I. STUDIES FOR DISCUSSION

Page 1 Lantuejoul, et al. Pulmonary Veno-occlusive Disease and Pulmonary Capillary Hemangiomatosis (AJSP 2006;30:850)


Page 5 Wright and Churg. Advances in the pathology of COPD. (Histopathology 2006;49:1)

II. OTHER STUDIES OF SIGNIFICANCE


III. NEW PROGNOSTIC MARKERS


Seto, et al. Prognostic value of expression of vascular endothelial growth factor and its FLT-1 and KDR receptors in stage 1 non small cell lung cancer. (Lung Cancer 2006;53:91)


IV. MISCELLANEOUS


Davies and Drobniewski. The use of interferon-gamma-based blood tests for the detection of latent tuberculosis infection. (Editorial. Eur Respir J 2006;28:1)


V. INTERESTING CASE REPORTS


**Purpose.** To study and compare cases of pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH). “To assess the relationship by undertaking a retrospective review of archival material for these disorders” (PVOD vs. PCH).

**Materials and Methods.** 38 samples of lung tissue from 35 patients collected over 24 years. 5 interpreted as PCH, 33 and PVOD. Some cases with 2 specimens included in both diagnostic groups. 15 autopsies, 15 biopsies, 7 explants, 1 pneumonectomy.

Clinical features are summarized in Tables 1 and 2 from the paper.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>PVOD (n = 30)</th>
<th>PCH (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>19/11</td>
<td>3/2</td>
</tr>
<tr>
<td>Mean age (n = 31)</td>
<td>34 (range 4 to 68 y)</td>
<td>42 (range 9 mo to 60 y)</td>
</tr>
<tr>
<td>Presenting complaints:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increasing dyspnea</td>
<td>20/20</td>
<td>1/2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8/20</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4/20</td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3/20</td>
<td></td>
</tr>
<tr>
<td>History of asthma</td>
<td>3/20</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2/20</td>
<td></td>
</tr>
<tr>
<td>Others (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>7/30</td>
<td>1/5</td>
</tr>
<tr>
<td>Biological data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycythemia (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet antibodies (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibodies (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin disease (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic idiopathic hilar fibrosis (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver transplant (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time duration before diagnosis (mo)</td>
<td>49 (0 to 480 mo)</td>
<td>71 (0 to 68 mo)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>15 DOD, 4 alive</td>
<td>3 DOD, one alive</td>
</tr>
</tbody>
</table>

Results. “In particular, it is notable that features of both diseases were found in the majority of cases. Capillary proliferation was seen in 24/33 (73%) of cases of venous occlusion, and venous occlusion was found in 4/5 cases of PCH…”

Conclusion. “The coincidental occurrence of PVOD and PCH in our material leads us to conclude that PCH represents a secondary angioproliferative response to pulmonary venous hypertension rather than a separate condition in the majority of cases.” The authors note that “PCH is also reported in association with pulmonary arterial thromboemboli and hereditary hemorrhagic telangiectasia.” The authors suggest that “the term “secondary PCH” or even PCH-like changes should therefore be considered or capillary proliferations seen in association with other disorders, such as PVOD, with the
term “primary PCH” reserved for those extremely rare cases of PCH without recognizable causative background disease.” This is illustrated in the following table:

**Take Home Message.** I essentially agree with this. I note in some of their figures that they are able to recognize small, interlobular venules on an elastic tissue stain. While I don’t disagree with them, I am not sure how they can be so certain.

Purpose. To assess fibroblast foci with semiquantitative scoring methods and compare them with qualitative scoring methods reported in the literature.

Methods. 15 patients with UIP in the setting of a collagen vascular disease compared with 16 patients with IPF. 10 fields at 100X magnification were randomly selected (honeycomb areas excluded) and digital photographs were taken and fibroblast foci were outlined and the area of fibroblast foci calculated (with a software program) and interobserver (between 2 pathologists) was scored and the optimal number of fields needed (10) was determined by comparing fibroblast foci area in 5, 10, and 20 fields in the same case at 2 different time points.

The area of fibroblast foci identified was then compared between the IPF and the CVD group. Their quantitative scoring method was also compared with semiquantitative scoring as described from studies from the Brompton, Denver, and University of Michigan. Interobserver variation was assessed with the kappa coefficient.

