# Pulmonary Pathology Journal Club
## (April 2007 articles)
### May 21, 2007

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### Original articles for discussion


### Articles for brief mention; non-neoplastic


Articles for brief mention; neoplastic


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I. Discussion Articles:


**Purpose:** To investigate whether the better prognosis of ILDs associated with CVD compared to idiopathic interstitial pneumonias (IIP) is due to higher frequency of NSIP in CVD or to a genuine difference in the same pathologic category (i.e. i-UIP vs. cvd-UIP; i-NSIP vs. cvd-NSIP)

**Methods:**
- **Subject:** 362 patients (269 IIP and 93 with cvd-IP) diagnosed using surgical lung biopsy as UIP (203 IPF and 36 with cvd-UIP) or fibrotic NSIP (66 i-NSIP and 57 cvd-NSIP) from 1990 to 2006 in a large (actually a huge) center in Korea.
- **Mean f/u:** 36.8 ± 2.1 m for IIP and 56.0 ± 4.2 for cvd-IP; chart review, telephone interview, clinical parameters were obtained within 1 month before surgical lung bx
- **Dx:** 2 pairs of pathologists (TVC & MK; \(\kappa\), 0.590 n=164; or TVC & SJJ; \(\kappa\), 0.429 ν=138), third opinion AGN, still controversial cases resolved by a final face-to-face meeting. Pathologists were blinded to the clinical information of most cases
- **PFT:** spirometry, lung vol, DLco
- **Stats:** chi-square test or Fisher’s exact test for categorical data and an unpaired Student’s t-test or Mann-Whitney test for continuous data. Survival by Kaplan–Meier survival curves and log-rank test, Cox proportional hazards regression analysis

**Results:**
- **Survival of pts with IP in general:** multivariate analysis revealed that age, FVC, DLco and the presence of CVD are independent marker for prognosis
- **Survival difference between pts with i-UIP and those with cvd-UIP**

![Survival curve graph](image-url)
### TABLE 3. BASELINE CLINICAL AND DEMOGRAPHIC FEATURES OF PATIENTS WITH A USUAL INTERSTITIAL PNEUMONIA PATTERN

<table>
<thead>
<tr>
<th></th>
<th>IPF-UIP</th>
<th>CVD-UIP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>203</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>59.2 ± 9.2</td>
<td>53.0 ± 12.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>144 (70.9%)</td>
<td>12 (33.3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking, current/ex/never</td>
<td>69/68/66</td>
<td>7/4/25</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>25.8 ± 21.1</td>
<td>15.4 ± 22.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Duration of dyspnea, mo</td>
<td>13.4 ± 17.1</td>
<td>8.8 ± 9.7</td>
<td>0.030</td>
</tr>
<tr>
<td>Dyspnea score</td>
<td>3.0 ± 1.3</td>
<td>2.7 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 191</td>
<td>n = 36</td>
<td></td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>72.2 ± 17.4</td>
<td>67.7 ± 15.7</td>
<td>NS</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>76.6 ± 16.6</td>
<td>74.9 ± 13.0</td>
<td>NS</td>
</tr>
<tr>
<td>DL\textsubscript{CO}, % predicted</td>
<td>62.9 ± 20.6</td>
<td>59.6 ± 16.3</td>
<td>NS</td>
</tr>
<tr>
<td>Pa\textsubscript{O2}/Fi\textsubscript{O2} ratio, mm Hg</td>
<td>435.1 ± 69.4</td>
<td>447.6 ± 51.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

-Survival difference between pts with i-NSIP and with cvd-NSIP: age and FVC (but not DL\textsubscript{CO} or the presence of CVD) were independent risk factors affecting the survival

-Survival difference between pts with cvd-UIP and with cvd-NSIP: unlike IIP patients, there was no difference between the two groups

**Take home message:** patients with cvd-UIP had significantly better survival than those with i-UIP, while there is no significant difference between the cvd-NSIP and i-NSIP.

