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Case Study

Solid Pseudopapillary Tumor of the Pancreas: Clinical Characteristics

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Abstract

Solid pseudopapillary pancreatic tumor (SPTP) is a rare heterogeneous pancreatic tumor with multicentric growth and low malignancy potential, with favorable prognosis after surgical treatment. A small percentage of patients exhibit aggressive behavior. The histogenesis of these epithelial neoplasms remains unclear, although it is likely that they originate from pluripotent immature cells of the pancreas. Grade criteria for SPTP have not been established. The prognosis of SPTP is generally favorable, with patients having a chance of long-term survival even with relapses and/or metastases after radical surgery.

The tumor is usually large and invariably a capsule. The diagnosis in most cases is based on symptoms of compression, pain, or detection of a palpable mass, while in about 20% of patients, detection is «incidental» during abdominal imaging performed for other conditions. CT and MRI are not always sufficient to distinguish this tumor type with certainty from other cystic neoplasms of the pancreas, such as pseudocysts, parasitic cysts, and congenital cysts. Cytological examination in most cases allows the diagnosis of SPTP. The malignancy of these neoplasms is not high and is determined by capsular invasion, proliferation of lymph nodes and, only in rare cases, metastases to the liver and peritoneum. Surgical treatment should be radical, since a malignant neoplasm can only be determined by postoperative histological examination.

This article reviews the clinical, pathological and visual characteristics of solid pseudopapillary pancreatic tumor (SPTP) used in routine clinical practice.

Keywords: Pancreas; Solid Pseudopapillary Tumour; Malignancy; Metastasis; Pancreas; Surgery; Multicentric Lesions; Solid Pseudopapillary Neoplasm; CT

Introduction

Solid pseudopapillary tumor of the pancreas (SPTP) is a rare tumor that accounts for only 1-2% of all pancreatic neoplasms. It is characterized by a low potential for malignant transformation and, in most cases, a favorable prognosis [1]. In 1996, the World Health Organization defined this type of neoplasia as a «solid pseudopapillary tumor of the pancreas» in the international histological classification of pancreatic tumors [2]. This name covers the most diverse macroscopic and microscopic aspects of neoplasia, that is, solid and pseudopapillary. Most often, this tumor occurs in women (82%) of all ages, in men - less than 10%. There is no clear ethnic predisposition or any association with known clinical or genetic syndromes. Some rare cases have been reported in patients with familial adenomatous polyposis (FAP) [3].

Recently, the number of SPTP has increased as a result of the wide availability of imaging techniques and greater awareness of the disease. These lesions are usually asymptomatic, and some patients may present with vague abdominal pain or a gradually increasing mass on imaging [3]. SPTP is characterized by a very low malignancy potential (no more than 10-15%), the medical literature indicates the following features: the presence of extracapsular extension, high expression of Ki-67 according to immunohistochemical analysis, pleomorphism and cellular, and to a high degree nuclear. The malignant course of SPTP is more common in the second to fifth decade of life and is usually seen in tumors 6 cm or larger. Metastases of SPTP are most often observed in the liver and less often in the lymph nodes and peritoneum [4].

Given their rare nature, clinical data on these tumors are most often limited to case reports or small series. However, the diagnosis of SPTP has been made more frequently due to awareness of its existence, increased use of immunohistochemical methods, and retrospective studies of tumors that have not been adequately identified [5].

Despite several studies using electron microscopy and immunohistochemistry, the cellular origin of this neoplasia remains uncertain. Some researchers support the hypothesis of a multipotential primitive cell as a source, especially due to the absence of a predominant lineage of differentiation and the found multidirectional differentiation [6].

Some authors suggest an extrapancreatic origin due to several reported cases of primary tumors in various areas of the pancreas such as the ectopic pancreas, retroperitoneum, gastroduodenal region, and ovary. Some authors consider the origin of primitive cells of the reproductive system, and not of the pancreas [7].

Given that solid pseudopapillary tumors of the pancreas (SPTP) are rare (the total number does not exceed 1-2% of all exocrine pancreatic tumors). This type of tumor has a favorable prognosis, and patients are most often young people who are indicated for organ-preserving surgical treatment and long-term follow-up, rather than the use of various neoadjuvant and adjuvant chemotherapy regimens. The purpose of writing this paper is the desire to present a detailed picture describing the characteristic clinical pathomorphological, immunohistochemical and molecular genetic, radiation and radiological aspects of a solid pseudopapillary tumor of the pancreas (SPTP).

Pathomorphology

Molecular genetic characteristics

Molecular genetic study of pancreatic tissue samples with Solid Pseudopapillary neoplasm of the pancreas shows its difference from adenocarcinoma. Expression of genes KRAS, CDKN2A/p16, TP53 and SMAD4/DPC4 are often present in ductal adenocarcinoma and have not been observed in SPNP. In SPNP tissue samples, somatic point mutations were revealed in exon 3 of CTNNB1, the gene encoding β-catenin [17]. Abnormal activation of the Wnt/β-catenin pathway has been consistently demonstrated in SPNP and is an important genetic event contributing to the development of solid pseudopapillary neoplasms [18]. A point mutation of exon 3 in the β-catenin gene is frequently reported in SPNP, and it is assumed that this leads to translocation of β-catenin into the nucleus [19].

