Workshop 12

Bridging the Gap Between Basic Histology and Cytohistology

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There are no disclosures necessary.

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Bridging the Gap between Basic Histology and Cytopathology
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OVERVIEW

Conflict of interest

1. General Cytohistology (LP)
2. Epithelial Morphology (LP)
3. Systemic/Organ-Based LUNG & PANCREAS (MS)
   HEAD & NECK (ZB)
INTRODUCTION

- Why do we need to know histology/histopathology?
  A. Better cyto-histo correlation
  B. Cell blocks with “microbiopsies”
  C. Concomitant core biopsies
- Welcome to the era of cytology + histology = i.e. Cytohistology
What is your diagnosis?

Intra-abdominal FNA – Cell Block (H&E)

What is your diagnosis?

Normal Renal Glomeruli

What’s in this cell block?
What’s in this cell block?

Metastatic breast carcinoma

What is your diagnosis?

Invasive Adenocarcinoma

Core (H&E)

Pankaratin IHC
**CYTO vs. HISTOLOGY**

<table>
<thead>
<tr>
<th>STUDY OF</th>
<th>HISTOLOGY</th>
<th>CYTOLOGY</th>
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<tr>
<td>TISSUES</td>
<td>CELLS</td>
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<tr>
<td>PROCUREMENT</td>
<td>INVASIVE</td>
<td>NON-INVASIVE</td>
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<tr>
<td>SAMPLES</td>
<td>MAINLY LARGE</td>
<td>MOSTLY SMALL</td>
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<tr>
<td>FIXATION</td>
<td>FORMALIN OR FROZEN</td>
<td>ALCOHOL</td>
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<tr>
<td>PREPARATION</td>
<td>SECTIONS</td>
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<tr>
<td>MORPHOLOGY</td>
<td>ARCHITECTURE BASED</td>
<td>CELLULAR BASED</td>
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<tr>
<td>STAINS</td>
<td>H&amp;E</td>
<td>DQ/PAP/H&amp;E</td>
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<tr>
<td>ARTIFACTS</td>
<td>SHRINKAGE &amp; FOLDS</td>
<td>AIR DRYING &amp; ROUNDED</td>
</tr>
<tr>
<td>ANCILLARY TESTS</td>
<td>OFTEN SUFFICIENT</td>
<td>USUALLY LIMITED</td>
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**Air Dried Material**

Wet fixation vs. Air-drying

- Lung Non-small cell carcinoma (Air dried, Pap stain)

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**Liquid-based Cytology**

Small cell carcinoma

- Shrinkage + Clustering = Darker

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**EPITHELIUM**

- Simple, stratified (transitional) & pseudostratified.
- Stratified >2 cell layers thick.
- Squamous, cuboidal & columnar.
- Epithelial cell polarity (apical & basal).
- Basement membrane separates basal layer from subjacent connective tissue (called the lamina propria for internal organs - GI, respiratory, & GU).
- Divided into lining (e.g. mucosa) & glandular epithelia.

**Mesothelium is Different**

**Mesos vs. Adenocarcinoma**

Peritoneal fluid with metastatic colon adenocarcinoma
Lining Epithelium

Flat (2D monolayer) sheet of monotonous bland cells with honeycomb arrangement.

Drunken Honeycomb

Irregular more 3D group of enlarged & crowded ductal cells with atypia.

Specialized Epithelia

Respiratory Epithelium
**Landmark Cells**

- Bronchial Brush (DQ stain)
- Small Cell Carcinoma
- Reactive Bronchial Epithelial Cells

**Creola bodies**

- Clumped columnar cells (balled-up).
- Introduced by Naylor (1962).
- Reactive (hyperplastic) process.
- Presence of peripheral cilia.
- May be mistaken for malignancy.

**Reserve cells**

- Mucous (Pap smear)
- Endocervix and Ectocervix
- MGH (Pap smear)
Reserve cell hyperplasia

- Small cells with increased N/C ratios.
- No pleomorphism, apoptosis, necrosis, or mitoses.

Lung - Reserve cell hyperplasia

Glandular epithelium

- Glandular epithelia form glands.

