PULMONARY PATHOLOGY JOURNAL CLUB
July 2007 articles

Featured articles


Articles for brief mention


Page 10 Primary pulmonary and mediastinal synovial sarcoma: a clinical pathologic study of 60 cases and comparison with five prior series. PH Hartel et al. Modern Pathology (2007) 20, 760-769.


Other articles
Page 12 Editorial - Resolving Dilemmas in Lung Cancer Staging and Histologic Typing. Kelly J Butnor, MD; Mary Beth Beasley, MD. Arch Pathol Lab Med 2007; 131:1014-1015


Acute Exacerbation of Interstitial Pneumonia other than Idiopathic Pulmonary Fibrosis
I-Nae Park et al.
(presented by Dr. Melanie Sackett)

**Background:**
- Acute exacerbation (AE) of interstitial pneumonia (IP) is relatively common and morbid in idiopathic pulmonary fibrosis (IPF), but can also be seen in idiopathic nonspecific interstitial pneumonia (I-NSIP) and collagen vascular disease related IP (CVD-ID).
- This study was performed to evaluate the frequency, clinical features, and outcome of AE in non-IPF interstitial pneumonia.

**Methods:**
- The authors followed 74 patients with I-NSIP and 93 patients with CVD-IP.
- Retrospective data collection.
- Biopsies reviewed independently by 2 pathologists and classified according to the American Thoracic Society/European Respiratory Society consensus classification.

**Results:**

<table>
<thead>
<tr>
<th>Frequency of Acute Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE/n</td>
</tr>
<tr>
<td>I-NSIP</td>
</tr>
<tr>
<td>CVD-IP</td>
</tr>
<tr>
<td>CVD-UIP</td>
</tr>
<tr>
<td>RA-UIP</td>
</tr>
</tbody>
</table>

Table 1—Clinical Data of 10 Patients With I-NSIP and CVD-IP*

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>Age, yr/Sex</th>
<th>Smoking Status</th>
<th>Duration of Interstitial Pneumonia Before AE, mo</th>
<th>Pathologic Pattern</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-NSIP</td>
<td>57/Male</td>
<td>Never</td>
<td>11 d after SLB</td>
<td>NSIP</td>
<td>Died</td>
</tr>
<tr>
<td>I-NSIP</td>
<td>75/Female</td>
<td>Never</td>
<td>34</td>
<td>NSIP</td>
<td>Died</td>
</tr>
<tr>
<td>I-NSIP</td>
<td>86/Female</td>
<td>Never</td>
<td>3</td>
<td>NSIP</td>
<td>Survived</td>
</tr>
<tr>
<td>I-NSIP</td>
<td>51/Female</td>
<td>Past</td>
<td>51</td>
<td>NSIP</td>
<td>Survived</td>
</tr>
<tr>
<td>I-NSIP</td>
<td>65/Female</td>
<td>Never</td>
<td>48 (SLB at the time of AE)</td>
<td>NSIP (plus DAD)</td>
<td>Survived</td>
</tr>
<tr>
<td>I-NSIP</td>
<td>58/Female</td>
<td>Never</td>
<td>7 (SLB at the time of AE)</td>
<td>NSIP (plus DAD)</td>
<td>Survived</td>
</tr>
<tr>
<td>RA-UIP</td>
<td>68/Male</td>
<td>Current</td>
<td>3</td>
<td>UIP</td>
<td>Died</td>
</tr>
<tr>
<td>RA-UIP</td>
<td>65/Male</td>
<td>Past</td>
<td>2</td>
<td>UIP</td>
<td>Died</td>
</tr>
<tr>
<td>RA-UIP</td>
<td>51/Female</td>
<td>Never</td>
<td>30</td>
<td>UIP</td>
<td>Died</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>47/Male</td>
<td>Never</td>
<td>Next day after SLB</td>
<td>NSIP</td>
<td>Died</td>
</tr>
</tbody>
</table>

*SLB = surgical lung biopsy.

2 patients had surgical biopsies at time of AE and showed DAD pattern superimposed on NSIP.

**Clinical features:**
- Median age 58, 60% female, 6/10 were taking corticosteroids.
- Sx: 10/10 dyspnea, cough, whitish sputum and inspiratory crackles. 5/10 fever.
Pulmonary function:
- 8/10 had a restrictive pattern with median FVC of 52% of predicted, diffusion capacity of 47%, and total lung capacity of 61%.
- 23% decline of FVC on spirometry.

