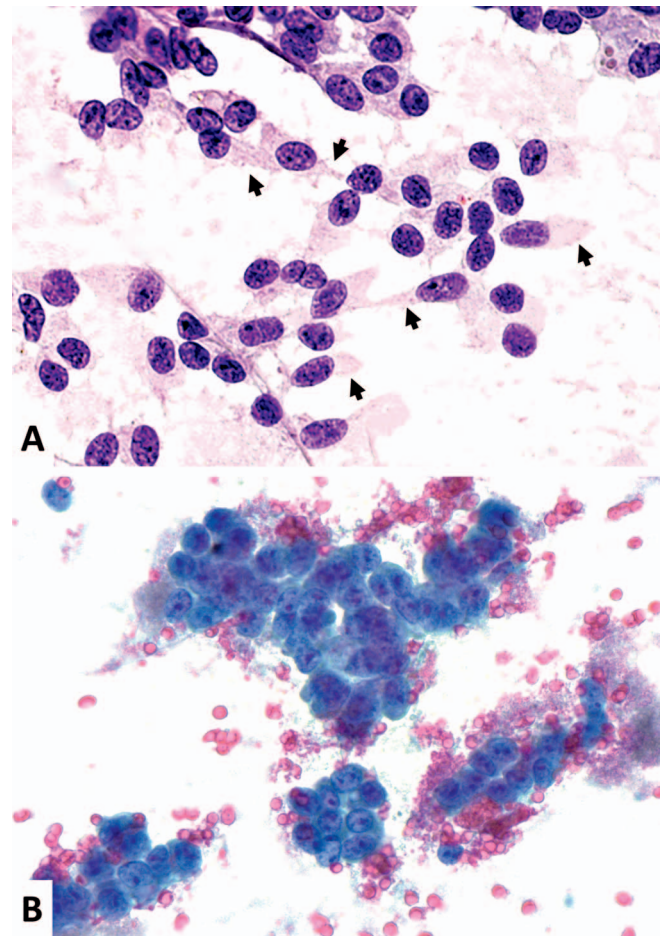
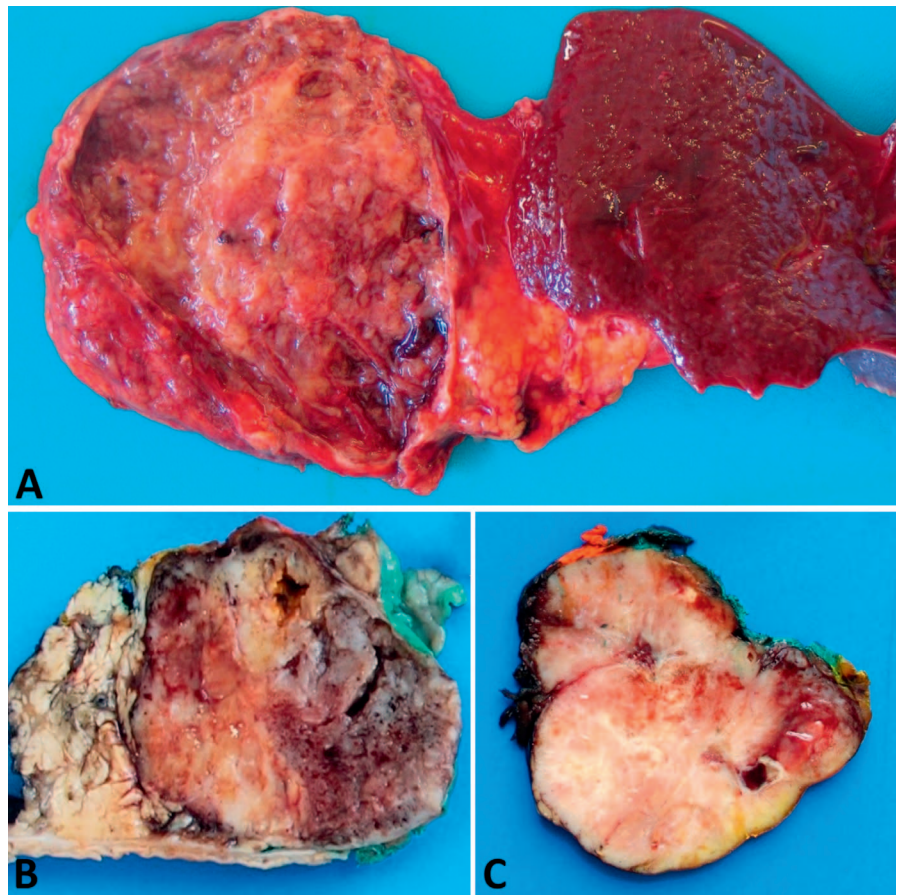


