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ORIGINAL ARTICLE

Retrospective analysis of clinicopathological features of solid pseudopapillary neoplasm of the pancreas

Nesrin Ugras [a,*], Ömer Yerci [a], Sinem Kantarcıoğlu Coşkun [a], Gökhan Ocakoğlu [b], Pınar Sarkut [c], Halit Ziya Dündar [c]

[a] *Department of Surgical Pathology, Uludag University Medical Faculty, Bursa, Turkey*
[b] *Department of Biostatistics, Uludag University Medical Faculty, Bursa, Turkey*
[c] *Department of General Surgery, Uludag University Medical Faculty, Bursa, Turkey*

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Abstract Solid pseudopapillary neoplasm (SPN) of the pancreas is a rare neoplasm that accounts for 2–3% of all primary pancreatic neoplasms. This study aimed to characterize clinicopathological features associated with SPNs and to retrospectively evaluate the relationship of these features with predictive parameters associated with aggressive behavior. We reviewed 16 cases of SPN of the pancreas that had been diagnosed between 2005 and 2014 at our pathology department. A total of 16 cases, 15 female and one male, were evaluated in this study. The patient age ranged from 13 years to 63 years with a median of 35.70 years. The mean tumor diameter ranged from 2 cm to 18 cm with a mean diameter of 5.90 cm. We identified a significant association between the presence of clear cells and perineural invasion ($p = 0.019$), which was considered to be a predictive factor for aggressive behavior. Other features (i.e., localization, nuclear grooves, central hyalinization, myxoid stroma, eosinophilic bodies, foamy histiocyte aggregates, multinucleated cells, and calcification) were not significantly associated with predictive factors for aggressive behavior. One patient died as a result of a pancreatic fistula that developed as a postoperative complication. The remaining 15 patients are alive and have not demonstrated any signs of recurrence or metastasis. The current study suggested that the presence of clear cells might serve as a possible prognostic indicator of perineural invasion, which is a predictive parameter associated with aggressive behavior in SPN.

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Pathology, Uludag University School of Medicine, Gorukle, Bursa 16059, Turkey.
E-mail address: nesrin_ugras@yahoo.com (N. Ugras).

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Introduction

Solid pseudopapillary neoplasm (SPN) of the pancreas is a type of pancreatic neoplasm with low malignant potential, and it represents 0.17—2.70% of all cases of pancreatic tumors [1]. This tumor type was first reported by Frantz [2] and was initially referred to by multiple names, including solid papillary cystic tumor, cystic epithelial neoplasm, and papillary cystic tumor, until the World Health Organization (WHO) designated and reclassified them as SPNs in 2010 [3]. The nature and clinical behavior of these tumors remains elusive. Pancreatic SPN is primarily observed in women and has a peak incidence in patients aged 20—40 years [4]. Most patients are asymptomatic and present incidentally with an abdominal mass that is detected by radiological imaging, and they exhibit levels of tumor markers within normal limits. WHO reported that perineural invasion, pancreatic paranchymal invasion, or lymphovascular invasion do not remark increased malignant behavior, but predictive factors for aggressive behavior [3]. SPN metastasis is rare, and in a recent study, some clinicopathological factors, such as male gender, younger age, large tumor size (>5 cm), and elevated mitotic rate are suggested to result in increased malignant behavior [5—7]. The main objectives of this study were to characterize clinicopathological features associated with SPNs and to retrospectively evaluate the relationship of these features with predictive parameters associated with aggressive behavior.

Materials and methods

We reviewed the cases of 16 patients diagnosed with SPN of the pancreas between the years 2005 and 2014 at our pathology department (Bursa, Turkey). Two pathologists reviewed and evaluated all the slides using light microscopy. Information regarding histological and pathological features, such as tumor size, presence of calcification, central hyalinization, multinucleated cells, histiocytes, nuclear grooves, clear cells, eosinophilic body, necrosis, myxoid stroma, mitotic activity, presence of perineural, lymphovascular, pancreatic parenchymal invasion, lymph node involvement, and metastasis were collected.

