PANCREATIC CYTOPATHOLOGY: PRACTICAL POINTS TO AVOID COMMON PITFALLS

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INTRODUCTION: CURRENT STATE OF AFFAIRS IN PANCREATIC CYTOPATHOLOGY

Fine needle aspiration (FNA) is the most commonly used technique to sample pancreatic masses. Guidance techniques include direct visualization during laparotomy, computed tomography (CT), transabdominal ultrasound (TUS), intraoperative ultrasound (IUS), and endoscopic ultrasound (EUS). EUS is becoming the most frequently employed at most large academic centers and now at large community hospitals. Review of the recent literature will show that most of the reported cases and series in the US are performed under EUS guidance.

EUS-FNA is performed by a gastroenterologist using an echoendoscope with a biopsy chamber through which the needle is passed. The mass is imaged with a radial scanner first and then a linear array scanner is introduced to guide the aspiration. Needles vary from 25 to 19 gauge. One of the manufacturers has developed a new prototype with a reverse bevel that on preliminary use appears to increase the cellular yield. This prototype is still being tested and is not yet available for routine use. The needle is passed through either the duodenum or stomach into the target organ under real-time imaging. Duodenal and gastric contamination are a constant problem with this technique.

Indications for FNA are the presence of a solid or cystic mass. The key problem is distinguishing benign, indolent or inflammatory processes, which may be treated with observation, from neoplastic processes, which require surgery or neoadjuvant or adjuvant therapy. Pancreatic masses may be discovered during the work-up for symptoms such as jaundice or abdominal pain, or may be discovered incidentally, during the work-up for an unrelated process. Increased utilization of CT scanning has lead to increased detection of asymptomatic masses and cysts. Cysts in the pancreas, in contrast to cysts in other organs, are more likely to be neoplastic rather than benign or insignificant, a very important point for the person reviewing the specimen from the cyst. In particular, there is a high incidence of IPMN, a pre-invasive precursor lesion, among incidental pancreatic cysts.1-3

The sensitivity for percutaneous pancreatic FNAB is approximately 80.5%, while the specificity is over 90%4. Ylagan et al reviewed the literature on EUS-guided FNA of the pancreas and reported on their own series of cases. Their sensitivity, specificity, PPV and NPV were 78%, 100%, 100% and 78% respectively. The sensitivity for EUS-guided FNAB ranges from 64-96% in all studies, with most series reporting a specificity of 100%5. At the Moffitt Cancer Center, our sensitivity for the diagnosis of pancreatic adenocarcinoma is 91% when cases interpreted as suspicious for malignancy are included in the calculation6. Others have obtained similar results6,7. The sensitivity for diagnosis of cystic lesions is much lower8-9, although the specificity for the diagnosis of malignancy is higher. Particularly problematic is the diagnosis of serous cystadenoma10,11.

Brushings are used to sample dilated or strictured pancreatic or bile ducts. This type of sampling technique requires a different interpretative approach than FNA. When a solid mass is present, FNA is preferred.

This discussion will focus on FNA of pancreatic solid and cystic masses and intraductal lesions. This will not be an overview of all of pancreatic cytopathology, but a focus on common pitfalls in evaluating pancreatic lesions.

ALGORITHMIC APPROACH

Assessment of a pancreatic FNA sample needs to begin before reviewing the slides. An integrative approach to the evaluation of pancreatic aspirates incorporating the clinical history, radiological findings, cytological findings and ancillary studies yields the most clinically relevant interpretation of the aspirate material.

