Special Course Cytomorphology II : FNA Cytology

Thyroid – Richard M. DeMay, MD
Lung – Kristen A. Atkins, MD
Salivary Glands – William C. Faquin, MD, PhD
Pancreas – Gregg A. Staerkel, MD

Disclosure information
“The speakers have no relationship that represents a possible conflict of interest with respect to the content of this presentation.”
Objectives:
* Learn diagnostic criteria for non-neoplastic lesions of the thyroid
* Learn diagnostic criteria for follicular lesions of the thyroid
* Learn diagnostic criteria for major forms of thyroid cancer

**Thyroid Cytology Made Easy**

There are only a few common, diagnostic categories in fine needle aspiration biopsy of the thyroid. These are:

- **Granulomatous thyroiditis**, a post-viral syndrome characterized by giant cells munching on colloid. If you see epithelioid giant cells, rule-out papillary carcinoma.

- **Hashimoto thyroiditis**, a classic autoimmune disease characterized by lymphocytes and oncocyes (Hürthle cells). 4 clues to chronic inflammation: lymphoid tangles, plasma cells, infiltration of lymphoid cells into groups of epithelial cells, and lymphoglandular bodies.

- **Papillary carcinoma**, characterized by papillary architecture, nuclear grooves and inclusions, and squamoid cytoplasm. Other clues: epithelioid giant cells, psammoma bodies, gummy colloid.

- **Medullary carcinoma**, a carcinoid tumor with amyloid stroma associated with calcitonin. The tumor cells are lymphoplasmacytoid or spindle shaped, with salt & pepper chromatin, finemetachromatic granules, and calcitonin expression. When it looks like a neoplasm, but you don’t know what, consider medullary carcinoma.

- **Anaplastic carcinoma**, characterized by “ugly” giant and spindle, or epithelioid, tumor cells. When “ugly” tumor cells are present, exclude metastasis.

**Follicular Lesions**

The basic clues to diagnosis of follicular lesions are: the more colloid that is present in the sample, the more likely the lesion is benign and the more cells that are present, the more likely that the lesion is neoplastic. Using these two simple, low power observations, aspirates of follicular lesions can be divided into three categories or zones. Zone I, a “colloid nodule” (or benign thyroid nodule) is dominated by colloid, and cells are scant. At the other end of the spectrum, Zone III, a “follicular nodule” (or suspicious for follicular neoplasm) is dominated by cells and colloid is scant. Zone II, a “cellular nodule” (or follicular lesion of undetermined significance) falls in between. This categorization roughly separates goiters (mostly zone I, colloid nodules) from neoplasms (mostly zone III, follicular nodules).
Colloid nodules have a very low risk of malignancy (<3%). Follicular nodules have a significant risk of malignancy (15%-30%). Note that a substantial number of follicular nodules (up to 35%) are nonneoplastic (ie, hyperplastic nodules in goiters or thyroiditis) and of the malignancies, up to 68% are papillary carcinomas, not follicular carcinomas.

Next, an attempt is made to refine the distinction between goiters and neoplasms. Nodules in goiters are formed by degeneration and regeneration. Therefore, signs of these processes are practically part of the definition of the disease, nodular goiter. Cytologically, evidence of hemorrhage, fibrosis, cystic degeneration, stromal calcification, repair, cellular pleomorphism and types of cells, together with a wide range in follicular size, usually characterize nodules of goiters. Also, the cells tend to form uniform, honeycomb sheets.

In contrast, neoplasms tend to form microfollicles. The nuclei tend to be uniform, though they may be enlarged. Nucleoli are infrequent. Atypical (but not frankly malignant-appearing) epithelium usually correlates with goiter, rather than neoplasm.

Clues to follicular carcinoma include marked architectural abnormalities, such as crowded, irregular microfollicles and increased single cells, and marked cytologic atypia, such as nuclear enlargement and pleomorphism, abnormal chromatin, prominent or multiple nucleoli, atypical mitotic figures, and necrosis.
DeMay: Follicular Thyroid Lesions

There are two forms of follicular carcinoma: a minimally invasive, minimally atypical, and minimally malignant form and a frankly invasive, frankly atypical, and frankly malignant form. The first type is difficult to recognize cytologically, but the second type is unlikely to be missed cytologically.

The final step in evaluation of follicular lesions is to take a close look at the nuclei. Nuclear grooves, when extensive, or even a single bona fide intranuclear inclusion strongly suggests papillary carcinoma. A helpful sign is that follicular nuclei, even in neoplasms, tend to be round and smooth, like oranges. Papillary nuclei tend to be irregular, more like potatoes.

The classic teaching is that follicular carcinoma comprises 15% to 20% of all thyroid malignancies and that zone III biopsies usually (80% to 90%) correlated with neoplasms, 20% to 30% of which were malignant. However, more recently, follicular carcinoma has apparently become rare (owing both to changes in definition and a true reduction related to adding iodized salt to the diet). Therefore, today, zone III biopsies are much less likely to be neoplastic, and <5% are malignant, assuming papillary carcinoma has been carefully excluded!

Advanced Topics

Hürthle cell lesions represent a mixed bag of entities, including goiters, thyroiditis, adenomas, and carcinomas. The common denominator is metaplastic (Hürthle cell or oncocyctic) change. As usual, colloid, inflammation, and honeycomb sheets of cells favor a benign/nonneoplastic interpretation, while numerous microfollicles, diffuse atypia, high N/C ratios, and features of papillary carcinoma favor a neoplastic/malignant interpretation. However, any thyroid lesion comprised exclusively, or nearly exclusively or Hürthle cells is likely to be neoplastic, and if neoplastic, there is a significant risk (~33%) of malignancy.

Poorly differentiated carcinoma includes insular and non-insular types. The diagnostic features are: 1. solid/trabecular/insular growth, 2. No nuclear features of papillary carcinoma, and 3. At least one of a. convoluted nuclei, b. increased mitotic activity, and c. necrosis. The tumor cells typically express thyroglobulin and TTF-1, but are negative for calcitonin.

Thyroid sarcomas are extremely rare. Most “sarcomas” are actually anaplastic thyroid carcinoma. Note that both thyroglobulin and cytokeratin can be negative in anaplastic carcinoma.

Metastases to the thyroid are not rare, but were formerly rarely diagnosed during life. However, the advent of FNA biopsy has increased the rate of antemortem diagnosis. Thyroid metastasis is a grave prognostic sign. Most of the cancers are poorly differentiated, unlike most primary thyroid carcinomas. Common sites of origin include: kidney, lung, breast, GI carcinomas; melanoma; and lymphoma.

