Solid-pseudopapillary neoplasm of the pancreas is a relatively uncommon tumor. It typically affects young women, has nonspecific clinical and radiologic manifestations, and can be readily diagnosed by ultrasound-guided fine-needle aspiration and histopathologic evaluation. Histologic features characteristically show loosely cohesive, relatively uniform polygonal cells surrounding delicate capillary-sized blood vessels. Other features include cytoplasmic vacuolization, finely stippled chromatin, nuclear grooving, eosinophilic hyaline globules, and degenerative changes. Almost all solid-pseudopapillary neoplasms harbor mutations in the β-catenin gene. They stain with β-catenin, CD10, and focally with neuroendocrine markers. Although previously considered benign, this tumor is currently considered a low-grade malignant epithelial neoplasm with low metastatic rate and high overall survival. Most patients are cured by complete surgical excision. Despite the characterization of the morphologic and molecular features of this enigmatic neoplasm, more work is needed to uncover its cell of origin and true histogenesis. (Arch Pathol Lab Med. 2009;133:1989–1993)

Solid-pseudopapillary neoplasm (SPN) is an uncommon pancreatic tumor whose cell of origin has yet to be elucidated. It has been known under different names such as solid-pseudopapillary tumor, papillary epithelial neoplasm, papillary cystic neoplasm, solid and papillary epithelial neoplasm, solid and cystic acinar cell tumor, papillary and solid neoplasm, papillary-cystic epithelial neoplasm, papillary-cystic carcinoma, solid and papillary neoplasm, papillary cystic tumor, solid and cystic tumor, solid and papillary neoplasm, low-grade papillary neoplasm, Hamoudi tumor, and Frantz tumor,1 but the current term, solid-pseudopapillary neoplasm, enjoyed the widest acceptance and has been retained in the latest World Health Organization classification.2 In contrast to the much more common pancreatic ductal adenocarcinoma, data on SPN are mostly based on case reports and small series. Despite this, clonality of this tumor has been lately confirmed.1 This short review covers the interesting clinical features of this tumor, its histopathologic and cytologic characteristics, immunohistochemical profile, molecular alterations, differential diagnosis, therapy, and prognosis.

GENERALITIES

Although some authors had reported SPN as early as 1927, its recognition as a distinctive entity came in 1959 by Franz.3 Since then, more than 750 cases have been reported in the English literature,1,4 predominantly within the last 20 years,5,6 reflecting the increased awareness of this uncommon neoplasm. The reported frequency is variable and ranges from as low as 0.17% to as high as 6% of excrine pancreatic tumors.1,8 Interestingly, 90% of patients are young women with a mean age of 22 years in one report4 and 28 years in another.1 The age of patients ranges widely, from 2 to 85 years.4 In a study of 17 pancreatic tumors in patients younger than 21 years—and representing the Memorial Sloan-Kettering Cancer Center (New York, New York) experience spanning more than 30 years—SPN represented slightly less than half of the cases and predominated in the second decade of life, whereas pancreatoblastoma predominated in the first decade.7

CLINICAL FEATURES

Most patients present with nonspecific symptoms, while the remainder are asymptomatic and their tumor is discovered incidentally. The most common symptoms are abdominal pain and palpable, nontender, upper abdominal mass.1,4,5 Many of the reported symptoms, for example pain, discomfort, nausea and vomiting, and early satiety, can be related to the intra-abdominal mass. Rarely, patients present with jaundice4 or with acute hemoperitoneum due to tumor rupture.8 Although this neoplasm has been reported in pregnancy and postpartum, this may only be a reflection of its peculiar predilection for onset in young women of child-bearing age.9 Solid-pseudopapillary neoplasm has not been linked to any known clinical or genetic syndrome.

