

Original Article

Clinicopathological features of solid pseudopapillary tumor of the pancreas: a multicenter study with 3,584 cases

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Abstract: Purpose: Solid pseudopapillary tumor of the pancreas (SPTP) is a rare type of pancreatic tumor. However, the diagnosis is challenging in clinic. Thus, the purpose of the current study was to investigate the morphological, immunohistochemical and molecular characteristics of SPTP. Methods: All cases of SPTP were collected in the First Affiliated Hospital of Guangxi Medical University, China during January 2008 to November 2016. Furthermore, SPTP from other centers reported in literatures were gathered up to November 2016. The clinical manifestations, macroscopic and microscopic morphological features, changes in immunohistochemistry and serum molecular characteristics were summarized and analyzed. Results: Altogether, 33 cases of SPTP in house and 3,551 cases from other centers were achieved. Most of the tumors were cystic-solid which had capsules and clear boundaries. The solid region mainly consisted of round or oval epithelioid tumor cells and showed a pseudopapillary arrangement surrounding the fibrovascular axis. The immunohistochemical staining of vimentin, NSE, AAT, β -catenin, CD56, CD10 and PR showed positive expression in most of tumor cells. On the contrary, E-cadherin, EMA and S-100 showed negative expression. No significant abnormalities have been found in the serum tumor markers of SPTP. Furthermore, WNT pathway and ER processing pathway might participate in the development of SPTP. Conclusion: The characteristics of morphological and immunohistochemical examination may aid in the diagnosis of SPTP. However, the molecular mechanism of SPTP remains to be further explored.

Keywords: Solid pseudopapillary tumor of the pancreas (SPTP), pathology, morphology, immunohistochemistry

Introduction

Solid pseudopapillary tumor of the pancreas (SPTP) is a rare type of pancreatic tumor that accounts for approximately 1%-2% of pancreatic exocrine tumors, which mostly occur in the head of the pancreas and are more common in young and middle-aged women [1]. In 1959, Franz first reported this type of tumor and named it papillary tumor of the pancreas [2]. In 2004, it was termed solid pseudopapillary tumor by the tumor histological classification of the World Health Organization, and this name has been generally accepted worldwide. To date, the pathogenesis of SPTP is not fully understood; however, it is suspected to be associated with mutations or abnormal expression of the β -catenin gene [3]. The degree of malignancy of SPTP is low, and its metastasis is rare; even if metastasis occurs, the prognosis is still good [4]. Because the clinical manifesta-

tions and signs of SPTP are not obvious and its specificity is poor, it is often difficult to diagnose and treat SPTP, and misdiagnosis tends to occur. Currently, the most clinically effective treatment method is surgical resection [5]. During the process of clinical setting, correct pathological diagnosis is the most important part. However, the pathological diagnosis is still challenging. Thus, the purpose of the current study was to investigate the morphological, immunohistochemical and molecular characteristics of SPTP based on the cases in our hospital, also the cases from other centers reported in literatures.

Materials and methods

Clinical cases in house

All cases confirmed as SPTP by pathological examinations were collected in the First

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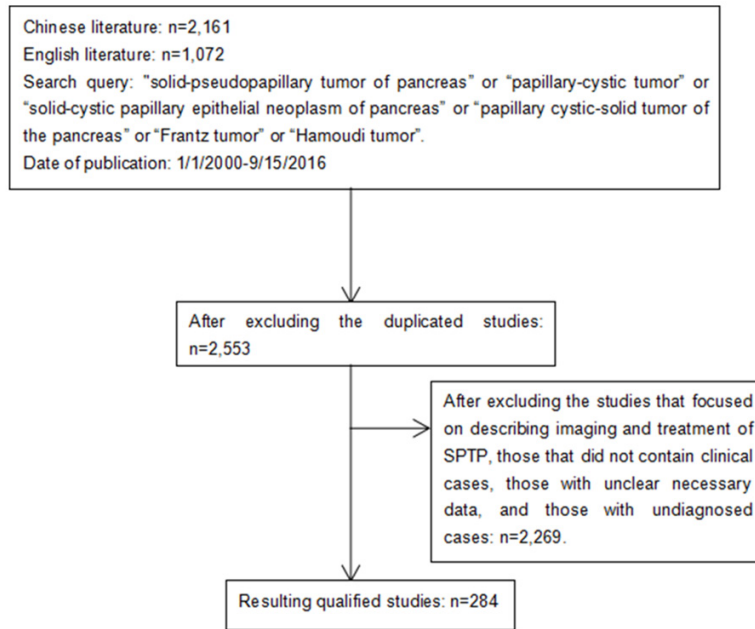