Immunohistochemical study

Furthermore, for differential diagnosis (i.e., pancreatic neuroendocrine neoplasms, adenocarcinoma, acinar cell carcinoma) immunohistochemical study was performed. Immunohistochemistry was carried out for a panel of markers, including progesterone receptor (PR), CD10, CD56, synaptophysin, CD57, chromogranin, epithelial membrane antigen (EMA), cytokeratin AE1/AE3, and Ki67 on a Leica Bond Max automated slide stainer system (Leica, Bannockburn, IL, USA). The primary antibodies used were NCL-L-PGR-312 (Novocastra, Newcastle, UK; 1:150 dilution) against PR, NCL-L-CD10-270 (Novocastra; 1:80 dilution) against CD10, NCL-L-CD56-1B6 (Novocastra; 1:100 dilution) against CD56, NCL-L-SYNAP-299 (Novocastra; 1:200) against synaptophysin, Clone-NK1 (Lab Vision, Fremont, CA, USA; 1:100) against CD57, NCL-L-CHROM-430 (Novocastra; pre-diluted) against chromogranin, NCL-L-EMA (Novocastra; 1:400) against EMA, NCL-L-AE1/AE3 (Novocastra; 1:200) against cytokeratin, and Clone SP6 (Lab Vision; 1:250) against Ki-67.

Statistical analysis

Variables were expressed as the median (minimum—maximum) or frequency. Between group comparisons were performed using Fisher's exact test. SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and $\alpha = 0.05$ was considered statistically significant.

Results

Clinical data

We evaluated a total of 16 patients, 15 female and one male, who were diagnosed with SPN of the pancreas at our pathology department. The patient age ranged from 13 years to 63 years, with a median of 35.70 years. The most frequently observed age range was 20—40 years. Nine patients were asymptomatic, and seven patients presented with symptoms of abdominal pain or vomiting. Four patients had a medical history of diabetes mellitus and hypertension. The tumors were located in the body or tail of the pancreas in 10 patients (62.50%) and in the head of the pancreas in six patients (37.50%). Serum tumor markers, such as carbohydrate antigen 19.9, carcinoembryonic antigen, and α-fetoprotein, were assayed. One patient with a tumor located in the head exhibited elevated levels of carbohydrate antigen 19-9 (73 U/mL; normal range $\leq$ 37 U/mL). A preoperative diagnosis of SPN was made in four patients (28.60%) based on the characteristic features revealed by radiological imaging. Surgical procedures included partial pancreatectomy in seven patients, distal pancreatectomy in six patients, and pancreaticoduodenectomy (Whipple procedure) in three patients. Abdominal ultrasonography computed tomography was used to evaluate patients during routine follow-up visits. The patients were followed for a median of 28 months (range 10—72 months). One patient died as a result of a pancreatic fistula that arose as a postoperative complication. The other 15 patients are living and have not demonstrated signs of recurrence or metastasis.

Pathological features

On a gross level, all of the tumors evaluated in this study were encapsulated and well demarcated from adjacent pancreas tissue. The mean diameter of the tumors was 5.9 cm, ranging from 2 cm to 18 cm. A tumor diameter $>$ 5 cm was observed in seven (43.70%) cases, and tumors $<$ 5 cm were observed in nine cases (56.30%).The cut surfaces of the tumors exhibited a reddish-white, spongy appearance and demonstrated signs of hemorrhaging.

Most tumors were composed of solid, cystic, and pseudopapillary components. The nuclei of all tumor cells were uniformly round and characteristic nuclear grooves were

observed in seven cases (43.80%). The cytoplasm was predominantly eosinophilic, but cells with a clear cytoplasm were observed in seven cases (43.80%). Mitotic activity was minimal (≤2/10 high-power fields). We observed various features associated with degenerative changes, including central hyalinization (4, 25%), myxoid stroma (5, 31.30%), eosinophilic bodies (11, 68.80%), aggregates of foamy histiocytes (6, 37.50%), multinucleated cells (6, 37.50%), and calcification (4, 25%) (Figure 1).

