Quiz Case

Pancreatic cyst endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA): Benign or malignant. Clues to cytological diagnosis with major consequences

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EUS-FNA of a 2.3 cm cystic lesion in tail of pancreas of 50 year old American woman showed cytopathologic findings seen in Figure 1. The Cyst fluid amylase was high (>20,000 units/L). Carcinoembryonic Antigen (CEA) was not raised.

Figure 1: Relatively hypocellular aspirates showed poorly preserved cells with myxoid debris and focal yellow refractile pigment (in both Pap and Diff Quik stained smears) without epithelial cells, except scant gastric mucosal contamination. [a (x 20)- Pap stain; b (x 20), c and d (x 100)- Diff-Quik stain].

QUESTION # 1
What is your interpretation?

a. Mucinous cystic lesion (mucinous cystic neoplasm [MCN]/intraductal papillary mucinous neoplasm [IPMN])
b. Pseudocyst
c. Carcinoma with cystic and necrotic changes
d. Cystic neuroendocrine tumor.

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Received : 12 February 2021
Accepted : 04 May 2021
Published : 02 April 2022

DOI
10.25259/Cytojournal_11_2021

Quick Response Code:
ANSWER

b. Pseudocyst.
The differential diagnosis of pancreatic cyst includes neoplastic and non-neoplastic categories. Although the majority of pancreatic cysts are benign, the survival after invasive carcinomas in potentially malignant mucinous cystic lesions either MCN or IPMN is often dismal. Distinction between a true cyst versus a pseudocyst can be challenging. The crucial role of cytology is to properly triage such patients.

EUS-FNA in the current case was relatively hypocellular with abundant thick myxoid material in the background without unequivocal epithelial cells (cyst lining cells). The polyhedral cells showed vacuolated/foamy cytoplasm with small, occasional folded nuclei consistent with reactive foamy histiocytes. Many spindle cells with repair-like pattern were also noted [Figure 2]. Cyst debris with occasional non-specific crystalline yellow pigment was noted in the background. The yellow pigment retained its yellow crystalline feature in Diff-Quik smear also. The cell-block (CB) showed stroma with reactive pancreatic ducts with mild chronic inflammation without pancreatic acini and malignancy [Figure 3]. The findings were consistent with pseudocyst in the background of chronic pancreatitis.

The patient had a medical history of alcohol abuse, pancreatitis, and ovarian borderline mucinous neoplasm status post-resection presented with upper abdominal pain. Based on the history of borderline mucinous neoplasm of the ovary, the differential interpretation included MCN and IPMN. However, the absence of epithelial lining and lack of thick viscid mucin ruled out MCN or IPMN.

Cystic neuroendocrine tumor would have shown singly scattered plasmacytoid neuroendocrine cells with focal cohesive pattern without significant proportion of myxoid material which was not seen in this case.

QUESTION # 2

Which are the diagnostic features of pancreatic pseudocyst?

a. Chemical analysis of cyst fluid with high amylase
b. Absence of epithelial cells with repair-like stromal cells
c. Foam cells and cyst debris with myxoid background
d. Presence of yellow crystalline pigment
e. All of the above.

The proper diagnosis of a pancreatic cyst should be based on the combination of pre-procedural findings (clinical and imaging) in conjunction with post-procedural findings (chemical analysis of cyst fluid and cytologic evaluation). The ultimate goal of such diagnostic tests is to distinguish benign cyst with malignant potential (IPMN and MCN) and to evaluate the morphological features of malignancy. The helpful features include the presence or absence of yellow pigment, the proportion and nature of background myxoid contents, and the presence or lack of epithelial lining.

The cytologic findings that distinguish pseudocyst from neoplastic cyst with malignant potential are summarized in Table 1. In addition to the cytologic features, cyst fluid analysis along with the clinical presentation and imaging is critical to make correct interpretation. Cytopathology of mucinous cystic lesions also allows evaluation and follow-up for neoplastic progression towards high grade dysplasia and invasive carcinoma.

Myxoid background in pancreatic pseudocysts may be difficult to distinguish from viscid mucin in mucinous cystic lesions [Figure 4]. In our case, it showed focal myxoid

![Figure 2: Cell-block of transgastric EUS-FNA cytology of cystic lesion in tail of pancreas. The sections showed reactive pancreatic ducts in ill-defined lobular architecture with sclerotic stroma without pancreatic acini. (H and E stained cell-block sections; (a) ×10, (b) ×20, (c) ×40, (d) magnification of cropped area).]