Graves disease is related to Hashimoto thyroiditis. The diagnosis is usually made based upon clinical and laboratory findings, not FNA biopsy. Occasionally, however, a patient with Graves disease will undergo FNA biopsy (usually to investigate a cold nodule). The cytologic findings in Graves disease include: high cellularity, pale watery colloid, flame and Hürthle cells, and inflammation, which may include granulomas.
Therapeutic effects, ie, owing to radiation or antithyroid medications, can cause marked cytologic atypia. However, this atypia is usually randomly distributed and mitoses are rare. Note that radiation is a risk factor for thyroid carcinoma, particularly papillary carcinoma.

Dyshormonogenetic goiter refers to thyroid enlargement due to congenital hypothyroidism. Autosomal recessive enzyme defects in hormone synthesis cause the goiter. The FNA biopsy is highly cellular, with microfollicles, cytologic atypia, and scant colloid mimicking a neoplasm, and carcinoma may be favored. However, actual malignant change is rare in this condition.

Pregnancy is associated with loss of iodine in the urine, leading to thyroid hyperplasia. Any pre-existing nodularity will be accentuated. The FNA biopsy is highly cellular, with watery colloid, and flame cells. Papillary hyperplasia (“polsters”) may suggest papillary carcinoma and women of childbearing age are at risk of papillary carcinoma. Look for the usually features of papillary carcinoma, such as nuclear grooves and inclusions, as previously discussed.

The Bethesda System
Diagnostic Terminology and Morphologic Criteria
A six tiered diagnostic system was suggested at the NCI conference. Briefly, the six categories are: Benign; Atypical; Follicular Neoplasm; Suspicious; Malignant; and Nondiagnostic. The categories also include an estimate of the risk of malignancy and management recommendations.

I. Non-Diagnostic
Nondiagnostic includes limited cellularity, absence of follicular cells, poor fixation, excessive blood, and poor cell preservation. The risk of malignancy is not applicable to this category. (Adequacy defined as at least 6 groups of at least 10 well preserved, well visualized follicular cells.

II. Benign
Benign includes colloid nodular disease (eg, nodular goiter, hyperplastic/adenomatoid nodule, macrofollicular adenoma) and thyroiditis (eg, acute thyroiditis, chronic lymphocytic thyroiditis). The risk of malignancy is low (<3%).

III. Atypical
Atypia is a heterogeneous category that includes atypical cells of undetermined significance (ACUS), follicular lesion of undetermined significance (FLUS), indeterminate follicular lesions, rule-out neoplasm, and cellular nodule. The cytologic findings are not convincingly benign, yet the degree of cellular or architectural atypia is not sufficient for an interpretation of “Follicular Neoplasm” or “Suspicious for Malignancy.” Some cases are placed in this category because the specimen was compromised (eg, low cellularity, poor fixation, obscuring blood). The use of this category is optional, but should be kept to a minimum (<7% of all thyroid FNA interpretations was arbitrarily chosen). The risk of malignancy is between 5% and 15%.
IV. (Suspicious for) Follicular Neoplasm (Specify if Hürthle cell type)
Follicular neoplasm includes suggestive or suspicious of follicular neoplasm, microfollicular lesion, and follicular lesion/ follicular nodule. This category applies to follicular patterned lesions, including Hürthle cell lesions, *lacking* nuclear features of papillary carcinoma. The risk of malignancy is between 20% and 30%.
Notes: Up to 35% are nonneoplastic; of malignancies, up to 68% are papillary carcinoma.

V. Suspicious
Suspicious for malignancy includes suspicious for papillary carcinoma (most commonly), suspicious for medullary carcinoma (material inadequate for calcitonin staining; recommend serum calcitonin to confirm), suspicious for other primary or metastatic malignancy, and suspicious for neoplasm due to lesion necrosis (anaplastic carcinoma). The risk of malignancy is 60% to 75%.

VI. Malignant
Malignant includes specimens diagnostic of malignancy. The type of malignancy, eg, papillary carcinoma, should be specified when possible. Risk of malignancy is 97-99%.

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<tr>
<th>Diagnosis</th>
<th>Cancer Risk</th>
<th>Management</th>
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<tr>
<td>I. Nondiagnostic</td>
<td>NA</td>
<td>Rpt w/ US</td>
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<td>II. Benign</td>
<td>&lt;3%</td>
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<td>III. AUS ACUS, FLUS</td>
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<td>IV. Follicular Neoplasm*</td>
<td>20%-30%</td>
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<td>V. Suspicious</td>
<td>60%-75%</td>
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<td>VI. Malignant</td>
<td>97%-99%</td>
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* Specify if Hürthle cell type

Final Topic: An Epidemic of Thyroid Cancer?
Pulmonary Cytology

Kristen Atkins, MD
University of Virginia

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Procurement of Tissue

- Bronchoscopic
- Brushings, EBUS, Washes, lavage
- FNA
- Thorocentesis for pleural fluid

Accuracy of detecting malignancy

- 1 Sputum < multiple sputums < brushing
- Transbronchial FNA < percutaneous FNA
Normal components

- Malignancies
  - Primary and metastatic
- Benign neoplasms
- Infections
- Oh no! The pitfalls.
Primary Malignancies

- Squamous
- Adenocarcinoma
  - Bronchoalveolar carcinoma
- Small cell
- Carcinoid
Small Cell Carcinoma

- Very blue
- Nuclear streaking artifact
- Variability
- Single cell apoptosis
- Nuclear molding, chromatin pattern
BAC

- VOLUME
- Columnar cells
- Inclusions, some atypia
- Not an outright diagnosis for cytology
BAC cytologic features

- Overlap with well-differentiated adenocarcinoma
- Columnar
- Enlarged nuclei (compared to internal control)
- Pseudonuclear inclusions, grooves
- Psammoma bodies

Metastasis
Ciliacytopthoria

- Traumatic
- Numerous should spark viral possibility
Peripheral Nodules
- Malignancies
- Metastases
- Benign neoplasms
- Mesothelioma
- Pleural fibrosis

Chondroid Hamartoma
Reactive Effusions

- Variable Cellularity
- Cell types: mesothelial cells, macrophages, inflammatory cells
- Architectural patterns: dispersed, papillary, sheets
- Mesothelial cells: Abundant cytoplasm, ruffled borders, vacuolization, nucleoli

“Microvilli”

Mesothelials, Breast, Pancreas, Stomach
“mesothelial like” pattern of breast cancer
Special Course Cytomorphology II:
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Salivary Glands
William C. Faquin, MD, PhD

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Cytomorphology II:

