Respiratory Tract Cytology

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Case 1

• 63 year old female with wheezing and had difficulty breathing. No history of smoking. She underwent a transbronchial fine needle aspirate of a central lung 4.0 cm. mass
Fine Needle Aspiration Assessment

Plasmacytoid Cells

Rosette Formation
Carcinoid Tumor

- Account for 2-3% of all lung tumors
- White adults, equal sex distribution
- Not related to smoking history
- 75% are central
- Well circumscribed
- Carcinoid syndrome
- Low metastatic potential
- 5 year survival ranges from 87-100%
Carcinoid Tumor

Plasmacytoid Cells

Rosette Formation
Carcinoid Tumor

Salt and pepper chromatin

Synaptophysin

Organoid Pattern
Carcinoid Tumor

Spindle cell carcinoid
Carcinoid Tumor

Central/well circumscribed

Organoid pattern with fibrovascular septa
Carcinoid Tumor

- 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
## Carcinoid Tumor

<table>
<thead>
<tr>
<th>Cytologic Features</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>Clean, no necrosis</td>
</tr>
<tr>
<td>Cellular arrangement</td>
<td>Three dimensional clusters, organoid, single cells, rosettes and palisading</td>
</tr>
<tr>
<td>Cell shape</td>
<td>Plasmacytoid, spindle, oncocytic</td>
</tr>
<tr>
<td>Cell size</td>
<td>Uniform cells, size ranges from 15-20 µm</td>
</tr>
<tr>
<td>Cytoplasmic detail</td>
<td>Homogeneous, scant to moderate</td>
</tr>
<tr>
<td>Nuclear detail</td>
<td>Uniform, salt and pepper chromatin, indistinct/small nucleoli, virtually absent mitotic activity</td>
</tr>
<tr>
<td>Stromal Elements</td>
<td>Fibrovascular cores with adherent tumor cells</td>
</tr>
</tbody>
</table>
Pulmonary Neuroendocrine Neoplasms (PNEN)

- Neuroendocrine tumors develop from primitive cells in the neural crest
- Neural crest cells have the ability for active amine precursor uptake and decarboxylation, which form biologically active amines
- Kulchitsky or K cell is thought to be the APUD cell of origin for PNEN
- K cells found widely in the tracheobronchial tree
- Chemoreceptors that sense oxygen and carbon dioxide levels and help regulate air flow
- K cells of endodermal origin
Cytologic Sampling and Evaluation

• Play a greater role in diagnosing these tumors in comparison to transbronchial biopsy
• Bronchial brushings sample a wider area
• Fine needle aspirates can be EBUS directed or CT scan directed and dependent on the location of the tumor mass
• Well sampled fine needle aspirates are hypercellular and effectively diagnose these tumors
• Fine needle aspirate yield is operator dependent
Clinical Symptoms of PNEN

- Tumor size, location and biologic activity
- Cough, wheezing and hemoptysis
- Obstruction of bronchial lumen can cause difficulty in breathing
- Paraneoplastic syndromes secondary to aberrant expression of peptide hormones
- Cushing’s Syndrome, syndrome of inappropriate secretion of anti-diuretic hormone
## Classification of PNEN

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
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</thead>
<tbody>
<tr>
<td>Dresler, et al</td>
<td>Neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma</td>
<td>Neuroendocrine carcinoma, small cell type</td>
<td>Neuroendocrine carcinoma, large cell type</td>
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<tr>
<td>(1998)</td>
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<td>(1989)</td>
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<tr>
<td>Travis, et al</td>
<td>Carcinoid tumor</td>
<td>Atypical carcinoid tumor</td>
<td>Small cell neuroendocrine carcinoma</td>
<td>Large cell neuroendocrine carcinoma</td>
</tr>
<tr>
<td>(1998)</td>
<td></td>
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</tbody>
</table>
Case 2

• A 52 year old male presented with a history of 20 year of smoking. Presented with cough, dyspnea and increased frequency of urination. The patient underwent a chest CT scan and a peripheral lung mass measuring 4.0 cm was discovered. The patient underwent a CT guided fine needle aspiration
Fine Needle Aspiration Assessment

Organoid Pattern
Atypical Carcinoid Tumor

- Males, 50-55 years
- Peripheral location
- History of cigarette smoking
- Multiple endocrine neoplasia syndrome
- Aggressive behavior
- Metastatic potential is high
- 5 year survival rate is approximately 70%
Atypical Carcinoid Tumor

Organoid Pattern
Atypical Carcinoid Tumor

Necrosis
Atypical Carcinoid Tumor

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

Well circumscribed mass
Atypical Carcinoid Tumor

Organoid pattern

Cell block

Organoid pattern
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)
Atypical Carcinoid Tumor

Central camedo type tumor necrosis is a key feature!
### Atypical Carcinoid Tumor

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<th>Cytologic Features</th>
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<tr>
<td><strong>Background</strong></td>
<td>Necrosis and inflammation</td>
</tr>
<tr>
<td><strong>Cellular arrangement</strong></td>
<td>Three dimensional clusters, organoid, single cells, rosettes and palisading</td>
</tr>
<tr>
<td><strong>Cell shape</strong></td>
<td>Variable, round, oval or spindle</td>
</tr>
<tr>
<td><strong>Cell size</strong></td>
<td>Variable, mostly medium size, larger than cell seen in carcinoid tumor</td>
</tr>
<tr>
<td><strong>Cytoplasmic detail</strong></td>
<td>Homogeneous, moderate</td>
</tr>
<tr>
<td><strong>Nuclear detail</strong></td>
<td>Pleomorphism, salt and pepper chromatin, generally prominent nucleoli, mitotic activity (2-10/10HPF on cell block)</td>
</tr>
<tr>
<td><strong>Stromal Elements</strong></td>
<td>Fibrovascular cores with adherent tumor cells</td>
</tr>
</tbody>
</table>
Case 3

