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**Articles for Discussion**


**Articles for Notation**


I. Articles for Discussion


Background: There are a number of anecdotal case reports or small series that suggest a relationship between cigarette smoking and eosinophilic pneumonia. Some of this information is an epidemiologic study of the US military in Iraq where 80% of the military personnel who developed acute eosinophilic pneumonia (AEP) had recently begun to smoke.

Patient population: 33 consecutive patients with AEP (by modified Philit criteria) were seen at a consortium of Japanese institutions between 1996 and 2006. 20 patients were retrospectively identified prior to 2002 and 13 patients prospectively identified after 2002.

Demographics: Most patients were young: mean 19.3 years (range 16-29). Can’t tell how many were on a ventilator. Other demographic data below:

Table 1. Clinical Characteristics and Laboratory Findings in Patients With AEP*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female gender, No.</td>
<td>23/10</td>
</tr>
<tr>
<td>Age, yr</td>
<td>19.3 ± 2.7</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>32</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>1</td>
</tr>
<tr>
<td>Underlying atopic diseases, %</td>
<td>15.2</td>
</tr>
<tr>
<td>Duration of symptoms, d</td>
<td>3.5 ± 2.1</td>
</tr>
<tr>
<td>Symptoms, %</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>93.9</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>81.8</td>
</tr>
<tr>
<td>Cough</td>
<td>66.7</td>
</tr>
<tr>
<td>Sputum</td>
<td>3.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>27.3</td>
</tr>
<tr>
<td>Signs, %</td>
<td></td>
</tr>
<tr>
<td>Crackles</td>
<td>30.3</td>
</tr>
<tr>
<td>WBC count, cells/µL</td>
<td>15,614 ± 6,440</td>
</tr>
<tr>
<td>Eosinophil count on hospital admission, cells/µL</td>
<td>623 ± 813</td>
</tr>
<tr>
<td>Maximal eosinophil count, cells/µL</td>
<td>2,050 ± 1,182</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>8.4 ± 5.9</td>
</tr>
<tr>
<td>KL-6, U/mL</td>
<td>131.7 ± 14.8</td>
</tr>
<tr>
<td>( \text{Po}_2 ) on room air, torr</td>
<td>60.3 ± 11.6</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± SD unless otherwise indicated.
Laboratory findings: Leukocytosis – 97%, elevated CRP – 96%, peripheral eosinophilia – 39% on admission (present in all patients at some point during their clinical course).

Smoking habits: All but 1 (97%) were smokers. 21 of 32 were new onset smokers, 2 had restarted smoking after a 1-2 year cessation, and remaining 6 had recently increased the quantity of cigarettes they smoked. For those who had recently started smoking, they had been smoking between 1 day and 2 months before the onset of AEP.

Cigarette smoke provocation tests were positive in all 9 patients tested. An example of a provocation test is shown in the following table.

HRCT scans: Ground glass opacity in 91%, interlobular septal thickening in 82%, airspace consolidation in 64%, pleural effusions and bronchovascular bundle thickening seen in 61% and 72% respectively.

Bronchoalveolar lavage: Marked elevation of eosinophils (52.8 +/- 18.6%); increase in total cell count. CD4/CD8 ratios variable.

Transbronchial biopsy: Done in 24 cases; all specimens showed marked eosinophil infiltration in the alveoli and interstitium.

Treatment: 11 patients (one-third) treated with steroids; all with rapid improvement. 22 patients had spontaneous recovery without treatment following cessation of smoking. 1 patient had a recurrence of AEP when he started smoking again. The remaining patients all quit smoking. No patient had lasting pulmonary impairment. No one died.

Take Home Message: Think about cigarette smoking in cases of eosinophilic pneumonia.
Background: There have been a number of reports of emphysema in HIV-positive individuals and the authors review the literature and postulate mechanisms.

Summary: Bullous disease in HIV-positive patients was first reported in the late 1980s. Subsequently HIV-associated emphysema was recognized and shown to develop in a much shorter period of time than smoking-related emphysema.

A survey of 327 HIV-positive patients revealed a greater incidence of cough, phlegm production, dyspnea, and wheezing compared to controls, independent of tobacco use.

Comparing 1,014 HIV-positive and 713 HIV-negative male veterans, HIV was identified as an independent risk factor for COPD, adjusting for age, pack years smoked, IV drug use, and alcohol abuse. HIV-positive individuals had significantly more emphysematous damage for a given level of tobacco use.