SALIVARY GLAND

William C. Faquin, M.D., Ph.D.
Director, Head and Neck Pathology
Massachusetts General Hospital
Massachusetts Eye and Ear Infirmary
Boston, MA
BACKGROUND TO SALIVARY GLAND CYTOLOGY

Salivary gland cytology represents one of the most challenging areas of all of cytopathology owing to the wide range of lesions that can be encountered and the significant degree of overlap between some benign and malignant tumors. In approaching a salivary gland FNA, it is useful to apply an algorithmic approach by attempting to place the lesion into one of several different broad categories:

GENERAL CATEGORIES FOR SALIVARY GLAND LESIONS:

- Matrix-containing tumors: e.g. pleomorphic adenoma and adenoid cystic carcinoma
- Basaloid neoplasms: e.g. basal cell adenoma
- Oncocytic lesions: e.g. oncocytoma and acinic cell carcinoma
- Mucinous cysts: e.g. low-grade mucoepidermoid carcinoma and mucocele
- High-grade carcinomas: e.g. salivary duct carcinoma
- Lymphoid lesions: LESA and lymphoma
- Clear cell tumors: e.g. epithelial-myoepithelial carcinoma
- Spindle cell lesions: e.g. myoepithelioma

RATIONALE AND INDICATIONS FOR SALIVARY GLAND FNAB:

FNA is widely used at many institutions for the evaluation of salivary gland lesions. Overall, FNA is safe, cost-effective, and accurate. Most often, FNA acts as a guide for the clinician in assessing the need for surgical or other clinical intervention for any unexplained salivary gland mass. When surgery is indicated, results from the FNA can assist in the pre-operative strategy. The primary goal of salivary gland FNA is to place the diagnosis into 1 of 3 categories that will dictate management:

- Non-neoplastic lesions (e.g. chronic sialadenitis) may not require surgical intervention
- Benign tumors (e.g. pleomorphic adenoma) and low-grade malignancies are usually treated with limited surgery such as superficial parotidectomy with disease-free margins
- High-grade carcinomas are usually treated with radical surgery
  - Facial nerve sacrifice may be necessary
  - Lymph node neck dissection and neo-adjuvant therapy are often indicated

ACCURACY

Overall, FNA is fairly accurate in the assessment of salivary gland lesions. In recent studies, sensitivity and specificity for neoplasia is >90%. The distinction between benign and malignant neoplasms has a sensitivity of 80-90% and a specificity of >90%. Diagnostic accuracy is lower for rendering a specific diagnosis.

- High diagnostic accuracy for neoplastic versus non-neoplastic lesions
- High accuracy for low-grade versus high-grade lesions
- Variable accuracy depending upon the specific entity (e.g. high accuracy for tumors such as pleomorphic adenoma & Warthin tumor, but lower for tumors such as basal cell adenocarcinoma, solid adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma)

IMPORTANT!!! SAMPLE PREPARATION:

Both Romanowsky-stained (Diff-Quik, Giemsa, MGG) and Papanicolaou stains are essential in the evaluation of most salivary gland lesions by FNA, especially those with matrix material. Air-dried Romanowsky-stained smears highlight diagnostically useful features of the matrix component that are poorly visualized in alcohol-fixed preparations of lesions such as pleomorphic adenoma, basal cell tumors, and adenoid cystic carcinoma. Romanowsky stains also aid in the evaluation of lymphoid lesions. Papanicolaou-stained smears are especially useful for
evaluating nuclear features and cytoplasmic differentiation. Yes, FNA of salivary glands can be done without both types of stains or even with thin-layer preparations, but depending upon the lesion, your diagnostic abilities may be limited.

THE NORMAL SALIVARY GLAND ASPIRATE:
Aspirates of normal salivary gland are comprised of groups of acinar cells, occasional ductal cells, and admixed adipose tissue. Acinar cells are usually present as cohesive polarized grape-like clusters with associated small inconspicuous tubules and small honeycomb sheets of cohesive ductal cells. Stripped nuclei from crushed acinar cells may be present in the background. The presence of normal salivary gland as the only cytologic finding warrants careful clinical correlation to exclude the possibility of a sampling error. Other explanations for normal-appearing salivary gland elements include a prominent but normal salivary gland, sialadenosis, and lipoma.

*Pitfall:* A pitfall for the diagnosis of normal salivary gland tissue is mistaking it for acinic cell carcinoma (and vice versa).

**Cytologic Features of the Normal Salivary Gland Aspirate**

- Serous and mucinous acinar cells in grapelike (lobular) clusters + background stripped nuclei
- Admixed small tubules and/or small sheets of ductal epithelium
- Adipose tissue

Normal salivary gland showing ductal cells (left) and acinar cells

**BASIC SALIVARY GLAND TUMOR CYTOMORPHOLOGY:**

1) MATRIX-CONTAINING TUMORS:
The differential diagnosis of matrix-containing salivary gland tumors includes a number of entities, but the most common and clinically significant differential diagnosis is between pleomorphic adenoma and adenoid cystic carcinoma.

**Differential diagnosis of matrix-containing salivary gland tumors:**

- Pleomorphic adenoma
- Adenoid cystic carcinoma
- Basal cell adenoma/adenocarcinoma
- Myoepithelioma
- Polymorphous low grade adenocarcinoma
- Epithelial-myoeplithelial carcinoma
**Pleomorphic Adenoma:**

Pleomorphic adenoma is the most common salivary gland tumor in both children and adults. Two-thirds of parotid tumors and 50% of all salivary gland tumors are pleomorphic adenomas. The most common site is the superficial parotid gland, often the tail of the gland at the angle of the jaw; occasionally, the latter are mistaken for a cervical lymph node. Approximately 50% of pleomorphic adenomas have been found to have specific gene rearrangements involving either the PLAG1 gene on chromosome 8q12 or the HMGA2 gene on chromosome 12q13-15.

**Cytologic features of pleomorphic adenoma:**

- Cohesive epithelial cells in honeycomb groups
- Myoepithelial cells, often plasmacytoid or spindled
- Chondromyxoid matrix - fibrillary and bright magenta using Romanowsky stains

**The hallmark of pleomorphic adenoma in FNA specimens is its characteristic fibrillary matrix material.**

Pleomorphic adenomas are characterized by an admixture of cohesive epithelial cells, usually in a honeycomb pattern, and myoepithelial cells, that can have a variety of appearances including epithelioid, clear, spindled, and plasmacytoid. Unlike epithelial cells, myoepithelial cells are commonly found individually, embedded within matrix material, in loose clusters, or in larger, haphazardly arranged clusters. In my experience, pleomorphic adenomas are more often composed predominantly of myoepithelial cells, but epithelial-predominant lesions do occur and appear somewhat basaloid. In addition to the cellular component, there is a characteristic matrix material, best appreciated in air-dried Romanowsky-stained preparations where it has a fibrillary or "wet yarn" appearance. It stains pale green or colorless in Papanicolaou-stained preparations, and it has an intense magenta (metachromatic) color in Romanowsky stained smears. The distinctive fibrillary nature of the matrix material with its frayed, indistinct margins and embedded myoepithelial cells is characteristic enough to distinguish a pleomorphic adenoma from other lesions that may mimic it, especially adenoid cystic carcinoma.