In some cases, tumor cells exhibited signs that have been linked to aggressive behavior [3]. Four cases (25%) presented with perineural invasion. A tumor diameter > 5 cm was observed in seven (43.70%) cases. Pancreatic parenchymal invasion was noted in 50% of the cases. Lymphovascular invasion, lymph node involvement, and metastasis were not observed.

We next examined the relationship between pathological features and predictive factors for aggressive behavior and identified a significant association between the presence of clear cells and perineural invasion (Figure 1; $p = 0.019$). Also, we found that there was a significant relationship between central hyalinization and the presence of perineural invasion. The other pathological features evaluated (i.e., localization, nuclear grooves, myxoid stroma, eosinophilic bodies, foamy histiocytes aggregates, multinucleated cells, and calcification) were not significantly associated with predictive indicators of aggressive behavior (Tables 1–3).

Immunohistochemical findings

The neoplastic cells in all cases were nuclear positive for PR localization in the nucleus and diffusely positive for CD10 and CD56. Six cases (37%) exhibited focal synaptophysin staining and CD57. Only two cases (12%) exhibited focal chromogranin staining. Focal positive staining for epithelial membrane antigen and cytokeratin AE1/AE3 was observed in 37% and 50% of cases, respectively. The Ki67 proliferative index ranged from 0% to 2%. Parameters of aggressive behavior (i.e., perineural invasion, large tumor size, and pancreatic parenchymal invasion) did not show any significant association with all immunohistochemical markers (Figure 2).

Discussion

SPN of the pancreas is a rare neoplasm that accounts for 2–3% of all primary pancreatic neoplasms. This disease predominantly affects young women, and it presents with nonspecific symptoms such as abdominal pain, distension, nausea, and vomiting [5,8]. The vast majority of cases in this study were female (male: female ratio 1:15).

In the current study, SPN was most frequently observed in the body or tail of the pancreas (62.50%). Previous studies have reported that 19.50–73.30% of the tumors evaluated were located in the body or tail of the pancreas,