Results. Interobserver and intraobserver correlations were high with the quantitative method (r = .877, .898, respectively). The quantitative fibroblast focus score was significantly higher (1.67% +/- 90%) in IPF than in CVD-associated UIP (.39% +/- .24%; p < 0.0001). In this small series the quantitative fibroblast focus score was a significant predictor of survival. The quantitative fibroblast focus score showed a correlation with the semi quantitative scoring previously reported “but patients with the same score assessed by the semi quantitative methods had widely varying scores assess by our method.”
The quantitative fibroblast focus scores and inter and intraobserver agreement are shown in the following graphs.

Survival for CVD-UIP versus IPF are shown in the following graph.

Comment. The Editorial by du Bois (Chest 2006;130:3) discusses this study. The cost ($10,000 for the technology) and time commitment (30-60 minutes of training and 20-30 minutes to assess 1 case) are considerable. Thus use of this technique for research is not unreasonable but it would be impractical for routine patient management.
C. Wright and Churg. Advances in the pathology of COPD. (Histopathology 2006;49:1)

**Purpose.** “This review is designed to help surgical pathologists evaluate the lungs of patients who have clinical manifestations of airflow obstruction so that appropriate clinical-pathological correlations can be performed.” (Methods don’t apply to most surgical specimens).

I am not sure how useful this is to the surgical pathologist for routine diagnosis. The standard definition of emphysema is used along with the traditional terms centriacinar/centrilobular, panacinar and panlobular.

To assess emphysema, it is suggested that inflation of the lung is required. Inflation with formalin is discussed with resection or autopsy specimens. The authors note that “the gold standard of emphysema classification and grading is the paper mounted whole lung (Gough) section by which the severity of emphysema in the test lung is compared with a panel of photographs ranked by severity…” This is not really practical for the surgical pathologist, and I don’t know anyone who does this anymore. The authors note that “no one does a surgical biopsy to diagnose emphysema.” They have aimed their comments at autopsies and resections.

The major forms of emphysema, including centri-acinar, pan acinar, distal acinar (paraseptal) and non-emphysema (simple airspace enlargement) are then addressed. Airspace enlargement with fibrosis is discussed and its distinction from honeycomb lung emphasized. The issue of airspace enlargement with fibrosis in the setting of emphysema in a patient a patient with interstitial lung disease is not really addressed.

Airways disease is discussed next, including large airway disease and small airway disease, primarily in their relation to COPD. It is emphasized the airflow resistance in patient’s with COPD is primarily in small airways less than 0.2 cm in diameter and this process has gone under a variety of names, including small airway disease, etc.

Finally, vascular disease in patients with COPD is discussed. The occurrence of pulmonary hypertension in COPD is noted.

The conclusions of this review are:

1) Evaluation of lungs for the presence of emphysema requires some method of lung inflation.
2) Simple enlargement of airspaces should not be confused with emphysema.
3) Revised airspaces due to fibrosis (honeycombing) should not be confused with emphysema but mild fibrosis in the setting of enlarged airspaces does not preclude a diagnosis of emphysema.
4) In COPD small airways are altered by inflammation and fibrosis.
5) Pulmonary vessels are altered in COPD with increased intima and media in muscular arteries.
II. Other Studies of Significance


**Materials.** 28 patients underwent bronchoscopic resection of endobronchial typical carcinoid tumors.

**Results.** The mean age was 49 years with a range of 11 to 82 years. Sex incidence was roughly equal. The tumors were left-sided in 61%. On average five bronchoscopic resections were required to achieve complete remission. It is not stated what the time was between first and last bronchoscopic resection. The median follow-up was 8.8 years (4.5 to 13.7). At 1 year and 10 years, the disease free survival was 100% and 94% respectively. The 1 and 10 year survivals were 89% and 84% respectively.

**Conclusion.** “In a selected group of patients, proximal polypoid typical bronchial carcinoid tumors can be treated bronchoscopically with good outcome.”

B. Dulu, et al. Prevelance and mortality of acute lung injury in ARDS after lung resection. (Chest 2006;130:73)

**Purpose.** To assess the frequency and outcome in patients with acute lung injury and ARDS after lung resection.

**Materials.** Retrospective review of all records of patients who underwent lung resection and developed ALI or ARDS and required ICU admission for a 3 year period from January 1, 2002 to December 31, 2004.

