Standardized Terminology in Pancreatobiliary Cytology: The Papanicolaou Society Guidelines

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Pancreatobiliary Masses: Differential Diagnosis

- **Inflammatory**
  - Pancreatitis
  - Biliary tract inflammation

- **Benign/Nonneoplastic**
  - Lymphoepithelial cyst of the pancreas
  - Ectopic Splenule
  - Squamoid cyst

- **Neoplastic**
  - Neuroendocrine Tumors
  - Solid pseudopapillary Neoplasm
  - Serous cystadenoma
  - Mucinous cystic neoplasm (pancreatic and biliary)

- **Neoplastic**
  - Pancreatic and Biliary Intraepithelial Neoplasia (BilIN)
    - Grades 1, 2, 3
  - Intraductal papillary Mucinous Neoplasms
  - Intraductal papillary Neoplasms-Biliary Tract (IPN-B)
    - LGD, MGD, HGD

- **Malignant**
  - Adenocarcinoma and variants
  - Acinar cell carcinoma
  - Neuroendocrine carcinomas
Algorithmic approach of pancreatic masses based on imaging features
Issues with Cytology Reporting of Pancreatobiliary Specimens

• Nonstandardized reporting lead to confusion for the clinicians treating the patient with a pancreatic mass or lesion

• Lack of epithelial cells used as criteria for nondiagnostic
  • IPMN and MCN not uniformly handled, thick mucin still indicative of underlying neoplasm, even without neoplastic cells
  • Pseudocysts will lack epithelial cells
  • Serous cystadenoma may lack neoplastic cells
  • Cases signed out as c/w cyst contents

• What cytological criteria should be used to interpret a lesion as IPMN or MCN?
  • Atypical mucinous epithelium classified as atypical, rather than neoplastic, or as suspicious for carcinoma
Issues with Cytology Reporting of Pancreatobiliary Specimens cont.

• Was high grade dysplasia in IPMN atypical, suspicious or malignant?
• Serous cystadenoma classified as negative or atypical
• Were neuroendocrine tumor and solid pseudopapillary neoplasms suspicious, positive, or other?
Standardized Terminology and Nomenclature for Pancreatobiliary Cytology: The Papanicolaou Society of Cytopathology Guidelines

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Purpose of Standardization

• Unify reporting of disease categories among pathologists
• Reduce and improve inter and intraobserver variability
• Provide clinically relevant information for patient management
• To reflect the current understanding of the biology of disease entities
Categories

- I. Nondiagnostic
- II. Negative (for malignancy)
- III. Atypical
- IV. Neoplastic: benign or other
- V. Suspicious (for malignancy)
- VI. Positive (for malignancy) or malignant

* only for laboratory systems where the information system requires it.
Nondiagnostic

Category I
Nondiagnostic

- **Definition:** A non-diagnostic cytology specimen is one that provides no useful information or diagnostic information about the sampled mass.
  - Discordant imaging and cytology findings
  - Cyst fluids that yield insufficient material for ancillary studies
- Any cellular atypia precludes a non-diagnostic category
- **Caveats:**
  - There are no established criteria for adequacy in pancreatobiliary specimens
  - Nondiagnostic does not equal unsatisfactory
    - Unsatisfactory indicates that a specimen cannot be processed and evaluated microscopically. There is no technical billing component.
    - A nondiagnostic specimen can be processed and assessed microscopically, but the sample does not provide information that is diagnostic of the lesion sampled. The technical component may be billed.
Nondiagnostic Cytological Criteria

• Preparation or obscuring artifact preclude evaluation of the cellular sample
• Gastrointestinal contaminant only
• Benign acinar and ductal epithelium derived from a clearly defined solid or cystic mass lesion
• Acellular aspirates of a pancreatic mass or pancreatic brushing
• Acellular aspirate of a cyst without evidence of mucinous etiology.
  • Lack of thick, background mucin and/or oncotic cells
  • Lack of elevated CEA
  • Lack of KRAS or GNAS mutations
Discordant Imaging and Cytology
Discordant Imaging and Cytology

• Imaging shows a well-defined mass
• Cytology shows benign pancreatic elements
• Report
  • Adequacy: Satisfactory for evaluation or evaluation limited by lack of representative cells?
  • Interpretation: Nondiagnostic: Benign acinar and ductal cells
  • Category: Nondiagnostic
  • Comment: The sample may not be representative of the targeted, well-defined lesion.
Nondiagnostic due to Preparation Artifact

• Adequacy: Evaluation limited by thickness of smear
• Interpretation: Nondiagnostic specimen
• Category: Nondiagnostic
GI Contaminant