Age and gender are important as some neoplasms show specific gender and age predilections. As an example, mucinous cystic neoplasms typically occur in middle-aged females. A history of pancreatitis, or a history of carcinoma are also beneficial. Most crucial are the imaging findings indicating whether the mass is solid or cystic, as this information will determine the cytopathological algorithm. Different entities are considered depending on whether the imaging studies show a mass that is solid, solid and cystic, purely cystic, cystic with a
connection to the ductal system (an intraductal lesion). Chronic pancreatitis, lobular atrophy, adenocarcinoma, pancreatic endocrine tumor, acinar cell carcinoma and metastases are among the entities that would be considered if the lesion is solid. Solid and cystic lesions include any solid tumor that has undergone cystic degeneration, such as pancreatic endocrine tumor, and also solid pseudo-papillary tumor. Purely cystic appearing lesions include mucinous cystic neoplasms, serous cystadenoma, side branch intraductal papillary mucinous neoplasms (IPMN) and pseudocysts. When a dilated main pancreatic duct is identified or a connection to the ductal system is demonstrated, a diagnosis of intraductal papillary mucinous neoplasms may be made. More specifics may be included by the person reporting the imaging findings, such as an impression of serous cystadenoma.

A stepwise analysis of the aspirate sample begins with an evaluation of the gross sample. This is particularly informative for cystic lesions. At low power, assessment of cellularity, architectural features and background yields a great deal of information, which may in itself be diagnostic. At intermediate power, architectural details can be assessed in greater detail. At high power, the nuclear, cytoplasmic and mitotic features are appreciated.

Ancillary studies include immunohistochemistry, flow cytometry for suspected lymphoma, cyst fluid analysis for CEA and amylase and possibly analysis of k-RAS mutations and loss of heterozygosity (LOH).

**PITFALLS**

1. Benign pancreas vs. neoplasia
2. Mucinous epithelium  
   a. Gastric or duodenal contamination  
   b. PanIN  
   c. Well-differentiated adenocarcinoma  
   d. Intraductal papillary mucinous neoplasm or mucinous cystic neoplasm
3. Inflammatory processes
4. Scant cellularity of neoplastic component in cysts

**WHAT IS NORMAL?**

The epithelium of the large pancreatic ducts is composed of columnar epithelium arranged in flat, honeycombed, two-dimensional sheets of cells. The nuclei are centrally located, or may be present in a palisaded "picket-fence" arrangement in which nuclei are basally located. The main pancreatic ducts may also contain goblet cells. In contrast to the epithelium of the large ducts, intralobular duct epithelium is composed of cuboidal shaped cells with scant basophilic cytoplasm, and is usually present as flat sheets, small clusters or tubular structures.

Aspirates of the normal pancreas consist predominantly of acinar type epithelium, typically arranged either singly or in small acinar shaped structures. The cells are pyramidal or triangular in shape and contain abundant, granular cytoplasm with numerous intracytoplasmic zymogen granules. The nuclei are round, have a granular chromatin pattern, contain prominent nucleoli, and are either central, or eccentrically located.

Islet cells are rarely detected in aspirates of the normal pancreas. They are more likely to be detected when there is pancreatic atrophy and the islet cells dominate. When present, they occur as loose aggregates of cells that contain wispy, ill-defined amphophilic cytoplasm and oval nuclei with a stippled chromatin pattern.

Distinction of normal ductal cells from adenocarcinoma usually does not present a problem. Potentially problematic are the over interpretation of benign acinar cells or islet cells as a neoplastic process. The neoplastic equivalent of islet cells includes pancreatic endocrine tumor and poorly differentiated neuroendocrine carcinoma. Aspirates of pancreatic endocrine tumor are typically very cellular, except when cystic, and composed of a predominantly dyshesive population of cells with monotonous nuclear features. The cytoplasm is variable in quantity and quality ranging from scant and amphophilic to abundant and oncocytic (Pacchioni, Papotti et al. 1996). The nuclei are round to oval with a salt and pepper pattern. These neoplasms are vascular and may show a vascular pattern. Aspirates of poorly differentiated neuroendocrine
carcinoma, small cell type, show fusiform nuclei with stippled chromatin. The cytoplasm is extremely scant to absent. In contrast to these neoplasms, aspirates showing islet cells are scanty cellular. The islet cells are arranged in loosely cohesive groups. The cytoplasm will be uniformly scant and amphophilic. Benign islet cells will be few in quantity and in loosely cohesive groups.

