Pancreatic Cytopathology

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KEYWORDS

• Cytopathology • Fine-needle aspiration • Pancreatic cytopathology • Cytology • FNA • Pancreas

Key points

- The sensitivity and specificity of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of pancreatic lesions both approach 95% with a low complication rate.
- Familiarity with benign elements, in particular contaminating gastrointestinal epithelium, is critical for arriving at an accurate diagnosis.
- EUS-FNA is the method of choice for the procurement of cytologic material for diagnosis in the setting of a cystic lesion; aspirates are often acellular and cytology alone is inferior compared to a combination of cytology with cyst fluid analysis.
- Well-established cytomorphological features of pancreatic adenocarcinoma include loss of organization, anisonucleosis, irregular nuclear membranes, nuclear crowding, nuclear overlap, high nuclear-to-cytoplasmic ratios, 3-dimensional architecture, and single cells.
- Recently, cyst fluid analysis has incorporated the detection of molecular markers through techniques such as gene sequencing, proteomic analysis, and detection of microRNA species to diagnosis premalignant and malignant cystic neoplasms, specifically in specimens with limited material.

ABSTRACT

Pancreatic cytopathology, particularly through the use of endoscopic ultrasound-guided fine-needle aspiration (FNA), has excellent specificity and sensitivity for the diagnosis of pancreatic lesions. Such diagnoses can help guide preoperative management of patients, provide prognostic information, and confirm diagnoses in patients who are not surgical candidates. Furthermore, FNA can be used to obtain cyst fluid for ancillary tests that can improve the diagnosis of cystic lesions. In this article, we describe the cytomorphological features and differential diagnoses of the most commonly encountered pancreatic lesions on FNA.

OVERVIEW TO PANCREATIC FINE-NEEDLE ASPIRATION

Current clinical management is dependent on the rapid and accurate diagnosis of pancreatic lesions. Although clinical and radiological findings can suggest malignancy, current management strategies rely on pathologic diagnosis, particularly in nonsurgical patients.[1–3] Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death with a projected rise to the second leading by 2020.[4,5] Survival is poor with a 5-year survival of 7% and less than 20% of patients considered surgically resectable at diagnosis.[4–6] Although surgical and neoadjuvant management of the disease has advanced, overall mortality has continued to increase.[4] However, patients with early localized disease have shown an improved 5-year survival, up to 30%, following complete surgical resection.[7,8] Therefore, an early definitive diagnosis appears to be the most critical step in current management algorithms.[9]

Initial evaluation of pancreatic lesions is performed with imaging studies, preferably multidetector computer tomography (CT), MRI, or magnetic resonance cholangiopancreatography

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(MRCP), depending on the presence of a cystic component.[10–12] Although biopsy may not be required in the setting of highly suspicious clinical and radiologic findings, it is necessary in most cases in which neoadjuvant therapy is the initial management.[13] Modalities for image-guided pancreatic tissue sampling have evolved over time from transabdominal ultrasound-guided and CT to more recently endoscopic ultrasound (EUS). Endoscopic retrograde cholangiopancreatography (ERCP) is restricted to ductal sampling in the setting of biliary stricture with cytologic sampling restricted to exfoliative cells in bile and/or brush samples. These samples have been shown to have low sensitivity (6%–32%) and have been replaced over time by EUS in the diagnosis of solid neoplasms.[14–17] Although transabdominal ultrasound biopsy is the least invasive, it has an overall low sensitivity for detecting small lesions, particularly in the pancreatic head/uncinate, the most common site for adenocarcinoma.[18–20] CT-guided biopsy also appears inferior because of its expense, radiation exposure, and lack of real-time guidance.[18] The advent of EUS has changed pancreatic lesion evaluation significantly by allowing for simultaneous nonradiation imaging combined with the ability for cytologic sampling. EUS has been shown to have greater accuracy for small lesions (<3 cm) relative to both ultrasound or CT with less risk for peritoneal seeding when compared with percutaneous core needle biopsy.[21–24] Multiple systematic reviews have shown the pooled sensitivity and specificity of EUS approach 95% with a complication rate similar to percutaneous FNA, ranging from 0% to 5%.[25–28] EUS-FNA, introduced more than 20 years ago, has accumulated extensive support in the literature and is now the modality of choice in procuring specimen material for diagnosing pancreatic neoplasia, including nonadenocarcinoma.[26,29,30]

Cytology specimens, therefore, play a key role in the initial diagnosis and management of solid and cystic pancreatic lesions, including pancreatobiliary strictures.[31] This has led to a particularly important emphasis on the terminology and nomenclature in pancreatobiliary cytology reporting. Currently there is no standard or universal reporting format for pancreas cytology; however, the Papanicolaou Society of Cytopathology recently published a proposed standardized nomenclature, see **Table 1**.[32] The proposed 6-tier scheme has divided the conventional *Other* category into Atypical (Category III) and *Neoplastic: Benign* or *Neoplastic: Other* (Category IV), creating, functionally, 7 discrete categories. This modification allows for the discrimination of "atypical" findings, not including reactive, from benign and low-grade neoplasms. This is particularly relevant to diagnosing specimens with limited material, whereby secondary to low cellularity or preparation artifact, a definitive diagnosis of premalignant, suspicious, or benign cannot be made. Lesions classified within the *Neoplastic* category have more cellularity that show specific architectural and cytologic features that allow for a reproducible diagnosis of a benign entity (cystadenoma, neuroendocrine microadenoma, and lymphangioma) or low-grade neoplasms (premalignant mucin-producing cystic lesions, intraductal pancreatic mucinous neoplasm [IPMN] and mucinous cystic neoplasm [MCN], pancreatic neuroendocrine tumor [PanNET] and solid pseudopapillary neoplasm [SPN]) specified as *Other*.[32,33] The authors' intent for this latter category IV was to allow for ease of correlation to the 2010 World Health Organization (WHO) classification of pancreatic lesions and thus drive cytologic diagnoses into a reproducibly correlative format.[32,34] Another advantage of the new classification scheme is that a lack of epithelial cells no longer precludes a diagnostic specimen but rather allows for ancillary fluid chemistry testing to have diagnostic value. This is reflected by the use of *Neoplastic: Other* in the setting of an elevated carcinoembryonic antigen (CEA) without an epithelial component. The remaining diagnostic categories show features consistent with conventional diagnostic criteria. The WHO and the Papanicolaou Society for Cytopathology have suggested classification of *Malignant* (category V) to include adenocarcinoma (and its variants), acinar cell carcinoma, poorly differentiated neuroendocrine carcinoma (including large cell neuroendocrine carcinoma), pancreatoblastoma, lymphoma, and metastatic lesions.[32,34] Recently, Saieg and colleagues[35] showed that reclassification of 55 specimens using the proposed Papanicolaou categories has the greatest effect on the atypical and suspicious categories. They found that reclassification allowed for 94% of their atypical specimens to be diagnosed as *Neoplastic: Other*, including 33% nondiagnostic and 23% of negatives.[35] The latter of which is the result of an elevated CEA value considered sufficient for the diagnosis.[35] The positive predictive value for their diagnoses was 88.9%.[35] Thus, in the context of a multidisciplinary and multimodality approach to pancreatic lesion diagnosis and therapy, a standardized nomenclature would have the benefit of predictably guiding management algorithms while improving the correlation of future studies.