Radiology:
- All patients had bilateral ground-glass opacity with either peripheral, multifocal or diffuse distribution
- +/- consolidation at time of AE, superimposed on chronic fibrotic changes.

Treatment and outcome:
- 9/10 were treated by antibiotics and systemic corticosteroids.
- 6 patients needed mechanical ventilation and all 6 died after a median of 26 days, including all 4 patients with CVD-IP.
- 4 other patients survived, all of which had NSIP.

Discussion and conclusion:
- Clinical, radiologic, and pathologic features of AE in I-NSIP and CVD-IP is similar to that of IPF, but the 1 year frequency may be slightly lower than that of IFP (15.4%).
- Survival of AE in NSIP seems to be better than that of AE in IPF. Survival of AE in CVD-IP, especially RA-UlP, seems worse than AE in IPF or AIP.

<table>
<thead>
<tr>
<th>Variables</th>
<th>I-NSIP (n = 6)</th>
<th>CVD-IP (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, $10^9$/μL</td>
<td>9,500 (4,000–18,900)</td>
<td>13,000 (5,900–17,100)</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>6.9 (0.5–9.6)</td>
<td>4.8 (2.7–6.9)</td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>199 (107–273)</td>
<td>146 (121–254)</td>
</tr>
</tbody>
</table>

*Data are presented as median (range).
**Two Dimensional Analysis of Elements and Mononuclear Cells in Hard Metal Lung Disease**  
Hiroshi Moriyama et al.  
Am J Respir Crit Care 2007; 176: 70-77.  
(presented by Dr. Melanie Sackett)

**Background:**
- Hard metal lung disease (HMLD) is caused by occupational exposure to hard metal, which is composed of about 90% of tungsten (W), about 10% of cobalt (Co), along with nickel, chromium (Cr), and tantalum (Ta).
- Pathological findings in HMLD are predominantly giant cell interstitial pneumonia (GIP).
- The purpose of this study was to elucidate the distribution of hard metal and inflammatory cells in lung biopsies of HMLD.

**Method:**
- 3 um sections from surgical lung biopsies of 17 patients with HMLD were analyzed by electron probe microanalyser (EPMA) with a wavelength-dispersive spectrometer (WDS) and immunohistochemistry was performed with antibodies directed against CD8, CD4, CD163 and CD20.

**Results:**
- 13/17 patients with HMLD had typical GIP pattern, consisting of centrilobular fibrosis and giant cell accumulation. 4 had an atypical pattern with various extents of interstitial inflammation and fibrosis similar to UIP.
- In patients with HMLD, W was found in all. Al, Si, Cr, Fe, and Ta were also found. Co was detected in only 4/17 patients and found in very low amounts.
- 5 control lungs from lobectomy for NSCLC contained Al, Ti, Fe, and Zn, but no Co or W.
- Al, Ti, Si and W were located in the peribronchiolar fibrosing tissue. Al and Si were also found in the surrounding alveolar areas.
CD8+ lymphocytes (but not CD4+) and CD163+ macrophages were found in alveolar walls, peribronchioles, and centrilobular fibrotic lesions, CD20+ lymphocytes in the lymphoid follicles, and alveolar macrophages were also CD163+.

Some CD163+ macrophages colocalized with W.

Discussion:

HMLD may develop through a hypersensitivity reaction.

Conclusion:

W is mainly found in centrilobular fibrosis and peribronchioles and was closely located with CD163+ macrophages surrounded by CD8+ lymphocytes. This suggests that CD163+ macrophages may phagocytose inhaled W and play a role in forming the fibrotic lesion of HMLD along with cytotoxic T lymphocyt
Local and Circulating Microchimerism is Associated with Hypersensitivity Pneumonitis
Martha L. Bustos, et al
Am J Respir Crit Care Med 2007; 176: 90-95.

Purpose: To evaluate the presence of circulating and local microchimeric cells in female patients with HP, in order to determine if microchimerism may be a factor involved in the pathogenesis of the disease.

Methods: Male microchimerism was examined in 103 females with HP, 30 with IPF and 43 normal controls. All had given birth to at least one son, and none had other known factors to account for acquired microchimerism. Microchimerism was examined by dot blot hybridization in peripheral blood and by FISH in cells from BAL and lung biopsy.
- Of 103 HP pts 46% had been biopsied.
- Of 30 IPF pts 36% had been biopsied.
- 14 pts with HP, 10 pts with IPF, and 0 controls had BAL cells tested for microchimerism
- DNA analysis for microchimerism on paraffin embedded tissue from lung biopsy performed in 5 HP pts who were positive for microchimerism in the blood had (different pts from those that had BAL fluid), and 3 IPF pts (status of microchimerism in peripheral blood not stated).