**Some common pitfalls in diagnosing pleomorphic adenomas include:**

- Cellular specimens with sparse or absent matrix material
- Lesions with focal adenoid cystic-like areas
- Lesions with focal cytologic atypia
- Lesions with metaplastic changes, especially squamous or mucinous features
Adenoid Cystic Carcinoma:

Adenoid cystic carcinomas represent 4-10% of all salivary gland neoplasms, usually occurring in middle-age women. Although the clinical course of adenoid cystic carcinoma is often protracted, long-term (15-20 year) survival is poor. Three histologic variants of adenoid cystic carcinoma are recognized and often present in combination: tubular, cribriform, and solid. Recognition of the solid pattern is important because of its more aggressive clinical course. The tendency of these tumors to invade nerves manifests itself clinically as a painful mass or as pain during the FNA, which should increase the clinical suspicion of malignancy.

Cytologic features of adenoid cystic carcinoma:

- Variably sized, often large, three-dimensional hyaline matrix spheres and linear branching structures
- Matrix is acellular with sharp borders, and metachromatic
- Surrounding basaloid cells with dark angulated nuclei and variable nuclear atypia

Aspirates of adenoid cystic carcinoma are classically comprised of acellular "cookie cutter-like" matrix spheres and tubules that are metachromatic in Romanowsky preparations and pale blue-green or colorless in Pap stains. The cellular component of adenoid cystic consists of small basaloid cells with angulated nuclei. The primary way that pleomorphic adenomas and adenoid cystic carcinomas are distinguished is based upon differences in their stroma. Romanowsky-stained preparations are essential for helping to make this distinction since it highlights the stromal features! Pleomorphic adenoma has fibrillar stroma with embedded cells, while adenoid cystic carcinoma has homogeneous acellular stroma in spheres and cylindrical shapes.

2) BASALOID TUMORS:

This category is among the most difficult in salivary gland cytology, because there are several entities that have overlapping features. By basaloid, we mean that the cells have small dark nuclei and scant cytoplasm. In a majority of instances, the diagnosis of a basaloid tumor will be descriptive rather than specific. Importantly, the differential diagnosis includes basal cell adenoma, cellular pleomorphic adenoma, and solid adenoid cystic carcinoma. In some cases, these entities can look nearly identical, so beware!

Differential diagnosis of basal cell tumors:

- Basal cell adenoma/adenocarcinoma
- Cellular pleomorphic adenoma
- Solid adenoid cystic carcinoma
Cytologic Features of the Membranous Subtype of Basal Cell Adenoma:

While the diagnosis of most basaloid tumors of the salivary gland will be descriptive, there is one form of basal cell tumor that is distinctive: the membranous subtype of basal cell adenoma. The characteristic cytology of this entity is the presence of a thick acellular ribbon of homogeneous matrix material surrounding large clusters of bland basaloid cells (see Figure below). No other tumor in the salivary gland looks like this:

![Image of membranous subtype of basal cell adenoma]

Pitfall: Mistaking chronic sialadenitis for a basal cell tumor

Beware of aspirates of chronic sialadenitis which can occasionally be mistaken for a basal cell tumor. Chronic sialadenitis does contain basaloid cells, but the aspirates are hypocellular in contrast to the cellular aspirates of most true basal cell tumors. In addition, chronic sialadenitis contains small angulated groups of basaloid cells in a background of mild chronic inflammation and fibrous tissue.

Cytologic Features of Chronic Sialadenitis:

- Hypocellular
- Small angulated groups of basaloid cells
- Mild chronic inflammation
- Fibrous tissue, crystalloids, and stone fragments

![Image of hypocellular aspirate of chronic sialadenitis]
3) ONCOCYTIC-APPEARING SALIVARY GLAND LESIONS:

The differential diagnosis of oncocytic salivary gland tumors includes a variety of entities, but the most common differential diagnosis is between oncocytoma and acinic cell carcinoma.

Differential Diagnosis of Oncocytic Salivary Gland Tumors:

- Oncocytoma
- Warthin tumor
- Acinic cell carcinoma
- Mucoepidermoid carcinoma, oncocytic variant
- Metastatic renal cell carcinoma

Acinic Cell Carcinoma vs Oncocytoma:

Acinic cell carcinoma is the second most common salivary gland malignancy, representing approximately 4-6% of all salivary gland tumors and up to 17% of salivary gland malignancies. It is generally a low-grade tumor although high-grade forms do occur. Acinic cell carcinoma typically presents as a circumscribed, mobile, slowly-growing mass which occasionally is painful. Acinic cell carcinoma is best recognized in Diff-Quik stained specimens, which highlights its cytoplasmic vacuoles distinguishing the tumor cells from oncocytes of Warthin tumor and oncocytoma. Oncocytes of oncocytoma have homogeneously dense and granular cytoplasm that lacks vacuoles. Cytoplasmic zymogen granules in acinic cell carcinoma are PAS-positive diastase-resistant and negative for PTAH…the opposite is true of oncocytomas. When acinic cell carcinomas show well-defined features of serous acinar differentiation, the tumor is easily recognized both cytologically and histologically. However, acinic cell carcinoma can show features of intercalated duct cells or of an adenocarcinoma, NOS, in which case, it is much more challenging to recognize the tumor specifically as acinic cell carcinoma.

Cytologic features of acinic cell carcinoma:

- Cellular smear of serous-type acinar cells
- Large polygonal cells with abundant finely vacuolated cytoplasm
- PAS+D resistant cytoplasmic zymogen granules
- Bland nuclear cytologic features
- Background stripped nuclei ± lymphocytes
- Psammoma bodies may be seen
Oncocytoma: Aspirates have a clean background and groups of oncocytes that lack cytoplasmic vacuoles.

Warthin tumor is an example of a salivary gland tumor comprised of oncocytes in a background of lymphocytes and abundant granular background debris. Most aspirates of Warthin tumor are easily recognized and accurately diagnosed.

Warthin tumor showing background debris, lymphocytes, and groups of oncocytes.

