Solid pseudopapillary neoplasia of the pancreas: a review

INTRODUCTION

Solid pseudopapillary neoplasm of the pancreas is a rare tumor, with low potential of malignancy, of uncertain lineage, and favorable prognosis in most cases. It has received different denominations, including “Frantz tumor”, “cystic solid tumor”, “papillary cystic tumor”, “papillary epithelial neoplasia”, among others. In 1996, it was defined by the WHO as a “solid pseudopapillary tumor” for the international histological classification of pancreas tumors. That name covers the most distinct macroscopic and microscopic aspects of the neoplasm, i.e., solid and pseudopapillary. It represents around 1-3% of all exocrine pancreatic neoplasias. It is most frequent in women (82%) of all ages. It is usually asymptomatic, but sometimes a palpable mass, pain, and abdominal discomfort, and
Solid pseudopapillary neoplasia of the pancreas is characterized by a solid-cystic growth pattern with pseudopapillary structures. Surgical resection is the treatment of choice and provides a good prognosis, even when there is distant metastasis or recurrence. The lack of apparent ethnic predilection or any association with known clinical or genetic syndromes, although some rare cases have been reported in patients with familial adenomatous polyposis (FAP). Due to its rarity, the clinical data regarding these tumors are most often limited to case reports or small series, especially in the Asian population. However, the diagnosis for SPNP has been more frequent due to the awareness regarding its existence, to the more widespread use of immunohistochemical methods, and retrospective studies on tumors that were not properly identified.

Despite several studies using electron microscopy and immunohistochemistry, the cell origin of this neoplasm remains uncertain. Several researchers favor the hypothesis of a multipotential primitive cell as an origin, particularly due to the absence of a predominant line of differentiation and the multidirectional differentiation found. In a recent study of 14 SPNP pediatric patients, no evidence was found of the PDX1, SOX9, PTF1A, and NKX2.2 transcription factors associated with pancreatic development. An extrapancreatic origin has been suggested by some authors due to several cases of a reported presence of primary tumors in different areas of the pancreas, such as the ectopic pancreas, retroperitoneum, gastroduodenal area, and ovary. The origin of the primitive cells in the genital system, over a pancreatic origin, has been considered by some authors.

**ANATOMOPATHOLOGICAL DIAGNOSIS**

SPNP can occur in any region of the pancreas, and, in general, one third occurs in the head, one third in the body, and another third on the tail. Macroscopic examination shows masses that vary from 0.5 cm to 25.0 cm in diameter (mean diameter of 8-10 cm). In general, they are rounded, well-circumscribed, and separated from the pancreatic parenchyma by a fibrous pseudocapsule; however, under microscopy, neoplastic cells can be seen infiltrating the pancreatic parenchyma, permeating acini, and pancreatic islets. The cut surface shows variable appearance, with yellowish or brownish solid areas, hemorrhagic foci, or cystic degeneration filled with necrotic debris. Smaller tumors tend to be more robust than those of larger diameter, and hemorrhagic-cystic areas, when extensive, may suggest a pseudocyst. They rarely spread to the stomach, the duodenum or to the spleen, and metastases occur in 5-15% of cases, mainly to the liver and peritoneum. The staging follows that of other pancreatic carcinomas.

The microscopic appearance of SPNP is heterogeneous, with a varied proportion of solid, pseudopapillary, hemorrhagic, and pseudocystic areas, representing the solid and cystic natures of the neoplasm. The solid areas, located mainly in the periphery of the tumors, when these are notably
hemorrhagic-cystic, are formed by little cohesive cells, polygonal, monomorphic, with eosinophilic cytoplasm, or with a light or spumous appearance, separated by delicate blood vessels amidst a variable amount of perivascular collagen. The pseudopapillary tumors are formed by the degeneration of the little-cohesive cells, leaving those who are closest to the conjunctive-vascular axis. These cells are frequently located perpendicularly to the axis, leaving the core in the apical position. The nuclei are rounded or oval, with disperse chromatin, and, at times, have longitudinal folds. Mitoses are rare (average of 0 to 10 in 50 fields of large magnification).