Results: Peripheral blood microchimerism was identified in 34/103 HP pts (33%) vs. 3/30 IPF pts (10%), vs. 7/43 controls (16%). BAL fluid cell microchimerism was found in 9/14 HP (64%) compared to 2/10 IPF (20%). Lung tissue microchimerism was identified in 5/5 HP pts and 0/3 IPF pts. HP pts with blood microchimerism showed decreased CO diffusing capacity compared to HP pts without microchimerism.

Figure 2. Detection of male microchimerism in bronchoalveolar lavage cells sorted by high-speed flow cytometer in two patients with hypersensitivity pneumonitis. Two microchimeric cells found in the alveolar macrophages and in the CD4 T-cell subpopulations are indicated by arrows. Original magnification: x100.

![Figure 2](image1.png)

Figure 3. FISH for centromeric regions of chromosomes X (green) and Y (reddish-orange signal) in lung tissues from three different patients with hypersensitivity pneumonitis. Light microscopy of the same tissue sections as in (A) and (B) counterstained with H&E. Arrows indicate the fetal male cells with chromosomes X and Y surrounded by XX bearing maternal cells in the inflammatory infiltrate (A1 and A2) and in the bronchiolar epithelium (A3).
<table>
<thead>
<tr>
<th>Variable</th>
<th>With Microchimerism $(n = 34)$</th>
<th>Without Microchimerism $(n = 69)$</th>
<th>p Value $^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>$48.3 \pm 12.5$</td>
<td>$49.0 \pm 13$</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of symptoms before diagnosis, mo</td>
<td>$28.1 \pm 22.0$</td>
<td>$31.1 \pm 23.6$</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>$53.8 \pm 15.4$</td>
<td>$55.5 \pm 15.8$</td>
<td>NS</td>
</tr>
<tr>
<td>$P_{aO_2}$, mm Hg $^*$</td>
<td>$50.8 \pm 7.1$</td>
<td>$50.2 \pm 11.0$</td>
<td>NS</td>
</tr>
<tr>
<td>$D_{LCO}$, %</td>
<td>$53.5 \pm 11.9$</td>
<td>$65.2 \pm 19.7$</td>
<td>0.02</td>
</tr>
<tr>
<td>SaO$_2$ rest</td>
<td>$85.1 \pm 6.6$</td>
<td>$84.6 \pm 9.3$</td>
<td>NS</td>
</tr>
<tr>
<td>SaO$_2$ exercise</td>
<td>$71.3 \pm 9.8$</td>
<td>$74.2 \pm 9.6$</td>
<td>NS</td>
</tr>
<tr>
<td>BAL macrophages, %</td>
<td>$34.0 \pm 17.5$</td>
<td>$44.0 \pm 16.2$</td>
<td>NS</td>
</tr>
<tr>
<td>BAL lymphocytes, %</td>
<td>$64.3 \pm 16.7$</td>
<td>$54.8 \pm 16.3$</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Conclusion of authors:

- Patients with HP exhibit increased frequency of fetal microchimerism.
- Microchimeric cells may increase the severity of the disease.
- Findings support the multilineage capacity of microchimeric cells.

<table>
<thead>
<tr>
<th></th>
<th>BAL neutrophils, %</th>
<th>BAL eosinophils, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 ± 2.0</td>
<td>1.2 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>0.8 ± 1.0</td>
<td>1.2 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Stem Cells for Lung Disease
MR Loebinger et al.

Purpose: To review advances and potential clinical implications of stem cell research pertaining to lung disease.

Abstract: Respiratory diseases remain one of the main causes of morbidity and mortality in the world. Interest has increased as to the possibility of optimizing the repair of the lung with the manipulation of stem cells. Embryonic and adult stem cells have been suggested as possibilities. Adult stem cells have traditionally been thought of as having limited differentiation ability and to be organ specific. However, a series of exciting reports over the last 5 to 10 years have suggested that adult bone marrow-derived stem cells may have more plasticity and are able to differentiate into bronchial and alveolar epithelium, vascular endothelium, and interstitial cell types, making them prime candidates for repair. This article critically reviews the evidence for this plasticity and the use of predominantly adult stem cells to help with lung regeneration and repair and assesses how this technology may be utilized in clinical medicine.

