PULMONARY PATHOLOGY JOURNAL CLUB
(May 2016 articles)
June 27, 2016

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Discussion articles

**Purpose:** To evaluate the utility of p16 FISH and BAP1 immunohistochemistry in the diagnosis of sarcomatous and desmoplastic mesothelioma (SM and DM).

**Methods:**

**Cases evaluated:**

- Sarcomatous/desmoplastic mesothelioma: N=20 (single institution) – 9 cases SM and 11 cases DM
- Sarcomatoid carcinoma: N=13 (2 institutions) - 5 cases lung, 5 cases non-lung primary (pancreas, bladder, breast and colon), 3 metastases (liver, cerebellum, bone)

**Testing performed:**

- p16 FISH (CDKN2A/CC9 probe – Cymogen Diagnostics): positive result defined as loss of 9p21.3 locus and retained centromeric signal in at least 12% of cells (50-100 nuclei counted / case)
- BAP1 IHC (C-4 clone – Santa Cruz Biotechnology Inc.): positive result defined as homogenous loss of nuclear staining in tumor cells
- Both tests performed on all cases EXCEPT p16 FISH not done on 2 cases of lung sarcomatoid carcinoma

**Results:**

- Sarcomatoid carcinoma patient demographics: ~1:2 M:F, age: 56-85 (average: 74)

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>SM</th>
<th>Sarcomatoid CA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P16 FISH (deletion)</strong></td>
<td>8/11 (73%)</td>
<td>8/9 (89%)</td>
<td>3/11 (27%)</td>
</tr>
<tr>
<td><strong>BAP1 IPOX (LOSS)</strong></td>
<td>1/11 (9%)</td>
<td>2/9 (22%)</td>
<td>0/13 (0%)</td>
</tr>
</tbody>
</table>

*p16 deleted sarcomatoid CA included: 1 lung, 1 breast, and 1 bone metastasis

Overall mesothelioma: p16 deletion in 16/20 (80%) and BAP1 IHC loss in 3/20 (15%)
- Only 1 case showed BAP1 loss without accompanying p16 deletion
- 17/20 cases showed at least 1 positive test result (85%)

**Take-home message:**

- p16 FISH and BAP1 IHC may be useful diagnostic adjuncts in the diagnosis of SM and DM
  - p16 deletion occurs frequently in SM/DM and occasionally in sarcomatoid carcinoma
  - BAP1 loss occurs only rarely in SM/DM, however if present favors mesothelioma over carcinoma
  - Combined testing may have mild improvement in sensitivity, and NEITHER is perfectly sensitive
  - Taken together: p16 is more sensitive & less specific, and BAP1 is very specific with poor sensitivity

**Issues:** problems with sarcomatoid carcinoma cohort include size, few primary lung tumors, no renal cell carcinoma, and (?) none actually occurred in pleura. Also no cases of organizing pleuritis included and no description given to specimen types (Bx vs other).

**Purpose:**

1. To provide more data on interobserver variability among pathologists using the new IASLC/WHO adenocarcinoma classification including: adenocarcinoma in-situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IA)
2. Provide further validation of superior survival in these patient groups

**Methods:**

- Retrospective resected lung adenocarcinoma cases identified in cancer database (1997-2009)
- AIS and MIA cases purposefully enriched by searching for “BAC” and “adenocarcinoma with BAC features”
- Cohort: N=296 tumors (254 patients; 35 patients had >1 nodule)
- Slides evaluated by 2 pathologists, blinded to gross size, stage & outcome
- New IASLC/WHO adenocarcinoma criteria applied and tumors graded and classified as AIS, MIA or IA
- Invasion noted (stromal, vascular, pleural) and largest focus (including central scar if present) measured
- Multiple tumor nodules were independently assessed if felt to be separate primaries
- Cases categorized as AIS and MIA had any residual gross tumor submitted for evaluation (if available); N=62
- Pathologist agreement measured by κ coefficient for tumor classification, and intraclass correlation coefficient (ICC) for invasion/scar measurement

**Clinical information:**

- Cases categorized as AIS/MIA with a preoperative CT were reviewed by radiologist to determine size and category (ground-glass opacity, subsolid, solid); N=91 (82 patients)
- General clinical information obtained, including disease-specific survival (DSS)
- Survival among groups assessed by log-rank tests (survival differences) and Kaplan-Meier estimates (survival percentage). Overall survival (OS) and DSS also analyzed.

