**Quiz Case**

**Endoscopic ultrasound-guided fine needle aspiration of a duodenal submucosal mass: Cytomorphological clues and radiological correlation**

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**CLINICAL HISTORY**

The patient was a 37-year-old male with a long-standing history of end-stage renal disease. He underwent workup for kidney transplantation, including a computed tomography (CT) of the abdomen. On CT, there was a 2.2 cm mass noted in the submucosa of the third portion of his duodenum. The patient denied any of the following symptoms including hypoglycemia, night sweats, diarrhea, or weight loss. The patient's blood chromogranin A level was normal. An endoscopic ultrasound (EUS) was performed and EUS-guided fine needle aspiration (FNA) biopsy of the duodenal submucosal mass was obtained with rapid on-site evaluation (ROSE). The ROSE evaluation by the cytotechnologist was “adequate sample, favor neuroendocrine tumor.” The direct smears showed cells with morphology as showed in Figure 1 (a-d).

**QUESTION**

What is your interpretation?

A. Positive for neoplasm, consistent with neuroendocrine tumor (NET)
B. Positive for neoplasm, consistent with gastrointestinal (GI) stromal tumor (GIST), epithelioid type
C. Positive for malignancy, consistent with metastatic acinar cell carcinoma
D. Benign, consistent with ectopic (heterotopic) pancreas tissue.

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ANSWER

The correct cytologic interpretation is:

D. Benign, consistent with ectopic pancreas (EP) tissue.

The EUS-guided FNA shows modest cellularity with an interesting mixed smear pattern with loosely arranged epithelioid cells showing abundant granular cytoplasm. This population of epithelial cells is consistent with acinar cells. In other areas, there are more cohesively arranged (more organoid arrangement) epithelioid cells with moderate amount of granular cytoplasm. Occasional single epithelioid cells with plasmacytoid morphology are noted. This is compatible with normal islet cells [Figures 1a-d].

a. The major differential diagnosis in this case is NET of the GI tract. The FNA of NET is usually richly cellular. Loosely cohesive sheets as well as many single tumor cells are often seen. The neuroendocrine cells are typically quite monotonous. Occasionally, significant pleomorphism (so-called "neuroendocrine atypia") can occur. Cell block showing a single population of neuroendocrine cells and immunostains of neuroendocrine markers can be helpful to make the correct diagnosis. In case there is not enough cells present on the cell block, an indeterminate diagnosis, such as suspicious for NET, is often rendered.

b. The main indication of EUS-guided FNA of GI submucosal mass is to rule in or rule out GIST. Spindle cell GIST is much more common than epithelioid GIST. However, when a GIST is predominantly epithelioid, it poses significant diagnostic difficulties. FNA of epithelioid GIST often shows a myxoid stromal background. The epithelioid GIST cells typically arrange in a loosely cohesive pattern. Intranuclear inclusions are noted in many cases. Again, cell block with immunostains of CD117 and DOG-1 can often confirm the diagnosis.

c. When epithelioid cells with abundant cytoplasm are identified in smears of a duodenal submucosal mass, the diagnosis of metastatic carcinoma, such as acinar cell carcinoma (ACC) of the pancreas, may be considered. However, metastatic ACC usually shows high cellularity with loose clusters and single tumor cells. Chromatin pattern is typically irregularly clumped and prominent nucleoli are often noted. Rare cases of pancreatic mixed acinar-neuroendocrine carcinoma have been reported.

Features favoring EP tissue are as follows:

- Patient is asymptomatic
- Patient's blood level of chromogranin A is normal
- Mixture of epithelioid cells, some with abundant granular cytoplasm (acinar cells), and some with moderate amount of cytoplasm and coarse nuclear chromatin (islet cells)
- The organoid arrangement of the uniform epithelioid cells.

RADIOLOGICAL CORRELATION AND FOLLOW-UP OF PRESENT CASE

This is quite a difficult case. The CT scan of the abdomen of the patient showed a definitive mass in the submucosal region of the duodenum [Figure 2a]. Since the EUS-guided FNA smears raised the possibility of NET, a cell block was attempted. Unfortunately, there were not enough cells on the cell block to perform immunostains. A diagnosis of "suspicious for neuroendocrine tumor" was rendered. The patient subsequently underwent a gallium-68 DOTATATE positron emission tomography/CT (PET/CT) scan, which showed that this mass had no DOTATATE uptake [Figure 2b]. Given this result, the clinical suspicion for NET was low. However, the patient decided to have this mass excised surgically anyway. Surgical pathology of the excised mass showed ectopic (heterotopic) pancreas tissue [Figure 3a and b].

ADDITIONAL QUIZ QUESTIONS

Q1. EP present as a subepithelial lesion (SEL) in the GI tract is being diagnosed with increasing frequency due to which of the following reason?

a. Most Eps are symptomatic
b. New molecular markers of EP
c. The incidence of EP is increasing due to dietary change
d. The liberal use and improved quality in radiology and endoscopy.

