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Original Article

Solid pseudopaillary neoplasm of the pancreas: analysis of clinicopathological and immunohistochemical features in 10 cases

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Abstract: Objective: The aim of this study was to investigate the clinicopathological features and immunomarkers of Solid Pseudopapillary Neoplasm of the Pancreas (SPN) and to find the best possible immunomarker combination that can accurately diagnose it. Methods: We retrospectively analyzed 10 patients who underwent surgery for pathologically confirmed SPN from August 2013 to August 2017. Follow-up of the patients was between 9 and 57 months. Results: Clinical symptoms and imaging were atypical. In general, the mass was encapsulated and clearly defined by the surrounding tissues. Cut surface was dusty-red and associated with hemorrhage. The neoplastic cell cytoplasm was eosinophilic or clear, and the nuclei were round or oval, presenting typical features of pseudopapillary distribution around a fibrovascular core. Immunohistochemical results showed that tumor cells were consistently positive for vimentin, CD56, CD10, PR, CD99, β-catenin and negative for E-cadherin (100%) and chromogranin. CD99 presented a unique dot-like staining pattern in tumor cells. Conclusions: In view of the atypical clinical manifestations and imaging features of SPN, accurate diagnosis mainly relies on the histomorphology and immunomarker combination including PR, CD99, β-catenin, and E-cadherin, which might be useful method in the diagnosis of SPN.

Keywords: Solid pseudopaillary neoplasm, pancreas, clinicopathology, immunohistochemistry, CD99

Introduction

The Solid Pseudopapillary Neoplasm of the pancreas (SPN) is a rare, low-grade tumor with good prognosis, typically afflicting young women aged 20-30 years. It accounts for 1-3% of all pancreatic tumors [1], which was firstly reported by Frantz [2] in 1959. The WHO classification named it as Solid Pseudopapillary Tumors (SPTs) in 1996 and Solid Pseudopapillary Neoplasm of the Pancreas (SPN) in 2010 [3]. SPN is rare tumor with atypical clinical manifestations and imaging features. Its accurate diagnosis still requires pathological examination. This study aims to explore pathological morphology and immunohistochemical features of SPN in order to improve the understanding of the tumor.

Materials and methods

A retrospective analysis was performed for 10 patients diagnosed in Anyang Tumor Hospital (Henan Province, China) from August 2013 to August 2017. Clinical and pathological data were collected. We conducted a retrospective descriptive analysis, including the following variables: sex, age, site of the lesion, clinical presentation, imaging features, diameter, morphological and immunohistochemical characteristics and follow-up. All tumors were resected, fixed in 10% fomalin, and then embedded in paraffin. Immunohistochemical analysis of tumor tissue was performed according to standard protocols. The following antibodies were used: Vimentin (Dako Denmark, prediluted), CD10 (Dako Denmark, prediluted), CD56 (Dako Denmark, prediluted), PR (Dako Denmark, prediluted), CD99 (Dako Denmark, prediluted), β-catenin (Dako Denmark, prediluted), E-cadherin (Dako Denmark, prediluted), Chromogranin (Dako Denmark, prediluted) and Ki67 (Dako Denmark, prediluted). All negative and positive controls were included. The specific part of the tumor cells were stained as brown and yellow, which was considered as positive expression.