![Figure 3: Transgastric EUS-FNA cytology of cystic lesion in the tail of pancreas. Focal collection of polyhedral stromal histiocytes should not be confused with epithelial cells with myxoid debris in the background. This may lead to misinterpretation as mucinous cystic lesion (MCN or IPMN). (Diff-Quik stained direct smear, ×40).]
Pancreatic pseudocyst results from reparative changes secondary to the pancreatic parenchymal injury. Typically, pseudocysts are the result of multiple episodes of acute and chronic pancreatitis. The pseudocyst contents are rich in amylase and/or lipase and lack epithelial lining. History of recurrent pancreatitis with unilocular simple cyst is the classic clinical scenario to trigger the clinical suspicion of a pancreatic pseudocyst. MCN and IPMN, on the other hand, usually present with a multilocular cystic lesion. IPMN communicates with the pancreatic ductal system and usually causes pancreatic duct obstruction with dilated duct on imaging (endoscopic retrograde cholangiopancreatography [ERCP] or magnetic resonance cholangiopancreatography [MRCP]). Thus, obstructive jaundice is the usual initial presentation of IPMN.

Serous cystic neoplasm composed numerous small cysts in a honeycomb-like formation of locules ranging from 1 to 20 mm size are typically seen on CT scan as a multicystic, lobulated lesion described as “bunch of grapes” with tendency for central scar and calcification. There is usually lack of the history of pancreatitis. Some pancreatic primary neoplasms can be associated with cystic degeneration, including neuroendocrine tumors of the pancreas. However, the presence of a previous neoplasm makes the possibility of a pseudocyst less likely.

### QUESTION # 3
What clinical/imaging scenario is typical for pseudocyst compared to neoplastic cyst?

- a. New, non-specific GI complaints with multilocular complex cyst in pancreatic head
- b. New, non-specific GI complaints with cystically dilated pancreatic duct
- c. History of recurrent pancreatitis with unilocular simple cyst
- d. History of pancreatic neuroendocrine tumor with a newly identified partially cystic mass.

### QUESTION # 4
What chemical markers are most helpful in distinguishing pseudocyst from neoplastic mucinous cyst?

- a. CEA and amylase
- b. Amylase and lipase
- c. CA 19-9 and CA-125
- d. Glucose.

Chemical analysis can be an useful ancillary test to support cytopathologic evaluation. The panel of chemical tests to be performed on cyst fluid should be directed based on
In the present case, CB was performed on the cyst fluid tissue material. Sclerotic stroma of pancreatic cystic lesions is expected in neoplastic mucinous cysts. However, gastrointestinal mucosal contamination (both epithelial cells and mucin) is very common and could be a significant diagnostic pitfall in some reports. It is crucial to discern non-neoplastic cysts from neoplastic lesions because the latter though considered benign, have malignant potential. International Consensus Algorithm for the management of mucinous cysts proposed management algorithm recommends that patients with cysts <1 cm should be re-evaluated after 1 year with MRI or thin-slice CT studies and should undergo resection if the cyst increases in size.

About 80% of pancreatic cystic lesions identified on imaging are non-neoplastic, including pseudocysts. Pancreatic pseudocyst is an encapsulated collection of homogenous amylase-rich fluid with little or without necrotic debris within it. Often, it is well-circumscribed and located outside of the pancreas, usually in the lesser sac. However, pseudocysts have been located in many areas in and around the pancreas. Pancreatic pseudocysts form as a complication of chronic pancreatitis and less commonly from acute pancreatitis. They are found in 0.5–1/100,000 adults per year with significant association with alcohol consumption.

Pancreatic cancer is arguably the deadliest cancer. Because of the malignant potential of neoplastic pancreatic cysts, familiarity of the cytomorphologic features of pancreatic pseudocysts are of momentous importance for practicing cytopathologists to make an accurate diagnosis that would affect the trajectory of the patient care. A comprehensive multimodal approach including a combination of clinical, imaging, chemical, cytomorphologic, and molecular findings needs to be applied to reach the final diagnosis.

The efficacy of EUS-FNA of cystic lesions of pancreas partly depends on the site, size, and characteristics of the target tissue as well as on the expertise, training, and interaction between the endosonographer and the cytopathologist. Acquisition of diagnostic samples is approached in different ways depending on the site and type of the lesion. Cytological samples are ideal for cyst fluid analysis, immunohistochemistry, and molecular testing. Direct smears are invaluable, both for immediate assessment but also for the final morphological diagnosis. The needle rinses can be processed as liquid-based cytology or CB. CB increases the diagnostic accuracy of EUS-FNA. It facilitates immunocytochemistry. A mixture of inflammatory cells, islet cells, and fragments of fibrous stroma is usually present in the aspirate from patients with acute pancreatitis. Cytopathology helps in distinguishing cyst types and also allows evaluation for dysplasia and invasive carcinoma in mucinous cystic lesions with the higher malignant potential. Cytology can be helpful in finding atypical epithelial cell clusters with drunken honey-comb pattern that has high nuclear-to-cytoplasmatic ratio, nuclear membrane irregularity, nuclear size, nuclear crowding, and hyperchromasia to clinch a diagnosis of malignancy.