Figure 2. A, Cells of solid pseudopapillary neoplasms are discohesive and show delicate cytoplasm with a peripheral tail (arrows). These cells are known as “cercariform cells.” B, Cells of neuroendocrine tumors tend to aggregate in small clusters and have a thin rim of cytoplasm all around the cells (hematoxylin-eosin, original magnification $\times 600$ [A]; Papanicolaou staining, original magnification $\times 600$ [B]).

cytoplasmic vacuoles, which seem to be the result of distended mitochondria or endoplasmic reticulum.¹⁸ In cases reported by Albores-Saavedra et al,¹⁸ clear cells represented more than 90% of neoplastic cells. However, in some cases the clear cell component may be less predominant and confined only to a few areas of the tumor (Figure 5). Clear cell SPNs or SPNs with clear cell areas can be a challenging task for pathologists because other pancreatic tumor types can show a more or less abundant clear cell component. Although ductal adenocarcinomas with clear cell features do not generally represent a difficult differential diagnosis, acinar cell carcinoma or pancreatic neuroendocrine neoplasms with clear cells can cause difficulties.^{19,20} Immunohistochemistry including acinar cell markers (trypsin, chymotrypsin, BCL10) or neuroendocrine markers (chromogranin and pancreatic hormones) is mandatory for the differential diagnosis. Solid pseudopapillary neoplasms with foci of high-grade malignant transformation (Figure 6), including high-grade (undifferentiated) histologic (diffuse growth pattern, extensive necrosis, significant nuclear atypia, and high mitotic rate) or sarcomatoid features, have been reported.²¹ This SPN

Figure 3. Solid pseudopapillary neoplasms are round, well-demarcated neoplasms. Some cases are completely cystic, as shown in image A (on the left the spleen). Other cases can show a variable combination of solid, cystic, hemorrhagic, and necrotic areas (B), whereas more rarely SPNs can be predominantly solid (C). Courtesy of Prof Christine Sempoux, MD, PhD, Institute of Pathology, University Hospital of Lausanne, Lausanne, Switzerland.



variant needs to be recognized because it is clinically aggressive.

Rare cases of SPN associated with a pancreatic neuroendocrine neoplasm have also been reported.^{22,23} These examples appear to be collision neoplasms rather than true mixed neuroendocrine-non-neuroendocrine neoplasms, in which by definition the 2 components should be clonally related.²⁴ However, additional molecular studies are needed to better define these rare neoplasms.

IMMUNOHISTOCHEMICAL PROFILE

During the last years, several attempts have been made to clarify the immunophenotype of SPNs (Table 2) with the aim of finding useful diagnostic and prognostic markers. Considerable data are now available, but the diagnostic and prognostic utility of all investigated markers needs to be critically evaluated.

It is well known that tumor cells characteristically show nuclear/cytoplasmic immunoreactivity for β -catenin (Figure 7, A). In addition, they are also positive for CD10 (Figure 7, B), progesterone receptor (Figure 7, C), cyclin D1 (Figure 7, D), and vimentin.¹ A very characteristic feature is represented by the immunoreactivity of CD99 that shows a peculiar dotlike paranuclear expression (Figure 8, A).^{25,26} Aberrant expression of E-cadherin is a typical feature of SPN, and 2 distinct patterns of immunoreactivity have been well documented and depend on the antibody used.²⁷ With the antibody directed against the cytoplasmic domain tumor, cells show nuclear E-cadherin positivity, whereas when using the antibody for extracellular fragments they are

