

The Papanicolaou Society of Cytopathology System for Reporting Pancreatobiliary Cytology

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The CSC endorses the Papanicolaou System for reporting pancreatobiliary cytology (2015). The following document is a short summary of the highlights of the Papanicolaou system guidelines. Further details can be found in the original document (reference).

The aim of this reporting system is to use terminology that correlates with the nomenclature of the 2010 W.H.O. classification of pancreatic tumors and to standardize the categorization of diseases involving pancreaticobiliary tract. It separates premalignant/preinvasive neoplasms of the pancreas and neoplasms with low-grade malignant behavior from high-grade malignancies. There are six diagnostic categories.

I-Non-Diagnostic

This category includes specimens that provide no diagnostic or useful information about the lesion sampled. Imaging features of the lesion sampled and cyst fluid analysis when dealing with a cystic mass should always be taken into consideration before giving this diagnosis.

There are no set adequacy criteria (i.e. number of cells) for pancreaticobiliary cytology; as certain lesions such as pseudocyst by definition do not require presence of epithelial cells and presence of colloid like mucin without epithelial cells supports a diagnosis of mucinous cyst. Contamination from the gastrointestinal tract during endoscopic ultrasound (EUS) guided fine needle aspiration biopsy (FNA) also contributes to specimen cellularity. The needle passes through the stomach and duodenum for lesions located in the body/or tail and head of the pancreas respectively.

Samples showing artifacts precluding evaluation, acellular aspirates of solid lesions and cystic lesions (without evidence of mucinous etiology), and presence of only gastrointestinal epithelium, and normal pancreatic tissue in a patient with a clear mass are some examples that are included in this category (Figure 1). Presence of atypia precludes this diagnosis.

II-Negative (for malignancy)

Samples with no atypia or features of malignancy fall into this category. A specific diagnosis should be given whenever possible. Examples include pseudocyst, lymphoepithelial cyst, accessory spleen, and pancreatitis (acute, chronic or autoimmune) (Figure 2A).

III-Atypical

This category includes samples showing cytologic and/or architectural changes greater than reactive, but falling short of the suspicious category. Cytologic criteria and types of lesions included in this category may vary among pathologists. It is also recommended that samples showing features suggestive but not diagnostic of neoplasms such as well differentiated pancreatic neuroendocrine tumor and solid pseudopapillary neoplasm to be included here.

IV- Neoplastic

This category is divided into two subcategories: benign and other.

Benign: Serous cystadenoma is the most commonly encountered benign tumor of the pancreas. FNA samples may be very scant or bloody and may show only hemosiderin-laden macrophages. Presence of small clusters or flat sheets of nonmucinous bland cuboidal epithelial cells are diagnostic (Figure 2B). Cyst fluid analysis for carcinoembryogenic antigen (CEA) is typically low.

Other entities that fall in this category are neuroendocrine microadenoma (<0.5cm), lymphangioma, schwannoma, and teratoma.

Other: This subcategory includes: 1- neoplasms with low-grade malignant behavior: well differentiated pancreatic neuroendocrine tumor (PanNET) and solid pseudopapillary neoplasm (SPN) and 2- mucin producing epithelial cystic neoplasms: Intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN).

FNA samples of **PanNETs** generally yield cellular samples showing monotonous population of polygonal cells in loose clusters, rosettes, or single cells with either scant or abundant cytoplasm and eccentric round/oval nuclei with finely granular chromatin pattern (Figure 3). Pleomorphism “endocrine atypia” and prominent nucleoli may be present. These tumors show positivity for neuroendocrine markers: synaptophysin and chromogranin.

SPN is a malignant neoplasm typically occurring in young females. Like PanNETs, FNAs of this tumor show cellular samples composed of uniform, bland cells with finely granular chromatin present in loosely cohesive or branching papillary clusters or as single cells. Hyaline globules may be seen within the cytoplasm of the cells or in the background. These tumors typically show β -catenin mutations.