Some of the neoplastic cells contain intracytoplasmic eosinophilic globules, positive to staining by PAS (Periódico-Schiff Acid), after digestion with diastole; these globules can also be found in the extracellular medium. Foci of calcification, foreign-body giant cells containing cholesterol crystals, and bizarre nuclei can also be observed. Cellular pleomorphism and cell atypia are not common but have been reported, mainly in the more aggressive forms of neoplasia. Perineural invasion, angioinvasion, and infiltration of the adjacent pancreatic parenchyma do not indicate a more aggressive behavior, since SPNPs without these characteristics can metastasize, which is why all these tumors are, therefore, classified as low-malignant neoplasms.

**IMMUNOHISTOCHEMISTRY**

Histologically, the SPNP phenotype does not resemble any of the pancreatic epithelial cells, but its histological appearance is very characteristic and, in most cases, can provide a diagnosis; immunohistochemistry is used to confirm the diagnosis or, in some cases, to assist in the differential diagnosis. A aberrant, nuclear, and cytoplasmic positive response to beta-catenin, the loss of membrane expression of E-cadherin, the characteristic perinuclear granular intracytoplasmic marking (dot-like) to CD99, associated with a positive response to the progesterone receptor, and, more rarely, synaptophysin. However, the nuclear expression of beta-catenin, the loss of membrane E-cadherin, positive CD10, associated with the absence of chromogranin and perinuclear granular expression of CD99 favor the diagnosis of SPNP.

**DIFFERENTIAL DIAGNOSIS**

The histopathological diagnosis for this tumor is sometimes difficult, since its histomorphology and immunophenotype may suggest other exocrine and endocrine pancreatic tumors. When in the SPNP there is a predominance of solid areas or light cells, or when there are pseudopapillary areas in neuroendocrine tumors, the immunohistochemical study is essential for the differential diagnosis, especially in specimens obtained by needle biopsy. The solid pattern resembles that of acinar cell carcinoma and neuroendocrine tumor, while the cystic aspect is observed in pancreatic adenocarcinomas and neuroendocrine tumors. This should be the primary neoplasm to be excluded in the differential diagnosis, because in addition to the morphological similarity, the solid pseudopapillary pancreatic neoplasia can express some neuroendocrine markers in the immunohistochemistry, such as CD56, neuron-specific enolase, progesterone receptor and, more rarely, synaptophysin. However, the nuclear expression of beta-catenin, the loss of membrane E-cadherin, positive CD10, associated with the absence of chromogranin and perinuclear granular expression of CD99 favor the diagnosis of SPNP.

**MOLECULAR PATHOLOGY**

Molecular analysis of SPNPs shows that they are distinct from pancreatic adenocarcinomas. Changes in genes KRAS, CDKN2A/p16, TP53, and SMAD4/DPC4, often present in the ductal carcinoma, have not been observed in SPNPs; however, almost all SPNPs feature somatic point mutations in exon 3 of CTNNB1, the gene that encodes beta-catenin. These mutations are related to the activation of the Wnt/β-catenin signaling pathway, preventing the intracytoplasmic phosphorylation and the subsequent degradation of the beta-catenin protein, which then accumulates in the nucleus of neoplastic cells. As a result, 90% of SPNPs present an abnormal pattern of nuclear marking of the beta-catenin protein, while in the healthy pancreas, the marking is on the membrane. This nuclear accumulation of beta-catenin stimulates the transcription of several genes, such as c-myc and cyclin D1, both involved in cell proliferation. In addition, β-catenin interacts with E-cadherin, so that the deregulation of the first also interferes in the expression of the second, and, as a consequence, no E-cadherin membrane expression is observed in most SPNPs. The loss of the normal expression of E-cadherin seems to be related...
to the lack of adhesion and cohesion of neoplastic cells among themselves, causing the typical pseudopapillary aspect of this neoplasm, like with the cystic degenerations observed in it\(^2\). In a study on methylation in three different areas of the same tumor, Chagas and col.\(^2^4\) found methylation of codifying genes of the protein p16 (cyclin-dependent kinase inhibitor 2A) and TIMP-2 (tissue inhibitor of metalloproteinase 2) in two areas, indicating a potential for malignancy and heterogeneous progression in this neoplasia due to the inactivation of the expression of these genes. The protein p16 is an important tumor suppressor, reducing cell proliferation and nontissue inactivation of metalloproteinase 2, encouraging the degradation of the extracellular matrix and the invasion and the occurrence of metastases. In a molecular study of three distinct areas of the tumor were identified by mass spectrometry (MS) 1,427, 5,786, and 4,298 proteins, respectively, being 1,337 common to all three fragments, showing the heterogeneity of tumor\(^2^5\).

