Bronchioloalveolar Adenocarcinoma

Samuel A. Yousem, MD
Pulmonary Pathology Society
USCAP, Atlanta, 2006
1. Definitions/rules.
2. Gross features/tissue processing.
3. Histopathology.
4. “Invasion”.
5. AAH/BAC.
6. Clinicopathoradiologic correlations.
7. Molecular issues.
BAC
Definitions and Rules to Diagnosis

“A bronchioloalveolar carcinoma shows growth of neoplastic cells along pre-existing alveolar structures (lepidic growth) without evidence of stromal, vascular or pleural invasion” –

- Implies no nodal disease and no extrapulmonary metastases.
- No papillary growth.

To make an unequivocal diagnosis, BAC must be

1. Completely excised (cannot diagnose on biopsy or cytology).
2. Completely embedded.
BAC
Definitions and Rules to Diagnosis

“Adenocarcinomas with prominent bronchioloalveolar pattern”.

1. What is “prominent”? Do we need to quantitate patterns in a lung adenocarcinoma?

2. We must not confuse a disease entity (BAC) with a growth pattern (lepidic) – for clear communication, I prefer to **not** use the term “BAC pattern”.
BAC

Gross Features

1. Classic (with radiologic correlation)
   - Solitary nodule.
   - Multiple nodules.
   - Pneumonic pattern – usually mucinous BAC.

2. Radiology – HRCT
   a. BAC without invasion or alveolar collapse = ground glass opacity.
   b. Adenocarcinoma with lepidic growth and central invasion/desmoplasia = nodule with central solid region and marginal GGO.
   c. Adenocarcinoma with minimal lepidic growth = solid.

3. Correlate gross specimen with HRCT to identify satellite lesions/other abnormalities.
**BAC**

**Histopathology**

- The importance of cell type needs to be emphasized as clinical stage, prognosis, and molecular biology is probably different.
  - **NON-MUCINOUS** – AII/Clara cell differentiation – low stage, ↑ EGFR mutation, good prognosis; includes a wide range of morphologies.
  - **MUCINOUS** – goblet cell differentiation.
    - Single cell vs stratified goblet cell types.
    - High stage, pneumonic infiltrate; ↓ EGFR mutation, worse prognosis.
  - **MIXED** type.
# BAC Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>Non-mucinous</th>
<th>Mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK7</td>
<td>+</td>
<td>- (+ in 30%)</td>
</tr>
<tr>
<td>CK20</td>
<td>-</td>
<td>+ (+ in 80%)</td>
</tr>
<tr>
<td>TTF-1</td>
<td>+</td>
<td>- (+ in 20%)</td>
</tr>
<tr>
<td>SPA</td>
<td>+</td>
<td>- (+ in 10%)</td>
</tr>
</tbody>
</table>

For mucinous tumors, always R/O metastases from extrathoracic malignancy; expressed mucin profile is also abnormal (MUC3/6).
BAC

The Problem of “Invasion”

1. Tissue orientation and assessment of invasion.

2. Does alveolar collapse = invasion?

3. Histologic features of invasion.

4. Quantifying invasion.
   a. % lepidic vs % solid growth.
   b. adjustments to gross diameter.
   c. “minimally invasive” adenocarcinoma – what diameter is the cut-off?
Adenocarcinomas often are associated with a central elastotic/fibrotic scar with entrapped neoplastic glands unassociated with desmoplastic reaction – are these “invasive”? Elastic tissue/BM stains show that many of these glands are within collapsed distorted airspaces, and have not “invaded” stroma and do not have a desmoplastic/stromal reaction.

How to document invasion in this setting? Disruption of elastica? Subtle evaluation of septal invasion?
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Localized bronchioloalveolar carcinoma (LBAC)</td>
</tr>
<tr>
<td>B</td>
<td>LBAC with foci of collapse of alveolar structure</td>
</tr>
<tr>
<td>C</td>
<td>LBAC with foci of active fibroblastic proliferation</td>
</tr>
<tr>
<td>D</td>
<td>Poorly differentiated adenocarcinoma</td>
</tr>
<tr>
<td>E</td>
<td>Tubular adenocarcinoma</td>
</tr>
<tr>
<td>F</td>
<td>Papillary adenocarcinoma with compressive and destructive growth</td>
</tr>
</tbody>
</table>
**BAC**  
**Alveolar Collapse**

**Noguchi/Shimasoto – B**

<table>
<thead>
<tr>
<th>Factor</th>
<th>A,B</th>
<th>C</th>
<th>D</th>
<th><strong>P value by chi-square test</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AB:C</td>
<td>AB:D</td>
<td>C:D</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>34</td>
<td>97</td>
<td>21</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage &gt; II</td>
<td>0</td>
<td>45</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>34</td>
<td>101</td>
<td>23</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>N1 and N2</td>
<td>0</td>
<td>40</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>31</td>
<td>82</td>
<td>21</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.20</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>51</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>32</td>
<td>72</td>
<td>23</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>67</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitotic rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5/10 HPF</td>
<td>29</td>
<td>80</td>
<td>16</td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt;5/10 HPF</td>
<td>2</td>
<td>28</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HPF: high power field

*Other primarily Japanese studies have shown A/B pattern is associated with an absence of nodal disease and intraparenchymal metastases.*
BAC

Defining Features of “Invasion”

1. Does not equate to alveolar collapse or to alveolar septal widening/fibrosis/sclerosis (“sclerosing BAC”).

2. Requires:
   - Angulated tubular glands or individual cell infiltration into stroma with an edematous fibromyxoid stromal reaction.
   - Cribriform/acinar growth with or without necrosis and high grade cytology correlates with invasion.

