Differential of Neuroendocrine Carcinoma

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Differential diagnosis of neuroendocrine carcinoma - Problems

1. Small cell carcinoma vs. large cell neuroendocrine carcinoma
   - Combined small cell or pure large cell neuroendocrine
   - Organ localized small cell carcinoma
2. Adenocarcinoma or large cell neuroendocrine carcinoma
3. Carcinoid tumors and large cell neuroendocrine carcinoma
   - Ki-67, mitoses
4. Mimics of neuroendocrine carcinoma
   - CD56 – perils and problems
   - Morphologic imitators

What is the problem?

- Partial sampling
- Small samples
- Crush artifact
- Morphologic overlap

Problem 1:

Small cell carcinoma vs. large cell neuroendocrine carcinoma vs. Combined small cell
Reproducibility in small cell carcinoma diagnosis

- Images of 79 tumors, mostly neuroendocrine in 3 tiers - morphology first tier then increasing number of IHC
- Moderate agreement (65%) improved to good (78%) with IHC
  - IHC Panel was variable
  - Often CK, TTF1 and at least one NE marker

Small cell carcinoma vs. Large cell neuroendocrine carcinoma - clinical

**Small cell carcinoma**
- Advanced disease
- Paraneoplastic syndrome – often
- Peripheral, early rare
- High PET SUV
- Smokers

**Large cell neuroendocrine**
- Early stage (50%)
- High recurrence rate
- Paraneoplastic syndromes rare
- Peripheral, lobulated/spiculated
- High PET SUV
- Smokers

Small cell carcinoma vs. Large cell neuroendocrine carcinoma - pathology

**Small cell carcinoma**
- Smaller cells, scant cytoplasm
- Fine “salt and pepper” chromatin
- Nuclear molding
- Crush artifact
- Apoptosis – frequent
- Mitoses – frequent (hard to see)
- Necrosis

**Large cell neuroendocrine**
- Larger cells, Visible cytoplasm
- Nucleoli, small (coarse chromatin)
- Rosettes, palisading (?related to cytoplasm)
- Apoptosis
- Mitoses – frequent
- Necrosis

Small cell carcinoma vs. Large cell neuroendocrine carcinoma - IHC

**Small cell carcinoma**
- Cytokeratin – weak, patchy, dot like
- Up to 10% of cases negative
- TTF1 – 90% positive
- Neuroendocrine markers
  - Often but not always positive
  - CD56 most sensitive
- Ki-67 high

**Large cell neuroendocrine**
- Cytokeratin – membranous
- TTF1 – 50% positive (or higher)
- Neuroendocrine markers
  - By definition
- Ki-67 high
Problem 1 – Small cell ca vs LCNEC

Take home lessons

- Mostly morphologic
- Don’t ignore clinical clues (paraneoplastic syndrome, organ localized)
- IHC pattern
  - Cytokeratin can reveal dual cell population
  - If Age <40 or more chest wall than lung (see Problem 4!)

DO NOT FORGET COMBINED SMALL CELL IS SMALL CELL!

LARGE CELL NEUROENDOCRINE AS PART OF COMBINED SMALL CELL CARCINOMA IS COMMON!
Problem 2:

Solid type adenocarcinoma vs. large cell neuroendocrine carcinoma

What is the problem?

• IHC definition of neuroendocrine differentiation
  • “NSCLC with neuroendocrine differentiation” vs. LCNEC
  • Morphologic overlap
    • What is the key criterion?
**Problem:**
Adenocarcinoma or squamous carcinoma with "neuroendocrine differentiation"

**Molecular story**
Do criteria for LCNEC determine molecular results?

**Definition of LCNEC**
- Any NAPSIN – then not LCNEC
- P40 – squamous
- Chromogranin – Neuroendocrine
- Focal NE staining did not exclude AdenoCA or Squamous CA

**Result:**
NO KRAS positive tumors

**Many KRAS positive “NSCLC-like”**

**Overview of key driver mutations and other activating mutations in LCNEC of the lung.**

KRAS 3 cases (6%)
All resected tumors
Two of three - one NE marker only
One combined with AdCa
### Solid adenocarcinoma vs. Large cell neuroendocrine carcinoma

<table>
<thead>
<tr>
<th>Solid adenocarcinoma</th>
<th>Large cell neuroendocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nuclear chromatin – vesicular with nucleoli</td>
<td>• Nuclear chromatin – coarse salt and pepper and small nucleoli</td>
</tr>
<tr>
<td>• Ample cytoplasm</td>
<td>• Identifiable cytoplasm</td>
</tr>
<tr>
<td>• TTF1 positive – about 70-80%</td>
<td>• TTF1 – &gt;50% positive</td>
</tr>
<tr>
<td>• Neuroendocrine markers</td>
<td>• By definition</td>
</tr>
<tr>
<td>• “neuroendocrine differentiation”</td>
<td>• Neuroendocrine markers</td>
</tr>
<tr>
<td>• Mitotic rate intermediate</td>
<td>• Mitotic rate high</td>
</tr>
<tr>
<td>• Ki-67 intermediate</td>
<td>• Ki-67 high</td>
</tr>
</tbody>
</table>

### Or in other words....

- For nucleoli – how big is too big?
- For cytoplasm – what is visible versus ample?