In normal cells, the absence of Wnt signaling leads to phosphorylation of catenin and the formation of a "kill complex" with other proteins such as APC, Axin1, casein kinase 1α and GSK3, which leads to ubiquitination and proteasome degradation of β-catenin. In the presence of Wnt signaling, this binding does not occur due to sequestration of the binding complex proteins (GSK3 and Axin1), which allows β-catenin accumulation and its transfer to the nucleus. It is here that it regulates the transcription of various genes through the formation of the β-catenin-T-cell factor (TCF) factor complex [20]. SOX11 can directly bind to -catenin or TCF, blocking their interaction and thus suppressing Wnt/β-catenin signaling [21].

These genetic changes lead to cytoplasmic and nuclear accumulations of catenin and, as a consequence, to immunohistochemical positivity (together with SOX11) [22]. Somatic mutations in CTNNB1 additionally lead to overexpression of cyclin D1, which is a key regulator of the cell cycle and an important downstream target for β-catenin [23].

Microphthalmia-associated transcription factor (MiTf) encodes a DNA-binding protein from the main family of leucine helix-loop-helix-zip (bHLH-Zip) that regulates gene transcription by binding to elements (M and E rectangles) in the flanking regions 5d 'their target genes [24]. This family is made up of four factors, including MITF, TFEB, TFE3, and TFEC. They have been shown to be enhanced in various malignant tumors. Overexpression of MiTF has been associated with Wnt signaling by increasing sequestration

of complex degradation proteins such as Axin1 and GSK3.9. It is possible that overexpression of other members of the MiT family (especially TFE3) may be associated with the Wnt/β-catenin signaling pathway. As we described in the previous paragraphs, TFE3 expression is observed using immunohistochemistry, although it is not known whether TFE3 is overexpressed in NSP [24].

Much remains unknown and further studies of molecular cytogenetics in SPNP are needed; in particular, the development of a molecular tumor biomarker to detect tumors with potentially aggressive behavior can be useful in patient management.

Pathomorphology

Macroscopic picture. SPTP can occur in any area of the pancreas and is typically one third in the head, one third in the body, and another third in the tail. Macroscopic examination reveals formations ranging in size from 0.5 to 25.0 cm in diameter (average diameter 8-10 cm). They are usually round, well-defined and separated from the pancreatic parenchyma by a fibrous pseudocapsule; however, under a microscope one can see neoplastic cells penetrating the pancreatic parenchyma, permeable acini and pancreatic islets [25].

The incision surface is different, with yellowish or brownish hard patches, hemorrhagic lesions, or cystic degeneration filled with necrotic debris. Smaller tumors tend to be more resistant than larger tumors, and hemorrhagic-cystic areas, if large, may indicate a pseudocyst. They rarely spread to the stomach, duodenum or spleen, and metastases occur in 5-15% of cases, mainly to the liver and peritoneum. The stages correspond to other pancreatic carcinomas [25].

The microscopic picture of SPTP is heterogeneous, with a different proportion of solid, pseudopapillary, hemorrhagic and pseudocystic areas, representing a solid and cystic nature of the neoplasm [25]. Solid areas, located mainly in the periphery of tumors, when they are especially hemorrhagic-cystic, are formed by small cohesive cells, polygonal, monomorphic, with eosinophilic cytoplasm, or have a light or spumous appearance, separated by thin blood vessels between them. variable amount of perivascular collagen [25]. Pseudopapillary tumors form as a result of the degeneration of loosely bound cells, leaving those closest to the connective-vascular axis. These cells are often perpendicular to the axis, leaving the nucleus in an apical position. The nuclei are round or oval, with scattered chromatin, sometimes with longitudinal folds. Mitoses are rare (average 0 to 10 in 50 high-magnification fields). Some of the neoplastic cells contain intracytoplasmic eosinophilic globules that are positive for PAS (Periodic-Schiff's acid) staining after digestion with diastole; these globules can also be found in the extracellular environment. There may also be foci of calcification, giant foreign body cells containing cholesterol crystals, and bizarre nuclei [38]. Cellular pleomorphism and cell atypia are uncommon, but are described mainly in more aggressive forms of neoplasia [39]. Perineural invasion, angioinvasion and infiltration of the adjacent pancreatic parenchyma do not indicate more aggressive behavior, since SPTP without these characteristics can metastasize, therefore all these tumors are classified as low-grade neoplasms [38].

Diagnostics

The prevalence of pancreatic cystic lesions is increasing due to more frequent detection with transverse imaging and that most pancreatic cystic lesions are neoplastic, accurate diagnosis with clinical information, radiographic imaging and endoscopic ultrasound (EUS) with analysis of cystic fluid can play an important role [13].

