



Endoscopic Ultrasound-Guided Fine Needle Aspiration Diagnosis of Pancreatic Endocrine Neoplasms: An Institution's Experience



Jane Bernstein, M.D., Berrin Ustun, M.D., Ahmed Alomari, M.D., Fang Bao, M.D.,
Harry R. Aslanian, M.D., David Chhieng, M.D., Guoping Cai, M.D.

Departments of Pathology & Internal Medicine, Yale School of Medicine, New Haven, Connecticut

ABSTRACT

Introduction. Pancreatic endocrine neoplasms (PENs) are rare tumors of the pancreas, which are increasingly diagnosed by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). In this study, we reviewed our experience in diagnosing PENs via EUS-FNA in 59 patients.

Methods. A search of the pathology database at Yale-New Haven Hospital revealed fifty-nine patients diagnosed with PENs via EUS-FNA between January 2005 and January 2012. The final diagnosis was based on cytomorphologic features and immunophenotypic findings if available. In this retrospective study, cytology diagnoses and immunocytochemistry results as well as clinical data, ultrasound findings, and surgical pathology follow-up from these patients were evaluated.

Results. Twenty-five of the patients were male and thirty-four were female with ages ranging from 26 to 85 years (median 58 years). The tumors were solid and cystic in 46 and 13 cases, respectively, with sizes ranging from 0.4 to 11 cm (mean 2.6 cm). Rapid on-site evaluation was performed for all cases. Based on cytomorphologic features and adjunct immunocytochemistry, when performed, 53 patients were diagnosed with PEN, while a diagnosis of "suspicious for PEN" was rendered in the remaining 6 patients. Thirty-three patients (56%) had surgical follow-up, which confirmed all cytological diagnoses of PENs.

Conclusions. The cytological findings in our series are similar to those previously described. When present in abundance, these features are characteristic of PENs. However, Immunocytochemical studies are often necessary to substantiate a definitive diagnosis. One neuroendocrine marker (chromogranin, synaptophysin or CD56) is sufficient to elucidate neuroendocrine differentiation in PENs, at least in well differentiated tumors. Our data demonstrate that EUS-FNA can reliably diagnose PENs. On-site evaluation is crucial to ensure adequate material for ancillary studies.

INTRODUCTION

Pancreatic endocrine neoplasms (PENs) are rare tumors of the pancreas which account for less than 2% of all pancreatic tumors¹⁻². These tumors are increasingly detected radiographically secondary to increased availability and improved sensitivity of imaging modalities³. Endoscopic ultrasound (EUS) has become accepted as an accurate and cost-effective method of detecting and staging pancreatic neoplasms. The sensitivity and specificity of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for diagnosis of PEN approach 98% and 100%, respectively⁴⁻⁶. On-site evaluation by a cytopathologist further enhances the diagnostic accuracy of this procedure and allows for the appropriate allocation of specimen material for ancillary testing. Assessment of cytomorphology in conjunction with immunocytochemistry helps to narrow the differential diagnosis raised in this scenario and can confirm the diagnosis. Accurate preoperative diagnosis of PENs allows for appropriate management of these lesions. Given the rarity of this entity, it is difficult to compile a large experience with PENs at a single institution. The aim of this study was to document a large series of PENs diagnosed by EUS-FNA with histologic follow-up.

METHODS

A search of the pathology database at Yale-New Haven Hospital revealed fifty-nine patients diagnosed with PEN based on EUS-FNA from 2005 to 2012. The biopsies were all performed in the endoscopy suite by an interventional gastroenterologist. The aspirated material was immediately transferred onto glass slides and smears were prepared, which were either air-dried or fixed in 95% alcohol. The air-dried smears were stained with Diff-Quik and assessed on-site for adequacy and preliminary interpretation. The alcohol-fixed smears were stained with Papanicolaou stain. Part of the aspirate was saved and processed for a compact cell block. Additional immunocytochemical studies were performed on cell block sections. The cytomorphologic and immunophenotypic findings were recorded. In addition, the clinical data, ultrasound findings, and surgical follow-up were retrospectively evaluated, when available.