**Results:**

- **Demographics:** M:F = 2:3, 92% Caucasian, prior or current smoker = 75%, age range: 17-91 (average: 68.3)
- **Tumor average size:** 2.0cm / Stage: I = 75%, II = 14%, III = 9%, IV = 2%
- **Gross pathology assessment (AIS/MIA):** 35/62 (56%) additional tumor submitted, 25/35 (71%) had no change in classification, 7/35 (20%) changed classification
- **Pathologist agreement:** 244/296 (82.4%) agreed upon (κ = 0.63, good agreement), when AIS/MIA grouped together (2 tier system) agreement increased to 84.5% (κ = 0.65, good agreement).
- **Invasion concordance:** average absolute difference in invasion measurement 3.4 mm (ICC, 0.80 – excellent)
- 9/296 nodules (3%) were AIS or MIA and >3 cm: 7/9 with more gross, 29% re-classified as IA with further gross evaluation, **remaining 5 cases of AIS/MIA all were alive** (8-9 years of follow-up)
- **Radiology:** AIS – correlated with GGO (9/10), MIA – heterogenous group (17 GGO, 21 subsolid, 8 solid)
- **Survival:** Mean followup (5.74 yrs), 45% deceased, OS significantly different among invasive categories (both observers), 5-year OS: 82-100% for AIS, 79-86% for MIA, and 62-63% for IA, 37 patients disagreement between MIA & IA → OS similar to agreed MIA cohort, 10-year DSS for AIS = 100% and ~97% for MIA

**Take-home message:** Good concordance using the new IASLC/WHO adenocarcinoma classification system is possible. AIS/MIA reaffirmed to have improved survival over cases of IA. “Borderline” cases between MIA and IA showed OS similar to “true” MIA cases. Total gross submission of the tumor is unlikely to change classification, however tumors >3 cm that show only AIS/MIA may be important.

**Purpose:** To clarify the significance of “UIP-like” histology in patients with hypersensitivity pneumonia (HP).

**Methods:**
- Previously reported retrospective cohort of patients with bird-related HP
  - + inhalational provocation test for avian antigen
  - recurrent symptoms with environmental or laboratory induced exposure to avian antigens
  - + serological/BAL fluid tests (ELISA, lymphocyte stimulation) for avian antigens
  - progressive deterioration in PFTs for at least 1 year
  - > 6 months of persistent symptoms
  - SLBx = “evidence of pulmonary fibrosis with or without granulomas”
- SLBx’s semi-quantitatively assessed for
  - centrilobular fibrosis [“peribronchiolar fibrosis with bronchiolar distortion and occlusion by scarring and smooth muscle hyperplasia”], bridging fibrosis [“linear fibrotic connection between centrilobular and perilobular areas or between centrilobular and adjacent centrilobular areas”], lymphoid follicles, fibroblast foci → quantity/cm²
  - perilobular fibrosis [“fibrosis in a subpleural or paraseptal region”], bronchiolitis, organizing pneumonia, honeycombing, granulomas, giant cells, fibroelastosis, lymphocytic alveolitis → 0 (absent), 1 (rare), 2 (occasional), 3 (marked)
- no control (e.g., UIP/IPF; HP without fibrosis) group

**Results:**
- n = 16

<table>
<thead>
<tr>
<th>men:women</th>
<th>14:2</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (mean ± STD; range)</td>
<td>58.3 ± 12.0 yrs (34 – 75 yrs)</td>
</tr>
<tr>
<td>dead (mean survival ± STD; range)</td>
<td>8 (34 ± 24.4 mos; range 9 – 82 mos)</td>
</tr>
<tr>
<td>interval from onset to SLBx (mean ± STD)</td>
<td>34.4 ± 25.9 mos</td>
</tr>
<tr>
<td>HRCT findings</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>upper:lower:no zonal predominance</td>
<td>2:8:6</td>
</tr>
</tbody>
</table>

