Solid-pseudopapillary, Acinar, and Other Cystic Neoplasms

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4.1 Solid Papillary Neoplasms

4.1.1 Definition and Epidemiology

Solid papillary neoplasms (SPNs) are a low-grade malignant neoplasm occurring predominantly in young women. The tumors are composed of poorly cohesive, monomorphic epithelial cells forming solid and pseudopapillary structures that frequently undergo hemorrhagic-cystic degeneration (WHO 2010).

Among the cystic neoplasms, SPNs of the pancreas are the least common. They were reported for the first time in 1959 by Franz [1]. Since then, this tumor has been described under different names: solid tumor, cystic-solid, papillary-epithelial, and cystic papillary. In the last few years, the number of literature reports of patients with SPNs has increased, owing to the improved recognition of these lesions.

SPN is a slow-growing, low-aggressive tumor, and even when malignant usually has a favorable prognosis [2]. However, 10–15% of all patients have metastases, which are frequently present at the time of first diagnosis [3]. From an epidemiological point of view, most (> 90%) of the patients with SPNs are young females, between 30 and 40 years of age. The relationship between tumor development and risk factors is not yet known.

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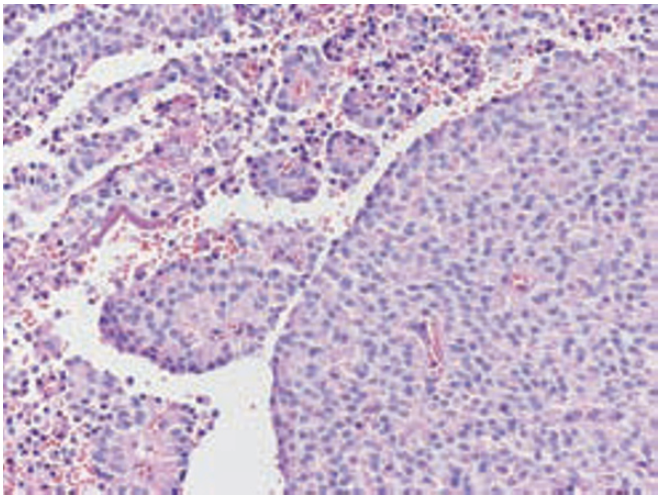

Fig. 4.1 Solid-pseudopapillary neoplasm. Pseudopapillary structures with fibrovascular cores (*left*) and a solid area showing small monomorphic cells (*right*)

4.1.2 Pathology

Macroscopically, SPNs are typically large, round, well-circumscribed masses that exhibit variable proportions of solid and cystic areas filled with hemorrhagic fluid and necrotic debris. Regarding their macroscopic appearances, at the extreme ends of the spectrum are the exclusively solid SPNs (usually the smaller lesions) and the entirely cystic SPNs (usually the larger tumors). The latter may be easily mistaken for a pseudocyst.

Microscopically, the tumors are composed of a mixture of solid and cystic areas, often surrounded by a fibrous capsule. The tumor cells, both in solid areas and lining the pseudopapillae, are monomorphous, with round to oval nuclei and an eosinophilic, granular cytoplasm (Fig. 4.1). PAS-positive globules, stromal myxoid degeneration, necrotic changes with foam cells, and hemorrhage are characteristically present. Mitotic figures are virtually absent, consistent with the low proliferative fraction (Ki-67 index < 2%). Pathologically, the most important differential diagnosis included with SPNs is endocrine neoplasms. The immunophenotype may help to distinguish the two, as SPNs are positive for CD10, vimentin, and nuclear β-catenin (Fig. 4.2). Progesterone receptor (PR) positivity supports the hypothesis of their pathogenetic role.

SPN should be regarded as a carcinoma of low malignant potential and a favorable clinical course, although both the invasion of vital structures and metastases have been reported [4-8]. Over 95% of patients with SPNs limited to the pancreas are cured by complete surgical resection. Only a few patients die of metastasizing tumor [9-11].