Figure 1. Flow chart of literature screening and selection. A total of 2161 Chinese studies and 1072 foreign studies were in the initial records. After removing duplicate studies, 2553 studies remained. Further scrutinizing excluded 2269 studies and 284 studies were finally included in our study.

Affiliated Hospital of Guangxi Medical University, the People's Republic of China during January 2008 to November 2016. The morphological features, the immunohistochemical and serum molecular characteristics were summarized.

Cases from other centers

Literature retrieval: An English and Chinese search query of "solid-pseudopapillary tumor of pancreas" or "papillary-cystic tumor" or "solid-cystic papillary epithelial neoplasm of pancreas" or "papillary cystic-solid tumor of the pancreas" or "Frantz tumor" or "Hamoudi tumor" were applied. The English databases PubMed, Wiley Online Library, Web of Science, Science Direct, Cochrane Central Register of Controlled Trials, Google Scholar, EMBASE, Ovid, and LILACS, as well as the Chinese databases CNKI, Chong Qing VIP, Wan Fang, and China Biology Medicine disc were searched up to November 30, 2016.

Inclusion criteria: The inclusion criteria were as follows: (1) studies with cases that had clinical records containing patient information regarding clinical manifestations, pathological characteristics, and results of immunohistochemis-

try and serum marker detection; (2) studies with cases that had been confirmed as SPTP by pathological examinations.

Exclusion criteria: The exclusion criteria consisted of the following: (1) studies that focused on describing imaging characteristics or treatment of SPTP; (2) studies in which cases had no clear diagnosis of SPTP; and (3) studies that had no clear description of clinical manifestations, pathological characteristics, results of immunohistochemistry or serum marker tests.

Comprehensive analysis of SPTP

The gender, age, and other information of the included patients were analyzed. The clinical manifestations, morphological features observed by macroscopy and microscopy, and changes in immunohistochemical and serum molecular characteristics of patients were summarized.

Results

The retrieval results and the basic information of the included cases

Altogether, 33 cases of SPTP in house and 3,551 cases from other centers were achieved. The literature retrieval process and results are shown in **Figure 1**. According to the above inclusion and exclusion criteria of literature selection, a total of 284 domestic and foreign studies were screened and selected. Among all the 3,584 cases of SPTP, 2,853 cases were Chinese and 731 cases were non-Chinese. Among these 3,584 patients, 449 were male, and 3,135 were female, with ages ranging from 8 months to 85 years and an average age of <40 years. Most patients showed no obvious or non-specific clinical symptoms, such as upper abdominal discomfort. Imaging studies revealed a pancreatic mass with clear lesion boundaries in most cases. A direct clinical diagnosis of SPTP was rarely provided.