*(Editorial by Barnes DJ. The staging system for non-small cell lung cancer. Time for an overhaul? 948-949)*

**Purpose:** Background of this study is that the current AJCC LN staging system has been considered inadequate because of the lack of consideration of the severity of LN involvement; patient survival might be quite different in the group of patients within the same LN stage. To examine the clinical impact of extranodal extension in the positive regional lymph nodes on the survival of NSCLC pts
Methods: a prospective study encompassing a 10-year-period (1/90-12/99), with the final f/u for survival at the end of 6/05

Patients; 199 pts who underwent a complete surgical resection of the primary tumor and had positive regional or mediastinal LNs by standard dissection of hilar, interlobar, lobar, intralobular, mediastinal LNs. No neoadjuvant or postop adjuvant therapy given

Specimens;
- routine exam for tumor cell type, grade, vascular invasion, node counts (number and station); they included only adeno and squamous ca (but not adenosquamous or large cell).
- additionally, size of the positive LN measured, then separated into 2 groups: <1cm and ≥1cm. extranodal extension assessed by serial section at intervals of 1-2 mm along the greatest diameter of each LN (I guess it is by gross exam), all the sections then examined by 2 pathologists for extranodal extension (illustrated figure does not seem to be convincing to me, though; they look like within the subcapsular sinuses).
- TNM staging done.
- IHC for p53 on tumor
- microscopic classification of LN involvement; intranodal (tumor cells within the capsule) vs. extranodal extension (beyond capsule), the number and % of LNs with extranodal extension in each pt
- extranodal extension status correlated with histologic type, grade, vascular invasion, tumor size, pathologic stage of the tumor; LN size group and presence of extranodal extension also studied; impact of LN station and number or percentage of extranodal extensions on pt survival also analyzed in relation to other prognostic parameters.

Results:
- ENE positive status in general was significantly higher in women, adenocarcinoma type, advanced stage, tumors with vascular emboli and p53 overexpression
- total number and percentage of ENE positive nodes correlated with advanced stage, tumors with vascular emboli, or p53
- + LNs ≥1 cm, the ENE+ seen in 79.6%; < 1cm, ENE+ in 90.8% (p=0.001); i.e. small positive LN has significantly higher chance of ENE+ than larger nodes.
- by multivariate analysis, the presence or total number of LNs with ENE, tumor stage, and p53 were significant prognostic factors
- ENE has an adverse impact on survival; stage IIIA without ENE did better than stage II disease with ENE!

Take home message:
- As stated in the editorial, time for an overhaul on the staging system for NSCLC?

Purpose: a prospective study to assess the value and practicality (i.e. cost and time) of TTF-1 ipox during frozen section as an adjunct within the intraoperative reporting process

Methods:
-subjects: over a 2-year-period, 33 pts were identified before surgery from requests for FS by the criteria including either a solitary mass or 2 masses in the lung and a history of carcinoma in different organ (large bowel n=23; 2 with additional hx of prostatic ca, renal n=2; 1 with additional hx of bladder ca, breast n=5, ovarian n=1, gallbladder n=1, bladder n=2; 1 with additional hx of renal tumor).
-routine FS with HE for dx; HE sections were independently assessed at the time of FS with the confidence in dx expressed as a percentage. Then, the dx was reevaluated using the additional evidence of TTF-1 staining, again expressed as a percentage. TTF-1 FSIHC was confirmed by subsequent IHC on paraffin using both frozen block and a separate un-frozen block. CK7, CK20 and PSA stains were also performed on paraffin-embedded tissues.
-rapid FSIHC method; sole aim of shortening the time while maintaining the sensitivity: by simple fixation in acetone, omission of blocking endogenous peroxidase, reduction of incubation times and increase of Ab concentration (1:5 as opposed to 1:80 in regular way), incubation at 37 degrees, EnVision detection system, subtle nuclear background stain with Mayer hematoxylin.

Results:
-10 of 33 cases were positive for TTF-1 by FSIHC, which was confirmed on subsequent paraffin sections. 9 of these 10 were primary lung adeno, but 1 proved to be a rare false-positive metastatic colonic ca. 23 were negative on FS and reported as favoring mets. In all cases, additional TTF-1 information increased the diagnostic confidence, but particularly positive cases and in cases from sites other than the large bowel
-Average time added was 24 minutes per test with a cost of US$57.

Take home message:
It is do-able, but do we really need it??


Purpose: to describe a distinct subtype of pulmonary tumors showing epithelial and myoepithelial differentiation with further pneumocytic specialization (pneumocytic adenomyoepithelioma, PAM)