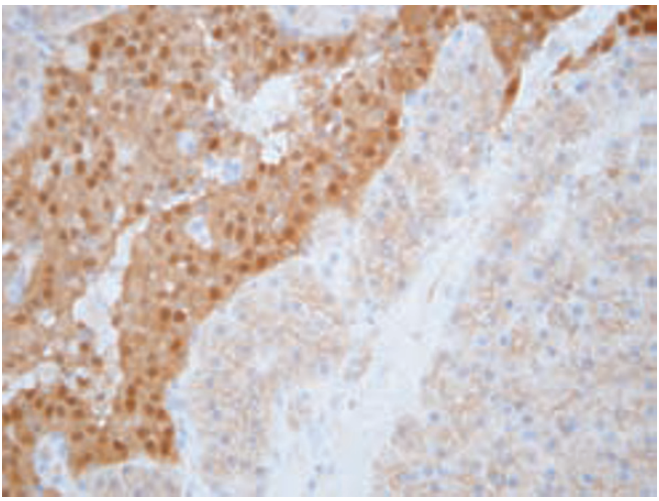

Fig. 4.2 Solid-pseudopapillary neoplasm. Cytoplasmic and nuclear β-catenin immunostaining in neoplastic cells (*left*); a weak membranous positivity is seen in normal pancreas (*right*)

4.1.3 Clinical Findings

Abdominal pain is the predominant and, sometimes, the only symptom present. The pain may be associated with a palpable abdominal mass, anorexia, or weight loss, but any of these signs may occur in isolation. The appearance of an abdominal mass is not considered to be a symptom. Rather, these patients usually complain of a full sensation and abdominal discomfort, and only on examination can a mass be appreciated, especially in the left upper quadrant. The simultaneous presence of pain and an abdominal mass does not suffice to confirm the pancreatic origin of the lesion.

The non-specific clinical features and the young mean age at the time of presentation are frequent reasons for the tendency to underestimate this tumor, by patients and doctors. For the latter, it could be useful to divide these patients based on the anatomical location of the lesion. In our experience, abdominal pain is more often present when the tumor is located in the body-tail of the pancreas, and in some cases is related to weight loss and abdominal discomfort, when a mean tumor diameter of 8.8 cm is reached. Fewer symptoms occur with tumors with a mean diameter of 5.4 cm and located in the head of the pancreas; in such cases, jaundice is seen in 4% of patients and gastrointestinal discomfort in 8%. Thus, it can be assumed that symptoms, in particular abdominal pain, are related to the size and behavior of the tumor, which involves near-by structures. This is different from the abdominal pain associated with ductal carcinoma of the pancreas, which is due to retroperitoneal nerve infiltration. The difference between the sizes and symptoms of SPNs are probably due to their slow evolution and low grade of malignancy.

4.1.4 Laboratory Findings

Laboratory data are not significant in these tumors due to the lack of a specific tumor marker. Chromogranin A, which has a higher sensitivity for endocrine tumors (68%), could be useful in the differential diagnosis between non-functioning endocrine neoplasms and SPNs [12], although the literature reports a positive result in the absence of an endocrine tumor in 19% of cases [13]. In our experience, the chromogranin A test was always negative in SPNs.

4.1.5 Diagnostic Imaging

Solid papillary neoplasms are well-vascularized and encapsulated masses with definite margins [14] (Fig. 4.3). Calcifications and septa may be seen inside the mass but they are not pathognomonic. Instead, the distinctive findings of these tumors are the alternation of solid and cystic areas, in which a necrotic hemorrhagic component may be present [15] (Fig. 4.4a, b). These findings may be seen in the same lesion, possibly with differences in the proportions of the two components.

The lesions are sometimes reported as cystic even though the finding of a rich vascularization could lead to their being mistaken for neuroendocrine tumors.

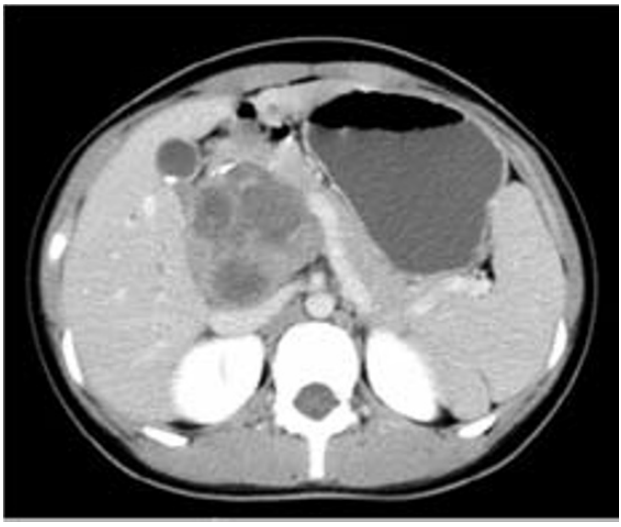

Fig. 4.3 Solid pseudopapillary neoplasm (SPN). Axial contrast-enhanced computed tomography shows a solid pseudopapillary neoplasm in the head of the pancreas that appears hypodense, with an heterogeneous pattern