RESULTS

The clinical data and EUS findings of the PENs diagnosed by EUS-FNA were summarized in **Table 1**. Fifty-six of the lesions (95%) aspirated were present within the pancreas itself and three of the EUS-FNAs were of peri-pancreatic lymph nodes. The classic cytomorphologic features are illustrated in **Figure 1**. The FNA smears were cellular in most cases. However, six (10%) of the cases showed only rare neoplastic cells and were diagnosed as suspicious for, but not diagnostic of, PEN. All the tumors stained with either synaptophysin or chromogranin were positive (**Figure 2**). Additional immunostains were performed in some cases to assess functional status of PENs or eliminate differential diagnoses (**Table 2**). Fourteen of the fifty-nine aspirates (24%) did not have enough materials available for immunocytochemical studies to be performed. All six cases diagnosed as suspicious for PEN were those without materials available for ancillary studies. Thirty-two of fifty-nine patients (54%) subsequently underwent surgical resection at our hospital. Histological examination confirmed the cytological diagnosis in all of these cases (**Figure 3**). Of the six cases with cytological diagnosis of "Suspicious for PEN", three had surgical pathology follow-up and all three were given a histologic diagnosis of PEN.

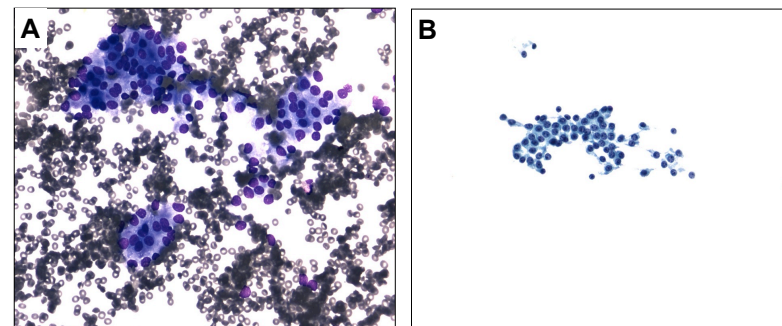


Figure 1. Cytomorphologic features of pancreatic endocrine neoplasms. The aspirate shows loosely cohesive clusters of relatively uniform epithelial cells in a bloody background (**A**, Diff-Quik stain, X200). The tumor cells have eccentrically located round to oval nuclei with speckled chromatin and small nucleoli (**B**, Papanicolaou stain, X400).

Table 1. Clinicopathologic Characteristics of Pancreatic Endocrine Neoplasms Diagnosed by Endoscopic Ultrasound-Guided Fine Needle Aspiration

Characteristic	
Age (years)	26-85
Range	58
Mean	
Sex	34
Female	25
Male	
Location	
Head/Neck/Uncinate	24
Body	11
Tail	18
Size, cm	
Range	0.4-11
Mean	2.6
Clinical History, Syndromes	
Hypoglycemia	4
MEN1	3
Hepatic Metastases	2
Severe Diarrhea	3

Table 2. Immunocytochemical Features of Pancreatic Endocrine Neoplasms Diagnosed by Endoscopic Ultrasound-Guided Fine Needle Aspiration

Immunocytochemical Stain	Number Positive/Total Number Tested (%)
Chromogranin	43/43 (100)
Synaptophysin	44/44 (100)
AE1/AE3	8/9 (89)
CD56	8/17 (47)
CK7	1/3 (33)
CK20	2/3 (67)
Glucagon	1/1 (100)
S100	0/2 (0)
NSE	1/1 (100)
Insulin	1/2 (50)
Gastrin	0/2 (0)
Vimentin	1/1 (100)
CD10	0/1 (0)
Cam5.2	1/3 (33)
Somatostatin	0/1 (0)
CD45	0/3 (0)
p63	0/1 (0)
Melan A	1/3 (33)
Inhibin	0/2 (0)
HMB45	0/1 (0)
C-kit	0/1 (0)
Beta-catenin	0/2 (0)