  - Exocrine glands:
    - E.g. salivary, pancreas, breast.
    - Tubular, acinar & alveolar glands.
    - Products (e.g. enzymes) from acini get secreted via ducts out the gland.

  - Endocrine glands:
    - Ductless and secrete hormones directly into the blood stream.

Gland Morphology
**Tubular Glands**

- Normal Colonic Mucosa

**Colon Adenocarcinoma**

- Cell block (H&E)
- FNA (Pap stain)

**Acinar Glands**

- Acinar (adjective: acinar, plural acini) = berry-shaped termination of an exocrine gland, where secretions are produced.
- Mucous (pale) & serous (dark) acini.
- Acinar cell neoplasms arise from (resemble) acinar cells.
- Pancreas: Acinar cell carcinoma
- Salivary gland: Acinic cell carcinoma
- Microglandular pattern:
  - Microacinar (e.g. prostate carcinoma).
  - Cribiform (sieve-like) carcinomas.
Salivary Gland

Normal Salivary Gland Acini

Acinic Cell Carcinoma

Acinar Features

Lung Adenocarcinoma (acinar pattern) vs. Lung Adenocarcinoma (solid pattern)

Microacinar Pattern

Prostate Adenocarcinoma
DUCTS

- Ducts become larger & their epithelium thicker.
- Myoepithelial cells between basal duct cells & basal lamina.

<table>
<thead>
<tr>
<th>Type of Duct</th>
<th>Location to Lobule</th>
<th>Epithelium</th>
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</thead>
<tbody>
<tr>
<td>Intralobular</td>
<td>Proximal</td>
<td>Simple cuboidal</td>
</tr>
<tr>
<td>Interlobular</td>
<td>Middle</td>
<td>Simple columnar</td>
</tr>
<tr>
<td>Interlobar</td>
<td>Distal</td>
<td>Stratified columnar</td>
</tr>
</tbody>
</table>

The Breast

Bile duct system

- Conveys bile from hepatocytes to intestine.
  - Hepatocytes arranged in "plates":
    - Apical surface faces sinusoids.
    - Basal surface forms canalicular.
- Bile canalicus is not a duct, but a dilated intercellular space between hepatocytes (no true epithelial lining).
- Bile flows parallel to blood (in sinusoids), but in the opposite direction.
- Bile then flows into bile ducts - true ducts lined with epithelium.
Normal Liver FNA

Benign hepatocytes & bile ductal cells (DQ stain)

Liver Architecture

Normal liver parenchymal architecture

Bile canaliculi

Hepatocellular carcinoma

Helpful immunostains for HCC

- Hepatic origin: pCEA/CD10 (canalicular pattern), CAM5.2+, AE1- (ducts stain), & HepPar-1+
- Malignant: AFP, Glypican-3, Arginase-1 (best)
**Papillary Proliferations**

- Papilla (plural: papillae) = exophytic (frond) growth.
- Stalk (fibrovascular core), but can be stroma poor.
- Surface, intraductal (e.g. breast, IPMN) or inverted (e.g. bladder).
- Macropapillary (large exophytic growths):
  - Non-neoplastic (e.g. papillary hyperplasia).
  - Benign neoplasm (e.g. papilloma).
  - Malignant neoplasm (e.g. papillary carcinoma).
- Micropapillary (many small papillae):
  - Carcinoma growth pattern.
  - In situ (e.g. DCIS) or invasive (e.g. micropapillary adenocarcinoma, serous carcinomas).
- Complex branches (arborizing) form secondary papillae (papillary tufts).
- Nonvillous papillae (small intraglandular papillary buds lacking cores).
- Pseudopapillary = solid tumor with degeneration, but leaving vessels.

**Papillae**

**STROMA-RICH**
- Branching
- Papillary tufts

**STROMA-FREE**
- Branching
- Papillary tufts

**Various Papillae**

- Papillary thyroid carcinoma (H&E)
- Ovarian serous papillary carcinoma (Pap)
- Well differentiated papillary mesothelioma (H&E)
- Micropapillary lung adenocarcinoma (Pap)
Degenerative changes result in tumor cell discohesion & cell loss, leaving capillary-sized vessels surrounded by a cuff of neoplastic cells. This leads to the characteristic pseudopapillary appearance of these tumors.

