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Solid pseudopapillary neoplasm of the pancreas with prominent atypical multinucleated giant tumor cells

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Abstract

Aims—Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare low-grade malignant neoplasm. SPN with prominent atypical multinucleated giant tumor cells (MNGTCs) has not been reported.

Methods and results—We identified four cases of SPN with prominent atypical MNGTCs in a cohort of 62 cases of SPN (6.5%). The MNGTCs contained multiple enlarged, hyperchromatic, irregular nuclei with ample eosinophilic cytoplasm, typically present in the solid area of the tumor. The MNGTCs had a typical immunohistochemical profile of the conventional SPN and were positive for vimentin, β -catenin, CD10, and progesterone receptor, but were negative for pan-cytokeratin chromogranin, synaptophysin, trypsin, Ki-67 and CD68 in all four cases. Patients of SPN with prominent MNGTCs were older than those with conventional SPN ($p=0.01$), tumors were incidentally discovered by imaging studies for an unrelated disease in all four cases, and with a female to male ratio of 1:1. The proliferation index (Ki-67) was $<1\%$ in all four cases. None of the three patients, whose follow up information was available, developed recurrence during follow-up of 2.7, 3.8 and 5.0 years.

Conclusions—The presence of MNGTCs in SPN most likely represents degenerative change of the tumor cells and does not seem to affect the prognosis.

Keywords

solid pseudopapillary neoplasm; multinucleated giant cells; prognosis

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Introduction

Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare low-grade malignant neoplasm that accounts for about 1% to 2% of all pancreatic tumors¹. The clinicopathologic features of SPN are distinctive from other pancreatic neoplasms^{1–3}. SPN occurs mainly in young women in their 20s and 30s of age with a median age of 28 years³. The tumor sizes are often very large at the time of presentation with a heterogeneous cut surface consisting of solid brown lobulated areas, hemorrhage, and cystic spaces containing necrotic debris⁴. Tumors are confined to the pancreas in 85% of patients. Patients with SPN have excellent prognosis after complete surgical resection with a five-year survival rate over 85%. Even the 10% to 15% of patients who developed recurrent SPN, liver or peritoneal metastases commonly enjoy long-term survival^{5–8}. Although there are no pathological factors that can reliably predict the clinical outcome of patients with SPN, Tang *et al* recently reported two rare cases of clinically aggressive SPN that were associated with diffuse growth pattern, extensive tumor necrosis, significant nuclear atypia, and high mitotic count. Both of their patients died of disease at 6 and 16 months after presentation⁹.

Despite numerous studies using immunohistochemistry markers, electron microscopy and molecular pathology, the cell origin of SPN remains unclear. Characteristically, SPNs almost always harbor β -catenin mutation and have nuclear localization of β -catenin by immunohistochemistry due to lack of degradation of mutated protein, but lack K-ras mutation that is a hallmark of pancreatic ductal adenocarcinomas. β -catenin immunohistochemistry has been widely used as one of the diagnostic markers for SPN^{10, 11}. The typical histologic pattern and cytologic features of SPN are characterized by numerous delicate blood vessels surrounded by variable amount of hyalinized stroma and relative uniform, non-cohesive polygonal cells forming pseudopapillae. Intra-cytoplasmic PAS-positive diastase resistant eosinophilic globules, foamy histiocytes, cholesterol crystals with foreign body giant cell reaction are commonly present in SPN. Rare cases of clear cell variant of SPN had also been reported. The clinical features, gross characteristics, and immunohistochemical staining profile of clear cell SPN are similar to those patients with conventional SPNs^{12–14}. Recently, we encountered an unusual case of SPN represented by numerous atypical multinucleated giant tumor cells (MNGTCs). This feature, to our knowledge, has not been previously reported. The purpose of this study is to investigate the frequency of SPN with MNGTCs and to describe the clinical and histologic features of four cases of SPN with MNGTCs and compared these to 58 patients with conventional SPNs. The significance of MNGTCs in SPN and the differential diagnoses are discussed.