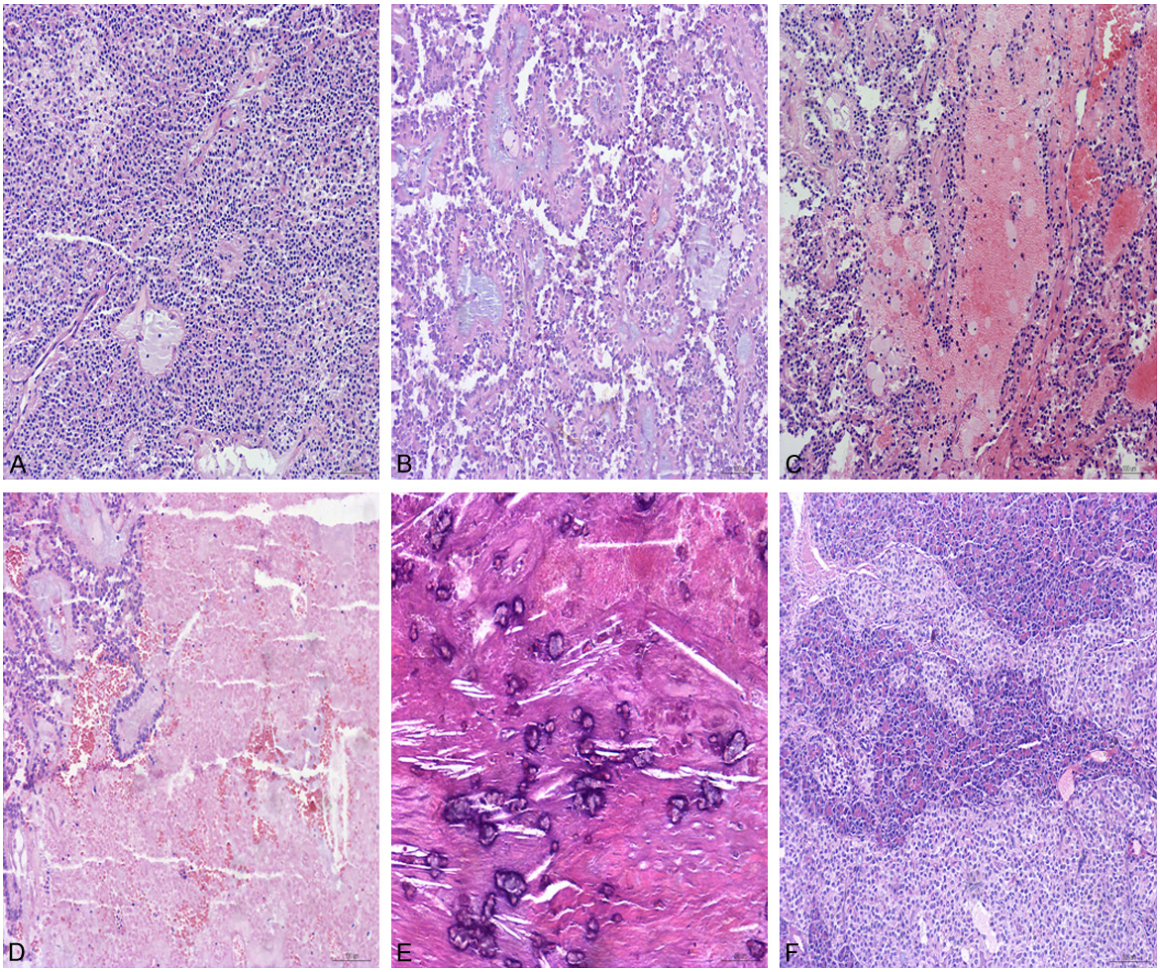

Figure 1. Histological Morphology of SPN (H&E × 100). A. The tumor cytoplasm is abundant, eosinophilic or bright. B. Pseudopapillary structures and the mucinous degeneration of fibrovascular cores. C. Cystic area with hemorrhage. D. Necrotic area. E. Calcification and cholesterol clefts. F. Tumor invasion of pancreatic parenchyma.

CD10, CD56 and E-cadherin were stained on cell membrane. Vimentin, CD99 and Chromogranin were stained in the cytoplasm. PR, β-catenin and Ki67 were stained in the nucleus. The results of immunohistochemistry were analyzed by two pathologists (Dr. Lanfang Miao and Ruixue Lei).

Results

Clinical features

Among the 10 patients, there were 8 females with average age of 28.9 years (ranged from 15 to 49 years), and 2 males with average age of 45 years (ranged from 44 to 46 years). The ratio of male to female is 1:4. Tumors were located in the head and neck of the pancreas in 2 patients (20%), and the body and tail in 8 patients (80%). Among clinical symptoms, 3 patients were accompanied with abdominal pain (30%), 3 cases were with palpable abdomen mass (30%), and 4 cases with absence of symptoms by physical examination (40%).

Imaging features

CT examination indicated that quasi-circular low-density solid cysts with clear boundary presented in 10 patients. The enhanced CT showed the area was uneven or mildly fortified and 3 cases were found with sporadic calcification. MRI examination showed neoplasm was found quasi-circular with clear boundary and uneven signal in 3 cases. Imaging diagnosis showed that there were 4 cases with SPN (40%), 3 cases with cystadenoma, 1 case with cystadenocarcinoma, 1 case with gastrointestinal stromal tumor, and 1 case with sarcoma.