CASES REVIEWED IN 21 YEARS IN THE PATHOLOGICAL ANATOMY SERVICE OF THE UNIVERSITY HOSPITAL CLEMENTINO FRAGA FILHO - UFRJ

Methodology

Were reviewed eight cases of SPNP diagnosed in the period of 21 years (1997-2018), in the HUCFF/UFRJ, of seven female patients aged between 12 and 46 years (project approved by the CEP HUCFF/UFRJ under CAE No. 64915717.0.0000.5257). We carried out a review of the medical records to retrieve the patients’ clinical and evolution information, post-surgery. We observed that the main clinical manifestations reported were abdominal pain, more precisely in the right hypochondrium (three cases), and on the left (one case), nausea, and vomiting. The presence of a palpable abdominal mass was observed in four cases. Three patients whose neoplasias were located in the head of the pancreas were subjected to duodenopancreatectomy (Whipple surgery) and two to body-tail pancreatectomy and splenectomy (neoplasia located in the body-tail region of the pancreas). Three patients were diagnosed by echoendoscopic pancreatic biopsy, and one was later submitted to surgery.

In the review of medical records, we observed that a patient was followed-up on an outpatient basis for four years, another for two years, and a third is still being followed-up (P16 5242), without any complications in this period. In the medical records of four patients, no information was found regarding the period after discharge (Table 1).

The paraffin blocks corresponding to the examinations were obtained from the archive of the Pathology Service, HUCFF/UFRJ, and their respective histological sections were submitted to routine techniques for conventional histopathology and immunohistochemistry assays (Table 2). In one case, a molecular biology assay was conducted\(^2^4,2^5\).

**FIGURE 1.**
TABLE 1. CASES REVIEWED IN TWENTY ONE YEARS IN THE ANATOMIC PATHOLOGY SERVICE - HUCFF

| Biopsy No | Age | Clinic Location of the neoplasia | Dimensions in cm | Previous diagnosis | Procedure |
|-----------|-----|----------------------------------|------------------|-------------------|-----------|
| B2116-97  | 27  | LH pain, LH palpable mass        | Head and body    | 10 x 7 x 6        | Cystadenoma, cystadenocarcinoma | Duodenopancreatectomy |
| P00 3249  | 46  | LH pain, palpable mass LH, vomiting | head             | 6.5 x 6 x 4.5     | Adenocarcinoma | Duodenopancreatectomy |
| P11 1978  | 14  | Abdominal pain, vomiting         | Body and tail    | 2.5 x 2 x 2       | Pancreatoblastoma | Body/tail pancreatectomy |
| C12 1733  | 13  | Abdominal mass                   | Body and tail    | NI                | SPNP       | Echoendoscopic biopsy |
| C15 1962  |     | Abdominal pain                   | Body             | NI                | SPNP, NET  | Echoendoscopic biopsy |
| C15 7785  | 23  | LH pain, nausea, vomiting        | Body and tail    | 7 x 4 x 7         | SPNP (previous cytopathological diagnosis) | Body/tail pancreatectomy |
| P16 5242  | 12  | LH pain, LH palpable mass, vomiting | Head             | 6 cm of diameter  | To be clarified | Duodenopancreatectomy |
| C18 113   | 34  | NI                               | Tail             | 3                 | Mucinous neoplasia | Echoendoscopic biopsy |

NI - no information; LH; left hypochondrium; SPNP - solid pseudopapillary neoplasm of the pancreas; NET: neuroendocrine tumor; HUCFF - University Hospital Clementino Fraga Filho