3. Elastic tissue/trichrome/BM stains can help demonstrate disrupted/fragmented septa.
BAC/Minimally Invasive Adenocarcinoma

If focal invasion is identified, what does it mean and how do we report it?

Options:

1. Report % lepidic growth and % invasion and normalize gross diameter (Cagle/Higashiyama).
2. Diameter of invasive focus:
   Invasive foci less than 5 mm in greatest microscopic dimension are associated with an absence of LN metastases despite rare angiolympathic and pleural invasion.
3. Use “comment” to define risk and therapy as adenocarcinomas with lepidic growth are often EGFR mutants.
Minimally Invasive Adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>LN (%)</th>
<th>Angiolympathic Invasion (%)</th>
<th>Visceral Pleural Invasion (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noguchi A/B/C</td>
<td>0% 27%</td>
<td>3% 55%</td>
<td>3% 44%</td>
<td>100% 63%</td>
</tr>
<tr>
<td>Sakumai G1 G2 G3</td>
<td>0% 0% 27%</td>
<td>3% 2% 68%</td>
<td>0% 0% 8%</td>
<td>100% 100% 59%</td>
</tr>
<tr>
<td>Terasaki BAC AD/BAC &lt;5 mm AD/BAC &gt;5 mm</td>
<td>0% 0% 35%</td>
<td>0% 18% &gt;55%</td>
<td>0% 2% 25%</td>
<td>-- -- --</td>
</tr>
</tbody>
</table>
AAH and BAC
How to separate these two entities.

- Size: in general, >0.5 cm makes a lesion BAC.
- For small lesions or potential satellites/T4 lesions:

<table>
<thead>
<tr>
<th></th>
<th>AAH</th>
<th>BAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphous population with respected cell borders and absent nuclear overlap</td>
<td>Monotonous population with densely packed and overlapping nuclei</td>
<td></td>
</tr>
<tr>
<td>Blends into surrounding lung</td>
<td>Sharply demarcated</td>
<td></td>
</tr>
<tr>
<td>May have grade 3 cytology in individual cells; ciliated, goblet cells</td>
<td>Uniform atypical cytology – may be mild to moderate</td>
<td></td>
</tr>
<tr>
<td>POLYMORPHIC HETEROGENOUS</td>
<td>UNIFORM MONOTONOUS</td>
<td></td>
</tr>
</tbody>
</table>
AAH and BAC

• May be difficult in assigning a stage: T1/2 vs T4 vs M1.
• On TBBx, may be difficult to separate
  – Must defer to larger biopsy/resection.
  – Correlate with HRCT.
• For isolated solitary lesion, AAH and BAC are non-invasive processes and should have benign clinical behavior if resected.
BAC

Clinicoradiologic Issues

1. Clinician/pathologist disconnect – clinical perception of BAC behavior needs to be adjusted to:
   • New definitions.
   • The possibility of cases behaving like a BAC (slow growth, multifocal, etc.) but being classified as “invasive” adenocarcinoma with lepidic growth.

2. Treatment:
   • Multifocal BAC is a surgical disease with a different clinical behavior than conventional TNM staging – pneumonic pattern is poor prognosticator.
   • Need for postop chemotherapy in BAC?
   • EGFR mutational analysis.
1. What is the relationship of AAH to BAC?
   • Do all BACs arise from AAH?
   • What molecular events are associated with this transition?

2. Are all invasive adenocarcinomas preceded by BAC?
   • Is there a difference between invasive cells and lepidic elements?
   • Molecular events associated with invasion and metastases?

3. Genes of interest.
BAC
Molecular Issues

1. Some BACs are preceded by AAH but this is not a mandatory route.
2. The molecular profile of AAH, BAC, and invasive adenocarcinoma is associated with increased genetic instability ($\uparrow$FAL) that decreases in LN and parenchymal metastases (clonal selection).
3. Microdissection studies show greater genetic instability in the invasive foci than in lepidic areas.
4. Early events: K-ras, 9p, 3p, 13q, 11q.
   Late events: 3p, 17, 18q, 22q.
5. Well-differentiated TRU adenocarcinomas (non-smoking Asian women) have highest incidence of EGFR mutation.
6. Different pathways of oncogenesis
   • EGFR.
   • K-ras/p53.
Summary

1. Non-invasive adenocarcinoma with lepidic growth.
2. Gross microscopic features correlate with radiology – GGO and solid zones.
3. Mucinous and non-mucinous BAC are different disease processes.
4. Invasion ≠ lobular collapse; <5 mm of microscopic invasion has excellent prognosis.
5. Ddx of AAH/BAC.
6. Need to educate clinicians/radiologists.
7. Molecular pathology of BAC is still unresolved.
REFERENCES


78. Yokose, T., et al., Favorable and unfavorable morphological prognostic factors in peripheral adenocarcinoma of the lung 3 cm or less in diameter. Lung Cancer, 2000. 29: p. 179-188.