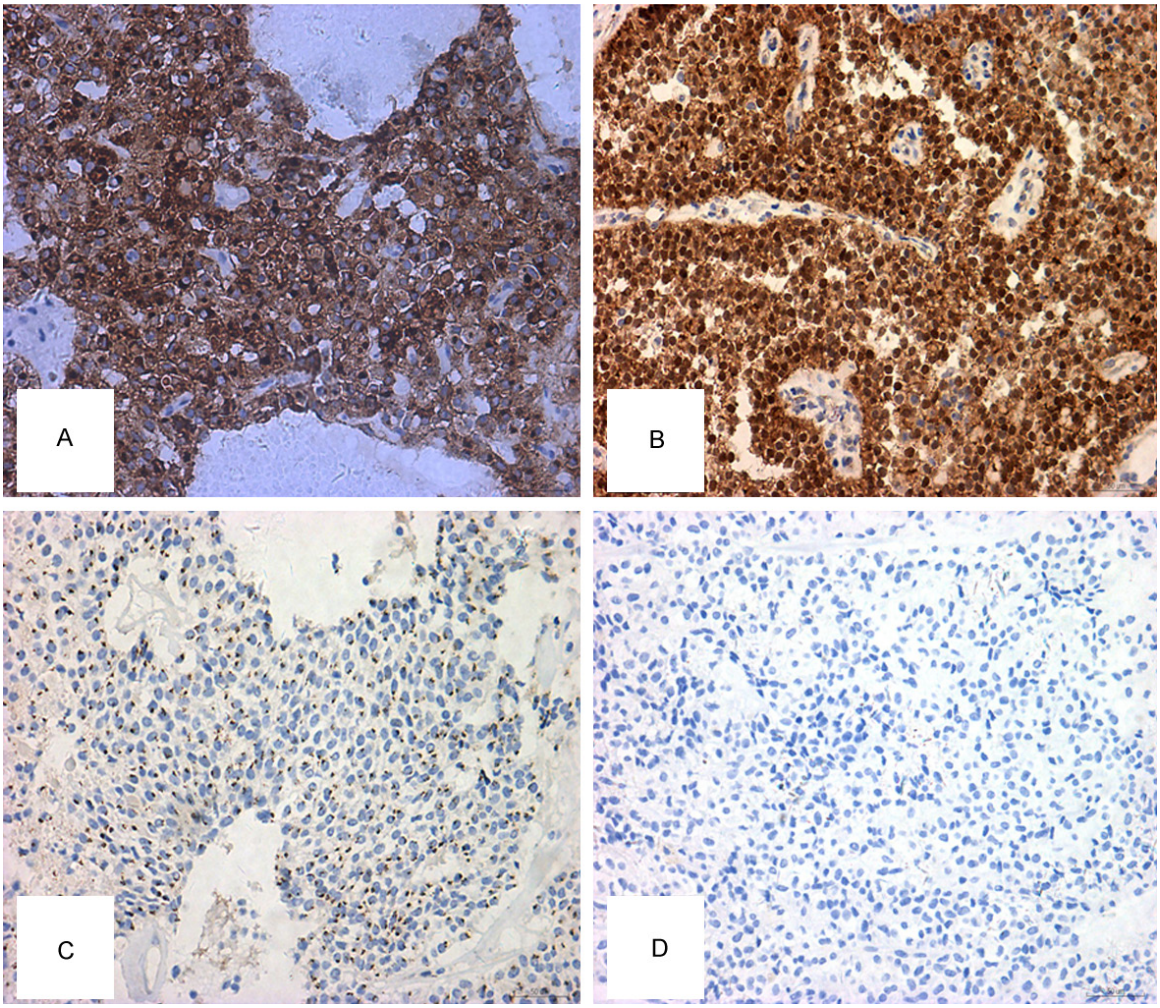

Figure 2. The immunophenotype of SPN (IHC with SP method × 200). A. Positive expression of CD10 in the cytoplasm. B. Positive expression of β-catenin in the nuclei. C. Dot-like positive expression of CD99 around the nuclei. D. Absence of expression of E-cadherin.

Pathological features

The general examination indicated that 6 cases were with solid-cystic masses (60%), which was dusty-red with hemorrhage and necrosis. 3 cases were with solid masses (30%), which were pale, dusty-red and crisp. 1 case was with cystic mass (10%), and section was multilocular. The masses were completely enveloped in 7 patients (70%), and partially enveloped in 3 cases (30%), which were closely related to the pancreas. The average tumor diameter was 7.95 cm (mean 3.5-13.0 cm).

