Prognostic Significance of PAX8, Survivin, and Ki-67 Expression in Pancreatic Endocrine Neoplasms: A Tissue Microarray Analysis

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INTRODUCTION

Pancreatic endocrine neoplasms (PENs) are are relatively uncommon tumors of the pancreas, which account for less than 2% of of all pancreatic neoplasm. PENs can be sporadic or associated with genetic syndromes including multiple endocrine neoplasia type 1, von Hippel-Lindau disease, von Recklinghausen disease, and tuberous sclerosis. They are typically seen in middle-age adults and are divided into functional and non-functional tumors.

Accurate classification/grading of PENs is important for appropriate clinical management and prognosis prediction of the patients. According to the current WHO classification, PENs include well-differentiated endocrine tumor with benign behavior, well-differentiated endocrine tumor with uncertain behavior, well-differentiated endocrine carcinoma, and poorly differentiated carcinoma. This classification is based on the presence or absence of local invasion, lymph node or distant metastasis, as well as expression of Ki-67. There are, however, no widely-accepted immunohistochemical markers that can reliably grade the tumors and predict tumor behavior.

In this retrospective study, we assessed the potential prognostic value of markers that are associated with cell proliferation, differentiation, and survival using a tissue microarray (TMA) prepared from surgically resected PENs.

METHODS

We searched the surgical pathology database for cases of PENs that were surgically resected at our institution from January 1998 to June 2011. A total of 58 cases were included and constructed for a TMA in which two 1-mm representative core tissue fragments from the tumor and corresponding non-neoplastic pancreatic tissue were included for each case. Immunohistochemistry was performed on TMA sections using antibodies against PAX8, NeuroD1, survivin, CD44 and Ki-67 with appropriate positive and negative controls. Expression of PAX8, NeuroD1, survivin, CD44 and Ki-67 was evaluated and semi-quantified. Nuclear staining for PAX8, NeuroD1 and Ki-67, cytoplasmic/nuclear staining for survivin, and cytoplasmic/membranous staining for CD44 were considered positive if >2% (for Ki-67) or >5% (for other markers) of the cells stained. Fisher's exact Chi-square analysis and Chi-square test for trend, where appropriate, were performed to correlate expression of these markers with the following: tumor functional status, lymph node metastasis, liver metastasis, and WHO classification. The markers significant on univariate analysis were included in exact logistic regression models.

RESULTS

The patients were 27 male and 31 female with ages ranging from 11 to 82 years (mean: 55 years). The tumors, ranging from 0.4 to 15 cm (mean: 3.4 cm), were classified as well-differentiated endocrine tumor with benign behavior (class IA), well-differentiated endocrine tumor with uncertain behavior (class IB), well differentiated endocrine carcinoma (class II) in 21, 20 and 17 cases, respectively. Eleven tumors were functional and forty-seven were non-functional. Lymph node and liver metastases were present in 15 (26%) and 7 (12%) cases, respectively. PENs showed PAX8 expression in 43 (74%) cases. NeuroD1 expression was positive and negative in 40 (69%) and 18 (31%) cases, respectively. Only 3 (5%) PENs expressed survivin while CD44 expression was evident in 17 (29%) cases. Eighteen (32%) PENs had a Ki-67 rate of >2%. On univariate analysis, expression of PAX8, survivin, and Ki-67 was associated with lymph node metastasis and WHO classification. Both survivin and Ki-67 expression were significantly associated with liver metastasis. On multivariate analysis, only Ki-67 remained significantly associated with lymph node and liver metastases. There were no associations between functional status and these markers.