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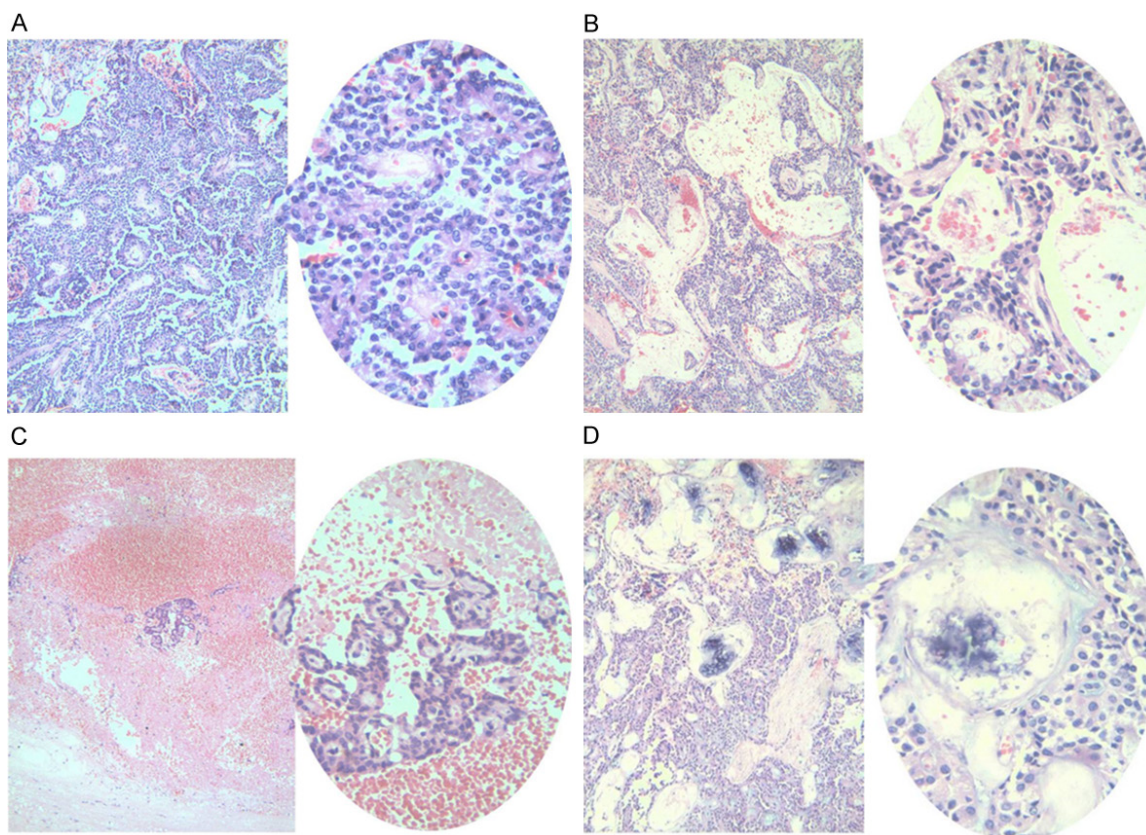


Figure 2. SPTP in microscopic ($\times 100$, $\times 400$). A: “Ependymoid-like” pseudo-papillary structure in a chrysanthemum shape and surrounding the fibrovascular axis, with a solid-sheet or nested arrangement; B: Lacunar structures of different sizes could be observed in the cystic region; C: Interstitial hemorrhage; D: Calcification.

Clinical characteristics

Of the 2,784 patients with clinical data, 1,211 had no obvious symptoms, but a painless abdominal mass was found on physical examination in all 1,211 cases; 1,302 patients experienced abdominal symptoms such as abdominal distension, abdominal pain, or abdominal discomfort; 159 patients had symptoms of nausea and vomiting; 45 patients complained of back discomfort or pain; 30 patients had obstructive jaundice; and 37 patients exhibited weight loss.

Site of the lesions

In 3000 cases, 1000 cases occurred in the head of the pancreas, 949 cases occurred in the body and tail of the pancreas, 527 cases occurred only in the pancreatic tail, 281 cases occurred in the pancreatic neck, 228 cases occurred only in the pancreatic body, and 15 cases occurred in the uncinate process of the

pancreas. In addition, 10 cases included SPTP at multiple sites (of these three cases occurred in which tumor almost invaded the whole pancreas), three cases occurred in the mesentery, 11 cases occurred in the retroperitoneal area, one case occurred in the right adrenal gland, and seven cases occurred in the peripancreatic tissues. However, the lesion sites of 559 cases were not provided.