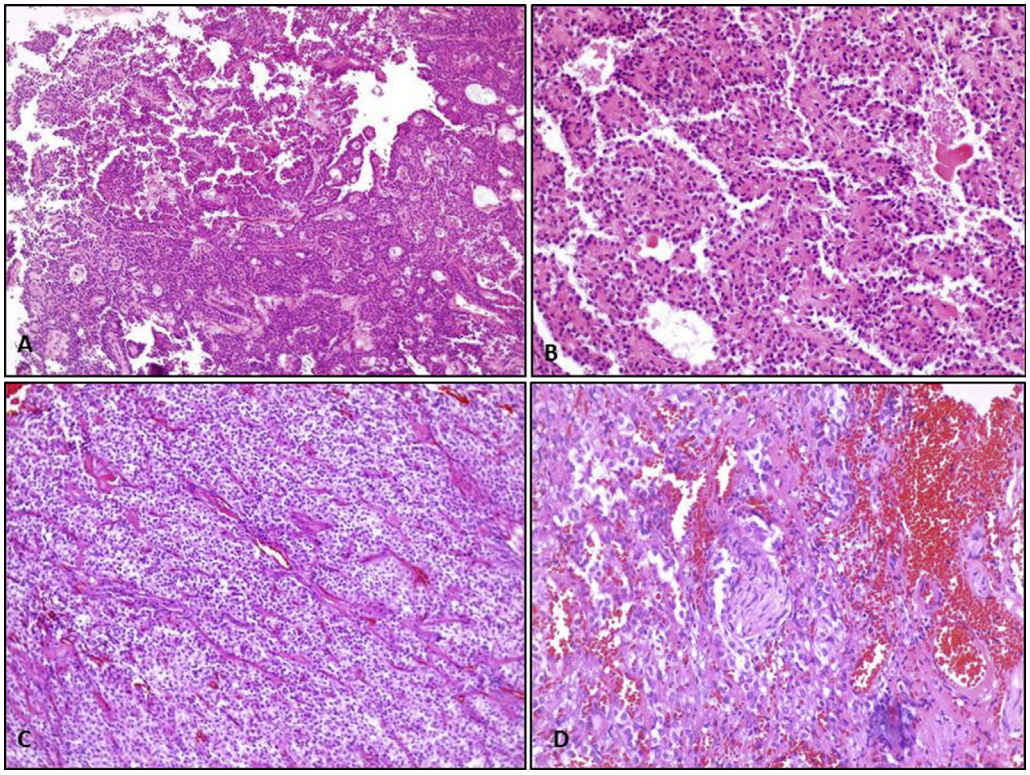

Figure 1. Pathological features of SPN. (A) SPN of the pancreas with characteristic pseudopapillary patterns (H&E, 100×). (B) Tumor cells exhibit uniformly round nuclei, eosinophilic cytoplasm (H&E, 200×). (C). Tumor presents with clear cytoplasm (H&E, 100×). (D) In the tumor, clear cells and perineural invasion are observed (H&E, 200×). H&E = hematoxylin and eosin; SPN = solid pseudopapillary neoplasm.

Table 1 Histopathological features of patients with tumor size > 5 cm compared with tumor size < 5 cm.

	Tumor size < 5 cm ($n = 9$)	Tumor size ≥ 5 cm ($n = 7$)	p
Multinucleated cells (presence)	4 (44.40)	2 (28.60)	0.633
Calcification (presence)	3 (33.30)	1 (14.30)	0.585
Perineural invasion (presence)	3 (33.30)	1 (14.30)	0.585
Lymphovascular invasion (presence)	0	0	NA
Central hyalinization (presence)	4 (44.40)	0	0.088
Myxoid stroma (presence)	2 (22.20)	3 (42.90)	0.596
Clear cytoplasm (presence)	4 (44.40)	3 (42.90)	>0.999
Eosinophilic cytoplasm (presence)	6 (66.70)	5 (71.40)	>0.999
Aggregates of foamy histiocytes (presence)	3 (33.30)	3 (42.90)	>0.999

Data are presented as *n* (%).
NA = Not Available (statistical analysis could not be performed because of insufficient sample size).

Table 2 Histopathological features of patients with perineural invasion compared with patients without perineural invasion.

	Without perineural invasion ($n = 12$)	With perineural invasion ($n = 4$)	p
Multinucleated cells (presence)	4 (33.30)	2 (50)	0.604
Calcification (presence)	2 (16.70)	2 (50)	0.245
Pancreatic parenchymal invasion (presence)	4 (33.30)	4 (100)	0.077
Tumor size (≥5 cm)	6 (50)	1 (25)	0.585
Lymphovascular invasion (presence)	0	0	NA
Central hyalinization (presence)	1 (8.30)	3 (75)	0.027
Myxoid stroma (presence)	3 (25)	2 (50)	0.547
Clear cytoplasm (presence)	3 (25)	4 (100)	0.019
Eosinophilic cytoplasm (presence)	8 (66.70)	3 (75)	>0.999
Aggregates of foamy histiocytes (presence)	3 (25)	3 (75)	0.118

Data are presented as *n* (%).
NA = Not Available (statistical analysis could not be performed because of insufficient sample size).

Table 3 Histopathological features of patients with pancreatic parenchymal invasion compared with patients without pancreatic parenchymal invasion.

	Without pancreatic parenchymal invasion ($n = 8$)	With pancreatic parenchymal invasion ($n = 8$)	p
Multinucleated cells (presence)	2 (25)	4 (50)	0.608
Calcification (presence)	2 (25)	2 (25)	>0.999
Tumor size (≥5 cm)	6 (75)	1 (12.50)	0.041
Perineural invasion (presence)	0	4 (50)	0.077
Lymphovascular invasion (presence)	0	0	NA
Central hyalinization (presence)	0	4 (50)	0.077
Myxoid stroma (presence)	2 (25)	3 (75)	>0.999
Clear cytoplasm (presence)	3 (37.50)	4 (50)	>0.999
Eosinophilic cytoplasm (presence)	5 (62.50)	6 (75)	>0.999
Aggregates of foamy histiocytes (presence)	2 (25)	4 (50)	0.608

Data are presented as *n* (%).
NA = Not Available (statistical analysis could not be performed because of insufficient sample size).

