

Ancillary Studies, Including Immunohistochemistry and Molecular Studies, in Pancreatic Cytology

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KEYWORDS

• Ancillary studies • Fine-needle aspiration • Pancreas

ABSTRACT

Fine-needle aspiration biopsy of the pancreas is indicated for sampling of solid and cystic masses. Preoperative cytologic diagnosis of pancreatic ductal adenocarcinoma and cystic lesions on cytology can be problematic, and ancillary studies may help confirm diagnosis. Ancillary studies in pancreatic cytology include special stains, immunohistochemistry, mutational analyses of specific genes, cyst fluid analysis of tumor markers and enzymes, and, in some instances, flow cytometry. Proteomics, microRNA sequencing, and whole-exome gene sequencing have been used to illustrate the progression of pancreatic neoplasms and identify key diagnostic markers. This article summarizes recent literature on ancillary studies in pancreatic fine-needle aspiration samples.

OVERVIEW

Fine-needle aspiration biopsy (FNAB) is the most effective procedure for sampling solid and cystic masses of the pancreas. Guidance techniques include intraoperative palpation and direct

visualization, CT, and ultrasound, including endoscopic ultrasound (EUS).

An integrative approach to the evaluation of pancreatic aspirates, incorporating the clinical history, radiologic findings, cytologic findings, and ancillary studies, yields the most clinically relevant interpretation of aspirate material. The most crucial of these are imaging findings indicating whether a suspicious lesion is solid or cystic, because this information determines the cytopathologic algorithm. Different diagnostic entities are considered depending on whether the imaging studies show a mass that is solid, mixed solid and cystic, purely cystic, or cystic with a connection to the ductal system (an intraductal lesion).

ANCILLARY STUDIES

Ancillary studies available for use with pancreatic FNAB include histochemical stains, immunohistochemistry (IHC), flow cytometry, and cyst fluid analysis for enzymes, tumor markers, and mutational analyses. Ancillary studies are used most routinely for the differential diagnosis of nonductal solid neoplasms and metastases and the work-up of pancreatic cyst fluids.

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ANCILLARY STUDIES IN SOLID PANCREATIC NEOPLASMS

Histochemical Stains

The use of special stains in the cytologic diagnosis of solid pancreatic neoplasms is somewhat limited and has been superseded by IHC. In tumors with ductal differentiation, including pancreatic ductal adenocarcinoma (PDA), intra-cytoplasmic mucin can be demonstrated with mucicarmine and periodic acid–Schiff (PAS) stains. PAS stain with diastase has also been helpful in diagnosing acinar cell carcinoma and solid pseudopapillary neoplasm (SPN). In acinar cell carcinoma, PAS-positive, diastase-resistant staining occurs in cytoplasmic zymogen granules, and in SPN, PAS-positive, diastase-resistant globules are seen in both cytoplasm and extracellular environ. Not all acinar cell carcinomas contain zymogen granules, however, making the diagnostic utility of PAS limited.

Immunohistochemistry

IHC studies have proven useful in the cytologic diagnosis of solid tumors. For PDA and its variants, ductal differentiation is supported by tumor positivity for carbohydrate cancer antigen (CA19-9), carcinoembryonic antigen (CEA), MUC1, cytokeratin (CK) 7, and CK19. Distinction of PDA from reactive ductal cells in chronic pancreatitis can be challenging on cytomorphology, and IHC can help distinguish the two. PDA is positive for p53 and negative or weakly positive for caudal-related homeobox 2 (CDX2) and often shows loss of deleted in pancreatic cancer (Dpc4) protein. In addition, PDA is positive for maspin, S100P, and insulin-like growth factor 2 mRNA-binding protein 3 (IMP-3) and negative for von Hippel-Lindau protein (pVHL), whereas reactive ductal cells show opposite results.¹ IHC markers of neuroendocrine differentiation include synaptophysin, chromogranin A, CD56, and CD57. In addition, some neuroendocrine tumors are positive for CK19, which is associated with more aggressive behavior. The ki-67 immunostain is critical for the grading of neuroendocrine neoplasms, through calculation of the ki-67 labeling index.² Markers of acinar differentiation include pancreatic enzymes trypsin and chymotrypsin. These are positive in acinar cell carcinoma and pancreatoblastomas with acinar differentiation. BCL10 is an additional marker of acinar cell carcinoma.³ For mixed acinar-neuroendocrine carcinomas, tumor cells express both acinar and neuroendocrine markers. SPNs are of uncertain lineage with no normal equivalent in the non-neoplastic pancreas.

These tumors show a unique immunoprofile and are negative or focally positive for pancytokeratin but stain positively for β -catenin (nuclear expression), CD10, vimentin, and progesterone receptor (PR).

Molecular Studies

Molecular testing has been used more recently in the diagnosis of multiple solid pancreatic neoplasms. Whole-exome sequencing in PDA has demonstrated somatic mutations in key driver genes, *KRAS*, *p16/CDKN2A*, *DPC4/SMAD4*, and *TP53*. MicroRNA (miRNA) sequencing has also shown alterations in PDA resections and needle aspirates.⁴ These involve many miRNAs, including miR-21, miR-155, miR-221,⁵ miR-200c, and miR-451,⁴ to name a few. Molecular analysis of pancreatic neuroendocrine tumors has demonstrated somatic mutations of death domain-associated protein (*DAXX*) and α -thalassemia/mental retardation syndrome X-linked (*ATRX*) genes, which result in loss of IHC expression of *DAXX* and *ATRX* proteins in tumor cells.⁶ Chromosomal studies have revealed numerous complex karyotypes in acinar cell carcinoma, including aneuploidy, loss of chromosome 11p, and mutations in the *APC/β-catenin* gene.

Flow Cytometry

Flow cytometry typically is not used in the diagnosis of solid pancreatic tumors. However because lymphomas⁷ and plasmacytomas may involve the pancreas⁸ and may resemble well-differentiated pancreatic neuroendocrine tumors (PanNETs), flow cytometry may play a critical role in distinguishing these differentials, by demonstrating clonal plasma cell or lymphoid populations.

CYTOLOGIC AND ANCILLARY FINDINGS IN SOLID PANCREATIC NEOPLASMS

PANCREATIC DUCTAL ADENOCARCINOMA

PDA accounts for 85% of solid pancreatic tumors. The cytologic diagnosis of poorly differentiated PDA is not typically a diagnostic challenge because neoplastic cells show overt malignant features (**Fig. 1**).^{9,10} Well-differentiated PDA is more challenging because the cytologic features are subtle and easily misinterpreted as benign or reactive cells of chronic pancreatitis. The most characteristic cytologic findings in well-differentiated PDA are poorly formed ductal sheets with focal nuclear crowding (so-called “drunken” honeycomb sheets) (**Fig. 2**),^{9,10} with only minimal deviation from normal duct morphology.

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