SPTPs are usually located in the tail of the pancreas. Large tumors contain solid and cystic components due to necrosis, bleeding, and cystic degeneration. Most cystic SPTPs do not have a connection with the pancreatic duct, which allows them to be differentiated from intraductal papillary mucinous neoplasms (IPMN) [14].

Small SPTPs (Ø < 3 cm in diameter) are often completely solid tumors with sharp edges and a tendency to enlarge. Atypical features of SPTP include extracapsular enlargement, invasion of neighboring organs, calcification, duct obstruction, and metastases. The differential diagnosis includes pancreatic lipomatosis (invagination of peripancreatic fat into the pancreas, which may mimic a mass); rupture of the pancreas in trauma; focal pancreatitis (useful correlation with history and laboratory data) [15].

Most pancreatic lesions that are large (Ø > 3 cm in diameter) have characteristic visualization features on radiological

examination, and the exact distinction between them is important for determining further patient management. SPTP tends to displace, rather than invade, surrounding vessels and organs, and only rarely is vascular coverage and mesenteric vessel invasion described [16].

Rarely, dissemination is described and, if present, most often affects the liver. Solid pseudopapillary carcinoma (SPTP) is diagnosed in 15% of cases. These tumors are usually larger than 5 cm, are more common in males, and are associated with vascular invasion and metastatic disease [17].

Ultrasound diagnostics (ultrasound)

On ultrasound, SPTP is a homogeneous or heterogeneous hypoechoic mass with a hyperechoic rim. Contrast-enhanced ultrasound (CEUS) shows rim perfusion in the arterial phase. CEUS can help identify cystic areas of the tumor and its peripheral margin.

Ultrasonography (ultrasound) is usually not helpful in differentiating SPTP from other types of pancreatic cystic lesions. On ultrasonography, a large, diffuse-echogenic or complex mass that is clearly demarcated in the upper abdomen has been described, with or without penetrating transmission, depending on tumor composition, but results suggest a definitive diagnosis is usually not made and additional study [18].

Contrast CT and MRI are superior to ultrasound in capsule identification as well as in intramural bleeding, which are more specific features for diagnosing SPTP [19].

Computed tomography (CT) is the primary imaging modality and demonstrates an encapsulated mass with various solid and cystic components. CT also reveals larger areas of necrosis and hemorrhagic degeneration [19].

Tumors seen on CT are usually described as well-differentiated, demarcated, encapsulated, large, cystic, and solid masses. In cystic and solid tumors, solid tissue components are usually noted in the periphery, and the central regions are represented by foci of hemorrhage and cystic degeneration. Calcifications and hard areas are visualized along the periphery of the neoplasm [20].

Multiphasic computed tomography shows weak early arterial enhancement compared to normal enhancement of the pancreatic parenchyma. However, the solid component shows a gradual increase in the portal-venous phase (Figure 1), exceeding the normal increase in the pancreatic parenchyma. Some case reports in the literature have reported associated dilatation of the pancreatic and bile ducts, which are rare secondary findings [21].

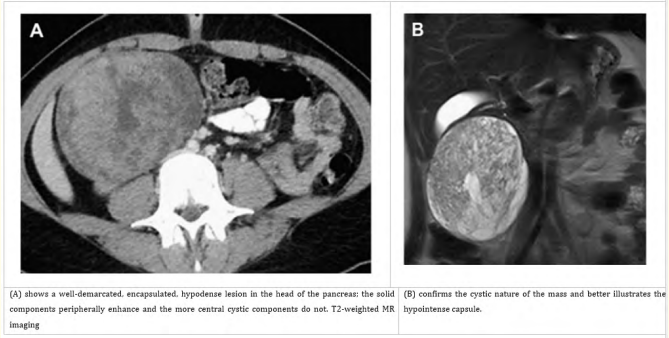

Figure 1: SPTP. Contrast-enhanced CT image.

Atypical SPTP may not have a well-defined capsule or a clear boundary between solid and cystic components. Studies have shown that the lobular shape is more common in men, while the oval shape is more common in women. Hemorrhagic degeneration of SPTP can be confused with postpancreatitis wall necrosis or pseudoaneurysm of the superior mesenteric artery [22].

Magnetic resonance imaging (MRI)

MRI is superior to other imaging modalities for characterizing pancreatic lesions with cystic components. In addition, it has an advantage over computed tomography due to the absence of radiation, as well as in the case of if the patient suffers from contrast allergy or renal insufficiency [23]. On MRI, SPTP is seen as an encapsulated lesion with solid and cystic components, as well as a hemorrhage without an internal septum [23].

MRI also usually shows a well-defined tumor mass, which usually has a heterogeneous appearance on both T1-weighted and T2-weighted images [24]. Areas of hemorrhage appear hyperintense compared to the pancreatic parenchyma on T1-weighted images and hypointense on T2-weighted images. images (Figure 2).