Occasionally the distinction from adenocarcinoma may be problematic, such as when the nuclei become significantly enlarged with coarser chromatin and with prominent nucleoli. In contrast to adenocarcinoma, the nuclear membrane remains smooth, and abnormalities of chromatin distribution are either absent of minimal. The finding of a neoplasm with round to oval nuclei with smooth nuclear membranes should prompt one to think of PET rather than adenocarcinoma. The prominent nucleoli may also lead to the consideration of acinar cell carcinoma, which will also have rounded nuclei. Immunohistochemistry for neuroendocrine markers and acinar cell markers will separate these various entities.

In the differential diagnosis of PET with oncocytic cytoplasm are oncocytic neoplasms which begin as an intraductal process. While their nuclei may appear bland, the chromatin will be pale, with grooves and pseudoinductions similar to those seen in IPMN. Immunohistochemistry will help with the differential.

The plasmacytoid appearance of PET may lead one to consider plasmacytoma. Plasmacytoma in the pancreas is extremely rare. Another consideration would be metastatic melanoma with a plasmacytoid appearance. Again, immunohistochemistry would be beneficial.

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The cellularity of normal pancreas with abundant normal acini may lead to the suspicion of acinar cell carcinoma. At low power, aspirate smears of acinar cell carcinoma will resemble pancreatic endocrine tumors because they are richly cellular and show a loosely cohesive population of cells with stripped nuclei. The cells form loose cohesive clusters of large and small acini. Nuclei are euchromatic, round to oval in shape, central or eccentrically located, and contain prominent cherry red nucleoli. The cytoplasm is scant to moderate in amount, amphophilic and slightly granular in appearance. A Romanowsky stain or a PAS stain (with diastase) can be used to highlight the granularity. Granularity is caused by the presence of cytoplasmic zymogen granules.

A diagnosis of acinar cell carcinoma should not be considered if there is not a mass lesion on imaging studies. In contrast to acinar cell carcinomas, benign pancreatic acini typically form more prominent organoid arrangements of acini with retention of the normal acinar architecture. In our laboratory, we encountered a potential pitfall. This was a case of a patient who presented with a mass in the tail of the pancreas. Aspiration showed benign acini. Resection showed a residual nodule of normal pancreas in a pancreas replaced by lipomatous hypertrophy.

MUCINOUS EPITHELIUM

Sources of mucinous epithelium on pancreatic aspirates include gastric epithelial contaminant, duodenal contaminant, pancreatic intraepithelial neoplasia, mucinous cystic neoplasm, intraductal papillary mucinous neoplasm, and adenocarcinoma. The pitfalls here are distinguishing gastric or duodenal contaminant from neoplastic process, and distinguishing the pre-invasive processes from each other and invasive carcinoma.

The surface mucus containing foveolar cells of the gastric epithelium appear as columnar cells arranged in large folded sheets, palisaded rows or single cells. Intact fragments may show the attachment of the surface epithelium to the lamina propria. A luminal border may be seen along one edge of the cellular aggregates. The sheets are typically monolayered, but occasionally may be folded or thick. The gastric pits may appear in some groups of cells as rosettes present in the center of a cellular sheet. Chief and parietal cells may be noted if the needle traverses the fundic region of the stomach. Gastric epithelium may occur as stripped nuclei with subtle nuclear membrane irregularities or grooves or both sitting in mucin. Degenerative changes in the gastric epithelium may produce nuclear inclusions.
Small intestinal epithelium will have a similar architectural appearance to the surface mucus epithelium of the stomach, but the epithelial component is composed of absorptive enterocytes with interspersed goblet cells. Goblet cells are always present if the needle tract enters non-gastric tissues. The brush border is visible when the cells are seen on edge. Paneth cells are occasionally seen and are identified by the presence of coarse granules in the cytoplasm.