In assessing an oncocytic lesion of the salivary gland, Diff-Quik stains for identification of cytoplasmic vacuoles is helpful, and sometimes, histochemical stains for intracellular mucin, PAS + diastase, and PTAH can be useful for narrowing the differential diagnosis. The differential diagnosis of metastatic renal cell carcinoma, raises the broader issue of metastatic disease in the head and neck region. The most common metastatic tumors encountered in periparotid and submandibular lymph nodes include:

- Cutaneous cancers (squamous cell carcinoma, melanoma, and Merkel cell carcinoma)
- Oropharyngeal squamous cell carcinoma
- Sebaceous carcinoma (eyelid)
- Breast carcinoma
- Small cell carcinoma
- Metastatic renal cell carcinoma

4) CYSTIC AND MUCINOUS SALIVARY GLAND LESIONS:

The differential diagnosis of non-neoplastic and low-grade tumors where mucus-containing cells predominate includes a mucocele (a pseudocyst because it lacks an epithelial lining), ductal mucinous
metaplasia (mucus retention cyst) in sialolithiasis, mucinous metaplasia in Warthin tumor or pleomorphic adenoma, and low-grade mucoepidermoid carcinoma. **Beware: The most important entity to consider in any salivary gland aspirate containing mucin is low grade mucoepidermoid carcinoma!** The key to distinguishing low-grade mucoepidermoid carcinoma from benign mucinous cysts is to search for the characteristic 3 epithelial cell types, and especially the combination of mucus-containing epithelial cells and squamoid or intermediate cells within a group. Sometimes a definite diagnosis is not possible, especially when cell block material is not available or only cyst contents are aspirated.

### Differential Diagnosis of mucinous cysts:

- Mucocele
- Mucus retention cyst
- Low-grade mucoepidermoid carcinoma
- Warthin's tumor with mucinous metaplasia
- Pleomorphic adenoma with mucinous metaplasia

### Low-grade mucoepidermoid carcinoma:

Mucoepidermoid carcinoma is the most common salivary gland malignancy in children and adults and the most common malignancy of the major and minor salivary glands. The cytology of these tumors is variable depending upon the grade of the tumor, but low-grade forms are the most frequently encountered. **Low-grade mucoepidermoid carcinoma is also the most common cause of a false-negative cytologic diagnosis,** in part because the lesion is cystic and aspirates may yield only cyst contents, and partly because the epithelial cells are bland, and the mucin-containing cells can easily be misinterpreted as histiocytes or muciphages. Cytologically, low-grade mucoepidermoid carcinoma is characterized by a combination of 3 epithelial components: bland cohesive squamous cells, intermediate cells, and mucus cells in a background of cystic mucinous material. These lesions can be extremely challenging, and when possible, material for a cell block preparation should be obtained. The latter can be quite useful since ancillary marker stains for keratins and for intracellular mucin can help to solidify the diagnosis.

### Cytologic features of low-grade mucoepidermoid carcinoma:

- Mucus-containing epithelial cells
- Epidermoid cells (squamous features)
- Intermediate cells
- Mucinous background

**FNA of low grade mucoepidermoid carcinoma**
Aspirates of mucoceles are hypocellular and contain histiocytes, mucinous background material, scattered inflammatory cells, and sometimes crystals.

Mucocele containing muciphages in a mucoid background.

5) HIGH GRADE SALIVARY GLAND CANCERS:

The differential diagnosis of high grade salivary gland cancers includes salivary duct carcinoma, high grade mucoepidermoid carcinoma, carcinoma ex pleomorphic adenoma, and metastatic disease. In some cases, it may be extremely difficult to distinguish salivary duct carcinoma from high-grade mucoepidermoid carcinoma and carcinoma ex pleomorphic adenoma, but clinical management tends to be similar for all of these cases. Distinction from distant metastasis is also difficult and depends on appropriate clinical information.

Differential diagnosis of high grade salivary gland carcinomas

- Salivary duct carcinoma
- High grade mucoepidermoid carcinoma
- Carcinoma-ex-pleomorphic adenoma (malignant mixed tumor)
- Metastatic carcinoma

Salivary Duct Carcinoma

Salivary duct carcinoma is an uncommon, clinically aggressive malignancy that most commonly occurs in the parotid gland of older men. It resembles high-grade comedo-type ductal carcinoma of the breast. The cytologic features are those of a high-grade carcinoma. Cells are polygonal with moderate to abundant vacuolated cytoplasm, enlarged hyperchromatic nuclei with prominent nucleoli, and background necrosis. The cells are present in cohesive groups that may form sheets, papillae, and cribriform clusters.

Cytologic features of salivary duct carcinoma:

- Overtly malignant cytology
- Polygonal cells with abundant vacuolated cytoplasm
- Prominent nucleoli
- Sheets, clusters, papillae, and cribriform groupings
- Background necrosis
Carcinoma ex pleomorphic adenoma:

Carcinoma ex pleomorphic adenoma (malignant mixed tumor) is a rare neoplasm. There are 3 types of malignant mixed tumor: metastasizing mixed tumor, carcinosarcoma, and carcinoma arising in a pleomorphic adenoma, the latter being the most common. When pleomorphic adenomas develop a malignant component, it is most commonly in the form of salivary duct carcinoma, although a variety of different salivary gland malignancies can arise, usually they are high-grade and clinically aggressive!

Cytologic features of malignant pleomorphic adenoma:

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<th>Carcinoma ex pleomorphic adenoma</th>
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<tr>
<td>• High-grade carcinoma (usually salivary duct carcinoma) juxtaposed with typical pleomorphic adenoma</td>
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<tr>
<td>Metastasizing mixed tumor</td>
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<tr>
<td>• Indistinguishable from pleomorphic adenoma</td>
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<tr>
<td>Carcinosarcoma</td>
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<tr>
<td>• Distinct, malignant epithelial and mesenchymal elements</td>
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Special Course Cytomorphology II: FNA Cytology

Pancreas

Gregg A. Staerkel, MD

Disclosure information

“The speaker has no relationship that represents a possible conflict of interest with respect to the content of this presentation.”
Fine Needle Aspiration of the Pancreas

Gregg A. Staerkel, M.D.

Fine-needle aspiration (FNA) has become the preferred method for evaluating a lesion of the pancreas suspected of being neoplastic in nature. The selection of FNA as a diagnostic tool has occurred because of radiologic technological advances. In addition, the utility of FNA has improved sensitivity/specificity for tumor detection while decreasing complications seen in traditionally performed biopsy procedures.