After the injection of the contrast agent, the capsule and solid components are enhanced (Figure 2) [24]. Following gadolinium infusion, there is usually a mild peripheral enhancement during

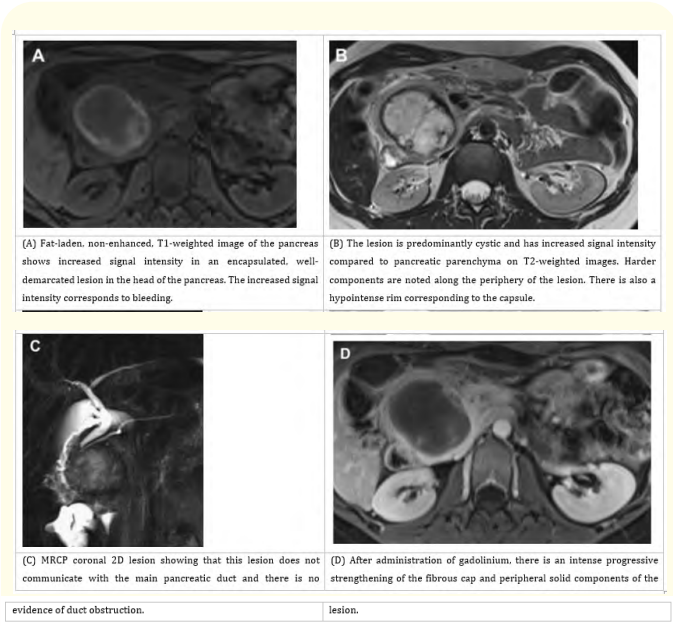

Figure 2: MRI picture of Solid pseudo-papillary carcinoma of the pancreas.

the arterial phase, with progressive dural enhancement during the portal venous and delayed phases. The key diagnostic feature of SPTP is the presence of a fibrous capsule that encloses and surrounds the tumor.

Criteria for FDG SPTP uptake on positron emission tomography (PET-CT) images have not been established. Literature review shows that SPTP FDG uptake on PET-CT is associated with tumor cellularity, proliferative index, or histological malignancy, however, high FDG uptake does not always indicate malignancy. Small SPTPs are likely to have increased FDG uptake due to very little or no cystic component within [22].

Significant advances have taken place in the field of imaging over the past few years, which have directly affected the imaging of the pancreas. In MRI, the use of stronger fields, tissue-specific contrast agents, new imaging sequences, including the use of parallel imaging and three-dimensional registration, as well as multi-channel magnetic resonance coils. Given the myriad imaging options available, radiologists must carefully specify the reasons for imaging a particular patient (eg, investigation of a pancreatic neoplasm, detection of liver metastases, etc.). Close attention must be paid to the optimization of technique to ensure good results. Following best practices, MRI/MRCP can make a significant contribution to the evaluation and management of patients with pancreatic cancer (Table 1).

Study type	Findings
Ultrasonography	Hypoechoic lesions Hyperechoic rim Homogeneous/heterogeneous Contrast enhancement of rim - arterial phase Advantage of CEUS over US: Superior characterization of cystic areas and rim
CT	Primary imaging modality Helps visualize capsule, distinguish solid and cystic portions, necrosis, hemorrhage, calcifications Hepatic venous phase: gradually increasing enhancement of solid components, exceeding normal pancreatic parenchymal enhancement
MRI	May be used in patients with contrast allergy, renal insufficiency Helps visualize capsule, distinguish solid and cystic portions, hemorrhage (hyperintense on T1) Heterogeneous signal intensity on T-1 and T-2 weighted imaging Helps identify Types 1, 2 and 3 SPN based on solid portions, extent of hemorrhage observed.
FDG-PET	Increased uptake may be seen in predominantly solid, small SPNs and malignancies

Table 1: Imaging characteristics of Solid Pseudopapillary Neoplasm of Pancreas.

Differential diagnosis

The differential diagnosis of SPNP includes several pathologies, including pancreatoblastoma, neuroendocrine tumor of the pancreas, and acinar cell carcinoma, and cystic neoplasms of the pancreas, such as mucinous cystic tumor, serous cystadenoma, cystadenocarcinoma, and pancreatic pseudocyst, should also be considered (Table 2) [25].

Pancreatoblastoma is a rare malignancy that occurs almost exclusively in patients under 10 years of age, and some of them are