The distinction of gastrointestinal epithelium from neoplastic epithelium from an MCN/IPMN is perhaps one of the most difficult areas of pancreatic cytopathology. Both gastric and duodenal mucosa will produce background mucin, typically present as thin or thick isolated clumps that does never develop the thick colloidy appearance characteristic of neoplastic mucinous cysts. The mucin is most prominent on air-dried smears, and most abundant from gastric mucosa. Epithelial cells will be admixed with the mucin, but it will lack oncocytic cells. Inflammatory cells may be present if there is an inflammatory process in the stomach or intestine.

Pancreatic Intraepithelial Neoplasia (PanIN)

PanIN is the pre-invasive precursor lesion arising in the intermediate pancreatic ducts that leads to invasive ductal carcinoma. The ductal epithelium becomes columnar and mucinous, with increasing degrees of atypia graded from 1-3. PanIN is most commonly encountered in aspirates of solid lesions for which the imaging differential diagnosis includes chronic pancreatitis or adenocarcinoma. Lobular atrophy with PanIN may also appear as a discrete mass that cannot be differentiated from adenocarcinoma on imaging.

PanIN may produce significant atypia on FNA samples that may be mistaken for adenocarcinoma. The groups will show features that resemble those of well-differentiated adenocarcinoma such as nuclear crowding and overlapping, nuclear enlargement, elongation of the nuclei, and pale chromatin. These groups may be admixed with acinar epithelium, and are scant in number [personal-unpublished data]. The only features that may distinguish these types of groups from ductal adenocarcinoma in my experience are that they are scant in number and completely cohesive. When a few groups of atypical ductal epithelium are present with these features, the sample is best interpreted as atypical with a comment stating that the differential diagnosis includes PanIN vs adenocarcinoma. The patient will need to be followed. PanIN may also serve as a source of false positive diagnoses on molecular tests, since these will have many of the same molecular alterations encountered in invasive pancreatic ductal carcinoma.

Well-Differentiated Adenocarcinoma

Well-differentiated adenocarcinoma may be very difficult to recognize in EUS guided aspirates since its features may be difficult to recognize as malignant and they most overlap with those of gastric epithelium. Particularly problematic is the adenocarcinoma with abundant cytoplasmic mucin resembling foveolar epithelium. On aspirate smears this type of adenocarcinoma will appear as crowded, hypercellular groups in which the cells have abundant cytoplasmic mucin. The mucin varies in quantity among the cells, imparting an uneven distribution of the nuclei. Other features in the group include cribriforming, acinar formations and loss of polarity. The nuclear to cytoplasmic ratio (N/C) may appear low, but the N/C will vary greatly among the individual cells. Close examination of the nuclei will show nuclear enlargement, anisonucleosis, nuclear elongation and membrane irregularities. When seen on edge, these may appear very bland. However, evaluation of the nuclei will show nuclear stratification, and the nuclear abnormalities described. These types of carcinomas may be difficult to recognize on cell blocks samples. Again, the architectural features of cribriforming, and nuclear stratification will be helpful in recognizing them. When examined closely nuclear enlargement and nuclear irregularities may be seen.

Mucinous Cystic Neoplasms and Intraductal Papillary Mucinous Neoplasms

Mucinous cystic neoplasms (MCN) and intraductal papillary-mucinous neoplasms (IPMN) have similar cytomorphological features consisting of neoplastic mucinous epithelium and dense background mucin. Diagnosis may begin at the time of aspiration, since the excessive viscosity of the fluid makes aspiration of the fluid from these neoplasms difficult. The material
may be expressed from the needle as a plug of mucin. This type of viscous fluid is considered diagnostic, regardless of the cellularity identified on the cytology. Gastrointestinal fluid is not viscous. Gross examination of the fluid will reveal highly viscous, clear fluid or clear fluid with strands of floating mucus plugs. Occasionally, the fluid may be hemorrhagic.