Cytologic features of SPN and PanNET show overlapping features. Immunohistochemistry for β -catenin is helpful as nuclear expression of this marker by neoplastic cells establishes diagnosis of SPN (Figure 4). Histologic diagnosis of **MCN** requires presence of an ovarian type stroma. Since this is almost never seen in FNA samples, cytologically it is not possible to differentiate IPMN from MCN. These lesions are diagnosed as “neoplastic mucinous cysts”. Diagnostic criteria for NMCs include; presence of thick colloid-like mucin or cyst fluid analysis showing mutations for KRAS/GNAS/ RNF43 or elevated cyst fluid CEA levels (>192 ng/ml is approximately 80% accurate) and/or presence of neoplastic epithelial cells. Elevated cyst fluid CEA levels can also be seen in lymphoepithelial cysts and duplication cysts and this may present a potential diagnostic pitfall. Absence of characteristic mutations or a low CEA level does not exclude a mucinous cyst. When a diagnosis of MCN is established, the grade of atypia/dysplasia should be stated. A two-tiered classification is used; low grade (including low grade and intermediate grade dysplasia) and high grade (atypia ranging from high grade dysplasia to potential adenocarcinoma). Low-grade atypia is seen as bland glandular epithelial cells with cytoplasmic mucin and sometimes it may be impossible to differentiate these from gastric contamination (mainly for cysts located in the body or tail of pancreas). The criteria for high-grade atypia/dysplasia include the following features: small cell size (<12 micron) with increase in nuclear to cytoplasmic ratios, nuclear membrane irregularities, abnormal chromatin pattern, and background necrosis (Figure 5).

V-Suspicious (for malignancy)

Suspicious (for malignancy) category is used for specimens showing changes suggestive but not unequivocally diagnostic of a high-grade malignant neoplasm such as ductal adenocarcinoma or acinar cell carcinoma. These samples show significant changes in morphology and architecture that are either qualitatively (not all criteria present) or quantitatively (rare cells) not enough for a definitive diagnosis. Also included is high-grade biliary intraepithelial neoplasia (BillIN) seen in brushings of pancreatic and biliary ducts. The malignancy risk associated with suspicious for malignancy is approximately 87% for EUS-FNA and 74% for duct-brushing specimens.

VI-Positive (malignant)

Samples showing diagnostic features of a high-grade malignant neoplasm are included in this category: pancreatic ductal adenocarcinoma, acinar cell carcinoma, pancreatic neuroendocrine carcinomas (small cell carcinoma & large cell neuroendocrine carcinoma), cholangiocarcinoma, pancreatoblastoma, lymphomas, sarcomas, and metastasis from other sites (Figure 6).

The most commonly encountered neoplasm is **ductal adenocarcinoma**. FNA samples show sheets of cells with crowding and overlap (loss of polarity aka drunken honeycomb). There is increase in the nuclear to cytoplasmic ratios, nuclear membrane irregularities, and chromatin clearing or hyperchromasia. Three-dimensional groups and single cells are present in poorly differentiated tumors. Also pleomorphism increases as the grade of the tumor increases. Mitosis and necrosis may be present.

Acinar cell carcinoma is a rare malignant neoplasm of the pancreas. FNA samples are generally cellular with loosely cohesive groups, acinar formations, and single cells or naked nuclei. The cells can have granular or dense cytoplasm with coarse chromatin and prominent nucleoli. This carcinoma shows positivity for trypsin, chymotrypsin, and BCL10. Cytology of acinar cell carcinoma may overlap with that of pancreatic neuroendocrine tumors. Use of immunohistochemistry can help differentiating these two entities (Figure 6).

Pancreatoblastoma is a rare malignancy primarily seen in children. Metastasis to pancreas is uncommon. Possible sites include lung, kidney, breast, and melanoma. The most common primary is renal cell carcinoma based on clinical series and cytologically it may mimic PanNET.