IMAGING

Solid-pseudopapillary neoplasms are commonly detected incidentally on imaging studies for other reasons (physical checkup, abdominal trauma, etc); often these studies are performed for nonspecific abdominal symptoms. Plain radiographs have limited value except when calcifications are seen.10 On computed tomography and magnetic resonance imaging, the tumor is often well cir-
PATHOLOGIC FINDINGS
Cytology
Endoscopic ultrasound-guided fine-needle aspiration and computed tomography–guided FNA can provide the cytopathologist with material that may help in establishing the right diagnosis. In addition, immunohistochemical staining can be performed on cell block preparations. The smears tend to be cellular. Delicate papillary fronds with branching capillaries and cell clusters are present. The tumor cells are usually bland and uniform with moderate cytoplasm (Figure 1). Large clear cytoplasmic vacuoles have been described and have been recently emphasized as a helpful distinctive finding. The nuclei are round to oval with finely granular chromatin. Other reported findings include cytoplasmic eosinophilic hyaline globules, nuclear grooving, and myxoid stroma.

Macroscopy
Solid-pseudopapillary neoplasm can occur anywhere in the pancreas and has no predilection for any specific location within it. Rare cases were reported outside the pancreas. On the basis of the largest review, the tumors ranged in size from 0.5 to 34.5 cm with a mean diameter of 6.08 cm. As its names indicate, SPN’s typical appearance is that of a solid and cystic tumor; to some extent, the size plays a role in its gross morphology. Smaller le-
sions tend to be more solid but less sharply circumscribed when compared to larger lesions. On the other hand, larger tumors demonstrate a fibrous pseudocapsule and have a variegated cut surface, with areas of friable and cystic degeneration and hemorrhage (Figure 2). These degenerative changes may be exaggerated and can simulate a pseudocyst.

### Microscopy

Histologically, SPN demonstrates highly vascular areas of polygonal epithelial cells alternating with cystic spaces. Degenerative changes result in tumor cell discohesion, leaving the capillary-sized vessels surrounded by a cuff of neoplastic cells, hence leading to the characteristic pseudopapillary appearance (Figure 3). A rim of tumor cell cytoplasm may separate the nuclei from the cuffed capillaries (Figure 4).

The cells have an eosinophilic cytoplasm that can be vacuolated. Clear cell variants have also been described, and the clearing is attributed to distended mitochondria and endoplasmic reticulum. The nuclei are usually uniform, round to oval, lack the endocrine salt-and-pepper type of chromatin, and harbor frequent nuclear grooves. Mitotic activity is low. Other degenerative changes that might be present include clusters of foamy macrophages, hemorrhage, and cholesterol clefts. Another characteristic feature of SPN is the focal aggregation of intracytoplasmic and extracytoplasmic hyaline globules (Figure 5). These globules are typically periodic acid–Schiff positive and diastase resistant. Stromal degeneration, such as myxoid change and microcalcifications, can also be seen.

Although the tumor is a well-defined lesion grossly, it is not unusual to find areas where it intermingles with the adjacent pancreatic tissue. Other findings, such as vascular invasion and perineural invasion, can be seen in otherwise indolent cases. Figure 6 demonstrates a tumor infiltrating the duodenal wall; however, it did not show other signs of aggressive clinical behavior.

Malignant transformation is exceptionally rare and was reported in 2 patients. In both cases, there were areas typical of SPN as well as atypical histologic and cytopathologic patterns, such as diffuse growth with more cellular atypia, tumor necrosis, and high mitotic activity. Focal sarcomatoid component was present in 1 of the 2 cases.

### Immunohistochemistry

Solid-pseudopapillary neoplasm has been tested for numerous immunohistochemical markers. In recent reports, most SPNs demonstrated nuclear localization of β-catenin and loss of membrane expression of E-cadherin with disruption of the activated Wnt pathway. One consequence of this disruption is cyclin D1 overexpression. In addition, results for CD10 are positive in a significant number of cases (Figure 7). Neuroendocrine markers are variably expressed in SPN. With the exception of the consistently negative results for chromogranin A, variable expression of other neuroendocrine markers, that is, synaptophysin, neuron-specific enolase, and CD56, was demonstrated; this staining profile complicates the distinction of SPN from pancreatic neuroendocrine tumor, the most important entity in the differential diagnosis. Similarly, cytokeratins (CK), mainly pancytokeratin, CK8, and CK18 are variably expressed. However, results for CK7 and CK19 are mostly negative. Solid-pseudopapillary neoplasm also stains for vimentin, progesterone re-
immunohistochemistry) hence the transcription of Wnt
nonspecific cellular junctions but not the typical desmo-
this study, chromosomal gains in 13q, 17q, 1q, and 8q and
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At the electron microscopic level, SPN demonstrates nonspecific cellular junctions but not the typical desmosome-like junctions. The cytoplasm is rich in mitochondria with variably sized electron-dense granules and some rough endoplasmic reticulum. Some of these granules were shown to contain α-1-antitrypsin. Nuclear indentation and cleaving are also present.