Methods: clinicopathologic description of a new entity based on 5 cases

Results:
-all were women, aged 52-63 years and
presented with single or multiple nodules
-grossly circumscribed, 0.8 to 2.6cm in greatest dimension
-histologically glandular and spindle cell proliferation, some glands filled with colloid-like secretion and had an inner, cuboidal epithelial layer (+ for pankeratin, EMA, TTF-1), surrounded by an outer layer of myoepithelial cells merging with foci of spindled myoepithelial cells (+ for hmwCK, s100, SMA, calponin, caldesmon, p63). Some glands lined by a single layer of plump cells that were positive for SP-A protein and other epithelial markers. EM confirms the pneumocytic features and myoepithelial cells
-all treated with wedge resection and followed benign clinical course
-ddx:
-pleomorphic adenoma (usually TTF-1 -, more chondromyxoid stroma
-sclerosing hemangioma (no myoepithelial element)
-salivary gland-type tumors with myoepithelial differentiation in association with pulmonary hamartomas (central location, primarily exophytic growth pattern and lacks spindle and glandular/pneumocytic areas)
-neuroendocrine tumor (IHC for neuroendocrine markers will help you, of course)
-metastatic thyroid ca including FVPTC, follicular ca (IHC for myoepithelial cells)
-metastatic ca from the salivary gland (hx and – stain for TTF-1 will help you)

Take home message:
We’ve got a name for those cases looking like a benign salivary-gland type tumor with TTF-1 positivity. (I had one case here and it was a man!).


**Purpose:** report of 5 patients presenting with signs and symptoms of mild restrictive lung disease and radiographic evidence of diffuse, bilateral reticulonodular lung infiltrates, in whom open lung biopsies revealed multiple meningothelial-like nodules in the absence of interstitial fibrosis, carcinomatosis, or other obvious pathologic abnormalities

**Methods:**
-case identification; found over a 10 year period (96-06) from Ohio State and M.D. Anderson. Medical records and imaging studies reviewed.
-all patients had VAT bx from RUL and RLL
-IHC; AE1/AE3, CAM5.2, vimentin, MSA (HHF35), S100, SMA, chromogranin, synaptophysin, EMA, CD34.
-EM on 1 case

**Results:**
-clinical; 4F 1M, with age range of 54-75
-all presented with dyspnea, SOB, fatigue
-none had a smoking or of occupational exposure
-all with available hx showed multiple underlying systemic diseases or cancers
-PFT; mild restrictive lung disease on PFT
- chest CT or x-rays; diffuse bilateral reticulonodular densities or ground glass opacities, with multiple small nodules measuring 2-3mm in diameter diffusely scattered throughout both lung fields, number of nodules ranging from 30 to >100, size up 8mm -Gross; multiple small gray white nodules scattered randomly throughout the lung parenchyma (like in the radiology) -Micro; we all know how it looks like (vimentin+, EMA+, the rest -) -F/U; 3 (of 5) lost in f/u, those 1 of 2 with f/u showed stabilization of the lesions in a surveillance CT scan , 92 months after the open lung bx. The remaining 1 patient showed scattered ground glass opacities and nodules that started to increase in number and develop respiratory symptoms, for which she underwent wedge lung biopsies. No additional f/u since.

**Take home message:**
While single or a few meningothelial-like nodules in the lung are extremely common but diffuse meningotheliomatosis is quite uncommon. This study reported 5 of these cases but could not provide us with solid information on its clinical behavior.

**II. Articles for brief mention**


This paper is based on the retrospective review of blastomycosis cases over a 20 year-period in a large community based general hospital practice. The cases were grouped as 8 localized to the lung (group 1), and 5 with extrapulmonary presentation (group 2) and 3 autopsy cases. 3 of the 8 group 1 cases were clinically mimicked tumors. Blastomycosis is seldom a fatal disease. Most patients are immune competent; immune compromise favors an aggressive course. Microbiologic culture and conventional morphologic assessment of routine samples have redundant utility in diagnosis.


Streptomyces species are gram-positive filamentous bacteria and soil inhabitants. They are famous for producing of antibiotics as secondary metabolites. They only rarely represent true infections, esp. in polymicrobial setting. However, it ay cause mycetoma; when it occurs in a lower extremity, it is know as Madura. Invasive infections other than mycetoma caused by Streptomyces species are rarely encountered in clinical practice. This study described 6 cases of their own and reviewed 13 other cases reported in the literature. A useful reference on this not so common subject.

This study assessed the prevalence of a medical diagnosis of GERD, reflux symptoms and acid-suppression therapy in patients with MAC lung disease (MAC+) and to compare these patients with control subject (MAC-). A cohort of 58 MAC+ patients and 58 age- and sex-matched MAC- patients who were asked to complete a DeMeester questionnaire of reflux symptoms and to identify and acid suppressive medication consumed. GERD, acid suppression and clinically suspected aspiration are more common in pts with MAC+ than in similar patients who are MAC-


Lately, the presence of PH in the setting of IIP as well as IP associated CVD has been implicated as an independent prognostic factor (Jeff has reviewed a few of them on this issue last week). 50 to 80% of all SSc pts have pulmonary involvement, with PH and ILD the most common manifestations and the leading causes of morbidity and mortality. Pericardial effusion is common in SSc pts with PH, which can be a presenting feature. This study showed that pericardial abnormalities are commonly seen on HRCT in pts with SSc-related ILD and their presence is strongly associated with echo evidence of PH.