E-cadherin negative (Figure 8, B). More recently, several other markers have been investigated. Solid pseudopapillary neoplasms have been found to be positive for glutamine synthase, α -methylacyl-CoA racemase (P504s; Figure 8, C), transcription factor E3 (TFE3; Figure 8, D), SOX11, lymphoid enhancer-binding factor 1 (LEF1), androgen receptor (AR), fused in sarcoma (FUS), WNT inhibitor factor-1 (WIF-1), CD138, and CD200.^{28–34} Immunoreactivity for cytokeratins, synaptophysin, and CD56 can be observed in 30% to 70% of cases, whereas chromogranin A is negative.¹ Up to 50% of SPNs can be positive for CD117, but *KIT* mutation has not been demonstrated.³⁵ Solid pseudopapillary neoplasms are negative for PDX1 and acinar cell markers, including trypsin and BCL10,^{1,36} whereas the diastase-resistant periodic acid-Schiff-positive hyaline globules, which ultrastructurally correspond to zymogen-like α 1-antitrypsin granules, are positive for both α 1-antitrypsin and α 1-antichymotrypsin.³

Because the specificity and sensitivity of each positive or negative marker used alone is variable, the use of panels increases the diagnostic power of immunohistochemistry.^{30,31} In Table 3 an immunohistochemical panel for the routine pathology workup is proposed, presuming that the listed antibodies are available in most pathology laboratories, including the smaller ones.

The prognostic role of the Ki-67 proliferative index in SPN is not clear. In one paper, a Ki-67 index higher than 5% has been demonstrated as a predictor of recurrent disease, but its prognostic role was not explored.³¹ In another study, a Ki-67 index higher than 4% was found to be associated with disease-specific survival.³⁷ However, although this marker seems interesting, it needs to be validated using a higher