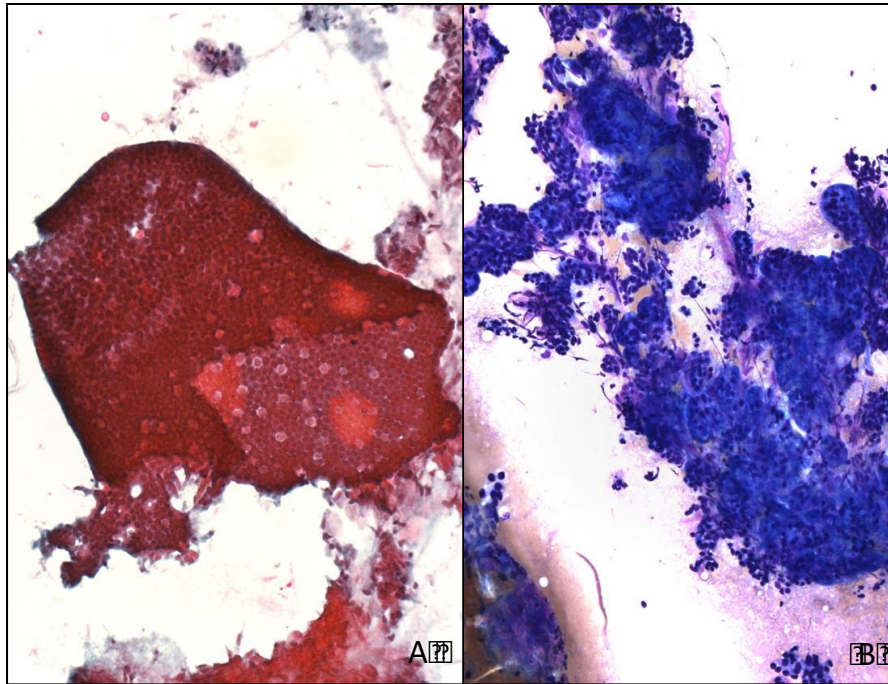


Figure 1 : Normal duodenal epithelium with a dual population of cells: enterocytes and goblet cells. (A). Benign acinar cells in a grape-like cluster (Diff-Quik) (B).

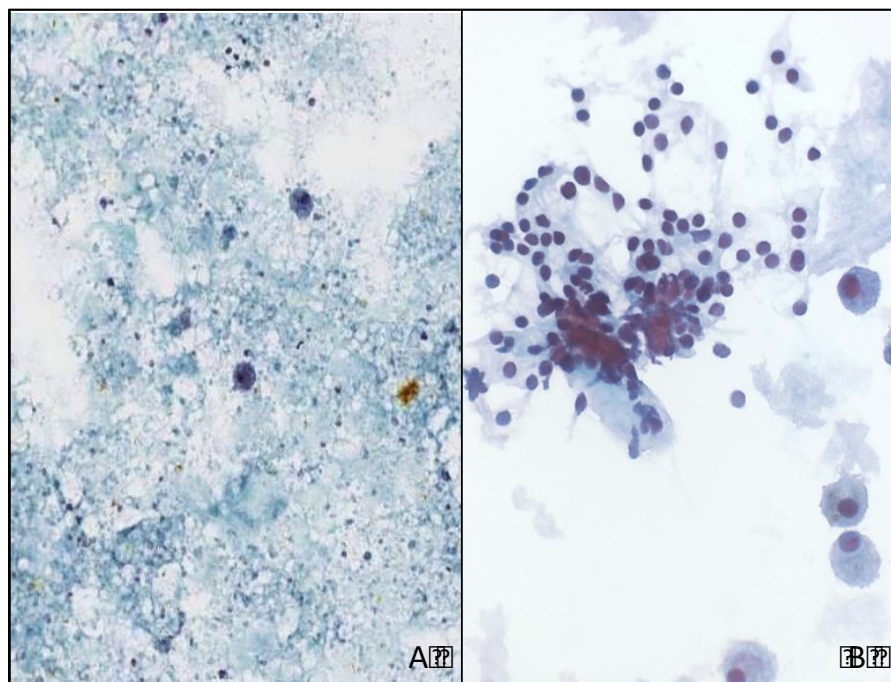


Figure 2: Pseudocyst showing necrotic debris, few histiocytes, and yellow pigment (A). Serous cystadenoma: A cluster of bland epithelial cells with round nuclei and abundant cytoplasm in a background of macrophages (B).