**Results.** 2,039 patients underwent a total of 2,192 lung resections. 50 (2.45%) developed ALI/ARDS; these included 7.9% of patients with pneumonectomy, 2.9% of patients with lobectomy/bilobectomy, and 0.88% of patients with sublobar resections. The sex incidence was roughly equal and the median age was 68.5 years (range 44 to 88). Median time of presentation to the ICU was 4 days, and median ICU length of stay was 10 days. 40% of the patients died and the highest mortality rate was among those that had had pneumonectomy.

**Conclusions.** “Our results confirm ALI/ARDS after lung resection is associated with a high mortality in patients who require invasive mechanical ventilation and ICU care.” I.e. Sick patients are sick!

Materials. 144 consecutive cases of LCNEC collected over a 16 year period. Diagnosis of LCNEC was based on 1999 WHO criteria. (Note: No central review of slides “although all involved pathologists discussed diagnostic criteria…”). Prior studies reviewed.

Results. 144 cases with a median age of 64 (range 35-80). 27 women and 117 men. 94% current or former smokers.

Stage 1A - 24%, 1B - 27%, 2A - 4%, 2B - 16%, 3A - 22%, 3B - 5%, 4 – 1.4%. 26% had significant postoperative morbidity. 40% of the patients relapsed with sites of recurrence in brain, multiple organs, lung, lymph nodes, bone, other single sites. Survival is shown in the following graph.

The mean follow-up was 27 months. The overall 5-year survival was 43% (52% for stage 1, 59% for stage 2, 20% for stage 3). Patients who “received induction or postoperative chemotherapy tended to survive longer than those who received no chemotherapy (p=0.077). “Poor outcome was predicted by age > 64 years, pathological stage 3, and pneumonectomy.”

Comments. The authors review the literature and their survival data is significantly better than for many of the other reported series in the literature. Their survival approaches that of other forms of non small cell lung cancer.

**Purpose.** “A systematic review and meta-analysis of randomized control trials was conducted to determine whether surgical resection improves disease specific mortality in patients with stages with I-IIIA non small cell lung cancer compared with non-surgical treatment, and compared to efficacy of different surgical approaches.”

**Results.** Only 11 randomized trials fulfilling the authors’ criteria could be identified. None had untreated control groups. Four year survival was superior in patients undergoing resection of stage I-IIIA NSCLC who had complete mediastinal node dissection compared with lymph node sampling (hazard ratio estimated at 0.78).

**Conclusions.** “It is difficult to draw conclusions about the efficacy of surgery for local, regional NSCLC because of the small number of participants studied and the methodological weakness of the trials.” The current evidence suggests that complete mediastinal lymph node dissection does improve survival in patients with stage I-IIIA NSCLC undergoing resection.

**Comment.** Given the relative frequency of lung cancer and the huge number of clinical studies in this area, it is remarkable (and somewhat disconcerting) to find that these authors could find only 11 randomized controlled trials. Indeed the authors state that “in summary, the current evidence from randomized controlled trial neither supports nor discounts the survival benefit of surgery for NSCLC.” They do conclude that more extensive (complete) surgery appears to be superior to less extensive surgery.
III. Prognostic New Markers


“The clinicopathologic features and immunohistochemical expression of levels of Jab1, p27, and Skp2 proteins were studied in 138 specimens from patients who underwent surgical resection for NSCLC.”

**Conclusion.** High Jab1 protein expression was associated with a poor outcome and this protein could be a target for therapy in NSCLC. (Jun activation domain-binding protein 1 [Jab1] is an activator protein that interacts with and potentiates transactivation by c-Jun and promotes cellular proliferation).

B. Seto, et al. Prognostic value of expression of vascular endothelial growth factor and its FLT-1 and KDR receptors in stage 1 non small cell lung cancer. (Lung Cancer 2006;53:91)

60 patients with stage 1 NSCLC who had no prior therapy were selected. The prognostic value of the expression of vascular endothelial growth factor (VEGF) and of the VEGF receptors (VEGFs are fms-like tyronase kinase receptor-1 (flt-1) and kinase insert domain containing receptor (KDR) are assessed in non small cell lung cancer.

Patients with tumors expressing VEGF or KDR tended to have a poorer outcome and those two markers were positively correlated. flt-1 expression was not correlated with VEGF expression or with outcome. Multivariate analysis identified expression of both flt-1 and KDR and VEGF and KDR as possible independent prognostic factors. Tumors expressing both flt-1 and KDR have a greater malignant potential and a poorer prognosis.