	Solid pseudopapillary neoplasm	Pancreatoblastoma	Neuroendocrine tumor	Acinar cell carcinoma	Mucinous cystic neoplasm	Serous cystadenoma	Pancreatic psuedocyst
Age	15-45 years	0-9	30-80	50-80	40-50	60	Middle Ages
Sex	Women	Men	No predilection	Men	Women	Women	Men
Location	Head and tail	Head and tail	No predilection	No predilection	Tail	Head	No predilection
Macroscopy	Bounded, heterogeneous, solid mass - cystic, with areas of necrosis	Solitary mass, delimited, lobed, partially encapsulated, gray, brown in color. Variable necrosis	Well circumscribed solid mass. 5% have cystic degeneration	Large, solid, circumscribed, fleshy, lobulated, reddish mass	Uni- or multilocular cyst, mucinous in content, surrounded by a fibrous capsule	Circumscribed mass with multiple cysts and a central scar	Uniloculated cyst with fibrous wall, without septa or nodules
Histology	Pseudopapillae, Discohesive cells, Nuclear clefts Variable stroma	Mix of solid nests, squamous corpuscles, and acini. Cellular stroma	Solid nests, and trabeculae. Nuclei with granular chromatin. Hyalinized stroma	Solid nests, acini, glands. Cells with broad granular cytoplasm with little stroma	Cysts lined by cubic to cylindrical cells, mucoproducing. Ovarian-like stroma	Cubic cell lined cysts with round nuclei	Wall made up of granulation and fibrosis tissue, without epithelium
Immunohisto-chemistry Cytokeratin	- / +	++	++	++	++	++	Does not apply
β - catenin	+	-	-	-	-	-	Does not apply
Chromogranin	-	+	++	- / +	- / +	-	Does not apply
Synaptophysin	+	+	++	-	-	-	Does not apply
Trypsin	-	++	-	-	-	?	Does not apply
α1-antitrypsin	++	+	- / +	+	-	-	Does not apply

Table 2: Differential diagnosis of pseudopapillary neoplasia.

associated with Beckwith-Weidemann syndrome and familial adenomatous colon polyposis. Microscopically, this neoplasm is highly cellular, formed by monomorphic epithelial elements located in a hard mantle with tubular formations and cell nests, with stromal hypercellularity that can sometimes represent cartilaginous or bony differentiation. It is characteristic that it contains flat nests (bodies) and, according to immunohistochemical analysis, shows signs of acinarity (trypsin, chymotrypsin and lipase), endocrine (neuron-specific enolase, synaptophysin, cromogrin and PGP 9.5) and pancreatic ducts (carcinogenesis, carcinogen 5), cytochertin antigen, AE1-cytokertin antigen), AE3 and CK7. There may be defetoprotein expression and nuclear positivity for β-catenin. In addition, it has nuclear expression of LEF1, but unlike NSP, it is weak and focal [26].

Acinar cell carcinoma is a malignant neoplasm that presents as a homogeneous cellular architecture with nests, acini, and occasional trabecular masses. Neoplastic cells are irregularly contoured nuclei, fine-grained PAS-positive, diastase-resistant cytoplasm that is positive for various pancreatic enzymes such as trypsin, chymotrypsin, and lipase, and has variable expression for lacatenin [27]. It should be borne in mind that acinar cell carcinoma has a cystic variant (acinar cystenocarcinoma), which can be pancreatoblastoma is a rare malignancy that occurs almost exclusively in patients under 10 years of age, and some of them are associated with Beckwith-Weidemann syndrome and familial adenomatous colon polyposis. Microscopically, this neoplasm is highly cellular, formed by monomorphic epithelial elements located in a hard mantle with tubular formations and cell nests, with stromal hypercellularity that can sometimes represent cartilaginous or bony differentiation. It is characteristic that it contains flat nests (bodies) and, according to immunohistochemical analysis, shows signs of acinarity (trypsin, chymotrypsin and lipase), endocrine (neuron-specific enolase, synaptophysin, cromogrin and

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Although morphology is key to differentiating SPTP from neuroendocrine tumors (NETs), they can sometimes show significant morphological overlap. Some cases of NET may have cystic and necrotic areas composed of discoghesive cells and, on the other hand, in some cases SPTP may have a predominantly continuous growth pattern without pseudopapillary structures, so that in some cases it is not possible to distinguish between these two types of tumors simply on the basis of their macro and micro pictures (Table 3).

Marker	Solid pseudopapillary neoplasm	Pancreatic neuroendocrine tumor	Pancreatic ductal carcinoma	Tumor de células epitelioides perivasculares (PEComas)	Metastatic renal carcinoma
R Progesterone	+	-/+	-	-	-
CK7	-	+/-	+	-	-
Cam5.2	-	-	+	-	+/-
CD99	+ (paranuclear point)	Diffuse	-	-	-
CD10	+	-	-/+	-	+
Vimentin	+	-	-/+	-	+
Galectin-3	+	-	+	?	-/+
Sinaptofisina	-/+	+	-	-	-
Cromogranina		+	-	-	-
β - catenin (nuclear)	+	+	+/-	-	-/+
E-cadherin	-	+	+	-	-
HMB45	-	-	-	+	-
Actin	-	-	-	+	-
PAX 8	up to 25%	-	-	-	+

Table 3: Indicators of immunohistochemical markers in clear cell tumors of the pancreas.

Histochemical analysis plays a critical role in differentiating these two tumor types. Synaptophysin, chromogranin A, pancytokeratin, and E-cadherin are markers for the diagnosis of NET, while progesterone receptor, vimentin, α-1-antitrypsin, CD10, and nuclear positivity with β-catenin are markers favoring the diagnosis of SPTP. However, caution should be exercised as the expression of all these markers may also show overlap between these two neoplasms [28]. There is a clear-cell variant of NSP described by Albores-Saavedra in 2006, which needs to be differentiated from metastases of clear cell renal cell carcinoma and perivascular tumor (PEComas) [29]. In this situation, careful histological analysis and reasonable immunohistochemistry allow for a correct diagnosis.

