Pulmonary Pathology Journal Club – Feb 4, 2019

January 2019 Journal articles – Table of Contents

Amir Lagstein, MD
Assistant Professor

Jian Jing, MD
Pulmonary Pathology Fellow

Department of Pathology, University of Michigan

Articles for Discussion:


Articles for Notation:

Neoplastic


Case Reports


Reviews and Consensus statements


Non-neoplastic


Aims/Background:
Better establish the mesotheliomatous nature of diffuse intrapulmonary malignant mesothelioma (DIMM), a rare variant of MM that simulates interstitial lung disease. Mesothelial origin has been based on morphology and conventional immunophenotype.

Materials and methods:
- 4 cases of DIMM (incl. 3 from original series) – 2 epithelioid, 2 biphasic
- BAP1 immunohistochemistry
- FISH of CDKN2A (p16) gene
- Ultrastructure (transmission electron microscopy)

Results:
- 4 of 4 - BAP1 loss (incl. sarcomatoid component)
- 1 of 4 – Heterozygous loss of p16 (epithelioid DMM)
- TEM: Numerous long microvilli, well-formed desmosomes, intracytoplasmic tonofilaments

Conclusions:
- DIMM shows molecular characteristics of typical MM and ultrastructural characteristics of mesothelium
- Immunohistochemistry sufficient to establish mesothelial nature of DIMM
- Other take-home points (more generally):
  - Retention of BAP1 does not exclude malignancy
  - Normal or heterozygous p16 FISH does not exclude malignancy

Aims/Background:

1) Evaluate the prevalence of PPFE in patients with autoimmune disease-related interstitial lung disease (AID-ILD). 2) Verify the increase in elastic fibers

Materials and methods:

- Case selection and definitions
  - Retrospective review of autopsies and lung explants from 1974-2018
  - Patients with diagnoses of “interstitial pneumonia” and “autoimmune disease” (CTD or vasculitis)
  - Excluded if upper or lower lobe not available
  - 24 patients with “AID-ILD”
  - Comparison groups
    - 49 “IPF or probable IPF” patients (autopsy or lung explant)
    - 9 non-pulmonary patients (autopsy)
  - “Interstitial pneumonia” – multidisciplinary approach using consensus classification criteria
  - “Histological patterns of fibrosis”
    - Definite UIP or probable UIP
    - NSIP
    - PPFE
      - Increased elastic fibers with septal elastosis in the subpleural area
      - Intraalveolar collagen deposition associated with septal elastosis
      - Collagenous thickening of visceral pleura
    (NB – did they exclude ILD with incidental apical cap? Or elastotic-rich UIP?)
    - “Unclassified fibrosis” (when predominant pattern did not fit)
    - “Undetermined fibrosis”
      - End-stage fibrosis, superimposed acute lung injury, “end-stage infection”
  - Quantification of elastic/collagen fibers using virtual slide software of EVG and Masson-stained section (in at least 1 section from each of the upper and lower lobes)
  - “Intralobar distribution” (subpleural vs diffuse)

Results:

- 24 AID-ILD: rheumatoid arthritis (8), poly/dermatomyositis (6), microscopic polyangiitis (4), systemic sclerosis (3), SLE (2), Sjogren’s (1)
<table>
<thead>
<tr>
<th></th>
<th>AID-ILD (n=24)</th>
<th>IPF (n=49)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Clinical info</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>67.3</td>
<td>69.4</td>
<td>ns</td>
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<tr>
<td>Female</td>
<td>11 (46%)</td>
<td>9 (18%)</td>
<td>0.024</td>
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<td>Smoking (curr/form)</td>
<td>15 (53%)</td>
<td>40 (82%)</td>
<td>&lt;0.01</td>
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<tr>
<td>FVC (% pred)</td>
<td>65</td>
<td>50</td>
<td>ns</td>
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<tr>
<td><strong>Histologic pattern</strong></td>
<td></td>
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</tr>
<tr>
<td>UIP</td>
<td>13 (51%)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>4 (17%)</td>
<td>--</td>
<td></td>
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<tr>
<td>Undeterm/unclassif</td>
<td>5 (20%)</td>
<td>--</td>
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<tr>
<td>PPFE</td>
<td>2 (8%)</td>
<td>--</td>
<td></td>
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<tr>
<td>“histologic PPFE”</td>
<td>12 (50%)</td>
<td>11 (22%)</td>
<td></td>
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<tr>
<td><strong>Elastic fiber score</strong></td>
<td></td>
<td></td>
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<tr>
<td>Whole lung</td>
<td>17.3</td>
<td>11.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upper lobes</td>
<td>16.6</td>
<td>11.2</td>
<td>&lt;0.01</td>
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<tr>
<td>Lower lobes</td>
<td>18.0</td>
<td>12.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upper/lower</td>
<td>1.07*</td>
<td>1.03*</td>
<td>ns</td>
</tr>
</tbody>
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* not sure how number arrived at