Materials and Methods

Four patients of SPN with MNGTCs and 58 patients with conventional SPN (control group) identified from the pathology file at the University of Texas MD Anderson Cancer Center from 1994 to 2011 were included in this study. The hematoxylin-eosin (H&E) stained slides from the pancreatectomy specimens of all patients were reviewed and the diagnosis of SPN was confirmed in all cases. Clinical and pathologic information, including patient age, gender, type of specimen, tumor size, tumor location in the pancreas, was collected from computerized patient medical record. The study was approved by the Institutional Review Board of the University of Texas MD Anderson Cancer Center.

All four patients of SPN with prominent MNGTCs were evaluated by immunohistochemistry for vimentin (clone V9, 1:900, Dako, Carpinteria, CA), CD10 (clone 56C6, 1:50, Novocastra, Buffalo Grove, IL), β -catenin (clone 14, 1:500, BD Biosciences, San Jose, CA), progesterone receptor (PR, clone 1294, 1:200, Dako), chromogranin (clone LK2H10, 1:4000, Chemicon), synaptophysin (clone 27G12, 1:600, Novocastra), trypsin

(1:130,000, Chemicon, Billerica, MA), Ki-67 (clone MIB-1, 1:100, Dako), and CD68 (clone KP-1, 1:900, Dako). The pancytokeratin cocktail consisted of a mixture of four different antibodies against cytokeratins: AE1/AE3 (1:50), CAM5.2 (1:50), MNF116 (1:50) and 8/18 (1:25). Standard immunohistochemical staining techniques were used as described previously with appropriate positive and negative controls¹⁵.

Patient follow-up information through April of 2012 was extracted from patient medical record and if necessary, by review of the U.S. Social Security Index. The overall survival was calculated as the time from the date of diagnosis to the date of death or the date of last follow-up if death did not occur. The Fisher's exact tests were used to compare categorical data. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to evaluate the statistical significance of differences. Statistical analysis was performed using Statistical Package for Social Sciences software (for Windows 12.0, SPSS Inc., Chicago, IL). A two-sided significance level of 0.05 was used for all statistical analyses.

Results

Prevalence and clinicopathologic features of SPN with multinucleated giant tumor cells

We reviewed the H&E slides from 62 pancreatectomy specimens with the diagnosis of SPN in the pathology file at our institution for the presence of multinucleated giant tumor cells (MNGTCs). We found 4 cases (6.5%) of SPN with prominent MNGTCs. In all four cases, many MNGTCs were present either in the solid area of the tumor or in area with conventional SPN histology. The clinicopathologic features of the four patients of SPN with prominent MNGTCs and their comparison with the patients with conventional SPN are shown in Table 1 and Table 2 respectively. The tumor was incidentally identified by computed tomography (CT) during work up for other unrelated diseases in all four cases (Table 1). All four patients had serum CA19-9 levels within the normal range. Fifty percent (2/4) patients of SPN with prominent MNGTCs were male compared to 13.8% (8/58) of male patients with conventional SPN ($P=0.06$, Table 1). Patients with SPN and MNGTCs had a mean age of 51.3 years (range 36 to 59 years) at the time of diagnosis and were older than those with conventional SPN, whose mean age was 32.1 years (range: 9.4 to 62.2 years, $p=0.01$).

Gross and morphologic features

SPNs with MNGTCs were located in the head of pancreas in 3 patients and in the tail of the pancreas in one patient. Grossly three tumors were well-circumscribed without capsule and with capsule in one remaining case (case #2). All four tumors showed tan, soft cut surfaces with areas of cystic degeneration and hemorrhage. The tumor size ranged from 1.8 cm to 10.3 cm (mean tumor size: 5.0 ± 3.8 cm), which was not significantly different from the mean tumor size of 6.7 ± 4.2 cm for the conventional SPN ($p=0.41$).

In all four cases, many atypical MNGTCs were seen in otherwise conventional SPN histology. However, MNGTCs were more prominent in the solid areas of the tumor (Figure 1). Most of the MNGTCs contained multiple enlarged, hyperchromatic, irregular nuclei with ample eosinophilic cytoplasm (Figure 1). While some of the MNGTCs had the nuclear features similar to the mononuclear tumor cells, most MNGTCs showed smudged chromatin, suggestive of degenerative changes. Intra-cytoplasmic eosinophilic hyaline globules were present in the MNGTCs in one case (Figure 1D). Areas of hemorrhage, collections of foamy histiocytes and foreign body multinucleated giant cells with cholesterol crystals were present in three of four cases. Focal calcification was identified in two cases. In all four cases, mitoses were rare and no mitoses were identified in the MNGTCs. Although the tumors were grossly well-circumscribed, microscopic tumor invasion into the

adjacent normal pancreas (Figure 1C) was present in three cases and peripancreatic soft tissue in two cases. Perineural invasion was present in one case. Lymphovascular invasion, lymph node metastasis or positive resection margin was not present in any of the four cases.

