PULMONARY PATHOLOGY JOURNAL CLUB
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Table of Contents

Discussion articles


Articles for notation
Page 6  Neoplastic diseases - histology

Neoplastic diseases – molecular diagnostics/precision medicine


Neoplastic diseases – miscellaneous


Page 7  Non-neoplastic diseases


Discussion articles

Purpose: Historical studies (eg, Roggli et al. Hum Pathol 1985; 16: 569) have indicated that extensively sampled lung carcinomas are histologically heterogeneous. These authors reviewed a modern consecutive series to see if that remains true today.

Methods:
• 172 consecutive primary lung cancers resected between 2010 and 2012 at Univ of Modena, Modena, Italy
• mean 13 blocks/case (range 3 – 44)
• definitions
  minor heterogeneity – 1 major histologic type (eg, adenocarcinoma), ≥ 2 subtypes (eg, acinar + solid)
  major heterogeneity - ≥ 2 major histologic types (eg, adenocarcinoma + squamous cell carcinoma)
• adenocarcinomas graded as per Sica et al. (AJSP 2010; 38: 1155)
• ≥ 1 block chosen for IHC in each case: CK7, TTF-1, napsin A, p63, CK5/6, CRG, SYN (“positive” = 2+ or 3+ staining in ≥ 10% of cells)
• clinical data from path reports, medical records, and referring physicians

Results:
Clinical
• 120 (70%) men; 52 (30%) women
• mean age 68 years (range, 33 – 84 years)
• mean tumor size 34 mm
  37 mm (men) > 28 mm (women) (P = 0.006)
Pathological
• 85% stage I (44%) or stage II (41%); PL1/2/3 – 93 (54%) including 5 cases that were “negative” with routine sampling
• 98 (57%) adenocarcinomas (adca), 46 (26.7%) squamous cell carcinomas (sqcellca), 8 (4.6%) sarcomatoid cas, 5 (2.9%) typical carcinoids, 8 (4.6%) SCLC (4)/LCNEC (4)
• 7 (3.5%) combined carcinomas (ie, major heterogeneity)
  3 adca + sqcellca; 2 adca + LCNEC; 2 SCLC + sqcellca
• minor heterogeneity in 81 (82.6%) adcas, 0 sqcellca, and 6 (75%) sarcomatoid cas (adca > sqcellca)?
  – acinar+lepidic (19) > acinar+papillary (13) > acinar+lepidic+papillary (11) > papillary+lepidic (10)
• CK7, CK5/6 and p63 showed less specificity than TTF-1 and napsin A

<table>
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<tr>
<th></th>
<th>CK7</th>
<th>TTF</th>
<th>NAP</th>
<th>P63</th>
<th>CK5/6</th>
<th>CRG</th>
<th>SYN</th>
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</thead>
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<td>adenocarcinoma (98)</td>
<td>98 (100%)</td>
<td>87 (89%)</td>
<td>84 (86%)</td>
<td>24 (24.5%)</td>
<td>6 (6%)</td>
<td>0</td>
<td>4 (4%)</td>
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<td>sq cell ca (46)</td>
<td>8 (17.4%)</td>
<td>0</td>
<td>0</td>
<td>46 (100%)</td>
<td>46 (100%)</td>
<td>0</td>
<td>2 (4%)</td>
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• biopsy/resection discordance in 4 (of 129) patients
  NSCLC, NOS (CK7/p63 pos) → adenocarcinoma (2)
  carcinoid tumor → LCNEC (1)
  mucoepidermoid ca → adenocarcinoma, solid type (1)
• only micropapillary pattern was significantly associated with pleural involvement and LN mets (P < 0.001)

Take-home message: Major heterogeneity is uncommon (< 5%) in resected lung cancers. Frequency of minor heterogeneity high in adenocarcinoma and low in everything else (depending on definition!).

Purpose: In January 2013 companion papers from two different laboratories (MCTP and Dana Farber) identified a unique NAB2-STAT6 fusion gene and corresponding fusion protein product in solitary fibrous tumors (SFT). Yoshida and colleagues set out to build on previous observations that nuclear staining using a commercially available STAT6 antibody is specific for SFT.