Microscopically, the tumor cells were monomorphic, the nuclei were in the middle of the cells presenting round or oval, and surrounded by abundant acidophilus or transparent cytoplasm. The cells were morphologically mild with rare mitotic figures. The tumor cells were arranged radially around the fibrovascular axis, forming pseudopapillary structures (**Figure 1A**). Hyaline degeneration or mucous degeneration presented in the axis of the fibrovascular (7 cases, 70%) (**Figure 1B**). The tumor cells were discrete away from the center of fibrovascular axis and the cytoplasm of discrete tumor cells were transparent, showing histocytes (6 cases, 60%) (**Figure 1A**), bleeding (7 cases, 70%) (**Figure 1C**), necrosis (4 cases, 40%) (**Figure 1D**), calcification (3 case, 30%), cholesterol crystals (6 cases, 60%) (**Figure 1E**), acidophilic corpuscle (2 cases, 20%), and multinucleated cells (1 case, 10%) were manifested in tumor tissues. 3 cases of the pancreas involvement (30%) (**Figure 1F**), and 1 case of nerve invasion (10%).

Immunophenotype

In terms of immunohistochemistry, vimentin, CD56, CD10 (**Figure 2A**), PR, CD99, and β-catenin (**Figure 2B**) were expressed in all 10 cases. It is worth mentioning that CD99 presented a unique dot-like staining pattern in tumor cells (**Figure 2C**). E-cadherin (**Figure 2D**) and chromogranin were negative in 10 cases, and Ki67 index was minimally expressed (< 5%).

Follow-up

10 cases were successfully followed up and follow-up time ranged from 9 to 57 months. No recurrence was observed in all the cases.

Discussion

Clinical features

SPN mostly afflicts young women aged from 20 to 30 years old, and the ratio of male to female is 1:5.8-1:10 [4, 5], which was 1:4 in our study. Studies have shown that male patients were older than female [6]. There were 8 female patients, aged 15-49 years old, with the average age of 28.9 years, and 2 males aged 44-46 years old, with the average age of 45 years, which is similar to that described in the literature. About 6-8% of cases occurred in children [7], and there was one case in our study (10%, 15 years old). The clinical features, comprising of abdominal pain, abdominal distention, diarrhea, nausea, vomiting, and abdominal mass are generally nonspecific. Among them, abdominal pain and mass are the most common [8-13]. In our study, 3 patients had abdominal pain, 3 cases had palpable abdomen mass, and 4 cases had no symptoms and diagnosis in physical examination. SPN mostly occurs in the tail of pancreas, followed by the head and neck [4]. In this study, 8 patients were located in the pancreatic body and tail, and 2 patients in the pancreatic head and neck, similar to that described in the literature. The previous study revealed that tumors also occurred in the uterus, omentum, peritoneum, liver, mesocolon and retroperitoneum [14-20]. The average diameter of the tumors were 4.9-9.5 cm [21, 22]. In our study, the diameters of the tumors were 3.5-13.0 cm with an average diameter of 7.95 cm, which were consistent with the literature.

Imaging characteristics

It is difficult to distinguish SPN from other cystic or solid tumor of the pancreas due to the limitations of imaging examination [23], which further lead to the inaccurate diagnosis in 80-90% of cases [24]. In this group, 4 cases (40%) were diagnosed as SPN and the accuracy was higher than previous reports.

General characteristics

The mass was enveloped and clearly defined by the surrounding tissues. Consistent with the literature [8, 11, 22], the section was solid-cystic, the solid area is gray-white and brittle, and the cystic area is gray-red, sponge-like, with hemorrhage and necrosis.

Histologic characteristics

The tumor cells were monomorphic, with round or oval nuclei and abundant acidophilus or transparent cytoplasm in the middle of the cells. The cells were morphologically mild and the mitotic figures were rarely found. The cells were surrounded by fibrovascular cores, radiating out and forming pseudopapillary structure. Hyaline or mucous degeneration can be seen in the fibrovascular cores. We also noticed that the tumor cells away from the blood vessels center were discrete and the cytoplasm of discrete tumor cells were transparent, showing froth histiocytes, which is consistent with report by Ud Din [22]. Such degenerative changes as hemorrhage, necrosis, calcification, cholesterol crystals and acidophilic corpuscle, multinucleated cells were manifested in tumor tissues [25, 26]. The indications of malignant SPN include: invasion of external pancreas, distant metastasis, invasion of pancreatic substance and vascular nerves [7, 23], the latter of which were found in our study. 3 cases of the pancreas involvement and 1 case of nerves invasion.