TABLE 2. HISTOPATHOLOGY

| Biopsy No | EC    | PSP    | LGT C | AP     | DGC   | HE    | F     | A     | M     | C     |
|-----------|-------|--------|-------|--------|-------|-------|-------|-------|-------|-------|
| B2116-97  | +     | +      | +     | ++     | AEG   | +     | +++   | +     | 0     | FI    |
| P00 3249  | +     | +      | +     | +      | CN    | +     | +     | -     | 2     | F     |
| P11 1978  | +     | +      | +     | +      | CN;C;GGCCC;GT | +     | ++    | -     | 0     | I     |
| C12 1733  | +     | ++     | -     | -      | -     | +     | -     | +     | 0     | ND    |
| C15 1962  | +     | +      | -     | -      | -     | +     | +     | -     | ND    |       |
| C15 7785  | +     | +      | +     | +      | GGCCC | +     | +     | +     | 0     | F     |
| P16 5242  | +     | +      | +     | +      | CV    | +     | -     | +     | 6     | I     |
| C18 113   | +     | +/-    | -     | -      | -     | +     | -     | +/-   | 0     | ND    |

EC: Eosinophilic cells; PSP: pseudopapillary formation; LGT C: light cells; AP: apoptosis; DGC: degenerative changes; HE: hemorrhage; F: fibrosis; A: atypia (multiple nuclei, increased volume, nuclei); M: mitosis (10 / large magnification field); C: capsule; AEG: eosinophilic granules; CN: coagulation necrosis; C: calcification; GGCCC: granuloma with giant cells and cholesterol crystals; GT: granulation tissue; CV: cellular vacuolation; FI: fibrous invasion; F: fibrosis; I: invasion; ND: Not determined; + positive; negative -

RESULTS

The macroscopic examination revealed rounded or oval masses, measuring between 2.5 x 2 x 2 cm and 10 x 7 x 6 cm, of a firm and elastic consistency, apparently encapsulated, three located in the head of the pancreas and two in the middle body/tail region of the pancreas. In the sections, it was possible to see clear and regular borders and whitish or yellowish surfaces, with solid areas located mainly in the periphery of the tumor, and areas sometimes grainy, others soft, associated with the hemorrhagic areas (Fig. 1A).

The histopathological examination of the slides stained with hematoxylin and eosin showed isolated neoplasms of the pancreatic parenchyma by fibrous pseudocapsule (Fig. 1B), which was permeated in three cases, but not crossed by neoplastic cells. They were polyedric, little cohesive, with eosinophilic (Fig. 2A) or light (Fig. 2B) cytoplasm, forming cell masses permeated by a delicate connective-vascular stroma. The nuclei were rounded or oval, with regular contours or slightly ribbed, or even with mild anisokaryosis. Cells with hyperchromatic nuclei, sometimes multiple, were present, focally, in one of the cases. The number of mitoses ranged from zero (five cases) to six (one case) in ten fields of large magnification. The neoplastic cells were frequently positioned perpendicularly around the axis, configuring pseudopapillary formations, on which occasion the cytoplasm appeared to be more elongated, and the nuclei were located in the apical edge of the cell.

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FIGURE 2.

FIGURE 3.
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TABLE 3. IMMUNOHISTOCHEMISTRY

| Biopsy No | B-catenin | CD99 | CD10 | CD56 | Progesterone receiver | Chromogranin | Synaptophysin | Ecaderin | Ki-67 | OBS |
|-----------|-----------|------|------|------|------------------------|--------------|--------------|----------|-------|-----|
| B2116-97  | NP        | POS  | POS  | NP   | POS                    | NEG          | NEG          | NP       | <2%   | 1 bl|
| P00 3249  | POS       | POS  | POS  | Focal| POS                    | NEG          | NEG          | NP       | <2%   | 1 bl|
| P11 1978  | POS       | POS  | POS  | NEG  | 2 bl                   | POS          | NEG          | NEG      | <2%   | 3 bl|
| C12 1733  | NP        | POS  | POS  | POS  | POS                    | NEG          | NEG          | NEG      | <2%   | 1 bl|
| C15 1962  | POS       | POS  | POS  | POS  | POS                    | NEG          | NEG          | NP       | <2%   | 2 bl|
| (C15-1962)| POS       | POS  | POS  | NEG  | 1 bl                   | POS          | NEG          | POS focal1 bl NEG 2 bl | <2%   | 2 bl|
| P16 5242  | POS       | POS  | POS  | 1 bl, NEG 1 bl | POS          | NEG          | NEG          | POS focal1 bl NEG 1 bl | <2%   | 2 bl|
| C18 113   | POS       | NEG  | POS  | POS  | POS                    | NEG          | NEG          | NEG      | <2%   | 3 bl|
|           |           |      |      |      |                        |              |              |          |       |     |