**Ultrastructure**

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**CHROMOSOMAL AND MOLECULAR ALTERATIONS**

Exon 3 of the β-catenin gene is the target of point mutations in most SPNs. This results in the accumulation of β-catenin in the cytoplasm; formation of a β-catenin–Tcf/Lef complex, which, after translocation into the nucleus, results in nuclear β-catenin expression detected by immunohistochemistry; and activation of several oncogenic genes such as cyclin D1 (explaining its overexpression by immunohistochemistry); hence the transcription of Wnt targets. No mutation in E-cadherin gene was found, and neither K-ras nor DPC4 were mutated or lost. No KIT/ PDGFRα mutations were detected in a series of CD117+ SPNs. Finally, a recent study with array comparative genomic hybridization analysis found variable chromosomal abnormalities, ranging from none to several per case. In this study, chromosomal gains in 13q, 17q, 1q, and 8q and losses in 11q were detected.

**HISTOGENESIS**

The histogenesis and the cell of origin of SPN have been, and still are, the subject of debate and speculations.

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**Comparison of Different Characteristics of Solid-Pseudopapillary Neoplasm (SPN), Pancreatic Endocrine Neoplasm (PEN), Pancreatoblastoma (PB), and Acinar Cell Carcinoma (ACC)**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>SPN</th>
<th>PEN</th>
<th>PB</th>
<th>ACC</th>
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<tbody>
<tr>
<td><strong>Gross</strong></td>
<td>Circumscribed; variegated, hemorrhagic, solid and cystic</td>
<td>Circumscribed; usually solid; possible cystic change</td>
<td>Circumscribed; usually solid; lobulated with fibrosis and necrosis</td>
<td>Circumscribed; nodular with or without necrosis and cystic degeneration</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Papillary fragments; cytoplasmic vacuoles; nuclear grooves</td>
<td>Monotonous, small or medium-sized cells with granular chromatin (salt-and-pepper) and plasmacytoid morphology</td>
<td>Primitive stromal elements; squa-moid corpuscles</td>
<td>Prominent acinar formation; cells with granular cytoplasm</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Pseudopapillae; discohesive cells; nuclear grooves; hyaline globules</td>
<td>Organoïd, trabecular, nested patterns; endocrine salt-and-pepper chromatin</td>
<td>Acini and sheets of cells surround-ed by fibrous bands; ductal, acinar and endocrine differentiation with squa-moid corpuscles</td>
<td>Acinar or solid patterns; cells with finely granular cytoplasm</td>
</tr>
</tbody>
</table>

**Immunohistochemistry**

<table>
<thead>
<tr>
<th>Marker</th>
<th>SPN</th>
<th>PEN</th>
<th>PB</th>
<th>ACC</th>
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<tbody>
<tr>
<td>β-catenin</td>
<td>+ Nuc</td>
<td>N</td>
<td>+</td>
<td>V</td>
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<td>E-cadherin</td>
<td>N</td>
<td>V</td>
<td>ND</td>
<td>ND</td>
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<td>Chromogranin</td>
<td>N</td>
<td>+</td>
<td>V</td>
<td>V</td>
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<tr>
<td>Synaptophysin</td>
<td>V</td>
<td>+</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>CD10</td>
<td>+</td>
<td>V, F</td>
<td>+, F</td>
<td>V</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
<td>V</td>
<td>+</td>
<td>V</td>
</tr>
<tr>
<td>Pancreatic enzymes</td>
<td>V</td>
<td>N</td>
<td>+</td>
<td>+</td>
</tr>
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</table>