11–20% were located in the body, 10–50% in the tail, and 20–39.80% in the head; rates that are consistent with those observed in this study [5–10].

Similar to other studies [6–9], the mean tumor size evaluated in this study was 5.9 cm. However, a study of patients from Pakistan by Din et al [10] reported a mean tumor size of 9.5 cm.

Macroscopically, all the tumors evaluated in this study were encapsulated and well demarcated from the adjacent non-tumor pancreatic tissue and they presented with large

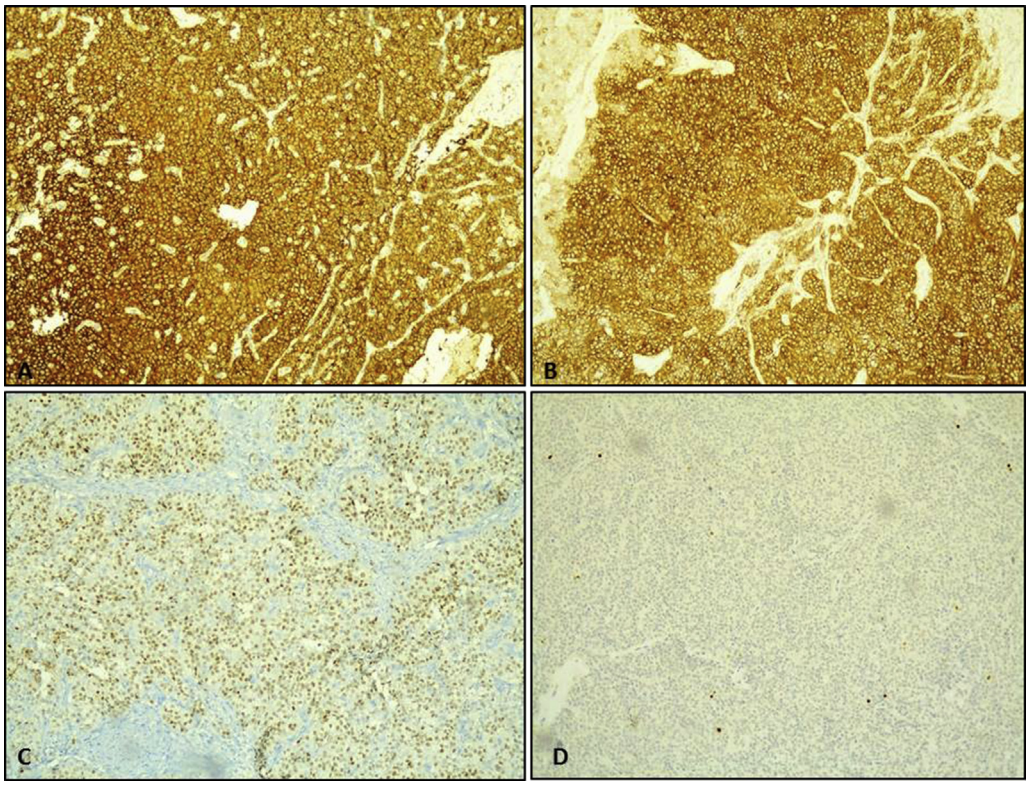

Figure 2. Immunohistochemical findings. (A) SPN tumor cells stained intensely with membranous pattern for strong positivity of CD56 (CD56, 100×). (B) Positive reaction for CD10 in SPN tumor cells (CD10, 100×). (C) Progesterone-receptor-positive nuclear expression (PR, 100×). (D) Ki-67 showing low cell proliferation index (Ki67, 100×). H&E = hematoxylin and eosin; SPN = solid pseudopapillary neoplasm.

spongy areas at the cut surface indicative of hemorrhage and solid and cystic degeneration. Similar macroscopic features have been reported in other studies [1,5,10].