Conclusion of the authors: There is evidence that bone marrow-derived stem cells are able to target areas of the body undergoing injury and contribute to repair. The exact mechanisms are not wholly understood, and different cell species may have different roles in certain situations. Nevertheless, this basic science research is likely to open up new and exciting avenues of pharmacologic, cellular, and genetic therapy for diseases in which they are greatly needed—no more so than in respiratory medicine.
ARTICLES FOR BRIEF MENTION - TIME PERMITTING

**Lobectomy or Pneumonectomy for Multi-Drug-Resistant Pulmonary Tuberculosis can be Performed with Acceptable Morbidity and Mortality: a Seven-Year Review of a Single Institution Experience**

T. Mohsen et al

This is a single institution retrospective study of the surgical management of multi-drug-resistant tuberculosis at the Kasr Al Aini Hospital of Cairo University in Egypt, over a seven-year period from 1999 to 2005. During this time 23 patients (of which 20 were male) underwent lobectomy or pneumonectomy for HIV negative multi-drug-resistant tuberculosis. The mean age of the patients was 24 years with a range of 7 to 48 years.

The patients operated upon had gross disease including cavities, bronchiectasis or destroyed lobes, 4/23 had hemoptysis and 3 had complicating fungus ball within the tuberculous cavity. Dense adhesions required an extra-pleural approach in 7 of 11 pneumonectomies to avoid spillage of cyst contents. There was one postoperative death and one relapse, and in the remaining 21 the treatment was considered successful, a 91% success rate in keeping with other series in the literature ranging from 83% to 93%.

**The Growing Burden of Chronic Obstructive Pulmonary Disease and Lung Cancer in Women**

S B Cohen et al

This review addresses the increasing incidence of chronic obstructive lung disease and lung cancer in women. Between 1980 and 2000, the mortality rates for COPD increased in women by 291% and in men by only 60%. Within the next 20 years, it is estimated that there will be more women than men with lung cancer. The epidemic of lung disease in women within the Western World appears to be not only due to an increase in the number of women smoking, but also due to an inherently greater biological susceptibility of women to the harmful effects of cigarette smoke.

The article references evidence supporting this susceptibility, including:

- Adolescent girls who smoke have been shown to have a 1.09% per year reduction in growth rate of FEV1 compared to only 0.02% per year in boys.
- Female smokers have a faster decline in FEV1 and FVC than male smokers
- For any given pack-year smoking history female smokers are 2 to 3 times as likely to die of COPD
- Compared to men smoking women with the same decrease in FEV1 adjusted for smoking history are twice as likely to develop lung cancer.
- There may be major sex differences in the expression of the p53 gene that predispose women to lung cancer.
- Female smokers have higher levels of DNA adducts in their lung tissue than male smokers.
- Epidemiologic studies showing an association between exogenous estrogen and increased risk of lung cancer in women.
Potential mechanisms for the increased vulnerability of female smokers are thought to include upregulated expression of cytochrome P450 enzymes in the lung compared with male smokers related to a positive feedback loop with 17 beta estradiol. Metabolism of foreign molecules by cytochrome P450 enzymes in liver and lung tissue results in “metabolic bioactivation” of several constituents of cigarette smoke, including benzpyrene and naphthalene, which are converted to potent carcinogens.

**Primary Pulmonary and Mediastinal Synovial Sarcoma: a Clinical Pathologic Study of 60 Cases and Comparison with Five Prior Series**

PH Hartel et al


A review from the case files of AFIP derived from a total of 119 cases diagnosed as “synovial sarcoma” or “sarcoma” from 1981 to 2006, excluding 59 cases that were either metastases, chest wall soft tissue tumors, or failed to meet histological or immunohistochemical criteria for diagnosis on review.

- Sex distribution was equal (29 male, 27 female).
- Age range 10 to 84 years (mean 42 years).
- Tumour distribution - lung (58%), pleura (33%), mediastinum (9%).

Radiographic findings are described for those cases that had imaging studies on file. At the time of the report 26% of patients were alive with NED, 26% were alive (disease status unknown), and 48% dead of disease. The 5 year dead of disease rate was 46% (consistent with survival data from other published series referenced in the paper) confirming that primary pulmonary and mediastinal synovial sarcoma is more aggressive than soft tissue synovial sarcoma, which has a 5 year DOD rate of 35%.

The chromosomal translocation t (x;18) was present in 92% (36/39) of cases studied, 58% fusion type SYT/SSX1 and 42% fusion type SYT/SSX2. A greater percentage of patients who died of disease within five years had tumors with SYT/SSX1, and this fusion type was associated with a mean age of 43 years compared to 54 years in patients with SYT/SSX2 positive tumors.