Macroscopic observation

The tumors exhibited expansive growth. The appearance of most tumors was round with smooth surface, which were nodular in some cases. Most of the small tumors had a capsule and clear boundaries of the surrounding tissues. Some of the large tumors exhibited a fibrous pseudocapsule with no intact capsule, and invasion of the surrounding pancreatic tissues and (or) vessels could be found. Rarely, the formation of tumor thrombus was noted in several cases. The cut-surfaces of the tumors

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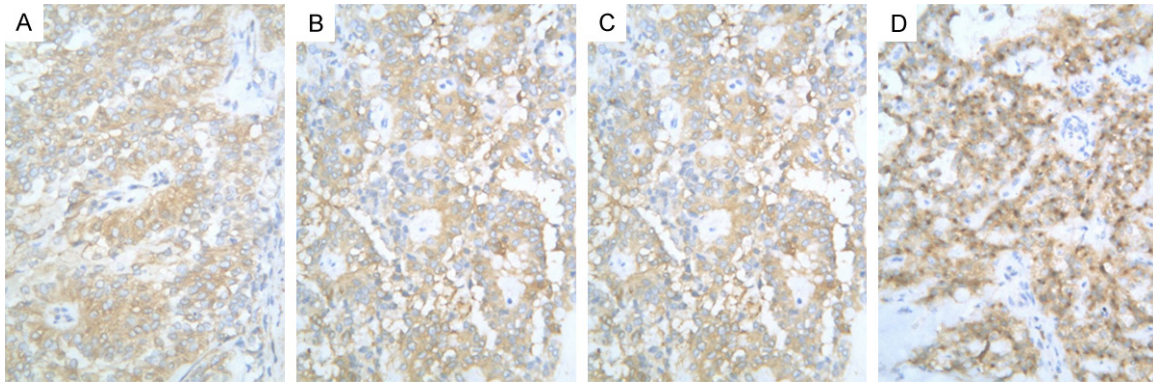


Figure 3. The positive rates for various antibodies in SPTP ($\times 400$). A: Vimentin (1052/1107); B: NSE (508/554); C: PR (482/673); D: CD10 (509/627).

were cystic or solid. Most of the small tumors were solid, and the large tumors were cystic. The solid area of the cut-surfaces was lobulated, gray, or gray-red and resembled fish meat. The cystic area resembled blood vessel lumen, commonly showing hemorrhage and necrosis, with yellow or dark brown turbid liquid. The cysts were often accompanied with soft cotton-like materials in the inner wall, with calcification in some cystic walls. Some tumors showed a high degree of cystic degeneration, with only a thin layer of residual tumor tissues in the cystic wall.

Microscopic observation

Microscopically, the tumor was composed of solid, cystic, and cystic-solid regions. The solid region mainly consisted of epithelioid tumor cells which were round, oval, or polygon shapes. The tumor cells showed no obvious atypia, with clear boundaries, rich cytoplasm, weak acidity and a transparent appearance in most cells. The cell nuclei were small and round or oval, which were located in the center of cells. Sometimes, fine chromatin and nuclear grooves could be found, as well as rare mitotic figures. Generally, the atypia of the tumor cells was slight. Most of tumor cells form a characteristic regular multilayered “ependymoid-like” pseudo-papillary structure in a chrysanthemum shape and surrounding the fibrovascular axis, with a solid-sheet or nested arrangement (**Figure 2A**). The tumor cells distal to the vascular axis exhibited retrograde degeneration. Lacunar structures of different sizes could be observed in the cystic region, with the mixed

cystic and solid structures in the junction area of the solid region and the cystic region (**Figure 2B**). Tumor stroma often displayed a high degree of edema or mucoid degeneration, with hyperplasia of some interstitial fibrous tissues, accompanied by hyaline degeneration, interstitial hemorrhage (**Figure 2C**), foamy macrophages, and localized calcification and cholesterol crystals in a small number of cases (**Figure 2D**). Large local coagulation necrosis surrounding connective tissues and containing hemosiderin and inflammatory granulation tissues was observed in some tumors. Obvious nerve invasion of the tumor was rare, and tumor cells were observed in individual vessels. Although all tumors had a capsule, a small number of tumors invaded the capsule or even broke through the capsule to invade the surrounding normal pancreatic tissues.