Abbreviations: F, focal; N, negative; ND, no data; Nuc, nuclear; V, variable.

ceceptor, and estrogen receptor β (but not estrogen receptor α). Findings for α-antitrypsin are positive, highlighting the periodic acid-Schiff–positive hyaline globules, and are negative for pancreatic enzymes. Other reported stains include DPC4, CD117, p21, p27, and to a lesser extent, p16. Expression of Ki-67 is usually low, although it was recently published work by Heiser et al, a causal relationship was demonstrated between β-catenin mutation and the development of SPN-like lesion in the pancreas of mice models. This study related the tumor to “cells residing within the ductal compartment,” a statement that needs further investigation, as indicated by the investigators.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of SPN can be quite challenging. The Table summarizes the gross, cytologic, histopathologic, and immunohistochemical features of SPN and its differential diagnosis. Pancreatic endocrine neoplasms can mimic SPNs, especially when the former are cystic or when the latter are solid. Both neoplasms are composed of clusters of uniform, homogeneous, round to oval cells; however, the presence of a pseudopapillary architecture, hyaline globules, foamy macrophages, and nuclear grooving with the absence of endocrine (salt- and-pepper) chromatin favors SPN. Despite this, immunohistochemistry is often needed for the distinction between the 2 entities. As previously discussed in this short review, nuclear β-catenin expression, loss of E-cadherin, positivity for CD10 and α-antitrypsin, along with negativity for chromogranin, can be of help in this differential.

Two other pancreatic neoplasms that can be included in the differential diagnosis are the uncommon pancreatoblastoma and acinar cell carcinoma. Pancreatoblastoma is very rare, usually affecting children younger than 10 years. Histologically, it shows nests of polygonal cells with areas of acinar differentiation in addition to the char-
acteristic squamoid corpuscles. These nests are separated by an often hypercellular stroma. Immunohistochemically, pancreaticoblastoma expresses markers of acinar differentiation (trypsin, chymotrypsin, and lipase) and markers of endocrine differentiation (chromogranin or synaptophysin); plus nuclear labeling for β-catenin. Acinar cell carcinomas grow in acinar, trabecular, or solid patterns, with granular cytoplasm and immunohistochemical expression of pancreatic enzymes. Nuclear β-catenin, however, is much less frequent.

Finally, when extensive cystic degeneration is present, SPN can be difficult to distinguish from pseudocysts. In this case, clinical history and extensive sampling are essential.

TREATMENT

Currently, the treatment of SPN consists of complete surgical excision. Depending on tumor location, different procedures are performed. Distal pancreatectomy and central pancreatectomy are done for tumors of the tail and body of the pancreas, whereas pancreaticoduodenectomy is reserved for tumors of the pancreatic head. Even locally invasive tumors and limited metastasis can be managed surgically.

PROGNOSIS

Despite the possibility of local invasion and distant metastasis, and because of its indolent behavior, SPN is regarded as a tumor of low malignant potential. No histologic parameters correlate with its behavior. When the tumor is confined to the pancreas, up to 95% of patients are cured by complete surgical excision. Metastatic spread or invasion may be present in up to 19.5% of patients. But even patients with metastasis or unresectable disease may achieve a long-term survival. One recently published case describes spontaneous tumor regression, with significant size reduction during a period of 10 years. At the other end of the spectrum, 2 previously reported cases demonstrated a malignant histology and an aggressive behavior at diagnosis, causing the death of both patients at 6 and 16 months following diagnosis.

CONCLUSION

Solid-pseudopapillary neoplasm of the pancreas is an uncommon pancreatic neoplasm with very good prognosis. It is important for the pathologist to be familiar with its salient clinical, cytopathologic, histopathologic, and immunohistochemical features. Such knowledge is essential to differentiate it from other potentially more aggressive pancreatic neoplasms.

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