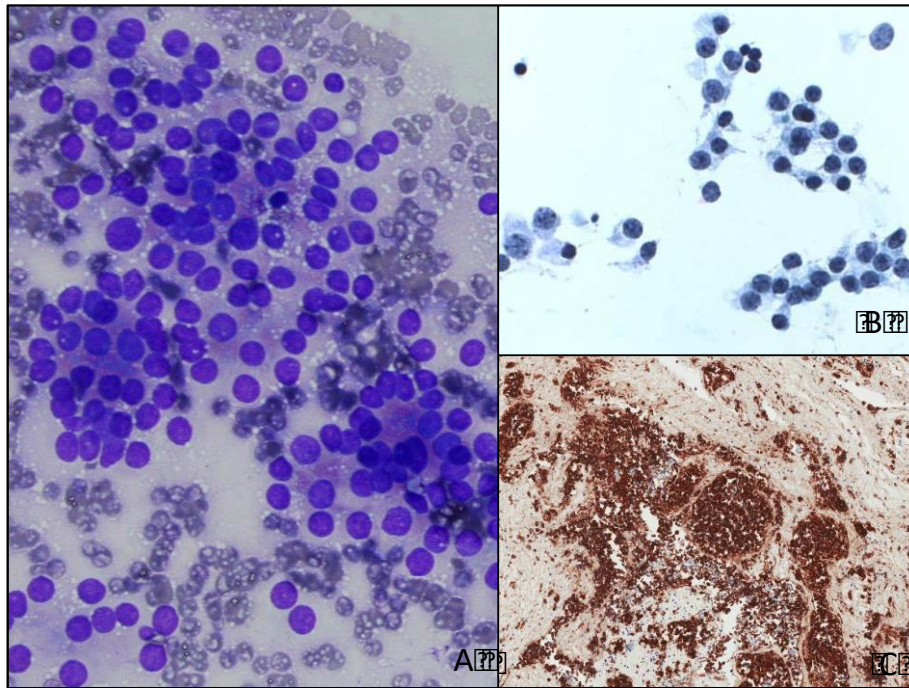


Figure 3: Well differentiated PanNET: bland uniform cells showing rosette-like arrangement (Diff-Quik) (A), salt and pepper type chromatin pattern (B), diffuse positivity for synaptophysin on cell block section(C).