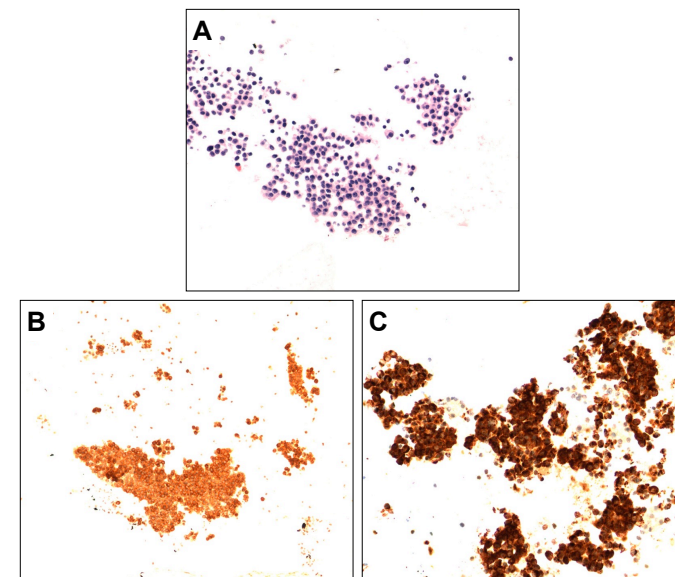


Figure 2. Immunophenotypic features of pancreatic endocrine neoplasms. The cell block section shows groups of epithelial cells with eccentrically located nuclei (**A**, hematoxylin-eosin stain, X400). The tumor cells are positive for synaptophysin (**B**, immunoperoxidase stain, X400) and chromogranin (**C**, immunoperoxidase stain, X400).

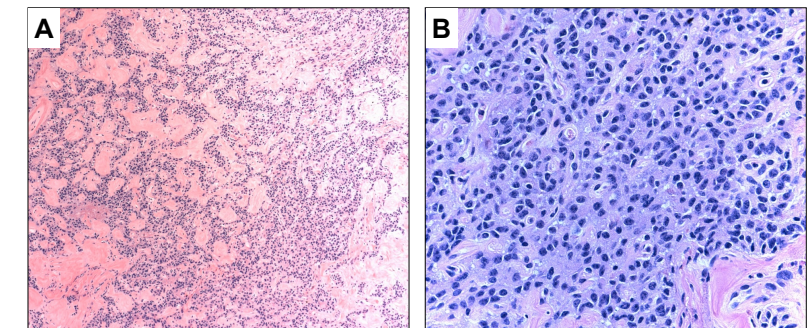


Figure 3. Histomorphologic features of pancreatic endocrine neoplasms in follow-up. The resected tumor was well circumscribed and had relatively uniform epithelial cells arranged in trabecular and gyriform growth patterns with eosinophilic stroma (**A**, hematoxylin-eosin stain, X100). The tumor cells have eosinophilic cytoplasm and eccentrically located round to oval nuclei with speckled chromatin (**B**, hematoxylin-eosin stain, X400).

CONCLUSIONS

The cytological findings in our series are similar to those previously described. When present in abundance, these features are characteristic of PENs. However, immunocytochemical studies are often used to substantiate a definitive diagnosis.

Our results suggest that one neuroendocrine marker, chromogranin or synaptophysin, is sufficient to elucidate neuroendocrine differentiation in PENs, at least in well differentiated tumors. Additional immunostains are sometimes necessary to assess functional status of the tumor or rule out other entities in the differential diagnosis.

It is crucial to save additional biopsy material for cell block during the procedure for immunocytochemical studies. All cases had either a cytopathologist or cytotechnologist on-site for immediate evaluation to ensure adequate sampling and specimen triage. Nevertheless, fourteen cases still did not have enough material to perform immunocytochemistry. Of these, only eight (57%) were signed out with a definitive diagnosis.

PENs can be accurately diagnosed via EUS-FNA based on cytomorphologic and immunophenotypic features. On-site evaluation is crucial to ensure adequate material for ancillary studies.

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