A positive correlation was noted between the presence of pneumocystis colonization and the GOLD stage of COPD. IV drug abusers, known to be a risk for developing HIV, is also a known risk factor for bullous lung disease. IV drug abuse has been associated with panlobular emphysema, predominantly affecting the lower lobes. Malnutrition has been implicated in emphysema.

Experimental Studies:

Epidemiologic, apoptotic, proteolytic, and oxidative stress responses all may be involved in the development of HIV-associated emphysema.

Apoptosis is known to be increased in emphysematous lungs. It is postulated that this causes inflammation and that this could lead to emphysema.

In the setting of HIV there is a persistent lymphocytic alveolitis (> 15% lymphocytes in BAL). These cells often express a cytotoxic T-lymphocyte phenotype resulting in the accumulation of CD8 positive cells in alveolar spaces. This is associated with the production of interferon gamma and alveolar macrophage activation and chronic inflammation which could potentially lead to emphysema. This also appears to cause the release of perforins and proteinases which can directly damage the lung, theoretically leading to emphysema.

It has been shown that HAART therapy decreases the number of CD8 positive cells in alveolar space and this is a potential mitigating factor for the development of emphysema in the setting of HIV infection.

HIV itself may infect alveolar macrophages and cause of an overexpression of matrix metalloproteinases ultimately leading to emphysema.

HIV infection can affect endothelial cell function and angiogenesis and this may be a factor in the development of Kaposi’s sarcoma. In the lung it is postulated that HIV-related apoptotic endothelial cells may trigger aberrant angiogenesis and this could be a factor in emphysema.
Finally, oxidative stress is thought to present in HIV positive individuals because of the lowered systemic levels of glutathione. Decreased levels of glutathione lead to oxidative stress, a potential factor in the development of emphysema.

The putative mechanisms involved in HIV-associated emphysema are summarized in the following diagram.

**Summary:** HIV-affected individuals appear to have a greatly likelihood of developing emphysema unrelated to their smoking status. Colonization by pneumocystis, drug abuse, and malnutrition may play a role in predisposition to emphysema, but HIV itself may be an independent factor via the mechanisms shown in the above diagram.

Background: The authors describe 31 cases of lung disease with features that they thought were distinctly different from bronchiolitis obliterans, BOOP, NSIP, ACIF, BRCIP, and CF. The cases disclosed both “bronchiolar disease and interstitial disease.”

Materials: 31 patients, open lung biopsies, seen between 1990 and 2006; 20 as consultation cases, 13 from MGH. 18M, 13F; symptoms: dyspnea (69%), cough (23%), hemoptysis (8%); duration of dyspnea: days to 4 years. Associated conditions in 12 (miscellaneous in type).

PFTs in 13 cases: restrictive in 8, obstructive in 1, mixed in 4.

Chest x-rays (21 cases): Increased interstitial markings (9), bibasilar haziness (5), bilateral patchy densities (6), focal nodular density (1).

CT scans in 18 cases: Most common findings were “interstitial process” in some regions in 14, diffuse ground glass opacities in 7, patchy alveolar infiltrates in 3, honeycomb fibrosis in 1. Chest x-rays and CTs were normal in 2 patients.

Clinical follow-up available in 19 patients (all treated with steroids): 1 stable, 12 improved after biopsy, 6 became worse. 4 of the 6 died of respiratory complications.

Pathologic findings:

“The most distinctive feature of the disease was noted at low magnification, where elements of BO for BOOP were associated with interstitial disease, which could be delicate or coarse.”

Purulent bronchiolitis in 4 cases; 3 regional, 1 widespread.

Bronchiolitis obliterans (with intraluminal polyps): 100%; regional in 29, widespread in 2.

BOOP (intra-alveolar organization): Present in 19; regional in 16, widespread in 3.

Bronchiolectasis (+- scarring): Present in 13, regional in 12, widespread in 1.

Interstitial fibrosis: Present in all cases, distant from the bronchiolar disease; immature/myxoid in 26 and judged to be slight or moderate in degree in 19.

Interstitial lymphoid infiltrate: Present in all cases; regional in 28, widespread in 3.

Architectural simplification: Present in all cases; regional in 24, widespread in 7.

Honeycomb fibrosis: Scarred airspaces greater than 0.3 cm in diameter in the subpleural regions; present in 7 cases.

Lambertos: Several in “several” cases.

Moderate hemosiderin deposition: Seen in “occasional” cases.