Immunohistochemistry

The immunohistochemical profile of the MNGTCs was similar to the mononuclear tumor cells for all four cases. Both mononuclear tumor cells and MNGTCs were diffusely positive for vimentin, beta-catenin (nuclear and cytoplasmic staining), CD10, and progesterone receptor (PR) in all four cases (Figure 2). Immunohistochemical stains for pancytokeratin and synaptophysin were focally positive in one case and were negative in the other three cases. All four cases were negative for chromogranin and trypsin. The MNGTCs were negative for CD68 in all four cases (Figure 2F). Thus the immunohistochemical staining profile suggests that the MNGTCs have similar origin as the mononuclear tumor cells, but not from the histiocytes that are commonly present in SPNs. Immunohistochemical stain for Ki-67 was performed on all four cases and all cases showed less than 1% nuclear staining for Ki-67 in the tumor cells, and no staining of MNGTCs (Figure 2E).

Clinical Outcome

The follow up information was available in three patients with the follow up time of 2.7, 3.8 and 5.0 years and one patient was lost to follow up one month after the surgery. During follow-up, one patient died of abdominal abscess at 2.7 years after the distal pancreatectomy. The other two patients were alive with no evidence of recurrence at 3.8 and 5.0 years after the surgery. Although there was no significant difference in overall survival compared to the 58 patients with conventional SPN, whose mean survival was 15.26 ± 0.72 years with a median follow up of 3.41 years ($P=0.21$), the number of patients with MNGTCs was too small to be meaningful.

Discussion

Multinucleated giant cells of histiocytic origin are common findings in SPNs. They represent a reaction to the necrotic and degenerative changes that are commonly seen in these tumors. However, MNGTCs have not been reported in SPNs of the pancreas. In this study, we reported four cases of SPN with prominent MNGTCs in a cohort of 62 patients with SPN. The index case of SPN with prominent MNGTCs was found incidentally during routine histologic evaluation of an otherwise usual SPN. Three additional cases of SPN with prominent MNGTCs were found in 61 pancreatectomy specimens with the diagnosis of SPN after retrospective review. The prevalence of SPN with prominent MNGTCs was 6.5% in our study population. We demonstrated that the MNGTCs in all four cases had the same immunohistochemical profile as the mononuclear tumor cells of SPNs and were immunoreactive to vimentin, beta-catenin, CD10, and PR, but not to histiocytic marker CD68. The MNGTCs are also negative for pan-cytokeratin, chromogranin, synaptophysin and trypsin. These findings suggest that the MNGTCs are originated from the mononuclear tumor cells, instead of histiocytic origin. Application of immunohistochemistry would help to differentiate SPN with prominent MNGTCs from other tumors with cells similar to those seen in our cases, including pleomorphic pancreatic neuroendocrine tumor¹⁶, pancreatic acinar cell carcinoma, undifferentiated carcinoma of the pancreas, undifferentiated carcinoma of the pancreas with osteoclast-like giant cells, metastatic carcinoma or sarcoma.

The MNGTCs in our cases showed multiple enlarged, irregular or bizarre, hyperchromatic nuclei with significant nuclear atypia. In addition, many MNGTCs were present in the solid areas of SPN in our cases. These findings raised the concern for an