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significant morphological overlap. Some cases of NET may have cystic and necrotic areas composed of discoghesive cells and, on the other hand, in some cases SPTP may have a predominantly continuous growth pattern without pseudopapillary structures, so that in some cases it is not possible to distinguish between these two types of tumors simply on the basis of their macro and micro pictures.

Clinical picture

A solid pseudopapillary neoplasm of the pancreas is usually discovered incidentally on routine physical examination or abdominal imaging studies performed for various reasons. Signs and symptoms are nonspecific and related to the intra-abdominal mass, including pain, dyspepsia, early satiety, nausea, and vomiting. Jaundice rarely occurs, even if the tumor is in the head of the pancreas. Serological tumor markers are normal, the relationship with functional endocrine syndromes has not been described [11]. Since in most cases surgical resection is curative and relapses can be treated surgically, it is important to have an accurate diagnosis6. SPTP should be considered in the differential diagnosis of any solid or partially cystic mass located in the pancreas or upper abdomen in young women [30].

The preoperative diagnosis can be made with an endoscopic ultrasound-guided fine-needle biopsy (echoendoscopy). Echoendoscopy has become very useful in evaluating pancreatic lesions seen on other imaging studies or when such lesions are suspected based on clinical and laboratory findings. Examination is generally safe and can be performed in most cases, and the material obtained should be evaluated by a cytopathologist using smears or cell blocks (cell block). The results allow treatment based on the diagnoses. Its use allows surgeons and oncologists to better plan their approach to the patient [31].

Treatment

Treatment for SPTP is usually surgical resection, but enucleation procedures have been described that are made possible by the fibrous cap surrounding the tumor. Overall, patients with this tumor have an excellent survival rate, including the rarer solid pseudopapillary carcinoma (15%), which has a 5-year survival rate of 96% [32]. Studies show that overall survival after surgical resection at 5 and 10 years was about 96% and 93%, respectively, including patients with malignant SPTP [21].

However, despite being a tumor with a low level of malignant potential, it is now well known that a small but significant percentage of these tumors exhibit aggressive behavior (5–15% metastases, 3–5% mortality) [32].

The optimal surgical approach can be controversial. Available surgical approaches include general partial pancreatectomy surgical approaches for SPTP, including distal pancreatectomy (DP), distal spleen-sparing pancreatectomy (Warshow/Kimmra), pancreatoduodenectomy (Whipple procedure), or pyloric-sparing pancreatoduodenectomy (PD/PPPD), glans-sparing resection pancreas (DPPHR) and middle pancreatectomy (MP) or enucleation, depending on the location of the tumor and the degree of invasion [21].

Distal pancreatectomy, whether open, laparoscopic, or robotic, involves removal of the tail and/or body part of the pancreas along with the spleen for tumors involving the tail of the pancreas. Spleen-sparing distal pancreatectomy involves the exclusion of splenectomy from surgery and can be safely performed with preservation of the splenic artery and vein. However, this operation is only possible in about one third of pancreatic tail SPN cases [4].

Duodenopancreatectomy or Whipple operation involves resection of the duodenum, pylorus and head of the pancreas along with a triple anastomosis - hepaticojejunostomy, gastroneunostomy and pancreatojejunostomy. This procedure can be performed in conjunction with pylorus sparing when the tumor does not involve the stomach and there are no enlarged perigastric lymph nodes. Preservation of the pylorus improves weight gain after surgery. Resection of the pancreatic head with preservation of the duodenum, first proposed by Beger H.G., *et al*. It is performed for low-grade pancreatic tumors [33].

Median, central, or medial pancreatectomy is performed for benign and low-grade malignancies of the middle pancreas and is associated with a low risk of exocrine and endocrine insufficiency. However, central pancreatectomy has a greater number of postoperative leaks from the pancreatic-intestinal anastomosis. This casts doubt on this surgical approach [21].

Small SPTPs with full capsules can be removed by enucleation. However, large tumors may require surgical resection even in the case of liver metastases or local metastases in order to reduce the tumor burden [3].

Complete resection requires a block synchronous portal vein - superior mesenteric vein or resection of an adjacent organ [4].

Very large SPTPs or SPTPs with extensive metastases can be treated with radiotherapy because these tumors are radiosensitive [3].

The most common site of SPTP metastasis is the liver. Depending on the biological behavior of the tumor, liver metastectomy with a margin of 1 cm may be sufficient [21]. Zhang Chi., *et al*. showed that, on average, 30 months of follow-up, all patients had no overt relapses or distant metastases, indicating a favorable prognosis with aggressive surgical resection, especially with resectable metastatic lesions [21]. Although surgical removal of liver metastases has shown long-term survival, in some cases long-term survival has been maintained even without removal of liver metastases. In some cases, removal of rare peritoneal metastases has shown long-term survival. Local spread to the stomach and spleen is treated by excision of the affected part of the organ. Extensive local organ involvement precludes resection in some cases, but long-term survival was likely due to the low malignancy potential and biological characteristics of the tumor [34].