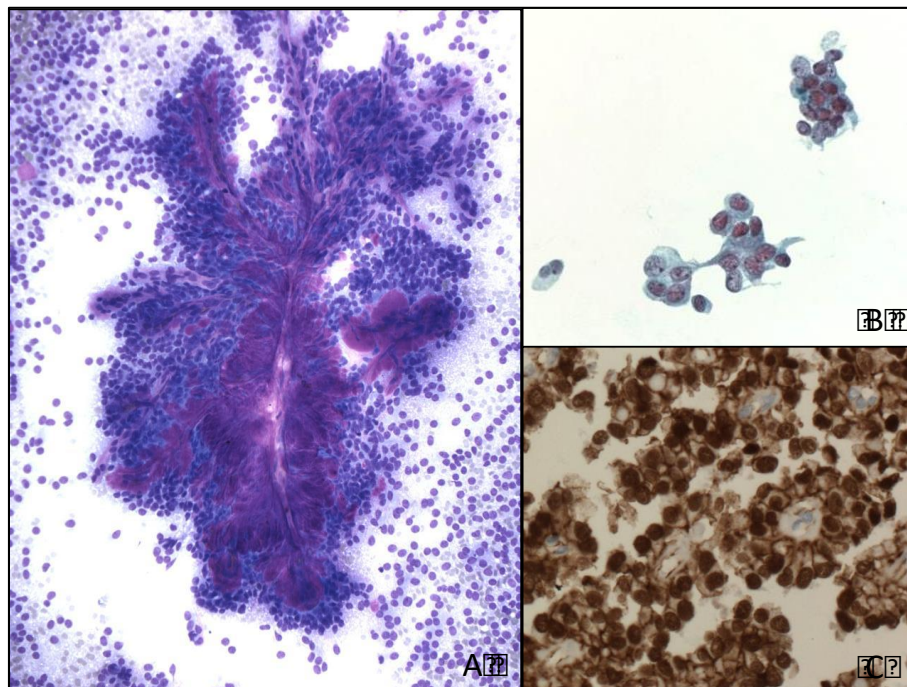


Figure 4: Solid pseudopapillary neoplasm: Branching papillary cluster with myxoid change (Diff-Quik) (A), Bland epithelioid cells with oval nuclei, open chromatin pattern, and occasional nuclear grooves (B), β-catenin (nuclear) positivity (cell block) (C).

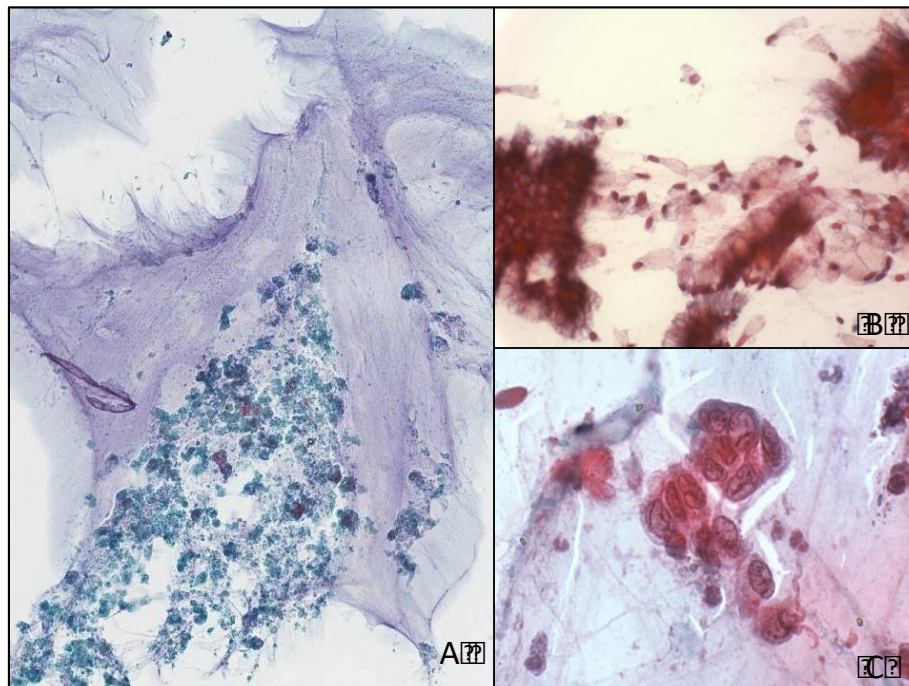


Figure 5: Neoplastic mucinous cyst: thick colloid like mucin admixed with debris (A), NMC with low grade atypia/dysplasia; bland mucinous cells (B): NMC with high grade dysplasia: glandular cells with high nuclear to cytoplasmic ratios, marked nuclear atypia with irregular nuclear membranes and hypochromasia (C).