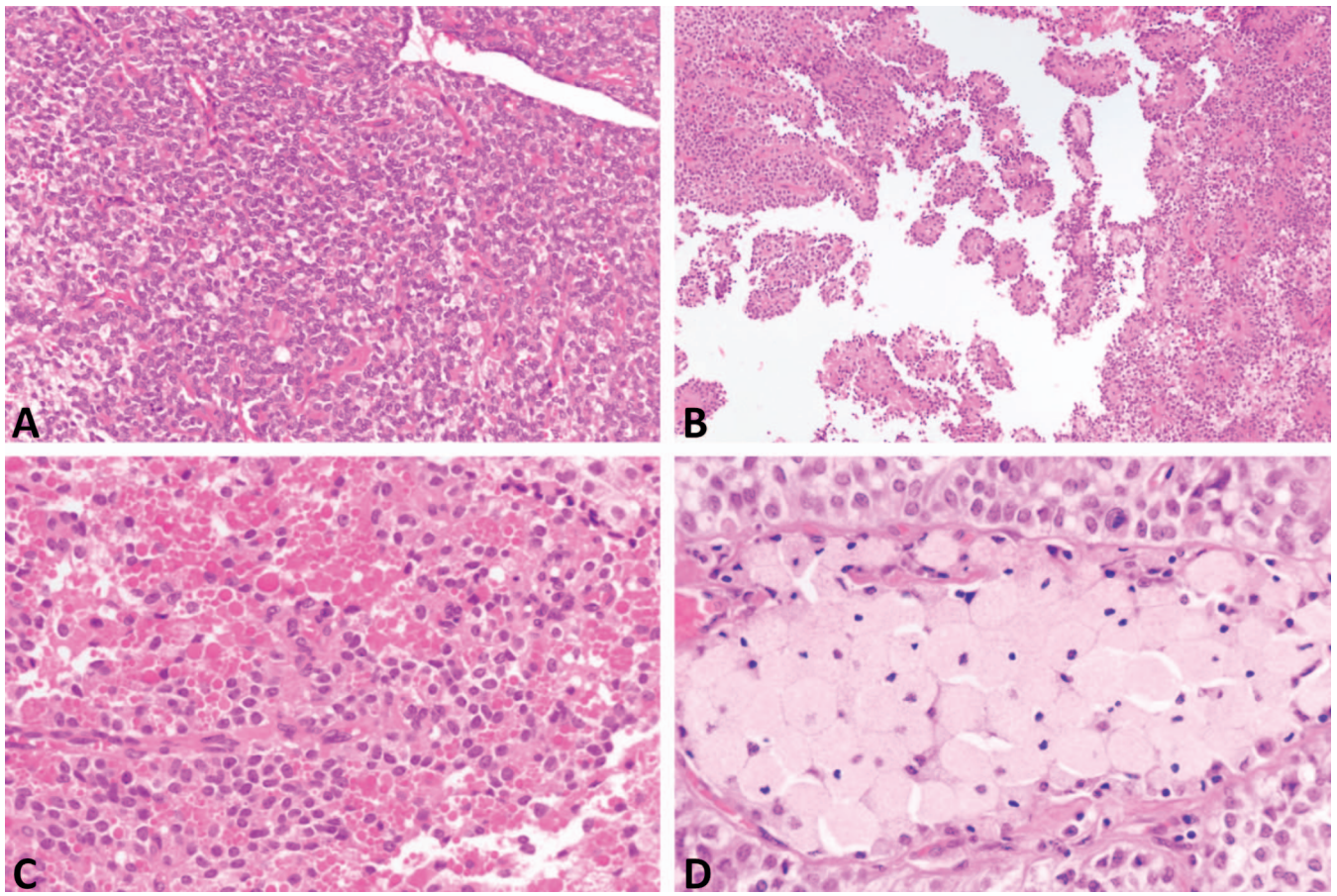


Figure 4. Solid pseudopapillary neoplasm shows various proportions of solid and pseudopapillary structures. A, The solid component is composed of uniform cells admixed with numerous delicate, capillary-sized blood vessels. B, Detaching of neoplastic cells from the capillary-sized blood vessels results in the pseudopapillary appearance. C, Some neoplastic cells may contain small hyaline globules. D, Frequently, foamy macrophages can be observed (hematoxylin-eosin, original magnifications $\times 200$ [A], $\times 100$ [B], and $\times 400$ [C and D]).

number of cases and a standardized method to count Ki-67–positive cells.

PATHOGENESIS

The cell of origin and the pathogenesis of SPN are still unclear. Some features, including sex and age distribution, the expression of progesterone and androgen receptors, the lack of expression of pancreatic markers like PDX1, SOX9, PTF1A, and NKX2.2,³⁸ and the regression of some cases after menopause³⁹ strongly support the theory that SPN may derive from pluripotent stem cells of the genital ridges that become attached to the pancreas during embryogenesis.⁴⁰ This hypothesis also seems to be supported by the fact that neoplasms morphologically identical to pancreatic SPNs arise in retropancreatic tissue, ovaries, and testes.^{41–46}

MOLECULAR FEATURES AND THEIR LINK WITH THE IMMUNOHISTOCHEMICAL PROFILE AND MORPHOLOGIC CHARACTERISTICS

Solid pseudopapillary neoplasms lack alterations in genes commonly found in ductal adenocarcinoma, such as *KRAS*, *TP53*, *P16/CDKN2A*, and *SMAD4*, and show low prevalence of abnormalities in chromosomes 11q, 13q, 17q, 1q, and 8q.^{47,48} The molecular hallmark of SPNs is represented by point mutations in exon 3 of the *CTNNB1* gene, which is involved in the Wnt/ β -catenin signaling pathway. This

genetic alteration is observed in more than 90% of cases.^{47,49} The consequence of these mutations is the cytoplasmic/nuclear expression of β -catenin. However, because *CTNNB1* gene mutations are lacking in about 10% of SPNs, in these cases the cytoplasmic/nuclear β -catenin expression remains unclear.²⁸ After mutations of the *CTNNB1* gene, β -catenin cannot be phosphorylated in the cytoplasm and translocates into the nucleus, where it activates the Wnt/ β -catenin signaling pathway and the transcription of several genes, including the cyclin D1 oncogene. The activation of the cyclin D1 gene results in the nuclear overexpression of cyclin D1, which is typically observed in SPN (Figure 7, D). However, although there is an activation of cell proliferation machinery, SPN paradoxically shows a very low proliferation, probably related to an unexplained overexpression of p21 and p27.⁵⁰ Mutations in the *CTNNB1* gene also explain the overexpression of glutamine synthetase, α -methylacyl-CoA racemase and AR, which represent downstream targets of the Wnt/ β -catenin signaling. The glutamine synthetase (*GLUL*) gene encodes *GLUL*, which is an enzyme involved in glutamine metabolism. The *GLUL* gene is a target gene of β -catenin,⁵¹ so its overexpression in SPN can be the result of β -catenin stimulation.²⁸ Similarly, the α -methylacyl-CoA racemase expression may be related to β -catenin mutations, as demonstrated in hepatocellular carcinoma.⁵² β -Catenin is involved in the regulation of AR function, playing a role in the pathogenesis of prostate cancer.^{53,54} A possible patho-