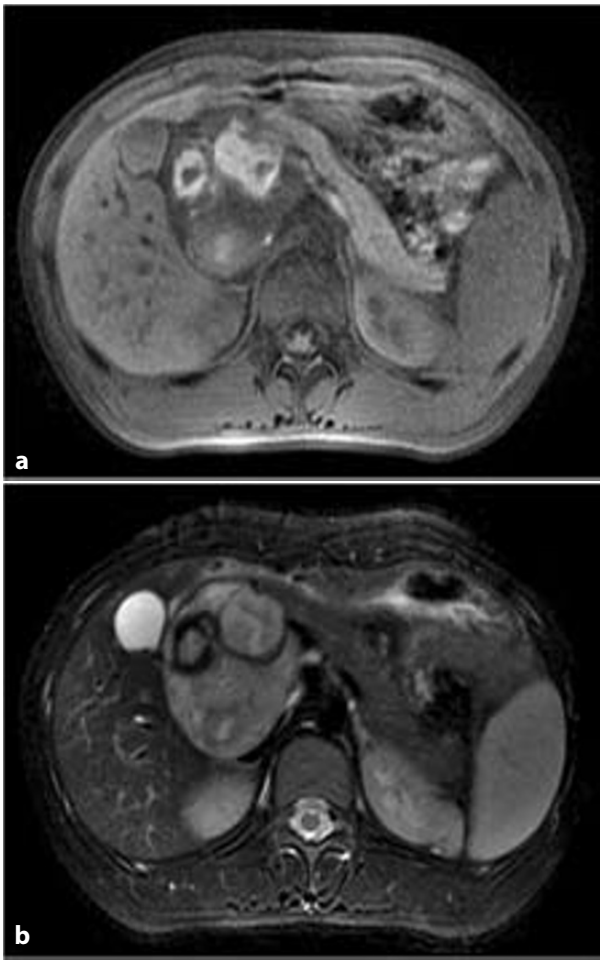

Fig. 4.4 Solid pseudopapillary neoplasm (SPN). **a** Axial fat-saturated T1-weighted magnetic resonance image shows hypointense solid pseudopapillary neoplasm in the head of the pancreas. The internal areas of the neoplasm are hyperintense on T1-weighted images, suggestive of the presence of methemoglobin. **b** On the axial fat-saturated T2-weighted image, the solid pseudopapillary neoplasm appears hyperintense, with an heterogeneous pattern

4.1.6 Treatment

Surgical treatment must be considered in all the patients diagnosed with SPNs, based on the still unknown biological behavior and potential malignancy of these tumors. The laparoscopic approach has been shown to be safe and feasible, if expertise is available; the median follow-up is 47 months (range 5–98). Care must be taken during surgery to prevent specimen rupture [16]. Metastatic disease is not considered a contraindication to surgery, as survival after the resection of liver metastases exceeds 5 years (range 6 months to 17 years). Recurrences are seen mainly in malignant SPNs but the long-term survival of these patients has been reported if they are treated [17-19].

4.2 Acinar Cell Cystadenoma, Cystadenocarcinoma, and Other Cystic Neoplasms

4.2.1 Acinar Cell Cystadenoma

Acinar cell cystadenoma (ACA) is a benign cystic lesion lined by cells with cytological features of acinar differentiation and evidence of pancreatic exocrine enzyme production [20]. ACAs show no clear age predilection; with patients ranging in age from 16 to 66 years, but there is a female predominance.

ACAs can be divided into two categories: clinically recognized macroscopic lesions and incidental microscopic findings. Macroscopically, the former are well circumscribed, cystic lesions with a thin, fibrous pseudocapsule that in some cases can instead be thick and contain calcifications. Microscopically, the cysts are lined by a single layer of cuboidal or columnar cells, with little tendency to pseudostratification or crowding, and with the typical features of acinar cells, i.e., cytoplasmic eosinophilic granules and immunoreactivity for the acinar marker trypsin (Fig. 4.5a, b). Thus, ACAs are thought represent the benign counterpart of the well-recognized acinar cell cystadenocarcinoma [21-24].