POS: positive; NEG: negative; NP: the exam was not performed; bl: block.

(Fig. 2C). Areas formed by granulation tissue and multinucleated giant cells containing cholesterol crystals were observed in two cases. Hemorrhagic foci and cell degeneration were observed in all cases, and fibrosis in four cases, with varying intensity. Eosinophilic granules, intra or extracellular, were observed in two cases and were positive to staining by PAS in one case and negative in another.

There were no significant histological changes in the pancreatic parenchyma adjacent to the neoplasms.

The immunohistochemical assay confirmed the diagnosis of SPNP by the positivity of the neoplastic cells, to the anti-beta-catenin antibodies in nuclear and cytoplasmic locations (Fig. 3A), the anti-CD99 of cytoplasmic granular pattern Fig.3B), the anti-CD-10 in cytoplasmic location Fig. 3C), the anti-progesterone receptor in nuclear location (Fig. 3D), and by the negativity to anti-E-cadherin, which are considered the main markers of this neoplasm (Table 3). The proliferative index assessed by the nuclear reaction in the neoplastic cells, with the anti-Ki67 antibody, was lower than 2% in three cases and 8% in one case. This also presented a high mitotic index (six mitosis/ten fields of large magnification) and is in regular outpatient monitoring since 2016, so far, uneventfully (Table 3 and Figure 3).

**CONCLUSION**

Solid pseudopapillary neoplasms of the pancreas have a heterogeneous pattern regarding their macroscopic, microscopic, immunophenotypic, and molecular aspects, as evidenced both in the bibliographical review, as in the cases studied. The histopathological diagnosis is guided by the presence of solid and pseudopapillary areas; however, the immunohistochemistry assists in the differential diagnosis with other pancreatic neoplasms, mainly by the aberrant nuclear expression of beta-catenin, associated to the lack of membrane expression of E-cadherin, the typical perinuclear granular marking of CD99, and CD10 positivity. Molecular biology is still poorly understood, although many studies on the subject have been published. Although rare and having, in most patients, good prognosis and excellent response to surgical treatment, it is a neoplasia that, due to its enigmatic cell origin and its morphological and molecular heterogeneity, encourages the search for a better understanding of its biology.

**Author Contribution**

Vera Lucia Chaças wrote the manuscript, and all authors reviewed it and made contributions.
RESUMO

OBJETIVO: Fazer revisão da literatura e do diagnóstico histopatológico convencional de rotina e de imuno-histoquímica dos casos diagnósticos da neoplasia sólida pseudopapilar do pâncreas (NSPP).

MÉTODOS: A revisão da literatura foi feita utilizando as bases de dados PubMed e Google Scholar, por meio do histórico, aspectos clínicos e métodos de diagnóstico da NSPP. A revisão dos casos de NSPP diagnosticados no Hospital Universitário Clementino Fraga Filho da UFRJ foi feita no período de 1997 a 2018.

RESULTADOS: A heterogeneidade fenotípica intratumoral da NSPP foi evidenciada nos casos estudados, levando-se em conta os padrões macroscópicos, microscópicos e imunohistológicos.

CONCLUSÕES: O conjunto de resultados evidencia a importância do exame de vários fragmentos obtidos de regiões distintas das neoplasias, uma vez que nem todos eles apresentam os mesmos alterações moleculares.

PALAVRAS-CHAVE: Pâncreas. Neoplasia sólida pseudopapilar.

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