Methods:
- 49 SFTs from the National Cancer Center Hospital in Tokyo
  - 26 (53%) pleural
  - 33 (67%) conventional histology
    - 16 (33%) unconventional (9 malignant, 3 giant cell angiofibroma pattern, 1 fat forming, 1 otherwise conventional SFT with pleomorphic cells, 2 with sheets of small cells)
- 159 non-SFT controls including monophasic synovial sarcoma (12), sarcomatoid mesothelioma (4), sarcomatoid lung cancer (5), spindle cell (WHO type A) thymoma (2) and Ewing sarcoma (6)
- IHC stains graded as negative, weak, moderate or strong; “positive” ≥ 5% tumor cells

Results:
- 49/49 SFTs showed diffuse (48) or focal (1) nuclear expression of STAT6 that was strong (45), moderate (3) or weak (1)
  - homogeneous in 40, heterogeneous in 9 (looked mostly like artifact)
- 4/159 (2.5%) non-SFTs showed focal (3) or diffuse (1), weak (4) nuclear expression of STAT6, but 74 (47%) showed diffuse (40) or focal (34) cytoplasmic/nuclear staining* that was weak (57), moderate (10) or strong (7)
  * interpretation of these cases required careful examination of the tumor cells that were optimally cut in full profile

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<th>Nuclear</th>
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<td>25%</td>
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|          |         |                     |
|          | synovial sarcoma (12) | 0 | 11 (92%) |
|          | mesothelioma (4)       | 0  | 2 (50%) |
|          | sarcomatoid ca (5)      | 0  | 2 (40%) |
|          | thymoma (2)             | 0  | 2 (100%) |
|          | Ewing sarcoma (6)       | 0  | 2 (33%) |

Take-home message: Strong diffuse nuclear staining for STAT6 is a sensitive and specific marker for SFT, including histologically unusual cases. But, differentiating nuclear staining from cytoplasmic/nuclear staining can be extremely difficult especially in those tumors with limited cytoplasm *(eg, monophasic synovial sarcoma).*

**Purpose:** To build on previous observations demonstrating BRAF V600E mutations in a subset of patients with pulmonary Langerhans cell histiocytosis (PLCH) using an IHC approach. A previous study by Yousem et al. used NGS to show BRAF V600E mutations in 7 separate nodules from 2 (of 5) patients with PLCH.

**Methods:**
- retrospective review of patients with LCH/PLCH in the Mayo Clinic files from 1991 to 2012
- clinical data from medical records
- IHC performed using commercially available monoclonal BRAF V600E antibody
  - “positive” = any cytoplasmic staining
  - reviewed blindly by 2 study pathologists
- PCR performed on FFPE tissue and results of IHC and PCR compared
- discordant cases were subjected to Sanger sequencing

**Results:**
- 25 PLCH/54 LCH
  - PLCH patients older (42.0 ± 11.4 yrs) than LCH patients (27.6 ± 21.8 yrs) \( (P < 0.001) \)
  - 25 (100%) of PLCH patients were smokers compared to 26 (48%) of LCH patients
- 7 (28%) PLCH cases IHC-positive (1 PCR negative)/19 (35.2%) LCH cases IHC-positive
  - BRAF V600E-positive PLCH patients had significantly higher cumulative tobacco exposure compared to BRAF V600E-negative patients (48.3 vs 23.7 pack-years, \( P = 0.012 \))
- 3 (4.4%) of 68 cases showed IHC/PCR discordance including 1 with PLCH (IHC-positive/PCR wild type)
  - Sanger sequencing unsuccessful in PLCH case

**Take-home message:** A subset of patients with PLCH have somatic BRAF V600E mutations. The likelihood of BRAF V600E mutations may increase with increasing cumulative tobacco exposure. Beyond a dose response relationship with lifetime tobacco exposure, the clinical significance of BRAF V600E mutations remain unknown.

Purpose: To validate prognostic significance of the previously proposed classification of lung adenocarcinomas in patients with early stage disease, focusing on those with lepidic-predominant histology.