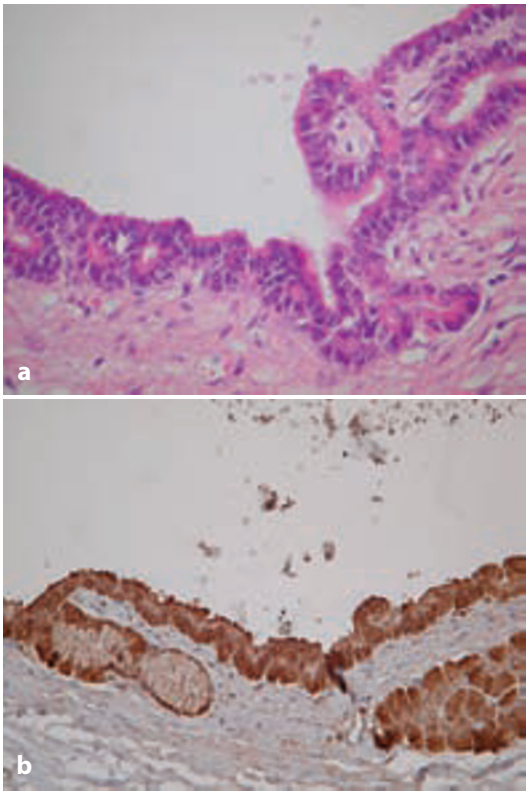

Fig. 4.5 Acinar cell cystadenoma. **a** Cyst lined by columnar cells (H&E staining). **b** Immunohistochemical expression of the acinar differentiation marker trypsin

4.2.2 Acinar Cell Cystadenocarcinoma

Rare examples of cystic acinar cell carcinoma have been reported as "acinar cell cystadenocarcinomas" [22, 25]. In contrast to ACAs, the patients are frequently men, with a mean age of 50–60 years. Macroscopically, these neoplasms are large masses, with diameters up to 35 cm, that contain multiple cysts, with a diameter ranging from a few millimeters to several centimeters. Hemorrhage and necrosis have been reported [26]. Microscopically, the multiple cysts, are admixed with tubular and solid areas. The lining cells show the typical acinar differentiation, with a cytoplasm filled with deeply eosinophilic granules in the apex and basophilic staining at the base. The cells composing cystic acinar cell carcinomas showed clear signs of atypia, with many mitoses; areas of necrosis are frequently present as well.

The prognosis of these patients, as reported in the literature, is similar to that of patients with the solid counterpart of these tumors. Most patients present with metastatic disease, either at the time of diagnosis or a few months post-operatively.

4.2.3 Other Cystic Neoplasms

This category includes very rare lesions, which account for less than 5% of cystic neoplasms.

Cystic endocrine neoplasms are characterized by solid growth, with massive degenerative changes. They may be confused with other cystic neoplasms but the preoperative diagnosis can be obtained with fine-needle aspiration biopsy, which reveals the characteristic cytology [27, 28]. The diagnosis may be confirmed by the immunohistochemical demonstration of endocrine markers, such as chromogranin A and synaptophysin, and of hormone production [29].

Lymphoepithelial cysts are benign, uncommon lesions characterized by mature squamous epithelium associated with lymphoid tissue [30]. They are more common in men, with a mean patient age of 56 years. Macroscopically, they may occur predominantly as extrapancreatic lesions and in any case are well demarcated from the surrounding pancreatic parenchyma. They are either multilocular (60% of cases) or unilocular (40% of cases), and their mean dimension is 4.7 cm. The cyst wall is usually thin and the inner surface of the cysts is smooth or finely granular. Microscopically, the lining epithelium of the cysts is stratified squamous epithelium, admixed with flat or cuboidal epithelium. The cyst wall and the septae are filled with dense lymphoid tissue composed of CD3-positive T cells, frequently associated with germinal centers formed by B cells. The differential diagnosis is essentially with serous cystadenoma and mature teratoma. These cysts have no malignant potential.

Mature teratoma is a benign extragonadal germ cell tumor with mature tissues derived from all three germinal layers [31]. They have no gender predom-

inance; the mean age of these patients is 29 years. Macroscopically they present both solid and cystic areas, with frequent calcifications. Microscopically, the cystic spaces are lined by squamous epithelium, admixed with respiratory and columnar epithelium. Suppurative inflammation is frequently present. Mature teratomas have no malignant potential.

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