The authors address the question of whether loss of expression of the mismatch repair system could lead to cancer refractory to some chemotherapeutic regimens but not others. Immunohistochemical expression of hMLH-1 and hMSH-2 (components of the MMR system) were studied immunohistochemically in 93 advanced non small cell lung cancers receiving chemotherapy that was either cisplatin or oxaliplatin in combination with gemcitabine.

The authors found that loss of hMLH-1 was associated with statistically significant improved survival when compared with normal expression of that protein. Biologic mechanisms that can be implicated in the survival were not identified. The difference in response observed hMSH-2 status in patients receiving oxaliplatin confirmed in vitro sensitivity studies that suggested the growth of cancer cells can be modulated by expression of mismatch repair proteins.
IV. Miscellaneous


**Purpose.** To investigate extracellular superoxide dismutase (ECSOD), the major antioxidant enzyme of the extracellular matrix of human lung, in usual interstitial pneumonia (UIP) in IPF.

**Methods.** Fibrotic areas and fibroblast foci in UIP were assessed for ECSOD by immunohistochemistry and Western blotting. The possibility of naturally occurring mutations in ECSOD were also addressed in studies of peripheral blood in 63 UIP patients and 61 unrelated controls.

Naturally occurring mutations in ECSOD were evaluated using DNA extracted from peripheral blood leukocytes.

The authors also exposed alveolar epithelial cells to tumor necrosis factor alpha and TGF beta and there was a trend toward decreased synthesis of ECSOD.

There has been no prior study of ECSOD in human interstitial lung disease.

**Take Home Message.** Another possible factor in lung injury in UIP: increased oxidant stress.


This is an Editorial regarding five papers in that issue or the ERJ investigating ex vivo cellular interferon-gamma-based blood tests to detect tuberculosis. These tests are based on detecting release of interferon gamma from a patient’s T cells when exposed to mycobacterial antigens.

Two methods are discussed and one appears to have greater sensitivity and the other greater specificity. Both appear to be more sensitive and specific than the tuberculin skin test.

**Purpose.** Carbon content of airway macrophages was studied as a marker of individual exposure to particulate matter and correlated with lung function impairment in children.

**Methods.** 114 children between 8 and 15 years of age were recruited from local schools and carbon content of macrophages (from sputum) was measured in 64 of them. Prior studies have shown that increased exposure to elemental carbon and gases from fuel combustion (and particularly material less than 10 microns in diameter) was associated with impaired growth of lung function.

Lung function was recorded at the same time induced sputum samples were taken. Airway macrophages were visualized light microscopically and the area occupied by black material in each macrophage was assessed. The annual mean level of respirable particulate matter was calculated for each child’s home address using previously described air sampling methods. Representative images of carbon in macrophages are shown in the following figure.

![Representative images of carbon in macrophages](image)

**Results.** There was an inverse dose dependent association between carbon content of macrophages and lung function. Increase carbon content was associated with a reduction in lung function as assessed with FEV1, FVC, and FEF25-75. This association was consistent with epidemiologic studies which have shown a long term effect in respirable particulate matter on lung function in the children. The authors’ data suggested no evidence that reduced lung function itself causes the increased carbon content.
V. Interesting Case Reports


Most previously reported acinic cell carcinomas of the lung had shown no evidence of recurrence. This report documents a recurrent acinic cell carcinoma 20 months after initial surgery.


In an 11 year period the authors identified 12 women with a history of breast cancer and biopsy proven pulmonary carcinoid tumorlets. In all cases the tumorlets were multiple radiologically and interpreted as suspicious for metastases. Misdiagnosis at frozen section was made 3 times.

Conclusion. “Pulmonary carcinoid tumorlets are radiologic and histologic mimickers of pulmonary metastases in patients with a history of breast cancer.” …. and mimickers of malignancy for a variety of other tumors, such as metastatic small cell carcinoma, metastatic carcinoid tumor.


An 83-year-old woman presented with hemoptysis and dyspnea and had a polypoid mass occupying 80% of the lumen of the upper trachea. The tumor proved to be a glomus tumor. Enough said.


A rare event following a rare tumor. A 47-year-old woman had had a stage 2 Wilms’ tumor resected via left nephrectomy at age 30. She presented with a left upper lobe mass and a diagnosis of metastatic Wilms’ tumor was confirmed by transbronchial needle aspiration. The tumor was excised surgically. The patient was alive one month following surgery.

The authors point out that the general prognostic principle for pulmonary metastasectomies is better when there is a long disease free survival from the initial tumor.