Immunohistochemistry

In the 3,584 SPTP tissue specimens, the positive rates for various antibodies were as follows: Vimentin (1052/1107) (**Figure 3A**), neuron specific endolase (NSE) (508/544) (**Figure 3B**), $\alpha 1$ -antitrypsin (AAT) (630/684), β -catenin (301/342), progesterone receptor (PR) (482/673) (**Figure 3C**), neural cell adhesion molecule (CD56) (458/555), and CD10 (509/627) (**Figure 3D**), $\alpha 1$ -antichymotrypsinase (AACT) (221/241), cyclinD1 (95/106), pan cytokeratin (AE1/AE3) (31/89), cytokeratin (CK) (163/519), chromogranin A (CgA) (215/873), synaptophysin (Syn) (39/776), S-100 (18/150), epithelial membrane antigen (EMA) (3/224), E-cadherin (6/159), estrogen receptor (ER) (28/272).

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The characteristics of peripheral blood markers for SPTP

Altogether, blood markers examination was performed for 1,092 cases. Of these 1,092 patients, no significant abnormalities of the tumor markers of carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), CA125, CA242, alpha-fetoprotein (AFP), CA724, and NSE were detected in the serum of 1023 patients. Serum CA19-9 levels were increased in 36 cases, AFP was slightly increased in six cases, CEA was increased in six cases, CA125 was increased in 15 cases, CA724 was increased in four cases, and NSE was increased in two cases.

Discussion

SPTP is a rare pancreatic tumor that accounts for only approximately 1% of all primary pancreatic tumors. However, studies have shown that the incidence rate of SPTP has been increasing [6]. A survey showed that this disease mostly occurs in young and middle-aged women, with a male to female ratio of 1:10 and a cure rate of 95% [7]. In the present study, the male to female ratio was 1:7, and the average onset age of males was higher than that of females.

The clinical symptoms of SPTP are not very specific and include abdominal discomfort such as abdominal distension and abdominal pain in 45.5% of patients. No clinical symptoms were found in 42% of the patients, and SPTP was usually found in physical examinations. In a small number of cases, the symptoms of nausea, vomiting, back discomfort, and pain were reported. Therefore, the diagnosis of SPTP cannot be based on its clinical symptoms. In addition, approximately 1% of patients exhibited jaundice, with a clinical diagnosis of obstructive jaundice, which may be due to the compression of the tissues near the hepatic portal by the tumor resulting in cholestasis. Additionally, in patients with jaundice, the jaundice gradually disappeared after the surgical resection of the tumor, thus confirming the explanation of tumor-induced cholestasis.

SPTP may occur in any part of the pancreas. In the present study, it was most commonly found in the pancreatic head, followed by the pancreatic body and tail, and the lowest incidence was found in the uncinate process of the pancreas.

Some studies have reported that SPTP was most commonly found in the pancreatic body and tail [8]. In some individual cases, SPTP could occur in the tissues adjacent to the pancreas, such as the retroperitoneal area and the right adrenal gland, which were presumably derived from the ectopic pancreas. The appearance of most tumors was round with smooth surface and had a capsule and clear boundaries of the surrounding tissues. The solid area of the cut-surface was lobulated, gray, or gray-red and resembled fish meat. The cystic area resembled blood vessel lumen, commonly showing hemorrhage and necrosis, with yellow or dark brown liquid, with calcification in some cystic walls.

A pathological diagnosis is the most reliable method of SPTP diagnosis. The typical histological characteristics mainly included solid nests with abundant cells and rich blood vessels. The tumor cells distal to blood vessels exhibited degeneration, and the tumor cells around blood vessels showed a pseudopapillary arrangement surrounding the small blood vessels. The tumor tissues exhibited no gland-like morphology, but the cells were often signet ring-like. The nuclei were usually consistent, eosinophilic, small, and round with eosinophilic transparent vesicles in the cytoplasm of typical tumor cells. The interstitial cells often showed varying degrees of hyaline or mucoid degeneration, with cholesterol precipitation and foamy cells [9]. When the gross and microscopic characteristics were different from other tumors, it will be relatively easy to make the morphological diagnosis. However, in some atypical cases, immunohistochemistry is needed to assist the pathology diagnosis.