Tumor size ranged from 0.6 to 17 centimeters. All were well circumscribed soft masses with areas of hemorrhage, necrosis, and cystic change. Histologically 88% were monophasic and 12% were biphasic. Cytomorphology was spindle cells in 58% and combined spindle/round cells in 42%.

Immunohistochemical and histological findings are summarized, highlighting potential diagnostic pitfalls in the differential diagnosis with malignant peripheral nerve sheath tumor, primitive neuroectodermal tumor, pleomorphic carcinoma, mesothelioma, and solitary fibrous tumor.
Pulmonary Lymphangioleiomyomatosis in Karyotypically Normal Man without Tuberculous Sclerosis Complex
M. Shiavina et al.

This is a case report out of Bologna Italy. The authors indicate that the literature contains reports of only nine men with possible pulmonary LAM between 1939 and 1997, and three probable or definite cases reported after 1997. They report the case of a 37 year old man, phenotypically normal, who presented with spontaneous pneumothorax and was subsequently discovered to have widespread thin-walled cysts throughout both lungs on HRCT, with characteristic features of LAM. Pleural abrasion and VATS biopsies were performed, and LAM was confirmed pathologically. The LAM cells were strongly positive for estrogen and progesterone receptors, smooth muscle actin and HMB-45. Extensive evaluation revealed no evidence of tuberous sclerosis. Cells from the cyst walls extracted by microdissection from the biopsy specimen and peripheral blood were tested for TSC1 and TSC2 germline mutations, which were not identified. A decision was made to treat with hormone manipulation (GNRH antagonist) and at nearly three years follow up the patient was reported to be clinically and functionally stable.

Upstaging by Vessel Invasion Improves the Pathology Staging System of Non-Small Cell Lung Cancer
T. Tsuchiya et al.
Chest Jul 2007: 170–177

The authors reviewed 995 cases of resected early stage NSCLC from two institutions in Japan, reclassifying them based upon the presence or absence of lymphovascular space invasion identified (VSI) on H&E with or without elastic stains. They compared survival statistics for these patients (median follow up 58.8 months and 39 months at institutions 1 and 2), and concluded that VSI provided significant prognostic information. They suggest that stage IA with VSI should be upstaged to IB, and IB with VSI should be upstaged to IIA in a new classification scheme for NSCLC.

Ozone, a Malady for All Ages
KE Pinkerton Ph.D. et al.

This is an editorial urging the United States Environmental Protection Agency to issue a more stringent ozone standard. It expresses concern for the respiratory health of US citizens under the current ozone standard, and suggests that children (due to their higher level of activity, higher minute ventilation and immature lung development throughout childhood) are particular risk from ambient air pollutants. Several studies are cited implicating ozone as a contributor to childhood asthma. The American Thoracic Society recommends that the EPA issue an ozone standard of 0.060 ppm/8 hours.
OTHER ARTICLES
Commonly Encountered Difficulties in Pathologic Staging of Lung Cancer
Douglas B. Flieder, MD
Arch Pathol Lab Med 2007; 131:1016-1026.

Editorial - Resolving Dilemmas in Lung Cancer Staging and Histologic Typing
Kelly J Butnor, MD; Mary Beth Beasley, MD
Arch Pathol Lab Med 2007; 131:1014-1015

Bronchioloalveolar Carcinoma - A review of Current Concepts and Evolving Issues
Samuel A. Yousem, M.D; Marybeth Beasley, MD

Sentinel Node Identification in Clinical Stage 1a Non-small Cell Lung Cancer by a
Combined Single Photon Emission Computed Tomography/Computed Tomography
System
Hiroaki Nomori, MD, PhD, et al.

Distinctive Evaluation of Nonmucinous and Mucinous subtypes of bronchioloalveolar
carcinomas in EGFG and K-ras Gene Mutation Analysis for Japanese Lung
Adenocarcinomas - Confirmation of the Correlations with Histologic Subtypes and Gene
Mutations
Yuji Sakuma, MD, PhD, et al.

Differences in Epidemiology, Histology, and Survival Between Cigarette Smokers and
Never-Smokers Who Develop Non-small Cell Lung Cancer
Ayesha Bryant and Robert James Cerfolio

Prognostic Value of Integrin beta1-I LK-pAkt Signaling Pathway in Non-small cell Lung
Cancer
Mayumi Okamura, MD, et al.
Human Pathology 2007; 38; 1081-1091.

Sources of Graft Restriction after Single Lung Transplantation for Emphysema