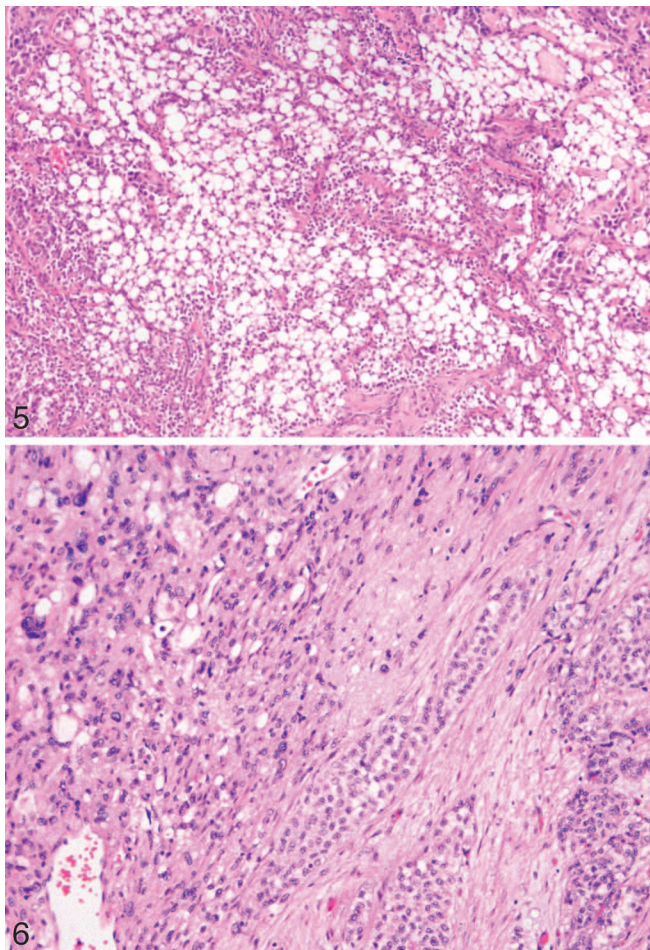


Figure 5. Solid pseudopapillary neoplasm showing a clear cell component. Courtesy of Prof Fausto Sessa, MD, Department of Medicine and Surgery, University of Insubria, Varese, Italy (hematoxylin-eosin, original magnification $\times 200$).

Figure 6. Solid pseudopapillary neoplasm (SPN) showing a sarcomatoid component composed of a solid proliferation of atypical spindle cells. In the center of the image, a residual conventional SPN pattern is visible. Courtesy of Prof David Klimstra, MD, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York (hematoxylin-eosin, original magnification $\times 400$).

genetic mechanism involving the interaction between β -catenin and AR may also be hypothesized for SPN, although it needs to be better studied and clarified. Alterations in the Wnt pathway are also involved in TFE3 and CD138 functions. Indeed, TFE3 contains the GSK3 phosphorylation site that cannot be phosphorylated by GSK3 when the Wnt pathway is activated,⁵⁵ whereas CD138 (syndecan-1) is a crucial component of the Wnt-signalosome as demonstrated in multiple myeloma cells.⁵⁶ Interestingly, recent findings have also demonstrated that β -catenin, LEF1, AR, and TFE3, which are all expressed in SPNs, interact with each other by diverse pathways, so they are functionally closely interrelated.^{57,58}

Transcriptome profiling analysis demonstrated, in addition to the expected activation of the β -catenin pathway, upregulation of members of the Notch pathway (HEY1, HEY2, NOTCH2).⁵⁹ More recently, gene expression analysis demonstrated that in addition to genes involved in the Wnt/ β -catenin pathway, genes involved in the Hedgehog and the

Table 2. Immunophenotype of Pancreatic Solid Pseudopapillary Neoplasms

| | Other Primary Pancreatic Neoplasms That Can Be Positive |
|--------------------------------------|---|
| Positive markers | |
| LEF1 | Ne |
| P504s | Ne |
| CD99 (dotlike pattern) | Ne |
| Vimentin | NET (rare) |
| CD138 | NET (rare) |
| Synaptophysin | NET |
| CD56 | NET |
| Progesterone receptor | NET |
| CD200 | NET |
| Cyclin D1 | NET (rare) |
| Androgen receptor | NET (rare) |
| CD10 | NET |
| WIF-1 | NET |
| β -catenin | NET (rare), ACC (10%) |
| TFE3 | NET |
| Negative markers | |
| E-cadherin (or nuclear) ^a | Ne |
| Chromogranin | NET (diffuse and strong) |
| Pancreatic hormones | NET |
| Trypsin | ACC |
| CEH | ACC |
| BCL10 | ACC |
| Lipase | ACC |
| Amylase | ACC |

Abbreviations: ACC, acinar cell carcinoma; CEH, carboxyl ester hydrolase; LEF1, lymphoid enhancer-binding factor 1; Ne, negative or not evaluated on large series of other primary pancreatic neoplasms; NET, neuroendocrine tumor; P504s, α -methylacyl-CoA racemase; WIF, WNT inhibitor factor-1.