Pancreatic Fine-Needle Aspiration:

Prior to FNA, cutting needle or wedge biopsy and endoscopic exfoliative cytology were widely utilized. For the pancreas, cutting needle and wedge biopsies yield complications that include hemorrhage, fistula formation, pancreatitis and death in 5 to 20% of cases. Furthermore, obtaining representative tissue for histologic examination can be problematic in up to half of cases sampled. In addition, histologic tissues obtained for frozen section evaluation can yield a false positive rate of 3%. Although endoscopic exfoliative cytology is a relatively safe method for tissue acquisition, sensitivity rates are low, in the neighborhood of 50%. Reaching the level of a stricture for sampling can be difficult because of the small size of pancreatic ducts.

The use of fine needle aspiration, in conjunction with computed tomography and ultrasonography, has maintained the reliability of diagnosing pancreatic carcinoma with specificity rates near 100%, while increasing sensitivity to 80 to 90%. Percutaneous computerized tomographic guided-FNA is technically easier to use than percutaneous ultrasound as it is unaffected by gas within the bowels and excessive adipose tissue. However, the lack of real-time imaging increases procedure time. The arrival of endoscopic ultrasonography eliminates the prior mentioned problem with percutaneous ultrasound. It also allows for the evaluation of the primary pancreatic lesion and, if malignant, simultaneous staging of the disease. In addition, smaller lesions can be detected and/or biopsied in less time with real-time imaging. It should be noted that with any technique employed, overall accuracy increases with aspirator experience and with the availability of a cytopathologist for immediate specimen adequacy assessment. Major complications for FNA are reported at less than a tenth of one percent. The relative non-invasive detection of malignancy by fine needle aspiration causes little or no change in the performance status of the patient for subsequent surgery or chemoradiation.
Fine Needle Aspiration of the Pancreas

I. Pancreas Aspiration

Increased diagnostic accuracy and decreased rate of complications, (e.g. hemorrhage, pancreatitis, death), when compared to core needle or wedge biopsy

II. Normal Pancreas

A. Exocrine Tissue
   1. Serous Acini
      a. Small cohesive, raspberry-like groups
         [Aggressive smears can disrupt groups giving impression of single cells (similar to cells of an islet cell tumor); recognition of the small nuclear sizes of these dispersed cells is key]
      b. Cell borders between cells, indistinct (margins of group, defined)
      c. Nucleus, eccentrically placed
      d. Nucleus, small, round to oval, smooth contour
      e. Chromatin, hyperchromatic, evenly distributed
      f. Nucleolus, small, inconspicuous
      g. Cytoplasm, granular and abundant (relative to size of nucleus)
   2. Excretory Ducts
      a. Monolayer sheets
         1) Uniform columnar to cuboidal cells
         2) Cell borders between cells, indistinct to honeycombed (margins of group, defined)
         3) Nucleus, round/oval, smooth contour, fine evenly distributed chromatin, indistinct nucleolus
         4) Nuclear spacing uniform throughout cell fragment with minimal to no overlap
      b. Cylindrical tubular structures
         [Cellular composition, same as monolayer sheets (see above)]

B. Endocrine Tissue
   [Not recognizable in cytology preparations due to sparse distribution and similarity to acinar cells that have been disrupted (special stains required)]

III. Pancreatic FNA Contaminants

A. Duodenum (approach to head lesions)
   1. Flat sheets showing goblet cells (appear to have zone of clear cytoplasm around nucleus) spaced at regular intervals.
   2. Three dimensional, “elephant trunks,” epithelial groups (represents the epithelial lining of villi)
3. Lamina propria fragments (recognized as stromal fragments containing inflammatory cells)

**B. Stomach (approach to body and tail lesions)**
1. Flat sheets of columnar cells with diffuse mucinous cell features (can be confused with mucinous neoplasms since background mucin can also be present)
2. Gastric glands either do not aspirate or are not recognized and therefore interpreted as normal pancreatic ductal epithelium.

**C. Differentiation of benign pancreatic ductal epithelium and gastrointestinal epithelium.**
1. B72.3 labeling
   - Benign pancreatic ductal epithelium: negative
   - Gastrointestinal contamination: goblet cells with strong, coarse granular pattern and other epithelial cells with finely granular, punctuate, perinuclear distribution
2. Mucin expression
   - normal duodenum
     - MUC1
     - MUC2 +
     - MUC5AC
     - MUC6 +
   - non-neoplastic pancreas
     - MUC1 +
     - MUC2
     - MUC5AC
     - MUC6 +

**IV. Reactive Pancreas (Pancreatitis)**
[Related to biliary tract disease, excessive alcohol intake and trauma]

**A. Acinar Tissue**
[Similar in appearance to normal pancreas (see above)]

**B. Ductal Tissue**
Atypia seen can cause confusion with malignancy, features to note:
1. Nuclear enlargement, relatively uniform throughout cells of the same fragment, with minimal nuclear overlap
2. Sizes of nuclei (total nuclear volume), within the same fragment, do not show differences of 4:1 or greater
3. Nuclear contours remain round/oval
4. Nucleoli may be prominent
5. Mitotic activity, infrequent
6. Necrotic debris, histiocytes and acute inflammatory cells can be seen
V. Tumors
A. Non-neoplastic Cysts
1. Congenital
   [Less than 5 cm., low cuboidal to no epithelium with fibrous connective tissue wall, filled with mucoid or serous fluid]
   a. Scant epithelium with features similar to those described under “Normal Pancreas/Excretory Ducts/Monolayer sheets” (see above)
   b. Proteinaceous background
2. Pseudocyst
   [5-10cm., fluid collection secondary to inflammation, necrosis or hemorrhage (history of pancreatitis), located adjacent to tail of pancreas, no lining cells (fibrous connective tissue only), filled with serous/turbid fluid – high amylase, normal CEA and viscosity less than serum (separates from cystic neoplasms)]
   a. No epithelium, although mesothelium may be inadvertently obtained
   b. Variable amounts of mixed inflammatory cells, fibroblasts and granular debris