The immunohistochemistry results of SPTP indicated that almost all cells expressed diffuse vimentin, with rare expression in pancreatic neuroendocrine tumors or acinar cell carcinoma. AAT and AACT were also positively expressed in the SPTP cells, while pancreatic ductal adenocarcinoma, acinar cell carcinoma, and pancreatic neuroendocrine tumors could also express AAT and AACT. NSE, CgA, and Syn were positively expressed in only a small number of cases, and most of these were focally positive, indicating that only a portion of SPTP cells are neuroendocrine cells; therefore, SPTP is not a neuroendocrine tumor. CD56 was posi-

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tively expressed in almost all SPTP cells, especially in the cell membrane. E-cadherin and EMA were negative in almost all cases. CD10 and β -catenin were positive in almost all cases. In most cases, the immunohistochemical signaling of PR was diffuse with positive expression, and ER expression was negative. Expression of cyclin D, AE1/AE3, CK, and S-100 was positive in some cases. In all cases, the expression of ki-67 was low, with a positivity rate of 1%-5%. Although many types of molecular markers are present in SPTPs, no antibody with specificity had been found. Therefore, many researchers have combined CD99, E-cadherin, β -catenin, and CD10 for the pathological and differential diagnosis of STPT, which has shown a relatively high specificity [10].

Regarding the detection of serum tumor markers, the vast majority of patients showed no significant abnormalities for the tumor markers CA19-9, CEA, CA125, CA242, or AFP. Only a small number of patients had a slightly increased CA19-9 level, and only few cases demonstrated increased levels of other molecules. However, there was no significant value for SPTP diagnosis.

SPTP is not sensitive to radiotherapy and chemotherapy, and surgical resection is the only effective treatment. The postoperative cure and survival rates are very high, and the prognosis is good [11]. In this study, only a small number of patients showed localized metastasis, and their disease-free survival was high after active surgical treatment. Few patients with highly malignant tumors died due to metastatic tumors.

In the past few years, the mechanism of SPTP has been explored by several research groups. Considerable attention has been attracted on β -catenin and E-cadherin in WNT signal pathway. E-cadherin is a type of trans-membrane glycoprotein that mediates cell adhesion in calcium dependent way. β -catenin binds to the cytoplasmic domain of E-cadherin and is also connected with cytoskeleton system via α -catenin [12]. The adjacent epithelial cells form tight adhesion via the extracellular region of E-cadherin and β -catenin is the molecule that plays key role in the entire complex function [13]. Abraham et al. had researched on 20 cases of SPTP patients, and it was found that the occurrence of SPTP was closely related to

mutations in exon 3 of the β -catenin oncogene which subsequently resulted in abnormal WNT signaling pathway [14]. In most of the immunohistochemical results of SPPT cells, β -catenin presented positive staining in nucleus or cytoplasm while E-cadherin showed negative staining. Therefore, it is presumed that the aberrant β -catenin protein expression in nucleus might contribute to the contractual damage and deactivation of E-cadherin. Tang et al. also proposed that the pseudopapillary pattern of SPTP could be accounted for by the disruption of intercellular adhesion induced by loss of E-cadherin expression due to the nuclear localization of β -catenin [15].

In addition, SPTP mainly occur in adolescence and young women, obviously to a certain gender and age, which may be related to factor of genetic and sex hormones. It has been reported that PR positivity, but ER negativity was predominantly related to SPTP, which suggests that sex hormone may be associated with the occurrence and development of SPTP [16, 17]. Furthermore, part of SPTP also showed the change of the adenomatous polyposis coli (APC) gene, and this change has not been found on pancreatic ductal adenocarcinoma [18].

In conclusion, the early diagnosis and treatment of SPTP is still challenging. The comprehensive application of imaging, pathological morphology, and immunohistochemical methods combined with the medical history and clinical symptoms is of great significance for the diagnosis of SPTP and can provide guidance for further treatment, thereby improving the cure rate.

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Disclosure of conflict of interest

None.

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