• Adequacy: Evaluation limited by lack of representative cells
Interpretation: Nondiagnostic, gastrointestinal contaminant only

• Category:Nondiagnostic

• Comment: The sample does not explain the mass lesion identified on imaging studies.
Negative

Category II
Negative

• **Definition:** Adequate cellular and/or extracellular material to evaluate and or define a nonneoplastic lesion identified on imaging
• The category must qualified by a diagnosis of a specific condition
• Includes the presence of normal pancreatic parenchyma in the appropriate clinical setting
  • Vague fullness of the pancreas
  • No distinct pancreatic mass
Differential Diagnosis

• Benign pancreas
• Acute Pancreatitis
• Chronic Pancreatitis
• Autoimmune pancreatitis
• Splenule/Ectopic spleen/Accessory spleen
• Pseudocyst
• Lymphoepithelial cyst
Negative Cytological Criteria

• Benign pancreatic ductal and acinar epithelium from a vague fullness
• Benign bile duct epithelium and bile
• Benign gastric or duodenal epithelium
• Aspirates showing cytological features of:
  • Acute or chronic pancreatitis
  • AIP
  • Pseudocyst
  • LECP
  • Splenule
Negative: Chronic Pancreatitis

• Imaging: Hypoechoic mass in a patient with a history of pancreatitis. CA19-9 levels normal.

• Cytology Report:
  • Adequacy: Satisfactory for evaluation
  • Interpretation: c/w chronic pancreatitis
  • Category: Neg.
Negative: Lymphoepithelial cyst

- Imaging: Well-defined cystic mass
- Cytology: anucleated squames, cholesterol crystals, debris
- Ancillary studies: elevated CEA, elevated amylase, no KRAS or GNAS mutations
- Report:
  - Adequacy: Satisfactory
  - Interpretation: Lymphoepithelial cyst
  - Category: Neg.
  - Comment: The cytomorphological findings are those of a lymphoepithelial cyst of the pancreas. These cysts present with elevated levels of CEA and amylase.
Negative: Pseudocyst

- Imaging: Cyst in the tail of the pancreas; aspirated abundant turbid, brown fluid
- Cytology: histiocytes, yellow pigment, debris
- Ancillary studies: amylase = 50,000 U/L; CEA= 3 ng/ml
- Report
  - Adequacy: Satisfactory
  - Interpretation: Inflammation, histiocytes, debris, and yellow pigment, no epithelial lining cells identified, c/w pseudocyst
  - Category: Neg.
  - Comment: The morphology, combined with the ancillary studies are supportive of a diagnosis of pseudocyst.

*Important caveat: Only diagnose a pseudocyst if it has the characteristic yellow pigment on cytology. Otherwise, be descriptive. Amylase and CEA levels in MCN and IPMN may be misleading. Other processes may have only histiocytes or hemosiderin laden macrophages.
Negative: Splenule

- Imaging: Well-defined mass
- Cytology: plasma cells and vascular structure on cell block
- Report:
  - Adequacy: Satisfactory
  - Interpretation: Splenule
  - Category: Negative
Atypical

Category III
Atypical

• *Definition*: Cells with cytoplasmic, nuclear, or architectural features not consistent with normal or reactive cellular components of the pancreas or bile ducts, and insufficient features to classify them as a neoplasm or suspicious for a high grade malignancy
  • The findings do not explain the lesion identified on imaging
  • Follow-up evaluation is warranted
Atypical

Cytological criteria for ductal epithelium

• Loss of architectural polarity
  • Mild loss of honeycombing
  • When seen on edge, cells remain at base
  • No crowded, three-dimensional groups
  • Absence of true nuclear molding

• Near normal N/C

• Slight nuclear membrane irregularities

• Mild parachromatin clearing

• Small nucleoli

• Minimal anisonucleosis, 2:1
  • 4:1 for carcinoma

• Clean or bloody background
  • Coagulative tumor type necrosis suspicious
Atypical Cytological Criteria

• Atypical mucinous epithelium in a pancreatic aspirate
  • PanIN
  • Gastric contaminant
  • IPMN

• Biliary brush specimens with mucinous epithelium and other atypical findings
  • BilIN
  • IPN-B

• Cellular component is suggestive of a PanNET or SPN but the sample is of insufficient quantity or quality for definitive diagnosis
Atypical