**Hyperplasia to Dysplasia**

**Hallmarks of dysplasia**
- Cellular pleomorphism
- Nuclear abnormalities
- Mitotic figures
- Loss of normal polarity

**Neoplasia**

**Components of a Tumor**

- **Desmoplasia**
  - CT response to (invasive) carcinoma
Desmoplasia
Pancreatic adenocarcinoma

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Goals and Objectives

• Review of Lung and Pancreas Histology
• Review of Commonly Encountered Benign and Neoplastic Lesions
• ROSE
• Expanding Knowledge Base
• Focus on Larger Tissue Biopsy Samples
Lung Histology

- Panoramic View
- Respiratory bronchioles
- Alveolar Ducts
- Alveolar Sacs
- Alveoli

Lung Histology

- Bronchioles with adjacent blood vessels
- Alveolar sacs with smaller alveoli

Lung Histology

- Cartilage and Sub mucosal glands
- Pseudostratified columnar ciliated cells
- FNA smear
Lung Histology

• Inter-alveolar walls
• Capillaries with blood cells

Organizing Pneumonia

• Radiologic pitfall for tumor
• Cough, hemoptysis and weight loss
• Exudate of fibrin and acute inflammatory cells
• Foamy macrophages appear in late stages as a result of bronchiolar obstruction

Lipoid Pneumonia

• Exogenous: Nasal spray
• Endogenous: Bronchial obstruction
• Sudanophilic lipoid material
• Inflammatory cells
• Hyperplasia of alveolar cells
Lipoid Pneumonia

- Numerous macrophages
- Pneumocyte hyperplasia
- Scattered inflammatory cells
- Rare multi-nucleated giant cells

Sarcoidosis

Aggregates of epithelioid histiocytes and multi-nucleated giant cells

Caseating Granulomas

- Caseous necrosis
- Tuberculosis
- AFB stain
Carcinoid Tumor

- Central/well circumscribed
- Organoid pattern with fibrovascular septa

Atypical Carcinoid Tumor

- Patterns
  - Organoid
  - Trabecular
  - Nested
  - Necrosis
  - Inflammation

- Well circumscribed mass

- Trabecular/organoid
- Fibrovascular septa
- Rosettes
- Plasmacytoid cells
- Scant cytoplasm
- Eccentrically placed nuclei
- No nuclear molding
- Salt and pepper chromatin
- Inconspicuous nucleoli
- Rare mitosis 1-2 (10HPF)
- No necrosis

- No necrosis
Atypical Carcinoid Tumor

- Pleomorphism
- Rosettes, acinar structures, palisading
- Oval, round, spindle, plasmacytoid cells
- Larger than CT/SCNC
- Moderate cytoplasm
- Variable sized nuclei
- Coarsely granular salt and pepper chromatin
- Prominent nucleoli
- Mitotic activity 2-10 (10HPF)

Central comedo type tumor necrosis is a key feature!
Small Cell Neuroendocrine Carcinoma

- Centrally located tumor
- Crush artifact and necrosis

• Round, oval or spindle cells
• 2-3 times the size of mature lymphocyte with rare intermediate size cells (3-4 times larger)
• Scant cytoplasm
• Round to oval nuclei
• Dense granular chromatin
• Nucleoli generally absent or inconspicuous
• Increased mitotic activity
  60 mitoses per mm²
• Nuclear molding
• Crush artifact
• Necrosis

Large Cell Neuroendocrine Carcinoma

- Infiltrating tumor cells
- Extensive necrosis
Large Cell Neuroendocrine Carcinoma

- Solid growth of confluent
- Organoid nests of cells
- Tumor cell palisading
- Rosettes
- Large cells, three times larger than SCNC
- Scant cytoplasm
- Large nuclei with fine chromatin
- Nucleoli present
- Nuclear molding
- Increased mitoses
- Necrosis