- A 60 year old male smoker who developed multiple liver lesions. CT scan of the chest showed a 3.5 central mass in the left lung, lower lobe as well. The patient underwent a fine needle aspiration of the largest liver lesion.
Fine Needle Aspiration Assessment
Small Cell Neuroendocrine Carcinoma

- Account for 20-25% of lung cancers
- 90% are centrally located and rapidly growing
- Male smokers account for 80% of the cases
- Widespread metastasis
- Treated with chemotherapy/radiation
- 5 year survival is less than 5%
Small Cell Neuroendocrine Carcinoma

- Small groups
- Nuclear Molding
- Hypercellular with crush artifact
Small Cell Neuroendocrine Carcinoma

- Round, oval or spindle cells
- 2-3 times the size of a mature lymphocyte with rare intermediate size cells (3-4 times larger)
- Scant cytoplasm
- Round to oval nuclei
- Dense coarse chromatin
- Nucleoli generally absent or inconspicuous
Small Cell Neuroendocrine Carcinoma

- Centrally located tumor
- Diff Quík stain
- Papanicolaou stain
- Crush artifact and necrosis
Small Cell Neuroendocrine Carcinoma

- Increased mitotic activity
  - 60 mitoses per mm$^2$
- Nuclear molding
- Crush artifact
- Necrosis
- IHC analysis

Chromogranin

Cell block
Case 4

A 45 year old male with a history of smoking presented with a new onset of coughing with blood. Further work-up included a CT-scan of the chest which showed a central well demarcated 3.8 cm mass lacking calcification and necrosis. The patient underwent a CT-guided fine needle aspiration
Fine Needle Aspiration Assessment
Large Cell Neuroendocrine Carcinoma (LCNEC): Clinical and Radiologic Features

• Initially described in 1991 by Travis et, al.*
• Male patients over 60 years of age
• History of smoking
• CT scan: Well demarcated and lobulated mass
• Size ranges from 2-5 cm
• Lacks internal calcifications
• Moderate enhancement which is more than the chest wall muscle
• Lymphadenopathy in ipsilateral hilar and mediastinal areas

Large Cell Neuroendocrine Carcinoma
Large Cell Neuroendocrine Carcinoma
Large Cell Neuroendocrine Carcinoma
Large Cell Neuroendocrine Carcinoma
Cytologic Features of LCNEC

- Tissue fragments
- Cellular clusters
- Rosettes
- Single cells
- Necrosis
Cytologic Features of LCNEC

Tumor cells are > 3 times the tumor cells in small cell carcinoma
Cytologic Features of LCNEC

- Moderate amount of cytoplasm
- Round to oval nuclei with thin membranes
- Finely granular chromatin
- Nucleoli are common and are large and single
Cytologic Features of LCNEC

- Nuclear molding
- Naked nuclei, nuclear crush artifact and extensive necrosis
Histologic Features of LCNEC

- Large confluent organoid nests of tumor cells
- The tumor cells are separated by thin septa of fibroconnective tissue
Histologic Features of LCNEC

- Palisading of tumor cells
- Rosette like structures
- Necrosis
Histologic Features of LCNEC

- Individual tumor cells are large with moderate cytoplasm
- Nuclei have large nucleoli
- Mitotic counts are 11 or more (average 75) per 2 mm²
- Large zones of necrosis are common
- IHC confirmation of neuroendocrine differentiation
Poorly Differentiated Squamous Cell Carcinoma

Diff-Quik Stain FNA

Infiltrating Squamous Cell Carcinoma
Poorly Differentiated Squamous Cell Carcinoma

CK5/P63

P40
Poorly Differentiated Adenocarcinoma

Diff Quik FNA

Infiltrating Adenocarcinoma
Poorly Differentiated Adenocarcinoma

TTF-1/Napsin A
## Differential Cytologic Features

<table>
<thead>
<tr>
<th>Cytologic Features</th>
<th>LCNEC</th>
<th>PDSQCC*</th>
<th>PDADC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Size</td>
<td>Mostly Large</td>
<td>Small to intermediate</td>
<td>Mostly Large</td>
</tr>
<tr>
<td>Single Cells</td>
<td>Prominently Present</td>
<td>Present</td>
<td>Rarely Present</td>
</tr>
<tr>
<td>Cellular Fragments</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Naked Nuclei</td>
<td>Prominently Present</td>
<td>Rarely Present</td>
<td>Rarely Present</td>
</tr>
<tr>
<td>Nuclear Molding</td>
<td>Prominently Present</td>
<td>Rarely Present</td>
<td>Rarely Present</td>
</tr>
<tr>
<td>Crush Artifact</td>
<td>Present</td>
<td>Rarely Present</td>
<td>Rarely Present</td>
</tr>
<tr>
<td>Rosettes</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Moderate</td>
<td>Scant</td>
<td>Abundant</td>
</tr>
<tr>
<td>Nuclear Membrane</td>
<td>Thin</td>
<td>Thick</td>
<td>Thick</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Fine</td>
<td>Dense</td>
<td>Fine</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Present</td>
<td>Rare</td>
<td>Present</td>
</tr>
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</table>

*PDSQCC*—Poorly differentiated squamous cell carcinoma  
*PDADC*—Poorly differentiated adenocarcinoma
Conclusion

• Cytology is sensitive in diagnosing pulmonary neuroendocrine tumors
• Procuring a cell block is important for ancillary IHC studies
• Flow cytometry important for excluding a lymphoma
• Core biopsy may have a helpful role