Nodal metastases are also rare in patients with SPTP, so extensive lymph node resection is usually not performed. Therefore, routine lymph node dissection is not recommended. However, removal of large suspicious lymph nodes is a prudent approach when found during surgery [21].

A study by Kim MJ., *et al*. showed that lymph node metastases may be associated with either tumor rupture during surgical removal or lymph node spread in a latent lymph node group. Patient c with SPTP greater than 5 cm, complete en bloc resection with lymph node harvesting from suspected lymph nodes and nodal dissection is recommended [4].

Conclusion

Solid pseudopapillary pancreatic tumors (SPTP) differ in clinical characteristics from other pancreatic tumors. Kosmahl M., *et al*. suggested that tumor cells have a different origin than the pancreas [35]. This type of tumor usually affects women in their second to fifth decade of life, but other age groups can also be affected. Since SPTP is predominantly found in women, it has been hypothesized that it develops from misplaced cells from the genital ovarian ridge, which is adjacent to the primordial pancreas, or from pluripotent fetal pancreatic cells under the influence of female hormones.

Histology

Gross anatomy usually reveals an encapsulated tumor with cystic degeneration and hemorrhage. Smaller tumors tend to be more solid while larger tumors are friable as they develop cystic degeneration and bleed as they grow.

SPTP is a cellular neoplasm with cells arranged in several layers around fibrovascular stalks, giving rise to a pseudopapillary structure. The histological presence of pseudopapillary architecture, hyaline globules, cholesterol clefts, foamy macrophages, and nuclear grooves with the absence of neuroendocrine (salt and pepper) chromatin are characteristic of SPTP [36]. The ultrastructure consists of non-desmosome-like compounds and electron-dense granules that may contain α-1-antitrypsin.

Immunohistochemistry

These tumors are usually positive for vimentin, α1-antitrypsin, α1-antichymotrypsin, and neuron-specific enolase. Nguyen N.Q., *et al*. showed 100% sensitivity and specificity of β-catenin in these tumors, while the positive predictive value for synaptophysin was 26% and for chromogranin was 15% [37].

The characteristic immunohistochemical pattern of SPTP is abnormal staining with nuclear and cytoplasmic positivity for β-catenin and loss of E-cadherin from the cytoplasmic membrane. Other common positive markers include the progesterone receptor, α-1 antitrypsin receptor, and CD10 [38].

SPTPs often show immunoreactivity for the neuroendocrine markers synaptophysin and neuron-specific enolase and chromogranin. If histological and immunohistochemical studies are insufficient for diagnosis, electron microscopy may help.

Common differential diagnoses are pancreatoblastoma, acinic cell tumor, and neuroendocrine tumor, which have several similarities radiographically as well as immunohistochemically. Nuclear and cytoplasmic expression of β-catenin has been reported in pancreatoblastoma, but the histological appearance with cells forming so-called squamous bodies and dense streaks of fibrous stroma are characteristic and distinct from SPTP [39]. Pancreatoblastoma is most common in children and, unlike SPTP,

occurs predominantly in men. Acinic cell tumors are rare in children, but have a histological appearance resembling pancreatoblastoma but without flat bodies. Neuroendocrine tumors (islet cell tumors) may or may not function with hormone secretion. Neuroendocrine tumor markers such as synaptophysin, chromogranin, and CD56 may be expressed differently in SPTP.

Differentiating SPTP with malignant and benign potential is difficult. Signs of malignant behavior, with the exception of metastases, are controversial. According to the WHO classification, clear criteria for malignancy are vascular invasion, nerve sheaths, metastases to the lymph nodes and liver. In these cases, the tumor is referred to as solid pseudopapillary carcinoma. Tumor size greater than 5 cm and invasion into the capsule and outward into the peripancreatic tissue are associated with malignancies [40].

The differential diagnosis should include microcystic adenoma, mucinous cystic neoplasm, nonfunctioning islet cell tumor, pancreatic adenocarcinoma, pancreatoblastoma, cystic degeneration of a solid neoplasm and calcified hemorrhagic pseudocyst, acinar and neuroendocrine tumors [41].

Ultrasound

Ultrasonography, computed tomography, and MRI usually show the same features with an encapsulated tumor composed of solid and cystic components, sometimes with encapsulated rim-shaped calcifications as well as intraparenchymal calcifications [42]. The lesion has well-defined margins, often without dilatation of the pancreatic duct. Ultrasonography reveals various echogenic and hypoechoic components.

CT

On computed tomography, imaging findings are nonspecific and suggestive (components of varying density and lesions).