The background mucin varies in quantity. The characteristic pattern is abundant, thick background mucin spread out over the entire slide forming a film, similar to colloid in thyroid aspirates, or it may be clumped. On Papanicolaou stains, it will have a characteristic pink hue. A characteristic feature is the presence of degenerated cellular debris, called oncocytic cells by one author\textsuperscript{20}, and macrophages. Ferning may be seen. Another feature of longstanding mucin is the appearance of dense material in a fan-like appearance, crystal-like appearance, or concretions with cracks. Psammomatous calcifications are a feature of intraductal papillary mucinous neoplasms. The background may also contain acute inflammation and coagulative necrosis, features associated with invasive carcinoma. Thick, colloidy mucin with a pinkish hue and thick concretions are not a feature of the mucin from the gastrointestinal tract\textsuperscript{21}.

The cellularity is variable. The higher the grade of dysplasia, the more cellular the samples tend to be, with invasive carcinomas typically being the most cellular. A varying degree of architectural and nuclear atypia will be encountered in aspiration samples depending on the grade of dysplasia. The characteristic cell type is a columnar cell with mucinous metaplasia characterized by abundant cytoplasmic mucin. The cells may be arranged singly, on edge, in sheets, papillary clusters, or small papillary tufts. The sheets or groups do not form a honeycomb pattern, but rather, are subtly hypercellular and crowded, in contrast to gastrointestinal epithelium. The cells may be rounder, with vacuolated cytoplasm. The vacuoles may not be as easily recognized on Diff-Quik stained smears. Signet ring cells are a feature of high-grade dysplasia or invasive carcinoma.

The nuclei show varying degrees of abnormalities. The subtlest are mild nuclear enlargement and hypochromasia with subtle nuclear membrane foldings. The hypochromatic nuclei may have small, peripherally located nucleoli, similar to those seen in papillary carcinoma. The nuclear atypia becomes more evident as the degree of dysplasia increases. Nuclear grooves and pseudo inclusions become more evident and are diagnostic of MCN/IPMN, although a pitfall is the presence of grooves and degenerative inclusions in gastric epithelium. The chromatin will become coarser, with abnormal paranuclear clearing and micronucleoli. Mitotic figures will be evident in high-grade dysplasia. The single dysplastic cell, which is a small cell with a high N/C ratio, and nuclear convolutions, is diagnostic of a neoplastic process, and it is typically associated with higher-grade dysplasias. These cells may be obscured by the cellular debris and histiocytes; therefore careful examination of the specimen, particularly in the areas of thick mucin, is needed.

The presence of background mucin with the features described should be considered indicative of the presence of neoplastic mucinous cyst even if diagnostic cells are not identified. Since aspirates are frequently scanty cellular, even a few cells should be considered diagnostic of a cystic mucinous neoplasm. Correlation with the imaging studies may lead to a specific diagnosis of IPMN vs. MCN\textsuperscript{21}.

**Invasive Carcinoma Associated with Mucinous Cystic Neoplasm or Intraductal Papillary Mucinous Neoplasm**

Aspiration of a solid area of an MCN/IPMN, when visualized by radiological guidance, may prove diagnostic of invasive adenocarcinoma. Occasionally, invasion can be determined on evaluation of cystic or ductal fluid only if abundant coagulative background necrosis and cytomorphological features typical of invasive tubular-type ductal adenocarcinoma are present. The intestinal type of intraductal papillary mucinous neoplasm is associated with non-cystic mucinous carcinoma. Cytology of mucinous carcinoma shows malignant cells floating in pools of mucin.