^a The lack of, or nuclear immunoreactivity for, E-cadherin depends on the antibody used (see text).

AR signaling pathways, as well as those involved in epithelial mesenchymal transition, are activated in solid-pseudopapillary neoplasms.⁵⁸ In addition, 17 microRNAs closely associated with the upregulation of genes involved in the Wnt/ β -catenin, Hedgehog, and AR pathways and epithelial mesenchymal transition have been identified.⁵⁸ All of these findings suggest a complex genetic background for SPNs.

Table 3. Proposed Immunohistochemical Panel for the Diagnosis of Pancreatic Solid Pseudopapillary Neoplasm

| | |
|--------------------------------------|--|
| Positive markers | |
| β -catenin | |
| CD99 (dotlike pattern) | |
| Negative markers | |
| Chromogranin | |
| Trypsin | |
| BCL10 | |
| E-cadherin (or nuclear) ^a | |

^a The lack of, or nuclear immunoreactivity for, E-cadherin depends on the antibody used (see text).

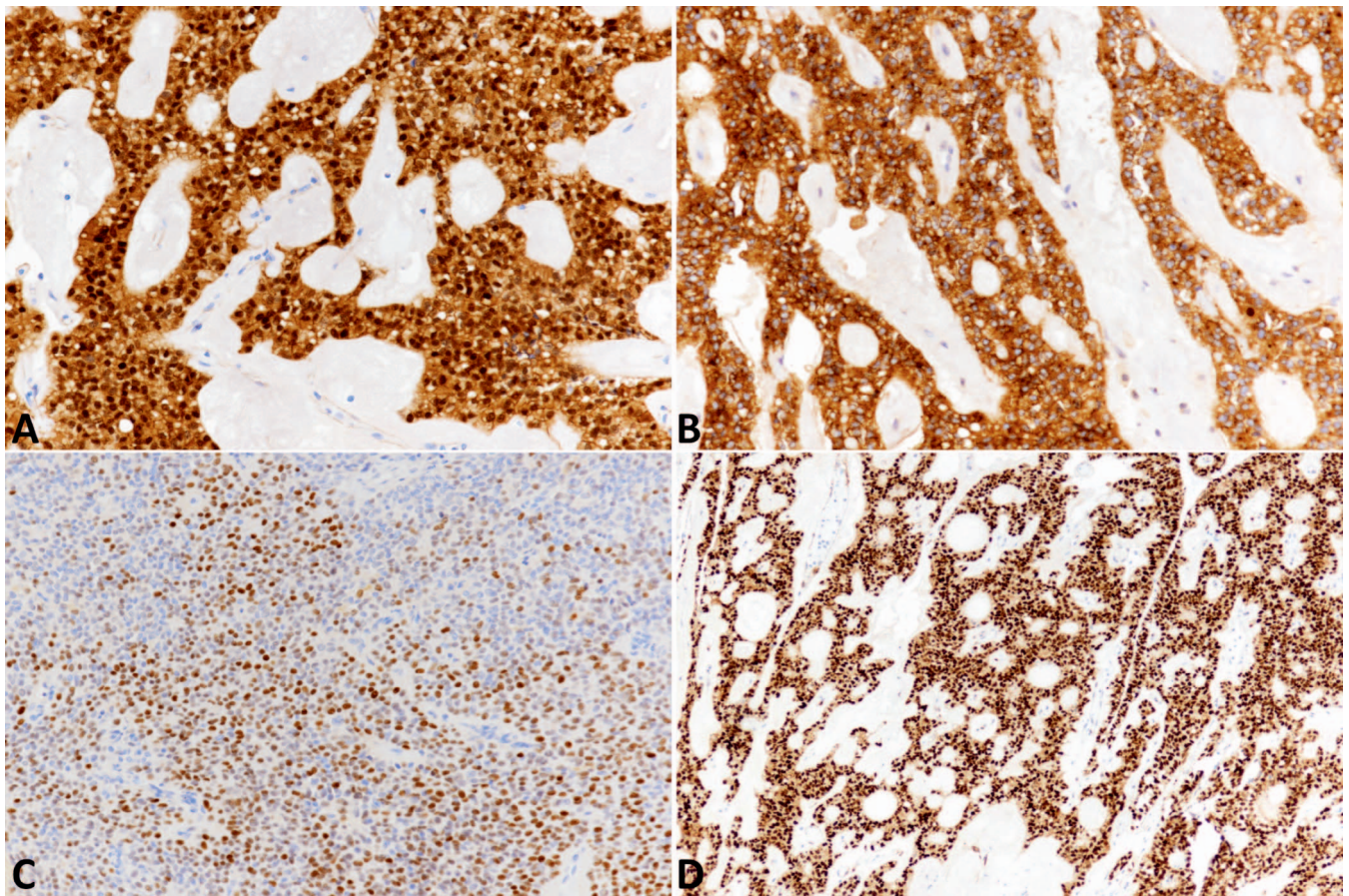


Figure 7. Solid pseudopapillary neoplasms characteristically show nuclear/cytoplasmic immunoreactivity for β -catenin (A), CD10 immunoreactivity (B), and nuclear positivity for progesterone receptor (C) and cyclin D1 (D) (immunohistochemical staining, original magnifications $\times 200$ [A through C] and $\times 100$ [D]).

Using whole-exome sequencing and copy number variation analysis it has recently been demonstrated that in metastatic SPNs, in addition to *CTNNB1*-activating mutations, inactivating mutations of epigenetic regulators (KDM6A, TET1, BAP1) are present in both primary and related metastases, suggesting a role of these genetic alterations in the metastatic dissemination of SPNs. Conversely, most copy number variations were not shared between primary and metastatic lesions from the same patients.⁶⁰ Interestingly, in a case showing high-grade morphologic features, loss of heterozygosity of chromosome 21 has been identified.⁶⁰

In a locally invasive SPN that progressed to liver metastasis an uncommon *EGFR* mutation at L861Q in the kinase domain of exon 21 has been identified, suggesting that this mutation may be involved in the metastatic progression of SPNs.⁶¹