MRI

Magnetic resonance imaging is preferred over computed tomography for demonstrating the presence of a well-encapsulated mass with p varying amounts of solid and cystic components, as well as bleeding without a clear internal septum and with peripheral or heterogeneous contrast enhancement [43].

On MRI with high signal intensity on T1 and low signal intensity on the T2 series, representing hemorrhagic areas [42].

These features help distinguish this rare tumor from other pancreatic neoplasms.

Angiographically, the tumor is usually avascular or hypovascular. However, none of the radiological features are characteristic of SPTP, and this statement occurs in other pancreatic tumors, especially cystic neuroendocrine tumors and pancreatoblastoma. 18F-FDG-PET differs in activity because tumor cells can have both high and low metabolism.

Abdominal CT, magnetic resonance imaging, ultrasound, and endosonography are used with varying success in the diagnosis of solid pseudopapillary neoplasms of the pancreas.

Clinic

Clinical symptoms are often nonspecific, which may delay the diagnosis. The most common symptoms are abdominal pain, followed by vomiting and nausea as a result of tumor compression of adjacent organs and a palpable mass. Almost 30% of patients are asymptomatic and the tumor is discovered incidentally during diagnostic imaging procedures [44].

Forecast

SPTP is characterized by a favorable prognosis. The survival period is 152.67 ± 12.8 months (approximately 13 years), with 5- and 10-year survival rates of 71.1% and 65.5%, respectively. Both inoperable and relapses within 3 years are independent factors in reducing the survival of patients with aggressive forms. Inoperability and the presence of metastases at the initial diagnosis are factors that can lead to recurrence [45].

The Ki-67 index may contribute to the classification of patients with SPTP to predict RFS and DSS. Ki-67 immunostaining should be done routinely in SPTP immunohistochemistry. A classification system based on distribution needs to be evaluated in order to identify patients at high risk in the future. Identification of a subset of patients at high risk of tumor recurrence may have some clinical implications. Tumor recurrence in these patients could be detected at an early stage with more intensive follow-up. Our study showed that recurrences/metastases and death in patients with a Ki-67 index >4% usually occurred within 2 years after surgery. Thus, such patients should be scheduled for follow-up visits every 1-2 months during the first and second years after surgery and

every 3-6 months for many years after surgery. Whether high-risk individuals should receive postoperative chemotherapy or chemoradiotherapy requires further study, as the role of adjuvant therapy for SPTP is unclear [46].

In conclusion, Ki-67 is a predictive factor for the clinical outcome of patients with SPTP. Although the World Health Organization classification includes well-defined histological criteria, there are a few unusual cases in which the diagnosis of malignant SPTP is extremely difficult to establish. The Ki-67 marker is considered as an additional support for SPTP histopathology to predict tumor recurrence. Improving relapse prognosis for patients with SPTP may change surveillance strategies, providing opportunities for effective adjuvant therapy for high-risk patients. Given the increase in SPTP reported in recent years and its malignant potential, it is important that criteria for predicting tumor recurrence and a consensus on the optimal follow-up strategy for high-risk patients be achieved.

Treatment

An effective treatment tactic is radical surgical treatment with free resection margins [47].

Adjuvant cancer therapy does not affect overall and recurrence-free survival. In most cases, this is possible due to the localized nature of SPTP growth. Local tumor infiltration or metastatic disease is not a contraindication for surgery since radical resection, including all metastatic tissue, may lead to long-term survival and cure. The overall 5-year survival rate is over 95.0% in large-scale reviews, and the recurrence rate is up to 6.6% [48].

Primary metastatic disease and recurrence are treated according to various oncological protocols, including 5-FU, S-1, gemcitabine, sunitinib, and transarterial embolization of liver metastases (TACE) [49]. However, the results are anecdotal, and the general consensus is that oncological treatment has a limited effect on SPTP, requiring aggressive surgical resection, including in cases with metastasis and progression.

The final

Knowledge of the clinical features and unique immunophenotype of SPTP allows differentiation to remove these tumors from other types of formations of this organ. The diagnostic panel should include, in addition to the already known markers (Ki-67), CD99 and claudin-3 (claudin-3). Proper diagnosis of SPTP is critical because these tumors have a favorable prognosis and patients are often young adults who require organ-sparing surgery and long-term follow-up rather than various neoadjuvant and adjuvant chemotherapy regimens. It should be remembered that, despite the rather favorable clinical course and slow growth of SPTP, they can eventually reach gigantic sizes and pose a threat to life when their radical removal is not possible.

Thus, SPTP is a rare neoplasm with malignant potential but a favorable prognosis. Radical surgery is associated with cure or long-term survival even in the event of metastasis. Recurrence after radical surgery is rare (5-6%) and should be treated surgically, since oncological treatment has a limited effect.

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Conflict of Interest

The review is part of the scientific research of M.N. Peshkov. The rest of the authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Contribution of the Authors

Peshkov M.N. - collection, analysis of literature data, writing an article. Reshetov I.V. - editing the article. All authors made a significant contribution to the research and preparation of the article, read and approved the final version of the article before publication.

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