### Solid Adenocarcinoma

Did not do neuroendocrine markers (should I have)?

### NO!

- Nucleoli +/-, vesicular
- Ample cytoplasm
- Not architecturally NE
- KRAS positive

### NO!

- Nucleoli +/-, vesicular
- Ample cytoplasm
- Not architecturally NE
- KRAS positive

### NO!

- Nucleoli – Yes, macro
- Cytoplasm - present
- Architecture - no
- KRAS positive

### NO!

- Nucleoli +/-, vesicular
- Ample cytoplasm
- Not architecturally NE
- KRAS positive
Nucleoli - no
Cytoplasm - present
Palisading - some
KRAS positive

MAYBE? Oops....

Did NE markers
? Regretted it

Nucleoli – yes, variable
Cytoplasm- present
Architecture – depends on who you ask
KRAS positive

Problem 2 – Solid adenocarcinoma vs. LCNEC
SUMMARY
• Adenocarcinoma, solid predominant –
  • Nuclear features, ample cytoplasm, lack of palisading/rosettes
• LCNEC – “molecular small cell-like”
  • Nuclear features, “less ample” cytoplasm, architecture
  • High mitotic rate/apoptosis
• “Solid adenocarcinoma with neuroendocrine IHC” vs. LCNEC
  “adenocarcinoma-like”
  • Napsin A and lower mitotic rate/Ki-67 = AdCA
  • KRAS rate seems similar - “Molecular adeno-like”
Problem 2 – Solid adenocarcinoma vs. LCNEC
Take home message
• LCNEC "small cell like" – criteria as in Problem 1
  • Molecular is small cell-like
• Blurring between some LCNEC "NSCLC-like" and solid adenocarcinoma
  • Molecular more AdenoCa-like
  • Criteria and clinical impact need further study

Problem 3:
Atypical carcinoid vs. large cell neuroendocrine carcinoma

What is the problem?
• Small samples
• Mitotic counting
  • Including undercalling carcinoids
• Ki-67

Atypical carcinoid vs. Large cell neuroendocrine carcinoma

Atypical carcinoid
• Nuclear chromatin – salt and pepper and small nucleoli
• Round nuclei
• Visible cytoplasm
• Necrosis
• Mitotic rate 2-9 in 2mm²
• Ki-67 low/lower

Large cell neuroendocrine
• Nuclear chromatin – coarse, salt and pepper and small nucleoli
• Irregular nuclear contour
• Visible cytoplasm
• Necrosis
• Mitotic rate 10 or greater in 2mm²
• Ki-67 high

Mitotic counting
• IASLC/WHO classification 2015
  • If initial counts are near the cutoff between categories, then the average of 3 sets of fields must be counted.
  • Impacts lower end more than upper
  • Upper end – most LCNEC have many more than 10 in 2mm²

Ki67 in pulmonary NE tumors

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>9-17.3</td>
</tr>
<tr>
<td>LCNEC</td>
<td>47.5-70</td>
</tr>
</tbody>
</table>

J Thorac Oncol. 2014 Mar;9(3):273-84
Problem 3 – Atypical carcinoid vs. LCNEC

Take home messages

- Careful mitotic counting when possible
- Ki-67 when small sample
- Rare LCNEC may arise from atypical carcinoids

Problem 4:

Mimickers of high grade neuroendocrine carcinomas

What is the problem?

- Not considered at sign out, especially when overlapping epidemiology with small cell carcinoma
- Presentation in metastatic sites
- Small samples
- Rare tumors
- IHC marker overlap
  - CD56
  - Cytokeratin

Mimics of neuroendocrine carcinoma

- Primitive neuroectodermal tumor (PNET)
  - Usually under age 40
  - Chest wall more often than lung
  - Pitfalls - Cytokeratin can be positive; calretinin can be positive; CD56 can be positive
  - TTF1 negative, WT1 negative
  - CD99 membranous; FLI1 positive
  - EWSR1 translocations
Mimics of neuroendocrine carcinoma

- **Pulmonary neuroblastoma**
  - Pediatric tumors often extra-pulmonary
  - Adult tumors can be pulmonary
    - Ganglion cells (ganglioneuroblastoma)
    - Neuropil

- **Pulmonary paraganglioma**
  - Rare
  - Depends on definition
    - Any trabecular pattern, spindle or oncocytic – carcinoid.
    - Cytokeratin negative
    - S100 sustentacular cells, even if only focal.
Panel approach for CD56 positive tumor
What trigger?

- Small cell is unusual (age, location, distribution, non-smoker)
- Morphology is variant or non-classical
  - E.g. no crush or molding, rare apoptosis
- CD56 is the only neuroendocrine marker positive

Panel approach for CD56 positive tumor
What panel?

- CD56, Cytokeratin and TTF1 positive combination favors small cell
- Rare exceptions
- Add WT1, desmin, SMA or actin/HHF35
- Molecular/FISH testing as needed
Problem 4 - mimics of neuroendocrine carcinoma

Take home messages

- High grade pulmonary neuroendocrine tumors – ALERTS!
  - Age <40, chest wall, no lung tumor
  - Diagnosis in metastatic site
  - Non-smoker
  - Variant histology

- Immunohistochemistry panels – be careful when single NE marker is CD56
- Molecular testing/FISH testing