Q2. Which of the following SELs, when diagnosed by EUS-FNA, most likely does NOT need surgical intervention if the patient is asymptomatic?

a. NET
b. EP
c. GIST

Figure 2: (a) Computed tomography scan shows the duodenal wall mass (arrow). (b) gallium-68 DOTATATE positron emission tomography/computed tomography scan shows no uptake (arrow).
Q3. Which of the following imaging diagnostic modality has the highest negative predictive value for NETs?

a. CT  
b. Magnetic resonance imaging (MRI)  
c. Gallium-68 DOTATATE PET/CT scan  
d. EUS.

ANSWERS TO ADDITIONAL QUIZ QUESTIONS

1. (d)  The liberal use and improved quality in radiology and endoscopy is the main reason for more and more SELs, such as Eps, are detected.[8]
   (a) Most of the patients with Eps are asymptomatic  
   (b) To date, there is no specific molecular marker for EPs of the GI tract  
   (c) The incidence of Eps is quite steady and not related to dietary change.

2. (b)  EP is benign. When EP is diagnosed by EUS-FNA, a surgical excision is often not necessary when the patient is asymptomatic[9]
   (a) (c) (d) NET, GIST, and leiomyosarcoma are malignant or having malignant potential. Surgical intervention is often needed.

3. (c)  The NETs typically express somatostatin receptor (SSTR) on the cell membranes. There are five known SSTR subtypes, the most popular subtypes of which are 2 and 5. Somatostatin analog-conjugated single-photon emission computed tomography/CT (SPECT/CT) and positron emission tomography (PET)/CT radiopharmaceuticals are successfully used for diagnostic and therapeutic purposes. Gallium-68 DOTATATE PET/CT uses a radiolabeled somatostatin analog to bind somatostatin receptor-2, which is expressed on the surface of well-differentiated and moderately differentiated NETs. Gallium-68 DOTATATE PET/CT has shown superior accuracy in detecting Grade 1 and 2 NETs. It has been reported in large clinical series that the false positive rate and false negative rate of gallium-68 DOTATATE PET/CT are 4.0% and 2.3%, respectively.[10,11]

   (b) (a) (d) Compared to gallium-68 DOTATATE PET/CT, CT, CT, MRI, and EUS are less specific in detecting GI submucosal NETs.[9,12]

BRIEF REVIEW OF THE TOPIC

EP, also known as heterotopic pancreas, is pancreatic tissue located outside the pancreatic parenchyma without vascular or ductal communication with the pancreatic gland. EP is rarely symptomatic, typically detected incidentally at surgery or autopsy. 85%–90% are in the upper GI tract.[13] The most common site of EP is the stomach or gastroesophageal junction and most of the case reports are from this site.[6,14-18]

The diagnosis of intraluminal EP can be challenging, but it is important.[19] When EP can be differentiated from a GIST or NET in an asymptomatic patient, a surgery usually can be avoided. Noninvasive imaging studies such as CT and MRI may show nonspecific enhancing thickening in the stomach or bowel, but many lesions are missed. Endoscopy typically reveals a SEL with bland, normal overlying mucosa. EUS-FNA has gained popularity in assessing the SELs and in obtaining cytological materials for accurate diagnosis.[3] The major differential diagnoses of EP on FNA cytology are NET and metastatic ACC. If a EUS-FNA shows a mixtures of glandular, acinar, and islet cells, the diagnosis of EP is usually evident. In our case, the cellularity is scant to moderate, and there is no glandular epithelium. Given the overlapping cytological features of acinar and islet cells, a more common SEL, NET, was suspected. However, cell block is insufficient for further studies. Nevertheless, the negative gallium-68 DOTATATE PET/CT should alert the pathologist that a NET is highly unlikely and the possibility of EP should be considered.

SUMMARY

- Although rare, EP must be differentiated from other GI SELs which have malignant potential
- EUS-FNA of the GI SELs is an effective diagnostic tool to establish the diagnosis of EP
- Pathologists should be aware of the morphologic appearance of EP on EUS-FNA and a cell block with immunostains may be helpful to differentiate EP from NET
- Correlation with gallium-68 DOTATATE PET/CT is helpful to rule out NETs.
COMPETING INTERESTS STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

All authors of this article declare that we qualify for authorship as defined by ICMJE http://www.icmje.org/#author. Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the content of this article.

ETHICS STATEMENT BY ALL AUTHORS

As this is a quiz case without identifiers, our institution does not require approval from Institutional Review Board.

LIST OF ABBREVIATIONS (In alphabetic order)

ACC - Acinar cell carcinoma
EP - Ectopic pancreas
EUS - Endoscopic ultrasound
FNA - Fine needle aspiration
GIST - Gastrointestinal stromal tumor
NET - Neuroendocrine tumor
SEL - Sub-epithelial lesion

EDITORIAL/PEER-REVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (the authors are blinded for reviewers and vice versa) through automatic online system.

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