**Role of Cytology in the Pre-Operative Work-up of IPMN**

IPMN may present either in the main pancreatic ducts or in the side branches. The Sendai criteria for the management of IPMN specify that resection is indicated for the following instances: main pancreatic duct diameter greater than 1.0 cm, side branch IPMN 3.0 cm.
or greater, solid nodule of positive cytology. What is meant by positive cytology may be open to interpretation, however, what is helpful is to identify significant atypia that may indicate the presence of high grade dysplasia in the cyst. At our institution, we assess the amount of dysplasia in the cells and report on whether there is at least moderate dysplasia or definitely high grade dysplasia present.

Features that represent moderate dysplasia include enlarged nuclei with a cigar shaped appearance in groups with nuclear overlapping or stratification. High grade dysplasia is characterized by groups forming small papillary tufts with nuclear membrane irregularity of high N/c within the cells. Other features that relate to high grade atypia include single dysplastic cells, signet ring cells, or groups with three dimensionality and crowding and anisonucleosis.

These criteria and management guidelines take some of the pathologist, particularly when trying to distinguish gastric foveolar epithelium from IPMN with low grade dysplasia, which in the side branches, has a foveolar phenotype. Making this distinction does not matter, and a report with a descriptive diagnosis and a differential diagnosis of gastric epithelium vs. IPMN with low grade dysplasia should be sufficient. The key is to identify neoplastic cells with significant atypia indicating the probable presence of high grade dysplasia in the cyst.

THE INFLAMMATORY ASPIRATE

Inflammatory processes most commonly in the differential diagnosis of solid masses in the pancreas include acute and chronic pancreatitis, autoimmune or lymphoplasmacytic pancreatitis. A dirty, necrotic background, necrotic cells, cellular debris, fat necrosis and calcifications characterize typical smears of cases with acute pancreatitis. Acute inflammation may be prominent. The normal pancreatic elements, when present, show evidence of necrosis and degeneration. Pancreatic ductal epithelium may show various degrees of reactive atypia.

In chronic pancreatitis, the cellularity of smears varies greatly depending on the stage of disease. In the earlier stages, which correspond to resolving acute pancreatitis, mononuclear cells with histiocytes, granulation tissue and early fibrous tissue are present. In the later stages of disease, the cellularity may be scant and contain only ductal epithelium, fibrous tissue and islet cells. The inflammation is lymphocytic and histiocytic.

Autoimmune pancreatitis is a recently characterized entity which may produce a mass in the head of the pancreas that mimics carcinoma. One study to date has reported on the cytological findings. Smears are typically paucicellular with fibrous stroma containing a lymphoplasmacytic infiltrate and eosinophils. Minimal ductal epithelium will be present. Recently, however, we had an FNA sample of a pancreatic mass which was interpreted as suspicious for adenocarcinoma due to the high cellularity and hypercellularity and crowding of the ductal groups. Fibrous tissue and a lymphoplasmacytic infiltrate with eosinophils were not identified in the background. Resection showed the characteristic histopathological features of autoimmune pancreatitis. Retrospective review of the smears showed that the while there was not background inflammation, the ductal groups were infiltrated by lymphocytes. Closer examination of the ductal groups showed uniform nuclear size and shape.

Acute inflammation may also be associated with ductal carcinoma, and is due to duct obstruction causing secondary acute pancreatitis or tumor necrosis with an inflammatory response. The acute inflammation may be abundant, obscuring the malignant cells. Careful examination of aspirates with abundant acute inflammation is warranted to identify obscured malignant cells.

Another pitfall resulting from inflammation is the presence of reactive atypia in ductal cells. Nuclear changes may be striking, and are characterized by nuclear enlargement, subtle anisonucleosis, and an increase in the coarseness of the chromatin including subtle abnormalities of chromatin distribution, and prominent nucleoli. These reactive changes may be a source of false positive diagnoses.