The cases were compared with cystic fibrosis (CF) and a number of similarities were noted although constrictive bronchiolitis was present in all cases of CF. Constrictive bronchiolitis was not seen in the cases of BIP.
Discussion: The authors separate bronchiolar intraluminal polyps (BO) from “intra-alveolar pneumonia known as BOOP.”

The authors separate pneumonitis from pneumonia, preferring to use the term “pneumonitis” to indicate an interstitial process.

The authors suggest they are describing a bronchiolar “disease”. I would suggest they are describing bronchiolar pathology.

The authors suggest their cases “differ from BO or BOOP both by the histologic prominence of interstitial component and the clinical course.” To me the numbers are too small to say anything conclusive.

The authors distinguish their cases from UIP. Fibroblast foci were not identified. They “entertain the possibility that some cases of BIP may represent a facet of NSIP or UIP but with prominent bronchiolar component…”

The authors suggest that some of their cases “might be categorized as NSIP or hypersensitivity pneumonitis by some observers because the pathology does not conform to other commonly accepted patterns.”

The authors distinguish their cases from examples of airway-centered interstitial fibrosis. To me there is very little similarity.

The authors suggest their cases have some similarity to idiopathic bronchiolocentric interstitial pneumonia of Yousem and Dacic.

Take Home Message: The variety of changes described in these cases are so many that I am not sure I feel comfortable recognizing a distinct morphologic phenotype. I suspect I would call most of these cases variants of either NSIP or COP. Some of them may represent examples of chronic bronchiolitis with some secondary interstitial changes.

Methods: A search of several databases revealed 125 articles from which 24 dealt with prognostic evaluation of pleural lavage cytology in patients with lung cancer. 9 articles were excluded for various reasons, and 15 articles were available for analysis. These are shown in the following table.

Some of the identified articles did pleural lavage cytology prior to resection, whereas the remainder did it following resection. As shown below, a positive pleural fluid cytology, either before or after resection, had a significant impact on survival as it appeared to show some correlation with T, N and pleural status. Taken together, the studies suggested that the overall hazard ratio for death for a positive pleural lavage cytology was 5.61 for patient with a positive result versus those with a negative result.

Comment: Interestingly, the risk of a positive cytology appeared to be more correlated with the lymph node status rather than the pleural status based on P0, P1, P2, P3 grading. In the report by Satoh et al., P0 is a tumor with no pleural involvement beyond its elastic layer, P1 is a tumor with extension beyond the elastic layer of the visceral pleura but with no exposure on the pleural surface, P2 is the presence of tumor on the pleural surface but no involvement of the adjacent anatomic structures, and P3 is a tumor that involves adjacent anatomic structures.

The majority of these studies come from Japan but even more prominent is the fact that all the large studies come from Japan and there is only 1 study from the USA and 1 from the UK.
II. Articles for Notation

**Stepwise Progression from Ground Glass Opacity Towards Invasive Adenocarcinoma:**
*Long-term follow-up with radiologic findings.*
*Soda H, et al. in Lung Cancer 2008;60:298-301.*

A case report of a case that showed radiographic ground glass change becoming a solid nodule on CT scan over a period of 4 years. Biopsy eventually showed poorly differentiated adenocarcinoma. He received stereotactic radiotherapy and was alive 3 years after treatment.

I include this simply because there is a nice series of six CT scans showing gradual development of a solid nodule from a region of ground glass change.

**Severe and Recurrent Episodes of Bronchiolitis Obliterans Organizing Pneumonia Associated with Indolent CD4 positive, CD8 positive T-cell Leukemia.**

A patient had a 10-year history of multiple (>50) episodes of sudden respiratory failure with fatigue, high fever, cough, dyspnea, hemoptysis, and myalgias. Transbronchial biopsy was interpreted as BOOP (but did show relatively prominent lymphocytes in the illustration). The patient was initially thought to have pneumonia but did not respond to antibiotics and ultimately showed prompt response to steroids for the multiple episodes. During his second hospitalization he was found to have a high percentage of double-positive (CD4 positive, CD8 positive) T cells in the peripheral blood and BAL (24% and 41%, respectively) and these were ultimately shown to be clonal (i.e. T-cell leukemia).

**Take Home Message:** A report based solely on transbronchial biopsy could be questioned. Hemoptysis is not typical of BOOP. The case does illustrate an unusual presentation for an indolent form of T-cell leukemia. Previous cases of “BOOP” have been reported with indolent leukemia.