**Frequency of histologic findings (%):**
- centrilobular fibrosis: 88%
- bridging fibrosis: 69%
- perilobular fibrosis: 81%
- honeycombing: 100%
- fibroelastosis: 44%
- fibroblast foci: 100%
- lymphoid follicles: 69%
- bronchiolitis: 44%
- organizing pneumonia: 75%
- granulomas: 25%
- giant cells: 31%
- lymphocytic alveolitis: 81%
- mosaic attenuation (mean score ± STD) |
- upper:lower:no zonal predominance |

- centrilobular and bridging fibrosis showed moderate correlation with PaO₂ and V₅₀/V₂₅, respectively
- high (≥ 2.2/cm²) FF correlated with
  - lower DLco, higher incidence of acute exacerbation, and mean survival (34.6 mos versus 92.7 mos)
  - HRCT findings of reticulation, honeycombing, and traction bronchiectasis

**Take-home message:** A UIP-like pattern is bad news for patients with HP, and may get worse if you have a lot of fibroblast foci!

**Purpose:** To review a retrospective cohort of patients with synchronously diagnosed mesothelioma and lung cancer.

**Methods:**
- Retrospectively identified 18 out of ≈ 3,800 (≈ 0.5%) medicolegal consultation cases from V. Roggli’s files with mesothelioma and lung cancer
- IHC in all mesotheliomas and 9 (50%) of lung carcinomas
- mineral fiber content analysis in 8 cases

**Results:**
- 3 patients had histories of prior extrathoracic malignancies (testicular seminoma and bladder cancer, prostatic adenocarcinoma (2)
- mesotheliomas: pleural (16), peritoneal (2)
- NSCLC (17): adenocarcinoma (12), squamous cell carcinoma (5)
  SCLC (1 – “collision tumor”)

<table>
<thead>
<tr>
<th>men:women</th>
<th>14:4</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (median; range)</td>
<td>68 yrs (58-84 yrs)</td>
</tr>
<tr>
<td>history of smoking (yes:no:NA)</td>
<td>15:1:2</td>
</tr>
<tr>
<td>documented asbestos exposure</td>
<td>15 (mean duration 24 yrs, range 3-45)</td>
</tr>
<tr>
<td>mesothelioma subtypes</td>
<td></td>
</tr>
<tr>
<td>- epithelial</td>
<td>11 (61%)</td>
</tr>
<tr>
<td>- biphasic</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>- sarcomatoid</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>histologic asbestosis</td>
<td>3 (17%) (absent in 9 and uninformative in 6)</td>
</tr>
</tbody>
</table>

| asbestos fiber burden (8) | elevated – 4 (22%)
|---|---
| background – 4 (22%)
| amosite (4), tremolite (5), crocidolite (3), actinolite (1) |

- Using Helsinki criteria,
  - mesotheliomas (pleural plaques, ↑ asbestos bodies, ↑ asbestos lung fibers) were attributable to asbestos exposure in 8 (44%), and
  - lung carcinomas (asbestosis, ↑ asbestos lung fibers = asbestosis) were attributable to asbestos exposure in 3 (17%).

**Take-home message:** Mesothelioma and synchronous lung carcinoma is rare, but could show up when you least expect it! Pay attention, and if you suspect it a combination of routine histology and IHC stains should sort it out.
Articles for notation


**Purpose:** To compare a less expensive antibody (1A4 – Origene, MD, USA) to the more expensive Ventana antibody (D5F3) and FISH for detection of ALK rearrangements in lung adenocarcinoma.