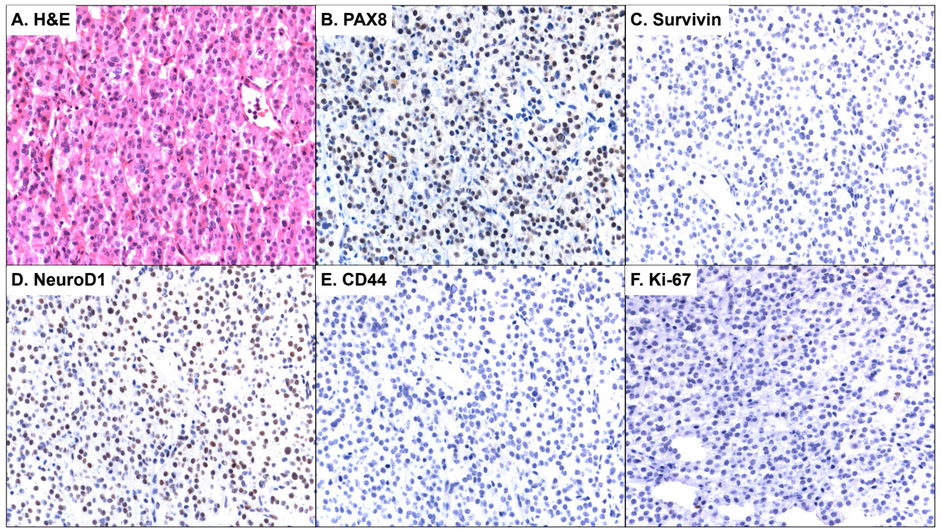

Figure 1. Expression of PAX8, survivin, NeuroD1, CD44 and Ki-67 in a well-differentiated pancreatic endocrine tumor with benign behavior (Class IA) (**A**, Hematoxylin-eosin stain, original magnification X400; **B**-**F**, Immunoperoxidase stain, original magnification X400).

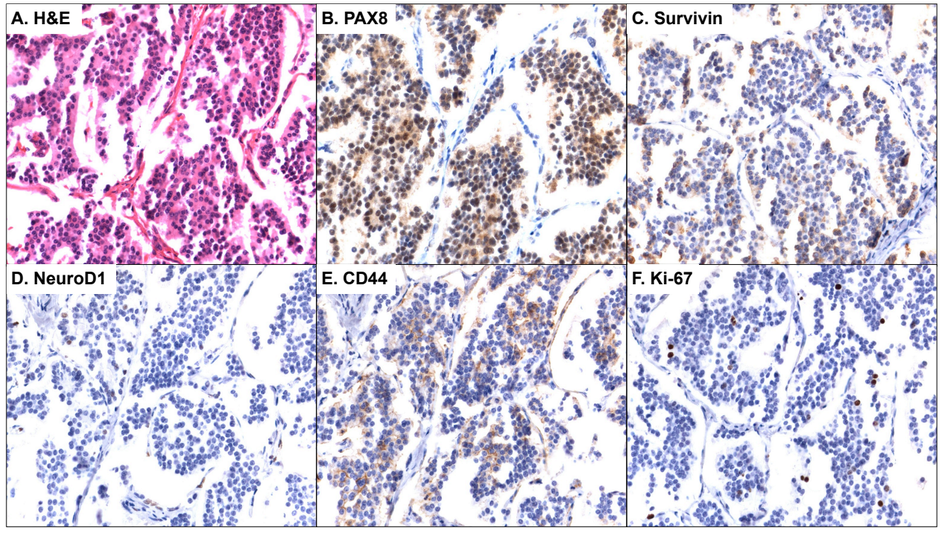

Figure 2. Expression of PAX8, survivin, NeuroD1, CD44 and Ki-67 in a well-differentiated pancreatic endocrine carcinoma (Class II) with lymph node and liver metastasis (**A**, Hematoxylin-eosin stain, original magnification X400; **B**-**F**, Immunoperoxidase stain, original magnification X400).

Table 1. Clinicopathologic Features of Pancreatic Endocrine Neoplasms (PENs)

Characteristics	Number	Percentage
Patient's Age (years)		
Range	11-82	N/A
Mean	55	
Patient's Gender		
Male	27	47%
Female	31	53%
Tumor Size (cm)		
Range	04-15	N/A
Mean	3.4	
Tumor Functional Status		
Functional	11	19%
Non-functional	47	81%
Lymph Node Metastasis		
Absent	43	74%
Present	15	26%
Distal (Liver) Metastasis		
Absent	51	86%
Present	8	14%
WHO Classification/Grading		
Well-differentiated Endocrine Tumor with Benign Behavior (IA)	21	36%
Well-differentiated Endocrine Tumor with Uncertain Behavior (IB)	20	34%
Well-differentiated Endocrine Carcinoma (II)	17	29%
Tumor Stage (AJCC, 2010)		
1A	22	38%
1B	15	26%
2A	5	9%
2B	9	16%
4	7	12%

CONCLUSIONS

- PAX8 and NeuroD1 are expressed in the majority of PENs while a small number of PENs express survivin and CD44. Increased Ki-67 proliferation rate (>2%) is seen in about one-third of cases.
- Altered expressions of PAX8, survivin and Ki-67 are associated with lymph node metastasis and WHO classification/grading. Survivin expression and increased Ki-67 proliferation are associated with liver metastasis.
- The results suggest that PAX8, survivin and Ki-67 can be potentially used as markers for predicting lymph node and liver metastasis.
- A larger scale study including the immunostains performed on routine tumor sections is needed to validate these findings.

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