• Imaging: mass lesion in the head of the pancreas
• Cytology: Scantly cellular smear, ductal group with nuclear overlap, nuclear membrane irregularity, infiltrated by neutrophils
• Report:
  • Adequacy: Evaluation limited by air-drying artifact
  • Interpretation: Atypical groups of ductal epithelium with acute inflammation
  • Category: Atypical
  • Comment: The findings may be related to reactive process, however, a neoplastic process is not excluded. Recommend correlation with clinical and imaging findings and follow-up as indicated.
Atypical

- Imaging: Stricture in bile duct
- Cytology: maintained honeycomb, with subtle loss of polarity, subtle nuclear angulations, parachromatin clearing

Report:
- Adequacy: Satisfactory
- Atypical ductal epithelium
- Category: Atypical
Atypical

- Imaging: well-defined, hypoechoic mass
- Cytology: few monomorphic cells
- Report:
  - Adequacy: Evaluation limited by scant representative cells
  - Interpretation: Few monomorphic neoplastic cells present
  - Category: Atypical
  - Comment: The differential diagnosis includes pancreatic neuroendocrine tumor and solid pseudopapillary neoplasm. The material is insufficient for ancillary studies to further define the lesion.
Neoplastic

Category IV
Neoplastic: Benign

• **Definition**: The cytological specimen is sufficiently cellular and representative, with or without the context of clinical, imaging and ancillary studies to be diagnostic of a benign neoplasm.

• Neoplasms included in this category:
  • Serous cystadenoma
  • Schwannoma
  • Cystic teratoma
Neoplastic: Benign
Report
Adequacy: Satisfactory
Interpretation: Nonmucinous cuboidal epithelium, c/w imaging impression of serous cystadenoma
Category: Neoplastic: Benign (Other)
Comment: The cyst fluid CEA level was 2.9 ng/ml and the amylase was 500 U/L. Caveat: CEA and amylase may be quite variable. Most aspirates yield only hemosiderin laden macrophages.
Neoplastic: Other

• **Definition:** Defines a neoplasm that is either premalignant, or a low grade malignant neoplasm.

• Neoplasms included in this category:
  • Neoplasm that is preinvasive cancer
    • IPMN or MCN with LGD, MGD, HGD
    • IOPN
  • Solid cellular neoplasm
    • Pancreatic neuroendocrine tumor
    • Solid pseudopapillary neoplasm
  • Extra-adrenal paraganglioma
  • Gastrointestinal Stromal tumor
Rationale

• Established to provide a category for neoplasms that were either not clearly benign, such as serous cystadenoma, nor clearly aggressive, and high grade in their behavior, such as ductal adenocarcinoma.
• Standardize cytological nomenclature and terminology to correlate with WHO 2010 classification and terminology.
  • The words tumor and neoplasm connote a neoplasm, but not a malignancy
• Patients with neoplasms in this category may have the option of being managed conservatively
  • PanNET may be observed
  • IPMN with low risk features may be observed.
• The categories of atypical and suspicious connote an indeterminate interpretation.
• Does not define these a benign or malignant
Neoplastic: Other

• Imaging: well-defined, solid, hypoechoic mass

• Report:
  • Adequacy: Satisfactory
  • Interpretation: Pancreatic neuroendocrine tumor, well-differentiated
  • Category: Neoplastic:Other (Other)
  • Ancillary Testing: CAM 5.2+, CD 56+, synaptophysin +, Chromogranin +
Neoplastic: Other

• Imaging: well-defined, solid and cystic mass

• Report:
  • Adequacy: Satisfactory
  • Interpretation: Solid pseudo-papillary neoplasm
  • Category: Neoplastic:Other (Other)
  • Ancillary Testing: beta-catenin nuclear (mutated)
Neoplastic: Other
Ferning

Psammomatous calcifications a feature of IPMN

Cell block showing thick, feathery type material
Neoplastic: Other

• Imaging: Large, multiloculated cyst in the tail of the pancreas with evident connect to the pancreatic ductal system

• Report:
  • Adequacy: Satisfactory
  • Interpretation: Thick background mucin, histiocytes, and oncotic cells, consistent with IPMN
  • Category: Neoplastic: Other (other)
  • Comment: No neoplastic epithelium is present for evaluation of dysplasia. The cytological findings correlated with the imaging findings support the above interpretation.
Incidental Cysts in the Pancreas

- Incidental cysts of the pancreas are common
- More likely to be neoplastic rather than benign
  - 30% of all incidental masses were IPMN in one series
  - 55% were MCN or IPMN (preinvasive precursors), only 4% were pseudocyst
- Pathologist is reviewing the cyst fluid to assess for the presence of pre-invasive precursors lesions
  - Pseudocyst diagnosis of exclusion
Cyst Contents
Criteria for Mucinous Cyst