<table>
<thead>
<tr>
<th>ALK FISH</th>
<th>N</th>
<th>1A4 – routine IHC</th>
<th>D5F3 – routine IHC</th>
<th>D5F3 Ventana detection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3+</td>
<td>2+</td>
<td>1+</td>
</tr>
<tr>
<td>+</td>
<td>58</td>
<td>17</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>–</td>
<td>424</td>
<td>0</td>
<td>19</td>
<td>107</td>
</tr>
<tr>
<td>Total</td>
<td>482</td>
<td>17</td>
<td>42</td>
<td>125</td>
</tr>
<tr>
<td>“sensitivity”</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Take-home message:** If your budget won’t allow Ventana, there is a cheaper alternative with reasonable performance for IHC screening of lung adenocarcinomas for ALK rearrangements.


**Purpose:** To share results of 3 IHC stains with scientific rationale for separating benign from malignant mesothelial proliferations.

**Take-home message:** None of them worked!


**Purpose:** To report a patient with long standing sarcoidosis who developed an enlarging lung nodule that proved to be sarcoidosis complicated by MALT.

**Take-home message:** Stuff happens . . . but does it really need to be published with a grand total of 11 authors?

**Purpose:** To review current state of PD-L1 IHC staining as a biomarker of potential value in selecting patients for targeted immunotherapy.

**Take-home message:** It’s a mess! And their recommendations leave me breathless and convinced that this is not something in which many labs will care to or can engage.

<table>
<thead>
<tr>
<th>ALK positive; negative =</th>
<th>1+/2+/3+; 0</th>
<th>2+/3+; 0/1+</th>
<th>3+; 0/1+/2+</th>
<th>3+; 0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>99%</td>
<td>86%</td>
<td>56%</td>
<td>99%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>98%</td>
<td>99%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*D5F3 and 5A4 much more sensitive than ALK1*


**Purpose:** Use previously published data to determine operating characteristics of IHC for ALK rearrangements.

**Methods:**
- Pooled data (meta) analysis using 12 studies accounting for 3,754 patients
- 3 IHC antibodies: D5F3, 5A4, ALK1 used according to manufacturers instructions compared to standard FISH assay

<table>
<thead>
<tr>
<th>ALK positive; negative =</th>
<th>1+/2+/3+; 0</th>
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<td>100%</td>
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</tbody>
</table>

Take-home message: IHC works already! Even in the absence of standardization the evidence base is sound – IHC a good testing strategy for ALK rearrangements.

**Purpose:** Compare effectiveness of mutant specific antibodies against sequencing for EGFR mutations in lung adenocarcinomas.

**Results:** Overall sensitivities and specificities 58.6% and 98.0%; better if restricted to tumors with E746-A750del.

**Take-home message:** IHC cannot yet replace molecular testing for EGFR mutations.


**Purpose:** Report potentially sensitizing mutations in 2 patients with SCLC, including one with a combined SCLC + adenocarcinoma (isn’t that kind of cheating??) and another in a never smoker (clearly a couple of highly selected tumors/patients!)

**Results:**
- combined SCLC/adenoca – novel exon 21 D855H point mutation in both components (really?)
- SCLC in non-smoker – exon 21 L858R point mutation
- neither patient was treated with tyrosine kinase inhibitor
- Adds to 59 previously reported cases of EGFR mutations in SCLC, heavily weighted toward never smokers and including a subset in whom “small cell transformation” was affiliated with TKI resistance.

**Take-home message:** It happens, it’s rare, and the impact on outcome completely unknown.


Case report of 27-year-old woman who turns out to have TSC-associated LAM and multifocal micronodular pneumocyte hyperplasia (MMPH).


Case report of 30s-year-old woman with HIV-associated pulmonary Kaposi sarcoma.


Case report of patient with concurrent KRAS and EGFR (exon 19 deletion) mutations and ROS1 rearrangement. After failing first line chemotherapy, crizotinib was met with no response. Disease stabilized (x 8 months) when switched to icotinib (EGFR-TKI) despite known KRAS-associate TKI resistance.


Case report of immunocompromised Brazilian patient who presented with hypoxemia that rapidly progressed to ARDS and proved to be paracoccidioidomycosis!