The characteristic poorly cohesive feature of SPNs (Figure 4) may depend on the mutation of the *CTNNB1* gene, causing in turn the loss of β -catenin membrane location. In addition, because the cytoplasmic C-terminal domain of E-cadherin directly interacts with β/γ -catenin, alteration in the cellular localization of β -catenin can alter the function of E-cadherin, the loss of which at the membrane level can also be related to p120 catenin alteration.⁶² Several proteins involved in cell adhesion have been found to be altered in SPN, when compared with normal pancreatic tissue, supporting their role in the poor cohesion of cells. In

addition, several endoplasmic reticulum-associated proteins were found to be altered, suggesting that endoplasmic reticulum stress may play an important role in SPN tumorigenesis.⁶³

PROGNOSIS

By definition SPN is a malignant neoplasm, albeit one associated with an excellent long-term prognosis even when metastatic,¹ with a reported 10-year disease-specific survival rate of 96%.⁶⁴ Pancreatic surgery, including resection of distant metastases when possible, is the treatment of choice, and it has been demonstrated to be associated with an excellent long-term survival.^{65,66} Furthermore, it is worth noting that patients who undergo limited resection with microscopically positive margins (R1) show outcomes similar to those who undergo large surgery with negative surgical margins (R0).⁶⁴

In about 10% to 15% of cases, SPNs are metastatic to the peritoneum or liver, whereas lymph node metastases are very rare.³ Several attempts have been made to identify markers predicting tumor recurrences or patient outcome. Sex, age, tumor size, positive surgical margins, and the presence of distant metastases, perineural invasion, angioinvasion, deep infiltration of surrounding structures, and Ki-67 proliferative index have been investigated, but published results are not concordant, and sometimes even contradictory. The SPNs showing undifferentiated/sarco-