III. Articles for brief mention; Neoplastic


An immunohistochemical study using MUC4 antibody on 343 cases of NSCLC arranged in tissue microarray. Long-term survival and tumor stage were correlated with MUC4 expression assessed by semiquantitative grading. MUC4 expression was most common in adenocarcinomas (81%) and there was a trend toward longer survival with higher levels of MUC4 immunoreactivity compared to lower levels in stage I and II adenocarcinoma (p=.11)


This study did an epidemiologic study over a 31-year period from 1973 to 2003 using the lung cancer incidence rates from the Surveillance epidemiology and End Results (SEER) program. From 1973 to 1998, the age-adjusted incidence rate of adenoca increased 83% in men and >200% in women. Interestingly, the rate declined 14% in men and 8% in women from 1999 through 2003. They looked into whether low-tar cigarette (tar ≤
(15mg) consumption/per capita by year was responsible for this trend by correlating with
the market share change of low-tar cigarette during this period. They concluded that
increasing low-tar cigarettes in the US and the decline in environmental tobacco smoke
may be contributors but not the driving force. Based on the striking similarities of
adenoca incidence curve changes in men and women, the major cause of adenoca might
be a more general phenomenon and has impacts on men and women in the same way,
such as air pollution.

In summary, this study described the fact that lung adenoca incidence has declined since
1999. The driving force for its long period increase and subsequent decline in recent
years is not clear. The possible causes may include air pollution, low-tar cigarette
consumption and environmental tobacco.

**Baser S, Onn A, Lin E, et al. Pulmonary manifestations in patients with cutaneous T-

A retrospective analysis on 710 pts with CTCL who presented to MD Anderson Cancer
Center between 1/1996 and 1/2005. 122 of 710 pts presented with pulmonary radiologic
abnormalities and 67 of these 122 pts had also respiratory symptoms. 27 had pneumonia
and 6 had CTCL involvement; both groups had high mortality rates. Radiologic findings
in pts with pneumonia were opacities. CTCL involvement was manifested by either a
solitary nodule or multiple progressing pulmonary nodules on radiologic studies.

**Tigrani DY, Weydert JA. Immunohistochemical expression of osteopontin in
epithelioid mesotheliomas and reactive mesothelial proliferations. Am J Clin Pathol
2007;127:580-584**

Osteopontin is a phosphoprotein with a variety of physiologic roles, including anchoring
osteoclasts to bone mineral matrix, functioning as a normal component of elastic fibers of
skin and aorta, and acting as a protein ligand of CD44. It has also been shown to be
expressed in a variety of carcinomas including lung, breast, and prostate. A recent study
showed that patients with pleural malignant mesotheliomas had significantly higher
osteopontin levels than those in a noncancer group with a history of asbestos exposure.
Given this recent findings linking increased serum osteopontin levels and mm, they
looked into the diagnostic utility of distinguishing epithelioid mm from reactive
mesothelial proliferations (what a wishful thinking….). The answer was very definite
“NO use”: 7 of 7 mesotheliomas and 19 of 20 reactive mesothelial proliferations showed
osteopontin immunoreactivity.

**IV. Review Articles**

**Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome.
Am J Pathol 2007;170:1136-1147**

Nice review from the heart of SARS epidemic, Beijing, China

-10-

Current view on atherogenesis has been shifted from a disorder of lipid accumulation to a disease caused by more dynamic interaction between endothelial dysfunction, subendothelial inflammm and the wound healing response of the vascular smooth muscle cells. Nice overview with recent literature.

Accurso FJ. Update in cystic fibrosis 2006. Am J Respir Crit Care Med 2007;175:754-757

Nawrot TS, Nemmar A, Nemery B. Update in environmental and occupational medicine 2006. Am J Respir Crit Care Med 2007;175:758-762

V. Case report


Despite the lack of bx confirmation, the clinical scenario was pretty good for the 2 cases that this paper reported: community-acquired pneumonia-like symptoms following smoking of flavored cigars, no response to antibiotic tx, BAL eos count >45%, response to steroid, and finally exclusion of all other possible causes. Who could ask for more?