Identifying adenocarcinoma in an inflammatory smear, where the differential diagnosis is with a reactive process, is problematic, but can be accomplished with a stepwise approach incorporating an assessment of the cellularity of the atypical groups, and their architectural and nuclear features. The criteria utilized in this stepwise approach have been analyzed in several retrospective pancreatic FNA studies trying to identify the minimal number of criteria needed to reliably separate benign processes from adenocarcinoma. While the accuracy of these
sets of criteria has not been proven in a prospective study, the results of these studies show that a systematic approach using a combination of these criteria, beginning with a low power assessment, leads to improved accuracy \(^{21}\). This approach is described below:

**Assessment at Low Power**

**Cellular composition:** Benign pancreas is composed of a mixture of ductal cells and acinar cells. This is most useful in aspirates obtained at laparotomy in which it is presumed that the surgeon is inserting the needle directly into the mass. Malignancy should show a predominance of ductal type cells, although chronic pancreatitis or atrophy may also have a predominance of ductal type cells. A distinguishing feature of pancreatitis is the scant cellularity.

**Cellularity:** Adenocarcinoma tends to produce cellular smears, although the minimum number of groups needed to diagnose adenocarcinoma has not been established in prospective studies. One retrospective study did establish 6 as the minimum number of atypical groups needed to diagnose malignancy \(^{28}\). However, tumors with a sclerotic stroma or necrosis may be low yield. In this case, close attention to the atypia of particular groups is needed.

**Architectural features:** Architectural features are the most helpful. Malignant groups lose the normal, honeycomb, two-dimensional patterns of normal ductal epithelium. Instead the cells lose their normal relationships, manifested as three dimensionality, crowding and overlapping of the nuclei, or an exaggerated honeycomb. The subtest of changes will be the folding and hypercellularity of groups. Loss of cohesion is a feature of malignancy, but well differentiated carcinomas may retain their cohesion.

**Background:** Coagulative necrosis is typical of malignancy. Other features that can be assessed as part of the background are inflammation, secretory products and dyshesion.

**Assessment at Intermediate Power**

**Architectural features:** Subtle alterations are the distribution of the nuclei in the groups, characterized as uneven distribution of nuclei in the groups, is appreciated at this power. Other features appreciated are loss of polarity and molding, acinar structures and cribriforming.

**Assessment at High Power**

**Anisonucleosis:** A nuclear size variation of greater than 4:1 is a very helpful feature, and when seen in a group with the architectural abnormalities described, is indicative of malignancy.

**Nuclear enlargement:** Criteria for nuclear enlargement are 1.5 X an RBC as seen on a Diff-Quik stain; other criteria include 2.5 X the size of a normal ductal nucleus as seen on a Papanicolaou stained smear.

**Nuclear membrane irregularities:** Normal nuclei are round and uniform. Nuclei from malignant cells lose that roundness, and become angulated, with sharp edges. These nuclear changes may be subtle in well-differentiated adenocarcinoma. The nuclei will become rectangular, with flattened sides, or more elongated and carrot shaped, or shows noses or blebs and nuclear membrane folding. Notches and convolutions become more apparent in higher-grade carcinomas.

**Abnormal chromatin patterns:** Hypochromasia is subtle, and most often seen in well-differentiated adenocarcinoma. Hyperchromasia becomes more apparent in higher-grade carcinomas. Abnormal chromatin clearing is a feature of malignancy.

**Single malignant cells:** These are diagnostic of malignancy, but are not seen in lower grade malignancies.

**Mitoses:** Abnormal mitotic figures are diagnostic when identified.

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**SCANT CELLULARITY OF PANCREATIC CYSTS**

Aspirates of pancreatic cystic lesions are frequently scantly cellular. The smears have to be carefully evaluated for the presence of characteristic neoplastic cells. In cyst aspirates, the threshold for adequacy needs to be lower. This is true for diagnosing serous cystadenoma, MCN/IPMN and cystic pancreatic endocrine tumor.
References


23 Pitman MB, Genevay M, Yaeger K, et al. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. *Cancer Cytopathol*.