**Respiratory Failure with Diffuse Bronchiectasis and Cryoglobulinemia.**

A 48-year-old woman with recurrent bronchitis and dyspnea. She was found to have a monoclonal gammopathy associated with type 1 cryoglobulinemia and a monoclonal immunoglobulin (IgM kappa). Biopsies showed deposition of an amyloid-like material that was negative for Congo Red.

**Take Home Message:** An unusual example of light chain deposition disease. The CT manifestation was as diffuse bronchiectasis with subpleural cystic change without nodules or diffuse interstitial infiltrates. Biopsies confirmed the presence of light chain deposition in the large airways. Plaque-like deposits were noted in the large airways by bronchoscopy.
Sex Differences in Physiological Progression of IPF.

A retrospective review of the University of Michigan’s database of patients with IPF assessing 6-minute walk test and survival. The authors showed that serial changes in maximal desaturation area and overall survival were worse for males than females.

Recent Chronic Beryllium Disease in Residents Surrounding a Beryllium Facility.
(Accompanying Editorial by Redlich and Welch in Am J Respir Crit Care Med 2008;177:936-937).

This is an interesting report looking at the incidence of definite or probable chronic beryllium disease among individuals living in a community near a beryllium manufacturing facility in Redding, Pennsylvania. The authors identified 16 potential cases of potential community-acquired chronic beryllium disease among patients who began residence in the area between 1943 and 1953 and who continued to reside in the area between 1956 until 2001. Among the 16 potential cases (not clear how they got here), 8 cases of community-acquired chronic beryllium disease (5 definite, 3 probable) were identified. 3 of the cases were among family members. 3 of the 8 cases were initially misdiagnosed as some other disease (sarcoid 2, silicosis 1).

Take Home Message: Chronic beryllium disease remains something we should keep in the back of our minds when considering a diagnosis of sarcoidosis.

Severity of Lymphocytic Bronchiolitis Predicts Long Term Outcome after Lung Transplantation.

770 transbronchial biopsies from 341 3-month survivors of lung transplantation between 1995 and 2000 were evaluated. Transbronchial biopsies were scored according to the degree of lymphocytic bronchiolitis (B0, B1, B2, B3, B4) for those with evaluable bronchioles and for which an alternative diagnosis was not made. Multivariate analysis showed that the risk of bronchiolitis obliterans syndrome had the highest association with B grade but that longer ischemic time and recent year of transplant were also risk factors. The risk for lymphocytic bronchiolitis was independent of acute vascular rejection.

Update in Lung Transplantation 2007
Corris PA and Christie JD. Am J Respir Crit Care Med 2008;177:1062-1067.

An update that includes outcomes, recipient selection, donor evaluation and management, primary graft dysfunction and ischemia/reperfusion injury, acute rejection, bronchiolitis obliterans syndrome, and other problems encountered.
Is Matrix Metalloproteinase-7 Specific for Idiopathic Pulmonary Fibrosis?

The background for this study is the fact that there are a number of reports suggesting that MMP-7 is a key molecule in the pathogenesis of IPF. The authors compared the expression of MMP-7 in UIP and COP and controls in BAL fluid. Diagnoses were based on surgical lung biopsies and BAL fluid was obtained within 2 weeks of the biopsy. BAL fluid was evaluated for MMP-2, MMP-7, MMP-9, TIMP-1, and TIMP-2.

There was no difference in BAL fluid MMP-7 levels between UIP and COP but both showed higher levels than normal controls. In addition, the pattern and degree of MMP-7 expression was similar in IPF and COP. In contrast, MMP-2 levels were higher in COP compared to IPF and MMP-7 levels were higher in IPF than COP.

MMP-2, TIMP-1, and TIMP-2 levels were higher in COP than IPF, whereas MMP-9 was higher in UIP compared to COP. The MMP-2/TIMP-2 ratio was higher in COP in contrast to the higher ratio of MMP-9/TIMP-1 in IPF. MMP-7 was weakly correlated with MMP-2.

Comment: There is probably something significant with MMP and TIMP expression in IPF but this paper leaves the waters still somewhat murky as to exactly what significance these play in IPF.

Population-Based Epidemiology in Prognosis of Mesothelioma in Leeds, UK.

A population-based study, retrospective from 2002 and 2003, and prospective from 2004-2005, looking at all patients who died with a diagnosis of mesothelioma in Leeds, UK.

Demographics: 77% male, median age 74 (range 36-93); survival from diagnosis: 8.9 months; 92% with histologic diagnosis and 8% cytologic diagnosis; 85% had definite or probable exposure to asbestos.