B. Benign Neoplasms
1. Serous Cystadenoma [synonyms: microcystic adenoma and glycogen-rich adenoma; serous oligocystic adenoma (large cysts present)]
   [Elderly female (F/M:3/1) individuals (mean age 66), frequently large, multicystic, involving head of pancreas, central scar, sun burst type calcifications on CT scan, clear fluid, sponge-like, vascular tumor (post contrast media enhancement, mucinous tumors do not)]
   a. Few cuboidal cells and small groups in monolayers
   b. Clear cytoplasm (glycogen)
   c. Honeycomb pattern
   d. Nucleus, round/oval, smooth contour, fine evenly dispersed chromatin, inconspicuous nucleolus
   e. PAS stain positive, not diastase resistant indicating glycogen and not mucin
2. Lymphoepithelial Cyst
   [Typically found incidentally or large in size, greater than 5 cm, when abdominal pain is complaint, peripancreatic, 80% occur in men]
   a. Anucleated squamous cells (ghost-like looking sometimes)
   b. Granular amorphous debris in background (looks like necrotic debris grossly when placed on slides; +/- cholesterol crystals)
   c. Lymphoid component sparse or not recognized (due to size of lesion, lymphoid component is stretched thin, needle passes quickly through)
3. Solid-Pseudopapillary Tumor (Synonym: Solid and Papillary Epithelial Neoplasm)
[Adolescent girls and young women (F/M: 9/1, mean age 28), usually discovered incidentally or during pregnancy or after trauma, tail of pancreas, greater than 10 cm., encapsulated, lesion is solid however cells furthest from small vessels are acantholytic-like and drop out of histologic sections creating a pseudopapillary pattern with cystic spaces]
   a. Slender papillary fronds
   b. Small cells
   c. Nucleus, round/oval, smooth contour, fine evenly dispersed chromatin, inconspicuous nucleolus
   d. Globules of myxoid material among cells (Pap: pale blue; Diff-Quik: reddish)
   e. Electron microscopy shows no neuroendocrine granules (helps distinguish from islet cell tumor which has cytologic similarity)
   f. Immunoperoxidase stains for B-catenin, CD56, CD10, alpha-1-antitrypsin and vimentin are positive, pan-keratin can be positive in 1/3 of cases and synaptophysin can be focally positive, chromogranin is negative

C. Mucinous Lesions
1. Pancreatic intraepithelial neoplasia (PanIN) - in-situ lesion, thought to give rise to invasive ductal carcinomas
   - Entity is not knowingly aspirated as they are clinically not detectable – grossly not visible (typically <0.5 cm) with no visible mucin
   - Classification
     - Normal: epithelium is low columnar with amphophilic cytoplasm and no mucinous cell changes, cellular crowding or nuclear atypia
     - PanIN-1A: mucinous metaplasia, lesion is flat composed of tall columnar cells with basally oriented nuclei and supranuclear mucin
     - PanIN-1B: same as PanIN-1A plus micropapillary to papillary or basally pseudostratified architecture
     - PanIN-2: mostly papillary, but, can be flat with nuclear abnormalities (enlargement, hyperchromasia, crowding, pseudostratification +/or loss of polarity); rare, non-atypical, non-apical mitoses
     - PanIN-3: micropapillary to papillary, only rarely flat with greater nuclear abnormality than PanIN-2; mitoses may be atypical and apical, cribriforming, budding off of small cell groups into lumen
(histologic sections), luminal necrosis, macronucleoli and subnuclear mucin

5. Intraductal papillary mucinous neoplasm (IPMN)
   - Grossly identifiable lesion (>1 cm), average age 68, affects men and women, typically located in the head (>80%), communicates to the ducts of the pancreas so mucin can be seen extruding from the ampulla on endoscopy and radiographically cystically dilated ducts (“cyst by cyst” or “cluster of grapes”) are seen
   - Histologically, villous projections are identified within dilated native ducts
   - Classification: IPM adenoma, IPMN with dysplasia (mild to severe) or IPMN-borderline and IPM-CIS
   - Invasive carcinoma is seen in approximately 30% of IPMNs (the presence of colloid carcinoma is almost always associated with IPMN; 5 year survival of resectable cases is 55% compared with 10% for conventional ductal carcinoma); the finding of a mural mass correlates with the likelihood of invasive carcinoma

6. Mucinous cystic neoplasms (MCN)
   - Grossly identifiable lesion, average age 50, affects perimenopausal women (>95%), typically located in the tail (>90%), no communication to native ducts of the pancreas and radiographically multiloculated thick walled cysts (“cyst in cyst”) are seen
   - Histologically, ovarian stroma surrounds cysts (>95%) that is estrogen and progesterone positive
   - Classification
     - AFIP: mucinous cystadenocarcinoma with low-grade malignant potential
     - WHO: Non-invasive [then based on degree of cytologic and architectural atypia subdivided into MC adenoma, MCN-borderline, MC adenocarcinoma (CIS)] and Invasive

7. Mucinous adenocarcinoma (MAC) or adenocarcinoma with mucinous features
   - Solid mass, no cystic features by imaging studies unless extensive cystic degeneration is present, do not typically see true papillary structures, no communication with the ductal system of the pancreas
   - Criteria for diagnosis is the same as conventional ductal adenocarcinoma of pancreas except mucinous cell changes and background mucin are identified in addition

8. Cytologic findings in mucinous lesions of the pancreas
   - Distinction between all mucinous lesions, based on cytologic review only is next to impossible, one must make a good correlation between cytologic, clinical and imaging findings to reach the correct
diagnosis; common cytologic findings for IPMN and MCN (cytologic features for MAC are as noted in paragraph above) are as follows:

a. Benign/low grade IPMN/MCN
   1. Solitary cells/small clusters/papillary groups
   2. Cytoplasm, abundant, filled with mucin
   3. Honeycomb fragments
   4. Single cells exfoliate, degenerate and look histiocytic
   5. Nuclear polarity, low nuclear/cytoplasmic ratio
   6. Nucleus, round/oval, smooth contour, fine dispersed chromatin, inconspicuous nucleolus
   7. Background mucin should be abundant and omnipresent (not just focally seen on rare slides only, especially if going through stomach for aspiration)

b. Malignant IPMN/MCN [cytologically similar to paragraph above except (at least focally):
   1. Increased nuclear/cytoplasmic ratios
   2. Loss of nuclear polarity
   3. Irregular nuclear size and shape
   4. Necrosis
   5. Mitotic activity
   6. Crowding of cells (pseudostratification) with papillary fronds
   7. Anisonucleosis

c. Ancillary studies in mucinous lesions of pancreas
   1. MAC usually expressed MUC1, whereas 80% of IPMNs are positive for MUC2 and MUC5AC
   
   • IPMNs exist in four subtypes with differing marker expressions:
       - pancreatobiliary (more aggressive)
         MUC1 +/-
         MUC2 -
         CDX2 -
       - gastric
         MUC1 -
         MUC2 -
         CDX2 -
       - oncocytic
         MUC1 -/+ 
         MUC2 -/+ 
         CDX2 -
       - intestinal
         MUC1 -
         MUC2 +
         CDX2 +
2. Expression of DPC-4 protein is seen in most cases of IPMNs and MCNs but only present in 40% to 50% of MAC
3. DUPAN-2, positive marker in most MAC and only few IPMNs
4. Other markers that favor malignancy in mucinous cystic lesions include:
   - expression of laminin-5-gamma-2
   - predominance of sulphomucin over sialomucin
   - expression of mammary-type and intestinal-type mucin core protein
   - stromal expression of gelatinase A

   d. Side branch vs. main duct IPMNs
   - more indolent tumors
   - progression slower
   - frequency of malignancy lower
   (reasons why some suggest watchful waiting in pure side branch tumors with benign cytology)

D. Cyst fluid analysis
Amylase levels below 250 U/L virtually exclude pseudocyst (some serous cystadenomas and mucinous lesions can have very high amylase levels).