Pseudocyst usually contains inflammatory cells, for example, histiocytes, neutrophils, or both on myxoid background focally in Diff-Quik stained preparation. On a Papanicolaou stain, abundant extracellular mucin with epithelial cells is a finding that strongly suggests a diagnosis of neoplastic mucinous cyst. However, gastrointestinal mucosal contamination (both epithelial cells and mucin) is very common and could be a significant diagnostic pitfall leading to atypical interpretations. Pseudocyst shows yellow crystalline material in both Pap stained and Diff-Quik stained preparations. This pigment is not hemosiderin (which stains blue-gray in Diff-Quik stain). The features suggest that it may be related to hematoidin which also retain its yellow crystalline nature in Diff-Quik stained smear.

It is important to consider preparation of CBs from all FNA specimens whenever possible. Specimens that have tissue material and/or blood are suitable for CBs following smear preparation. Recently described method, with ready to use kits allows quantitatively and qualitatively optimum CBs from most of the cytology specimens including EUS-FNA aspirates of pancreatic cystic lesions. In the present case, CB was performed on the cyst fluid tissue material. Sclerotic stroma with reactive pancreatic ducts was noted. The duct lumens were irregular and lined by epithelial lining with polymorphic cells with dense nuclear chromatin. Spindle cells and foamy histiocytes are present with a repair like pattern.

Not all cysts could be characterized by FNA and cytopathology alone. An elevated CEA level (>192 ng/mL) and v-Ki-ras2...
mutation in the aspirate are confirmatory of a mucinous cyst. Overexpression of DNA oncogenes (e.g., GNAS, KRAS) and/or loss of heterozygosity of tumor suppressor genes (e.g., tumor protein [p53], cyclin-dependent kinase inhibitor 2A [p16], ring finger protein 43) detected in cyst fluid also aid to the diagnosis and determination of malignant potential.\(^4\)

**SUMMARY**

The primary role of cytology is the exclusion of cyst with malignant potential (IPMN and MCN) or malignant cystic lesion. Pseudocysts usually show cytologic features which are frequently nonspecific and are primarily interpreted in correlation with clinical (alcoholism and pancreatitis) and imaging (gland atrophy with calcification and a unilocular cyst without a mural nodule) features with chemical analysis of cyst fluid.

Yellow pigment which continues to be yellow crystalline in Diff-Quik stained smears is important clue as surrogate marker of a pseudocyst. Myxoid background focally should not be confused for viscid and abundant mucin in cysts with malignant potential (IPMN and MCN).

Answers for Question 2 through 4:

2. e  
3. c  
4. a.

**COMPETING INTERESTS STATEMENT BY ALL AUTHORS**

The authors declare that they have no competing interests.

**AUTHORSHIP STATEMENT BY ALL AUTHORS**

Each author has participated sufficiently in the work and takes public responsibility for the appropriate portions of the content of this article.

**ETHICS STATEMENT BY ALL AUTHORS**

As this is case report without identifiers, our institution does not require approval from the Institutional Review Board (or its equivalent).

**LIST OF ABBREVIATIONS (IN ALPHABETIC ORDER)**

- CAT – Computerized axial tomography  
- CB – Cell block  
- CEA – Carcinoembryonic Antigen  
- CT – Computed tomography  
- DNA – Deoxyribonucleic acid  
- ERCP – Endoscopic retrograde cholangiopancreatography  
- EUS-FNA – Endoscopic ultrasound guided fine needle aspiration  
- HP – High power  
- IPMN – Intraductal papillary mucinous neoplasms  
- LP – Low power  
- MCN – Mucinous cystic neoplasm  
- MR – Magnetic resonance  
- MRCP – Magnetic resonance cholangiopancreatography  
- PAP – Papanicolaou smear  
- HP – High power

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How to cite this article: Alrajjal A, Choudhury MS, Bandyopadhyay S, Shidham VB. Pancreatic cyst endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA): Benign or malignant. Clues to cytological diagnosis with major consequences. CytoJournal 2022;19:26.

HTML of this article is available FREE at: https://dx.doi.org/10.25259/Cytojournal_11_2021