Squamous Cell Carcinoma

- Cell Block
- Invasive Squamous Cell Carcinoma

Mucinous Adenocarcinoma

- Invasive adenocarcinoma
- TTF-1/Napsin A
- Glandular differentiation of tumor cells
Bronchioloalveolar Carcinoma

- Non-mucinous BAC grows in a lepidic fashion along preexisting airways
- Clara cell or type 2 pneumocyte differentiation

Bronchioloalveolar Carcinoma

- Uniform cell size
- Columnar cells (Clara)
- Cuboidal cells (Type 2 pneumocyte)
- Round nuclei
- Small nucleoli
- Nuclear grooves
- Pseudoinclusions

Large Cell Carcinoma

- 9-10% of lung cancers
- Lack cytologic and architectural squamous and glandular features
- Undifferentiated cells
- Moderate cytoplasm
- Prominent nucleoli
- Ancillary studies
- IASLC recommendation “non-small cell carcinoma not otherwise specified”
Malignant Mesothelioma

- Clinical history and presentation
- Radiologic Findings
- Immunohistochemistry

Sarcomatoid Mesothelioma
Epithelioid Mesothelioma

Malignant Lymphoma

- Cartilage and glands
- Solid and diffuse
- Dense and mononuclear infiltrate of tumor cells

Pancreas Histology

- Lobulated parenchyma
- High magnification
It is critical to know where the aspirated lesion is located as this determines the type of contaminant.

- Lesions aspirated in pancreatic head and uncinate process → duodenal contaminants.
- Lesions aspirated in pancreatic body/tail → gastric epithelial contaminants.
Duodenal Epithelium

- Duodenum epithelium forms flat honeycomb sheets
- Composed of bland, evenly spaced cells
- Tissue edges have distinct brush border best seen at very high power

Gastric Epithelium

- Cytoplasmic mucin in gastric epithelium does not fill the entire cell
- Mucin is confined to the superficial 1/3rd of the cell
- Forms distinct mucin-cup

Chronic Pancreatitis

- Retention of lobular architecture with dense stroma separating each lobule
Serous Cystadenoma

- Size variation of cysts

- Cuboidal cells

Mucinous Cystic Neoplasm

- Thick mucin

- Columnar cells

- Tall columnar mucin containing cells and hypercellular sub-epithelial stroma resembling the ovary

Well Differentiated Pancreatic Adenocarcinoma

- Four fold variation of nuclear size

- Anisonucleosis

- Nuclear grooves

- Lack of lobularity
Moderately Differentiated Pancreatic Adenocarcinoma

- Diff-Quik stain
- Invasive moderately differentiated carcinoma

Poorly Differentiated Pancreatic Adenocarcinoma

- High grade cytology
- Infiltrating tumor cells and desmoplasia

Undifferentiated Carcinoma

- Osteoclast-like giant cells
Acinar cell carcinoma

Pancreatic Endocrine Neoplasm

Solid Pseudopapillary Neoplasm
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Objectives

Basic Concepts
- Thyroid histology – "the so called normal"
  - Architecture vs. Cytomorphology
  - Cells vs. Cytomorphology
  - Common Lesions vs. Cytomorphology
- Salivary Gland Histology
  - Architecture vs. Cytomorphology
  - Cells vs. Cytomorphology
  - Common Lesions vs. Cytomorphology
- Neck Cysts

Thyroid Gland

Thyroid gland
Anatomy vs. Ultrasound

Normal Thyroid

Thyroid Histology
Thyroid Histology

**Oncocytic cell** (AKA Hürthle cell)
- Metaplastic follicular cell
- Eosinophilic (pink) cytoplasm
- Round nucleus
  - Prominent Nucleus
  - Seen in both benign and malignant lesions

Thyroid Histology

**C-cells** (Parafollicular cells)
- Produce Calcitonin
- Located at the lateral aspect of thyroid gland
- Rarely seen in regular histology until hyperplastic
- Best seen with immunostains for calcitonin.
- Not seen in cytologic preparations.
Follicular cells & colloid