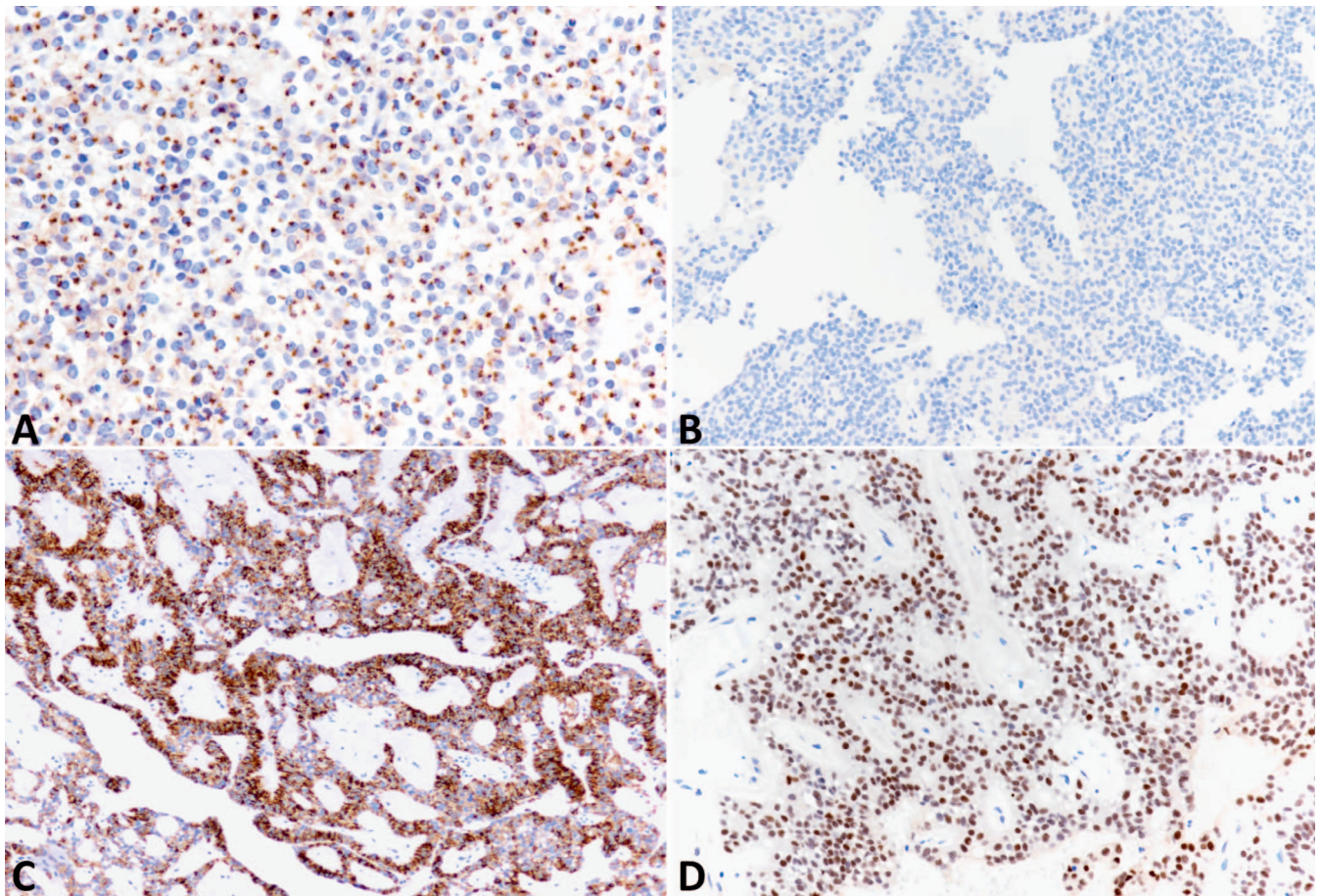


Figure 8. A, Solid pseudopapillary neoplasms (SPNs) show a peculiar dotlike paranuclear immunoreactivity for CD99. B, SPNs are E-cadherin negative when using antibodies directed against the extracellular fragment of E-cadherin. C and D, SPNs are also generally positive for α -methylacyl-CoA racemase (P504s) (C) and for the transcription factor E3 (TFE3) (D) (immunohistochemical staining, original magnifications $\times 400$ [A], $\times 200$ [B], $\times 100$ [C], and $\times 200$ [D]).

matoid features (Figure 6) present with worse behavior than SPNs lacking them,²¹ so the careful search for these high-grade morphologic features is very important to identify aggressive cases.

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