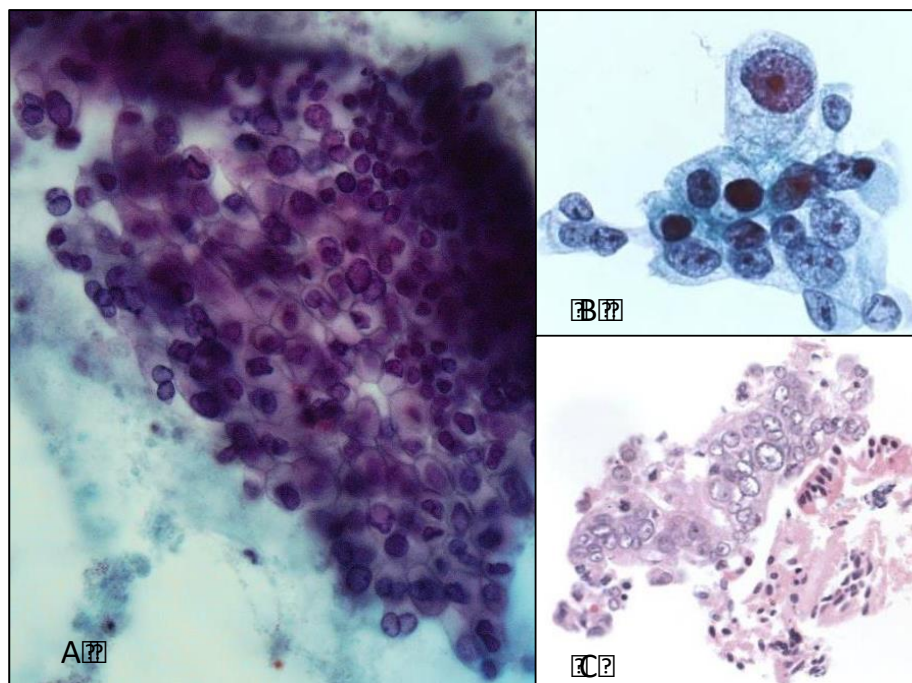


Figure 6: Pancreatic ductal adenocarcinoma: A sheet showing loss of polarity, variation in nuclear size, nuclear membrane irregularities and hypochromasia (A), Bile duct brushing: Adenocarcinoma (B), adenocarcinoma and benign biliary epithelium (cell block) (C).

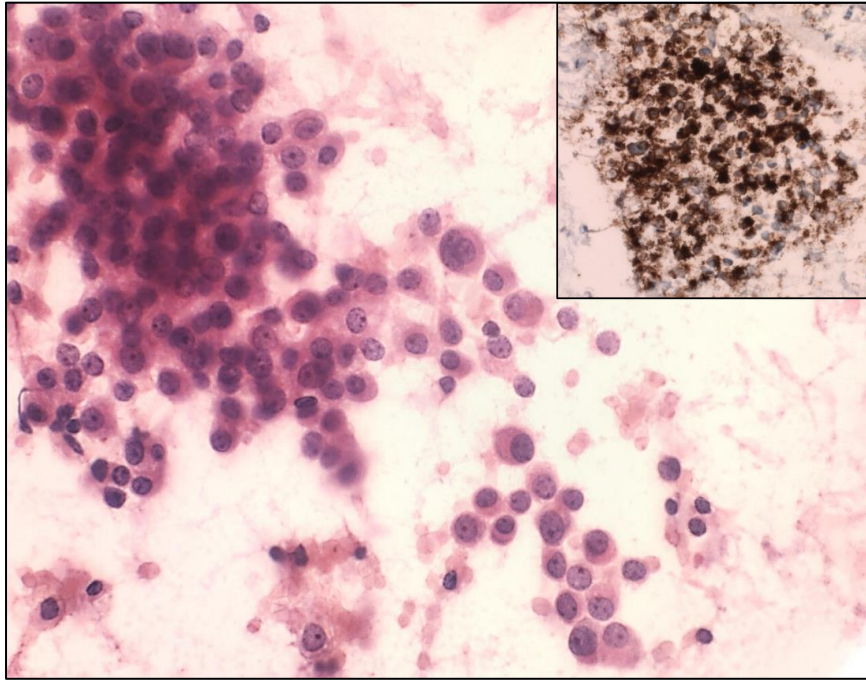


Figure 7: Acinar cell carcinoma: loosely cohesive group of epithelioid/plasmacytoid cells with round nuclei and small nucleoli, positive immunohistochemistry for trypsin (inset).

Reference: Pitman MB, Layfield LJ. *The Papanicolaou Society of Cytopathology System for Reporting Pancreaticobiliary Cytology*. New York, NY: Springer; 2015.