Follicles, Papillae & Colloid

Microfollicles & Microfollicles
Oncocytic cells & Lymphocytes

Thyroid Lesional Heterogeneity

Cytomorphology vs. Cytopreps
Cytomorphology Vs. Cytopreps
ThinPrep®

Cytomorphology vs. Cytopreps

Smears
ThinPrep

Correlation all the way
Normal Salivary Gland Cytology

- Acinar Cells
  - Serous
  - Mucinous
- Ductal epithelium
- Oncocytic cells
- Adipose tissue

Normal Salivary Gland Histology

The Major Salivary Glands
1. Parotid
2. Submandibular
3. Sublingual

The Minor Salivary Glands
• Acinus has acinar cells – grape like clusters
• Myoepithelial cells constrict intercalated duct & squirt saliva into striated duct.
• Acinar epithelium secretes proteins and isotonic filtrate
Histo-Cyto Correlation

Cyto-Histo Correlation

Mimic of Normal Salivary Gland
Acinar Tissue = Acinar cell carcinoma
**Acinic Cell Carcinoma**

**Cytology**
- Cellular smear of serous-type acinar cells
- Sheets and single cells
- Polygonal cells with abundant finely vacuolated cytoplasm
- PAS-positive diastase-resistant cytoplasmic zymogen granules

**Acinic Cell Carcinoma**

**Cytology**
- Tumor cells with indistinct cell borders
- Bland nuclear cytology
- Background containing naked nuclei & lymphocytes

**Normal Salivary Gland Tissue vs. Acinic Cell Carcinoma**
Lymphocytes in Salivary Gland

- It is not uncommon to encounter few lymphocytes & plasma cells in normal in FNA of normal salivary gland

Too many lymphocytes:
- Intra-parotid lymph node
- Chronic Sialadenitis
- Epithelial tumors with lymphocytes
  - Warthins
  - Mucoepidermoid carcinoma
  - Acinic cell carcinoma

Common Lesions In Parotid with Lymphocytes

- Chronic Sialadenitis
- Warthin Tumor

Neck Cysts

Embryologic Structures
Congenital / Developmental

• Branchial Cleft Cyst
• Thyroglossal duct cyst
• Lymphatic malformations
• Epidermoid or Dermoid
• Bronchogenic & Esophageal duplication cysts

Congenital Cysts

Branchial Cleft Cysts
Thyroglossal Duct Cyst

Branchial Cleft Cysts

External auditory canal
First branchial fistula
Stomachomochidial remnant
Second branchial fistula
Third branchial fistula
Branchial Cleft Cysts

- Type II – 95% of all branchial cleft lesions
  - Cystic mass at the antero-lateral border of SCM
- Type 1 Branchial Cleft Cyst
  - Extends from external auditory canal (EAC) through the parotid gland to the submandibular region
  - Type 1 – Periauricular & Type 2 – Periparotid
- III, IV branchial cleft cysts

Branchial Cleft Cyst

Thyroglossal Duct Cyst

- Most common congenital neck mass
- Located in mid-line or paramedian (left side)
- Closely related to hyoid bone
  - 20% suprazygoid, 65% infrahyoid & 15% at the level of hyoid bone (Bonvouloir & Yousem 1988)
- Characteristic appearance on US, CT and MRI
  - Hypoechoic thin walled cyst
  - Debris – hemorrhage or infection
  - Solid mass – Carcinoma (95% PTC & 5% SCC)
Differential diagnosis
- Dermoid cyst
- Necrotic lymphadenopathy
- Cystic goitrous nodule arising from thyroid isthmus
- Thymic cyst
- Branchial cleft cyst – paramedian location
- Cystic hygroma – paramedian location

Conclusions
- Knowledge of histology leads to better cyto-histo correlation and more accurate interpretation of cell block material & concomitant core biopsies.
- Architectural patterns and cell distribution among true tissue fragments is as important as the nuclear cytology of single cells.
- The best way to learn cytology is through knowledge of normal histology and histopathology of commonly occurring lesions.
- In this era of interventional cytopathology basic knowledge of anatomy & radiology (e.g. ultrasound) is essential.
• Histology for Pathologists
• Mills SE. *Histology for Pathologists*, 3rd edition. 2007. Lippincott Williams & Wilkins.