• Fluid viscous, clear or white
• Cytology shows mucinous background as described, +/- neoplastic epithelium
• Ancillary studies
  • CEA elevated
  • Mutational analyses will identify neoplastic processes
    • KRAS mutated in IPMN and MCN
    • GNAS mutations in IPMN
    • RNF43 mutations in IPMN and MCN
Mucinous cysts

- Nonneoplastic and neoplastic mucinous cysts
  - Nonneoplastic mucinous cyst (mucinous duct lesion)
  - Foregut cysts
  - Nonneoplastic cysts lack mutations
- Cytological and cyst fluid features may overlap
  - Mucin only
  - Elevated CEA
  - Lack KRAS and GNAS
- Mucinous cyst, not otherwise specified
  - Characteristic mucin with oncotic cells, no epithelium for evaluation
- Mucinous cyst with low grade epithelial atypia (low grade and moderate grade dysplasia) (IPMN or MCN)
- Mucinous cyst with high grade epithelial atypia (high grade dysplasia and adenocarcinoma)
Low-Grade Dysplasia

Abundant columnar mucin containing cytoplasm

Basally located nuclei

Columnar cytoplasm with mucin

Basally located nuclei
Moderate dysplasia
High-Grade Dysplasia

Papillary tufts, nuclei extend to luminal border

Mitoses
Adenocarcinoma
High-grade epithelial atypia

• Includes high grade dysplasia and invasive carcinoma

• Criteria
  • High N/C
  • Nuclear membrane irregularities
  • Abnormal chromatin
    • Hypo- or hyperchromasia
  • Background necrosis

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Suspicious
Category V
Suspicious

• **Definition:** Some, but not all of the criteria of a specific malignant neoplasm are present, mainly for pancreatic adenocarcinoma diagnosis. The features are qualitatively or quantitatively insufficient for a conclusive diagnosis.

• Confirmatory ancillary testing or substantial clinical and radiological findings must be present and discussed during a treatment planning conference, or similar correlation conference.

• Indeterminate category
Suspicious Cytological criteria

• Sufficient cellular or architectural atypia to be derived from a malignancy
• Suspicious for ductal adenocarcinoma
  • Significant loss of group and cell polarity, significant anisonucleosis, increased N/C, nuclear membrane irregularities, moderate to marked coarsening of the chromatin
• Suspicious for acinar cell carcinoma
  • Cytological features of acinar cell carcinoma, cannot confirm with ancillary studies
• Cyst aspirates with a solid mural nodule and cytological features suspicious for invasive carcinoma
• Other
  • Lymphoma
  • Metastases
Suspicious Management

• Management decisions based on correlation with other clinical and imaging findings
• Cannot be used as a basis for surgical intervention or adjuvant therapy
• Ancillary testing, expert consultation, repeat sampling, or discussion at a treatment planning conference, such as the Moffitt multidisciplinary tumor boards
Suspicious

• Imaging: Ill-defined, hypoechoic mass with evidence of invasion
• Cytology: Few cell groups with features of adenocarcinoma partially obscured by abundant acute inflammation
• Report
  • Adequacy: Evaluation limited by scant cellularity
  • Interpretation: Suspicious for adenocarcinoma
  • Category: Suspicious
Ancillary Testing

• Immunohistochemistry
  • DPC4/SMAD4, S100P, mesothelin

• FISH
  • Same probes as in UroVysion
    • 3, 7, 17, 9p21

• miRNA
Positive

Category VI
Positive/Malignant

- **Definition:** Unequivocal display of malignant cytological change
- **Diagnoses:**
  - Adenocarcinoma and its variant
  - Neuroendocrine carcinoma, small and large cell type
  - Pancreatoblastoma
  - Acinar cell carcinoma
  - Lymphoma
  - Metastases
  - Sarcomas in this region, secondarily involving the pancreas
Positive

• Imaging: Ill-defined pancreatic mass
• Report
  • Adequacy: Satisfactory
  • Interpretation: Poorly differentiated neuroendocrine carcinoma, small cell type
  • Category: Positive (Diagnostic for malignancy)
  • Comment: The carcinoma is positive for cytokeratin, CD 56 and synaptophysin, confirming the above interpretation.
Summary

- The PSC guidelines developed 6 categories with criteria for each category
  - Restricted the use of nondiagnostic
  - Clarified the categorization of PanNET and SPN
  - Defined criteria for reporting and work-up of preinvasive cysts
- The reporting terminology and categories will clarify communication of pathology results to the treating physicians.
- Reporting needs to incorporate correlation of clinical, imaging, cytological and ancillary findings.