The pathogenesis and immunophenotype

Currently, the origin and pathogenesis of SPN remain unclear. In view of the high correlation and significant gender differences in cancer incidence between tumor and ovarian cells in the immune phenotype, it was speculated that SPN may originate from the genital ridge-ovary primordium cells, existing in the process of embryogenesis [27]. The immunophenotype

showed pleomorphism, including pancreas exocrine indexes (vimentin, α1-AT, α1-ACT), pancreas endocrine indexes (NSE, SYN), and partially broad-spectrum epithelial markers, which suggested that SPN might be derived from the development of pancreatic embryo [28].

In terms of molecular pathology, the mutation of somatic cells in the third expression region of CTNNB1 genes encoding β-catenin in SPN led to difficult degradation of β-catenin protein escaping from phosphorylation in the cytoplasm. The β-catenin-Tcf/Lef complex, that is, β-catenin combined with T cell factor (Tcf), lymphatic enhance factor (Lef) was abnormally transported to the nuclei, which induced the positive expression of β-catenin in nuclei. The β-catenin-Tcf/Lef complex activated the transcription of oncogenes such as myc, and cyclinD1, which further activated the signaling pathway of Wnt/β-catenin. Activation often leads to proliferation in other tumors, while the expression of P21 and P27 may block the pathway of SPN, which result in low activity proliferation [2]. As important components of Wnt signaling pathway, E-cadherin and β-catenin participate in differentiation and growth of cells [29]. E-cadherin is a transmembrane protein, closely related to catenin, that plays an important role in cell adhesion, and the absence of membrane expression of E-cadherin explains the dyscohesive nature and cystic change of these cells [30]. CD99, the gene product of MIC2, is a 32 kDa transmembrane glycoprotein formed by glycosylation of 30 kDa precursor molecules [36]. Functioning as an adhesion molecule or a signal transduction molecule, CD99 was found to be critical for the regulation of apoptosis [36]. CD99 was expressed in lymphocytes, thymic cortex cells, ovarian granulosa cells, islet cells, Sertoli cells are also expressed in Ewing's sarcoma, primitive neural ectodermal tumor, and lymphoblastic lymphoma located in the cell membrane. Recent studies have found that CD99 was not located in the cell membrane, while positively expressed around the nuclei in SPN as dot-like pattern [37, 38], which was clearly observed in this study. The unique expression pattern of CD99, positive expression of β-catenin in the nuclei and loss of membrane expression of E-cadherin can be a reliable immunohistochemical approach to the diagnosis of SPN [37].

Differential diagnosis

There are many similarities between SPN and neuroendocrine tumors. In addition to the special tissue morphology of SPN, immunohistochemistry can help. Most studies hold that neuroendocrine indicators such as chromogranin and synaptophysin are not expressed in SPN [33, 34], which distinguishes SPN from pancreatic neuroendocrine tumor. In this study, chromogranin was not expressed, SYN and NSE were expressed in different degrees. Further identification is needed in combination with other immunohistochemical markers, such as CD99, E-cadherin, and β-catenin. The positive expression of β-catenin and vimentin in the tumor were able to distinguish SPN from pancreatic ductal adenocarcinoma, acinar cell carcinoma, and pancreatoblastoma.

Treatment and prognosis

Surgical resection is the only effective method for SPN, which is not sensitive to radiotherapy or chemotherapy [39, 11]. 95% patients can survive a long time with good prognosis after complete tumor removal [39], even if they relapse or metastasize [3]. 10 patients were performed with surgical treatment, 5 cases of which were carried out with the removal of pancreatic body and tail, 2 cases with removal of tumor and a small amount of pancreas, 2 cases of tumor removal and pancreas to jejunum anastomosis, 1 case of partial pancreas removal and pancreas to stomach anastomosis. Patients in this group including 3 cases with pancreatic parenchymal and neuro-aggression were followed up 9-57 months, none of which had any recurrence or metastasis.

Conclusion

SPN is a low-grade malignancy, mostly afflicting young women, with ICDO code: 8542/3. In view of the limitations of imaging diagnosis in CT and MRI, the final diagnosis also requires pathological examination. The tumors are generally encapsulated by a cystic mass, forming morphologically typical pseudopapillary structures, with immunohistochemical specific expression. Surgery is a preferred treatment with good prognosis.

Disclosure of conflict of interest

None.

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