Conclusions: Survival is worse than in selected series. Thoracoscopic pleurodesis was associated with fewer recurrences than “bedside pleurodesis.”

11 cases of LCNEC that had had prior fine needle aspiration cytology. All cases were completely examined histologically.

Demographics: All male, mean age 65 (55-73).

Original cytologic diagnoses: NSCC -5, LCC with NE features – 3, undifferentiated Ca – 2, small cell Ca – 1.

Key cytologic features: Hypercellular smears with numerous single medium to large cells; naked nuclei; subset of cells with cytoplasm; three-dimensional groups of variable size; nuclear pleomorphism; molding and mitotic figures; necrotic background; peripheral nuclear palisading; rosette-like structures.

<table>
<thead>
<tr>
<th>Table 2. Cytomorphologic Features</th>
<th>Morphologic variable</th>
<th>No. of cases/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent cellular dissociation</td>
<td>9/11</td>
<td></td>
</tr>
<tr>
<td>Nuclear molding</td>
<td>9/11</td>
<td></td>
</tr>
<tr>
<td>Hypercellularity</td>
<td>8/11</td>
<td></td>
</tr>
<tr>
<td>Abundant naked nuclei</td>
<td>7/11</td>
<td></td>
</tr>
<tr>
<td>Nuclear palisading</td>
<td>6/11</td>
<td></td>
</tr>
<tr>
<td>Lymphoid cells</td>
<td>6/11</td>
<td></td>
</tr>
<tr>
<td>Necrotic background</td>
<td>6/11</td>
<td></td>
</tr>
<tr>
<td>Rosette-like structures</td>
<td>5/11</td>
<td></td>
</tr>
<tr>
<td>Large cellular aggregates</td>
<td>5/11</td>
<td></td>
</tr>
<tr>
<td>Crushing artefact</td>
<td>5/11</td>
<td></td>
</tr>
</tbody>
</table>

The authors include a table of differential diagnoses:

<table>
<thead>
<tr>
<th>Table 4. Differential Diagnosis</th>
<th>Feature</th>
<th>LCNEC</th>
<th>SCC</th>
<th>NSCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Intermediate to large</td>
<td>Small</td>
<td>Large</td>
<td></td>
</tr>
<tr>
<td>Prominent cellular dissociation</td>
<td>Yes</td>
<td>Yes</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Large cellular aggregates</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Nuclear palisading</td>
<td>Yes</td>
<td>Rare</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Nuclear molding</td>
<td>Yes</td>
<td>Yes</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Crushing artefact</td>
<td>Possible</td>
<td>Yes</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Rosette-like structures</td>
<td>Yes</td>
<td>Possible</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Present</td>
<td>Rarely seen</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Variable</td>
<td>Rare</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

LCNEC indicates large cell neuroendocrine carcinoma; SCC, small cell carcinoma; NSCC, nonsmall cell carcinoma.

Comment: The authors have identified traditional criteria that can be ascribed to "neuroendocrine" lesions. I am not sure how reliable and discriminatory these would be in a prospective study.
Infections in Lung Allograft Recipients: Ganciclovir Era.

202 patients who received 208 lung allografts between 1990 and 2005 were studied. A total of 178 patients developed 859 infections with 944 pathogens identified. 559 infections (65%) were pulmonary, with a majority of pathogens being bacterial (84%); the majority of these were due to *Pseudomonas aeruginosa*. Fungal infections comprised approximately 11% with Aspergillus being most frequent. CMV was seen in 4.3% of respiratory infections. These are summarized in the following tables:
Conclusion: There is a notable decrease in CMV in the Ganciclovir era. Filamentous fungi are becoming proportionally more prevalent.

Comment: A nice review of infection in the lung transplantation population.

**EGFR FISH vs. Mutation: Different Tests, Different Endpoints.**


A review of assessing EGFR status by FISH gene copy number vs. mutational analysis. Mutational analysis is better at identifying responders (i.e. those whose tumors shrink), whereas FISH is probably the best for patient selection when the mean endpoint is survival (in which case tumor shrinkage may not be apparent). FISH was the only EGFR test significantly associated with prolonged survival in large randomized trials with control arm of placebo. The author also noted that patients with clinical or biologic predictors for TKI sensitivity (e.g. nonsmokers, women, Asian, etc.) also survived longer when exposed to standard chemotherapy, representing a confounder when trying to assess the effects of TKI therapy.