Most tumors were composed of solid, cystic and pseudopapillary parts. The nuclei of all tumor cells were uniformly round, and characteristic nuclear grooves were observed in seven cases (43.80%). The cytoplasm of the tumor cells was predominantly eosinophilic, but clear cells were observed in seven cases (43.80%). Various factors associated with degeneration were observed, including central hyalinization (4, 25%), myxoid stroma (5, 31.30%), eosinophilic body (11, 68.80%), aggregates of foamy histiocytes (6, 37.5%), multinucleated cells (6, 37.50%) and calcification (4, 25%).

The neoplasms demonstrated relatively discrete microscopic features. SPN cells demonstrated various combinations of solid, cystic and pseudopapillary configurations. In the cystic and cystic—solid components, one or several layers of tumor cells discohesively covered the fibrovascular cores and formed characteristic pseudopapilla [3,11]. Microscopically, the neoplasms were cellular and consisted of regular-shaped, polygonal tumor cells that were uniformly round, and exhibited folded nuclei and abundant cytoplasm. The cytoplasm of most cells is eosinophilic; however, clear, basophilic and vacuolated cells are observed in some cases [3]. Among the samples we evaluated, seven (43.80%) tumors contained cells with a clear cytoplasm. Ud Din et al [10] reported that clear cells were observed in 60% of the cases evaluated in their study. The presence of nuclear grooves, another characteristic histological feature observed in SPN of the pancreas, was observed in seven cases (43.80%) in this study. Degenerative features, such as central hyalinization, myxoid stroma, eosinophilic bodies, foamy histiocyte aggregates, multinucleated cells, calcification, cholesterol clefts, and mucoid degeneration, are also frequently observed [12,13].

SPN of the pancreas is a rare indolent neoplasm and is associated with good prognosis. Studies that investigated the clinicopathological features associated with malignant behavior have reported different results [5—7,14,15]. Some studies demonstrated that potentially malignant SPNs were associated with larger tumor size [7,14,16] and vascular invasion [7,15]. In another study, Chung et al [17] reported that tumor size $>$ 5 cm; elevated mitotic rate, presence of lymphovascular, perineural, and pancreatic parenchymal invasion, nuclear atypia may predict aggressive behavior, similar to WHO report which the above- referred histopathological factor of agressive behaviour. As none of the cases in this study were considered malignant SPN (defined as unresectable tumors, metastases, and disease recurrence), we only examined the relationship of pathological features and predictive factors of aggressive behavior.

In this study, the clinical parameters and pathological features evaluated were not significantly associated with predictive factors of aggressive behavior in SPN. The only significant association we identified was between the

presence of clear cells and perineural invasion ($p = 0.019$). In 2006, Albores-Saavedra et al [18] first described neoplastic SPN cells as large cytoplasmic empty vacuoles and referred to a clear cell variant of SPN in three cases. Hav et al [19] and Tanino et al [20] observed two cases of this variant. In these reports, clear cell variant of SPN was a histological variant based on >90% of the isolated neoplastic cells containing large cytoplasmic empty vacuoles [18–20]. However, in this study, 20–25% of cells in these cases were clear cells; therefore, they cannot be considered clear cell variants of SPN. Similar to the results in our study, Hav et al [19] evaluated and identified perineural invasion in a case of clear cell SPN. Albores-Saavedra et al [18] reported vascular invasion in one case of clear cell variant of SPN. Tanino et al [20] did not observe perineural invasion, vascular invasion, or increased mitotic activity in clear cell SPN.

In conclusion, SPN of the pancreas is a rare indolent neoplasm with low malignant potential, consistent with the cases evaluated this study. The current study demonstrated that the presence of clear cells might serve as a possible prognostic indicator of perineural invasion, a feature associated with aggressive behavior in SPN. The elusive nature of SPN makes it an interesting neoplasm for clinicians and pathologists.

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