Methods:
- 1038 patients with stage I lung adenocarcinoma resected with curative intent at MSKCC from 1995-2009
- all slides reviewed by 2 pathologists and histologic pattern recorded in 5% increments
  - predominant pattern = “the morphologic subtype present in the greatest proportion”
  - invasion = 1) histologic pattern other than lepidic (ie, acinar, papillary, micropapillary, solid); 2) myofibroblastic stroma (ie, desmoplasia); 3) lymphatic, vascular or pleural invasion
  - AIS (nonmucinous + mucinous) - ≤ 3 cm, pure lepidic growth pattern
  - MIA (nonmucinous + mucinous) - ≤ 3 cm, lepidic predominant pattern, ≤ 0.5 cm invasion, and no necrosis, lymphovascular or pleural invasion
  - lepidic predominant adenocarcinoma (LPA) (nonmucinous only) - > 3 cm and/or > 5 mm invasion, any tumor with necrosis, lymphovascular or pleural invasion
- total tumor size = “recorded on gross finding by use of a ruler”
- invasive tumor size: 1) if “small” (ie, 1 slide) measured on a single slide “using a ruler”; 2) if “large” (ie, > 1 slide), invasive tumor = % invasive x total tumor size
- also recorded, 1) visceral pleural, lymphatic and vascular invasion, 2) necrosis, 4) nuclear atypia (mild, moderate, severe), and 5) mitotic count (low 0-1/10 hpf; intermediate 2-4/10 hpf; high ≥ 5/10 hpf)
- cumulative incidence of recurrence (CIR) used to calculate probability of recurrence (ie, death from causes other than recurrence considered a competing event)

Results:
- women (62%) > men (38%)
- stage IA (70%) > stage IB (30%)
- AIS, MIA and LPA were uncommon, accounting for 2 (0.2%), 34 (3%) and 103 (10%) of cases
- acinar was the most common (31) invasive growth pattern in MIA followed by papillary (3)
- LPA tumors showed average of 50% lepidic pattern (range 40% to 85%)
- AIS/MIA/LPA more frequent in Asian (P < 0.001) and never smokers (P = 0.011) compared to non-LPA
- smaller tumors more likely to have higher percentages of lepidic pattern (P < 0.001)
- LPA less likely to have pleura/lymphatic/vascular invasion and necrosis compared to non-LPA and were more likely to have mild nuclear atypia (P < 0.001) and lower mitotic counts (P < 0.001)
- 5-year CIR 0% for AIS/MIA and 8% for LPA compared to 19% for non-LPA (P = 0.003)
  - 4/103 (3.9%) LPAs recurred: 2 after sublobar resection with close (0.2 & 0.5 cm) margins, and 2 with “substantial” (30% and 20%) micropapillary components and lymphatic invasion.
- risk of recurrence correlated with % lepidic pattern: > 50% (84) = 0; >10%-50% (344) = 12%; ≤10% (610) = 22% (P < 0.001)
- total tumor size and invasive tumor size correlated with recurrence

Take-home message: Turns out Liebow was right. Small tumors that are mostly lepidic (ie, >50% in this study, ≥75% in others . . . which was Liebow’s definition) have the same low risk of recurrence, although micropapillary component and close margins shift the odds. In other words, AIS/MIA/LPA = BAC! But why use one term when you can invent three . . .
Articles for notation

**Neoplastic diseases - histology**


**Take-home message:** Rarely lung cancer can look like hepatocellular carcinoma and express both AFP and HepPar1. Grand total of 16 in the world literature, including the 5 patients reported here (15/16 men, 9/9 smokers). The histologic findings may be “pure” or focal in tumors showing other growth patterns (eg, acinar, papillary). Key to distinction is radiological distribution of disease and immunostains (hepatoid adenocarcinomas usually positive for CK7, MOC31, CEA, and TTF1 – cytoplasmic?).