- 22 of 24 AID-ILD had above-average (vs normal lung) elastic fiber scores on whole lung analysis (“AID-ILD with elastosis”)
  - 10 upper-lobe predominant elastosis (“ratio >= 1”)
  - 12 lower-lobe predominant (ratio < 1)
    - 5 UIP, 2 NSIP, 2 undetermined fibrosis

**Conclusions:**
- Increased lung elastosis generally and PPFE specifically may be a marker for underlying autoimmune disease, irrespective of final histologic diagnosis

**Problems:**
- Methods of diagnosis (multidisciplinary consensus vs pathologic, diagnoses vs patterns etc.)
- “Garbage in = garbage out”
- Convoluted (non-practical) way of measuring elastosis
- So is apical cap a marker of autoimmune disease?

Aims/Background:
Perform genomic analysis on WDPM of peritoneum (WDPM-P) in order to determine neoplastic nature of the lesion and assess molecular pathogenesis

- TRAF – tumor necrosis factor alpha receptor-associated factor (E3 ubiquitin ligase)
  - TRAF7 mutation – adenomatoid tumor, perineurioma, meningioma
- CDC42 – Rho family GTPase

Materials and methods:

- 10 WDPM-P from pathology archives (1993-2014)
- Targeted next-gen DNA sequencing
- Immunohistochemistry for Bap1 and L1CAM
  - L1CAM – marker of NF-kB pathway activation, + in adenomatoid tumor

Results: Clinical -

- 3 males, 7 females; all incidental discoveries at surgery for another indication
- 8 solitary (2-12 mm), 1 two nodules (5 mm), 1 “several” nodules (2-10 mm)
- No specific therapy
- No recurrences (3.1 year median f/u)

Histological – simple papillary structures, fibroedematous core, no atypia, no invasion

Genomic –

- 7 cases (TRAF7 mutation), 3 cases (CDC42 mutation) – verified somatic (tumor-specific)
- All missense mutations (1 also had focal gene amplification (TRAF), 1 also multiple missense (TRAF))
- CDC42 mutations not previously known but equivalent to very common NRAS/HRAS/KRAS mutation (homologous proteins)
- Allele frequencies (all <50%) suggest clonal heterozygous alteration
- No anomalies in genes (BAP1, CDKN2A, NF2, DDX3X, SETD2 TP53, ALK) altered in DMM

IHC – Positive BAP1 and L1CAM (9 of 9)

- Normal mesothelium – Positive BAP1, Negative L1CAM
- DMM – Negative BAP1, Negative L1CAM

Conclusions:

- WDPM-P is clonal and neoplastic; defined by TRAF7 or CDC42 mut
- WDPM-P and adenomatoid tumor of genital tract may be related/ morphologic variants (though 31 adenomatoid tumor of genital tract did not show CDC42 mut)

**Purpose:** To quantify the impact of pirfenidone or nintedanib treatment on lung histopathology and molecular mediators of fibrosis in patients with idiopathic pulmonary fibrosis (IPF).

**Methods:**

- 28 IPF patients who underwent lung transplantation at UCSF, 11 of whom were treated with pirfenidone and seven with nintedanib.
- P16 and P21 expression levels as senescence makers were quantified with immunoblot by densitometry from lung lysates and *in vitro* induced cellular injury.
- P16 and P21 expression levels were compared by immunohistochemistry under microscope and confocal microscope.
- Levels of p-SMAD as marker of TGF-β signaling pathway were quantified by immunoblot in untreated and treated IPF patients.

**Results:**

- There were no significant differences in age, smoking history, FVC or diffusion capacity of carbon monoxide (DLCO) between groups. Eight patients were found to have histopathological evidence of acute lung injury.
- Quantification of the senescence markers p16 and p21 expression in lung lysates and *in vitro* demonstrated no difference in the lungs of untreated or treated IPF patients.
- Lung sections were immunostained for p16 and p21 of alveolar type II cells in the lungs demonstrated similar immunoreactive to p16 and p21 among untreated or treated IPF patients.
- IPF patients treated either with pirfenidone or nintedanib tended to have higher levels of p-SMAD than untreated controls.

**Take-home message:**

- Pirfenidone and nintedanib do not modulate expression of senescence markers, levels of p-SMAD3 or the amount of fibrosis in IPF lungs.
- Treated patients have less histopathological evidence of acute lung injury at the time of lung transplantation.
- Limitations of the study include small number of sample, variable length of treatment, fixed evaluation time at the transplantation.