CEA levels below 10 mg/ml are associated with serous cystadenomas and pseudocysts and only rarely with mucinous lesions; levels below 100 mg/ml and 800 mg/ml exclude most serous cystadenomas and pseudocysts, respectively; levels in excess of 800 mg/ml are most consistent with mucinous lesions, but, these lesions can have levels in the 10 to 100 mg/ml range too.

E. Malignant Neoplasms
1. Pancreatic (Ductal) Adenocarcinoma
   [80-90% of malignant tumors, frequently involving head of pancreas causing obstructive jaundice]
   Aspirates to be evaluated need good cellularity (the less nuclear atypia, the more groups required)
   a. Nuclear features include:
      1. enlargement
      2. size variation (4:1 or greater within the same cell group)*
      3. crowding/overlap*
      4. contour irregularity*
      5. irregular nuclear distribution in groups*
      6. hyperchromasia
   b. Three-dimensionality of cell groups*
   c. Mucinous metaplasia
      1. diffuse
      2. isolated engorged cells*
   d. Single malignant cells/small clusters
e. Cribriform pattern
f. Mitotic activity (significance increases when many fields show mitotic figures or several mitoses are seen in one high power field)
g. Ancillary studies in ductal adenocarcinomas of pancreas (many are under investigation and have in initial studies shown promise, however, virtually all do not have 100% sensitivity and specificity, widespread use and experience or do not assist in the most difficult area of recognition of well differentiated adenocarcinomas of the pancreas

- Markers favoring ductal adenocarcinoma over benign/reactive ductal epithelium
  - Loss of cytoplasmic and nuclear reactivity for DPC4 (Smad4)
  - Expression of cytoplasmic reactivity for monoclonal CEA
  - Expression of mesothelin
  - Reactivity in greater than 20% of nuclei for p53
  - Expression of B72.3
  - Mucin positive (PAS and/or mucicarmine)
  - Expression of carbohydrate antigen 19-9 (elevated serology for Ca19-9 over 200 U/ml and most notably over 1,000 U/ml favors pancreatic cancer)
  - Expression of DUPAN2 (elevated serology for DUPAN2 over 300 U/ml favors pancreatic cancer)
  - Expression of MUC1, MUC4, and MUC5AC (few express MUC2 or MUC6)
  - Absence of clusterin
  - Expression of prostate stem cell antigen (PSCA)
  - Expression of L523S
  - Expression of S100P by immunohistochemical staining
  - Expression of K-ras gene mutation
  - Expression of p16 mutation
  - Loss of chromosome 9p (site of p16 gene and/or chromosome 18q (site of DPC4 gene)

2. Pancreatic (Ductal) Adenocarcinoma Variants
   a. Signet ring cell carcinoma
      1. Single cells
      2. Nucleus so eccentric that nuclear border becomes one with the cell's cytoplasmic border (this distinguishes from histiocytes)
      3. Cytoplasm varies from clear (vacuole) to “tissue paper” consistency
      4. Mucin present within cells often deforms nucleus creating a crescent shape
   b. Undifferentiated (anaplastic giant cell) carcinoma
1. Poorly cohesive cell groups and single cells
2. Nuclei show great irregularity, bizarre giant forms and/or multinucleation
3. If reactive multinucleated giant cells are present then termed “undifferentiated carcinoma with osteoclast-like giant cells”
   c. Adenosquamous carcinoma (in addition to features of adenocarcinoma, a coexistent malignant component shows squamous differentiation)
   d. Colloid carcinoma (neoplastic cells are seen within a background of abundant mucin; 80% of tumor must be floating in mucin on resection to be designated colloid carcinoma; most colloid carcinomas arise from IPMN, typically exhibiting intestinal type papillae)
3. Pancreatic Endocrine Tumor (Islet Cell Tumor)
   [Adults, occurs anywhere along the length of the pancreas with greater percentage in the body and tail where a greater number of islets reside, variable in size when detected, slow growing (long survival even with metastasis)]
   a. Hypercellular
   b. Often a 50-50 mixture of single cells and cohesive groups
   c. Acinar-like formations
   d. Thin-walled branching vessels with arborizing cells
   e. Individual cells, round to cuboidal, with well defined cytoplasm
   f. Nucleus, small, eccentric, round/oval, fine evenly dispersed chromatin, nucleolus usually inconspicuous
   g. Exception for tumors with a trabecular growth pattern – aspirates yield large, three-dimensional groups of small uniform cells which appear in syncytium (few or no single cells present)
   h. Chromogranin, synaptophysin, CD56, pan-keratin and neuron specific enolase positive
   i. Electron microscopy demonstrates neurosecretory granules
4. Acinar Cell Carcinoma
   [Less than 5% of malignant tumors, children to adults, occurs anywhere along the pancreas, survival as poor as pancreatic ductal carcinoma]
   a. Single cells/small groups
   b. Stripped nuclei in background
   c. Acinar structures, loosely configured
   d. Large nucleus (relative to normal acini), fine, evenly distributed chromatin, mildly irregular contour, conspicuous nucleolus
   e. Cytoplasm varies from foamy to granular
   f. Trypsin, chymotrypsin, alpha-1-antitrypsin and keratin are positive
   g. Electron microscopy demonstrates zymogen granules
5. Other Malignancies
a. Undifferentiated small cell carcinoma (high grade carcinoma with neuroendocrine differentiation that is morphologically similar to small cell carcinoma of the lung)

b. Pancreatoblastoma (large mass in young children, mean age 4, some occur in adults, associated with Beckwith-Weidemann syndrome and AFP elevation)
   1. Cells are undifferentiated to tubuloglandular and/or squamoid (multidirectional differentiation with acinar predominating)
   2. Morphology similar to islet cell tumor and acinar cell carcinoma
   3. Trypsin, chymotrypsin, chromogranin, synaptophysin, CEA, keratin and AFP (only 15%) are positive
   4. Electron microscopy can show bi-directional differentiation with both neurosecretory and zymogen granules identified

c. Metastatic tumors and lymphomas (suspect when morphology is not consistent with typical pancreatic lesions or when patient has a known prior malignancy)
FNA REFERENCES:

PANCREAS REFERENCES:

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