**Neoplastic diseases – molecular diagnostics/precision medicine**


**Take-home message:** EGFR mutations occurred at the same rate in Hispanic (15.0%) and non-Hispanic (18.6%) patients in this cohort from San Antonio, TX. Interestingly, exon 19 deletions (6/14) and exon 21 point mutations (1/14) together accounted for only 50% of patients. The remainder were mutations in exons 18 (4/14) and 20 (3/14).


**Take-home message:** Bronchioloalveolar carcinomas (“pulmonary nodules resembling bronchioloalveolar carcinoma”)/AIS have been reported in children/adolescents with other malignancies. In this report a combination of CGH, SNP oligonucleotide microarray analysis (SOMA) and FISH/SISH demonstrated copy number variations (mostly gains) and LOH in chromosomes 1, 4, 8, and 17 in a 15-year-old discovered to have a solitary lung nodule in the course of staging for acral melanoma. Some of the genes affected have been linked to lung adenocarcinomas in adults.

**Neoplastic diseases - miscellaneous**


**Take-home message:** Metastases to extralobar lymph nodes (stations 10 and 11 – separately submitted or identified as definitely extralobar in path reports) predict lower rates of disease-free survival compared to mets to intralobar lymph nodes (stations 12-14 – intrapulmonary parenchyma) in patients with stage II (T1/T2, N1, M0) disease (HR 1.83, P = 0.01). Only tumor size (HR 1.21, P = 0.02) and squamous cell histology (HR 0.49, P = 0.007) fell out as other significant drivers of disease-free survival in multivariate analysis. Number of positive nodes and number of nodes samples had no effect.


**Take-home message:** More is better when it comes to margins in wedge resections for small (≤ 2 cm) non-BAC (reason for this exclusion unclear) non-small cell lung cancers . . . but not much more! Risk of recurrence diminished from 2 mm to 5 mm to 15 mm but then flattened (ie, 15 mm distance had a 113% lower risk of recurrence than patients with a margin of 2 mm, but was no different than 20 mm). Suggests that one needs a tumor-free margin, but not a big one!
Non-neoplastic diseases


**Take-home message:** Don’t drink the water (or eat the crustaceans!). Beautifully illustrated comprehensive review of more parasitic infestations than I would have thought possible. Aside from the anticipated ascariasis, strongyloidiasis, dirofilariasis and hydatid cysts the authors (Carol Farver the pathologist) review many others including hookworm, syngamosis, tropical pulmonary eosinophilia (*Brugia malayi, Wuchereria bancrofti*), visceral larva migrans, schistosomiasis, paragonimiasis and rhinosporidiosis. Only reference you’ll ever need on the topic!


**Take-home message:** Sensitization to flour contaminated with fungi and the flour mite (*Acarus siro*) was apparent driver for HP in a 30-year-old non-smoking baker. I’ll never look at a cupcake the same again . . .


**Take-home message:** Perhaps one of the most important secondary benefits from modern clinical trials of patients with UIP/IPF is opportunity to learn more about mortality in untreated controls. This analysis of control groups from three different trials, which selected for patients with mild to moderate disease at entry, found all-cause mortality rates of 6.6% and 13.7% at 1 and 2 years, respectively. That means that to appropriately power a study to detect a 25% reduction in all-cause mortality would require enrolling 2,582 patients over 3 years with maximum follow-up of 5 years!


**Take-home message:** On average the cysts of BHD are different than the smoking-related emphysema more common in patients with spontaneous pneumothorax. The cysts of BHD are basal predominant, have a “punched out” appearance in otherwise normal lung, are lined by pneumocytes (not systematically compared to smoking-related emphysema in this study), and lack associated respiratory bronchiolitis (except, of course, in BHD patients who smoke) and fibroelastotic scars.


**Take-home message:** If you’re willing to look at an average of 5.6 slides from 982 adult autopsies, you can expect to find either bone marrow (29) or bone fragment (5) emboli in about 3.4% of patients. Turns out bone marrow emboli (BME) are associated with rib fractures (we knew that already, right?) while bone fragment emboli (BFE) tended to be associated with osteomyelitis (2/5) and/or femoral nailing (1/5), and may actually be a cause of death.