aggressive behavior of this tumor. Rare cases of clinically aggressive SPN of the pancreas that are associated with diffuse growth pattern, extensive tumor necrosis, significant nuclear atypia, and high mitotic count have been reported ⁹. However, all four patients of SPN with prominent MNGTCs in this study were identified incidentally by CT scan during work up for other unrelated diseases (three patients during work up for inflammatory conditions and one during follow-up for breast cancer after lumpectomy and cyclophosphamide/epirubicin/5-fluorouracil therapy) and two of the tumors were less than 3.0 cm in size. None our patients had tumor invasion to the other organs, lymphovascular invasion or lymph node metastasis. In addition, all four cases of SPN with MNGTCs showed very low proliferation index and all giant cells were negative for Ki-67 in this study. No recurrence was detected during the follow up of three patients whose follow up information were available, which was similar to those with conventional SPN. These findings argued against the possibility that the presence of prominent MNGTCs in SPN was associated with more aggressive behavior of SPN. Long term follow-up and more cases are needed to further confirm the indolent behavior of this tumor. The histologic appearance and clinical follow-up data in our study of SPN with prominent MNGTCs bear analogy to the degenerative, pleomorphic atypia seen in pleomorphic pancreatic neuroendocrine tumors ¹⁶, symplastic leiomyomas ¹⁷, symplastic glomus tumor ¹⁸, symplastic hemangioma ¹⁹, and bizarre giant cells of mammary fibroadenomas ²⁰. The presence of atypical cells in these tumors has also been shown to have no significant effect on the prognosis, but the demographic trend appeared to be similar to their conventional counterparts.

In summary, we identified, for this first time, four cases (6.5%) of SPN with prominent MNGTCs of the pancreas in a cohort of 62 patients with SPN at our institution. The patients of SPN with prominent MNGTCs were older, slightly more frequent in males and located in the head of the pancreas compared to the patients with conventional SPN. The patients of SPN with prominent MNGTCs seem to have a good prognosis similar to those with conventional SPN. We speculate that the MNGTCs in our cases may represent degenerative changes in tumor cells.

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Figure 1.

Representative micrographs showing many atypical MNGTCs in case #4 present in the solid area of the tumor (A), in area with conventional SPN histology and foamy histiocytes (B), and tumor invasion into the adjacent pancreatic parenchyma (C). D. Representative micrograph from Case #3 show atypical MNGTCs present in area with conventional SPN histology with intracytoplasmic globules (H&E stain, original magnification, 200x).

Figure 2.

Representative micrographs from Case #1 show immunohistochemical staining for pan-cytokeratin (A); β -catenin (B), CD10 (C), PR (D), Ki-67 (E) and CD68 (F). Normal pancreatic acinar cells as internal control were marked with dot line in A, B, and C. The atypical MNGTCs were marked with arrows in B–F. (Original magnification, 100x for A and E; 200x for B, C, D and F).

Clinicopathologic features of solid pseudopapillary neoplasm with prominent MNGTCs.

Table 1

Case number	Age at diagnosis	Gender	Clinical presentation	CA19,9 (unit/ml)	Type of surgery	Location	Tumor Size	Percentage of tumor with MNGTCs (%)	Follow-up (months)	Vital status
1	52.7	Female	Incidental finding by CT during follow up for breast cancer	10.7	Pylorus-preserving pancreaticoduodenectomy	Head	1.8 cm	60	45.2	Alive with no evidence of disease
2	36.0	Female	Pneumonia, incidental finding by CT	15.2	Distal pancreatectomy	Tail	10.3 cm	90	32.4	Dead of abdominal abscess
3	59.0	Male	Kidney stone and lithotripsy, incidental finding by CT	11.2	Pancreaticoduodenectomy	Head	5.0 cm	30	60.0	Alive with no evidence of disease
4	57.2	Male	Diverticulitis, incidental finding by CT	16.6	Pancreaticoduodenectomy	Head	2.7 cm	25	1.1	Lost to follow-up

Table 2

Comparison of the clinicopathologic features of SPN with prominent MNGTCs with conventional SPN

Clinicopathologic features	SPN with prominent MNGTCs	Conventional SPN	p value
Number of cases	4	58	
Female: male ratio	1:1	4:25	0.06
Mean age $\pm$ SD (years)	51.3 $\pm$ 10.5	32.1 $\pm$ 14.1	0.01
Location			0.13
Head	3	16	
Body	0	12	
Tail	1	30	
Mean tumor size $\pm$ SD (cm)	5.0 $\pm$ 3.8	6.7 $\pm$ 4.2	0.41
Liver metastasis or other organ involvement at the time of presentation	0/4	5/58	1.00
Recurrence	0/3 [*]	10/57 [*]	0.42

^{*} Number of patients whose follow-up information is available.