PULMONARY PATHOLOGY JOURNAL CLUB
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I. DISCUSSION ARTICLES

- **Background:** Hydrophilic coatings are used on intravascular devices to facilitate ease of manipulation and to minimize complications.
- **Purpose:** The authors report a case of embolization of hydrophilic coating of a central venous catheter to the lung that resulted in cavitary lung nodules in a 34-year-old woman.
- **Histologic features:**
  - Angiocentric granulomas with multinucleated giant cells.
  - Microabscesses containing numerous neutrophils and scattered eosinophils.
  - Numerous ill-defined serpiginous structures: the material is amorphous, nonrefractile, nonpolarizable, and pink-purple to blue-gray with H&E staining.

- **Take-home message:** Be aware of this embolic foreign material.

- **Purpose/Methods:** The authors undertook a 20-year (1988-2007) retrospective review of all autopsies performed on hematopoietic stem cell transplant (HSCT) recipients at the University of Minnesota Medical Center, with emphasis on infections, especially fungal infections, as the cause of death.

- **Results:**
  - The most common causes of death were pulmonary complications, occurring in 247 (62.5%) of 395 cases.
  - In 178 cases (45.1%), microorganisms (viral, bacterial, and/or fungal) were documented at autopsy in one or more organs and contributed to the cause of death.
  - Fungal infections were found in 23.5% of cases, but their frequency as a cause of death decreased throughout this study, from 30.3% in the 1988-1992 period to 10.9% in the 2003-2007 period.

- **Take-home message:**
  - Infections in general and, especially, invasive fungal infections continue to be a significant cause of death in HSCT recipients.
  - However, a decline in the rate of invasive fungal infections as a cause of death has occurred during the 20 years covered by this study.

- **Purpose:**
  - To determine the frequency of sarcoidal reactions in lymph nodes of patients with NSCLC.
  - To report the frequency of co-involvement of sarcoidal reactions with metastatic NSCLC in regional lymph nodes.

- **Methods:**
  - The authors prospectively examined 50 consecutive patients undergoing EBUS-TBNA for staging of suspected or confirmed NSCLC.
  - The authors also performed a retrospective chart review of 187 patients undergoing lobectomy or mediastinoscopy for NSCLC.

- **Results:**
  - EBUS-TBNA (n = 50) revealed non-necrotizing granulomas in one patient and metastatic NSCLC in 45 patients.
  - Surgical lymph node sampling (n = 187) revealed non-necrotizing granulomas in 8 patients (4.3%) with all lymph nodes free of metastatic NSCLC. Four of these patients were pre-operatively assessed as Stage III (cN2/3). None had a prior history of sarcoidosis or other granulomatous diseases. All eight patients remain alive and recurrence-free.

- **Take-home message:**
  - Sarcoïdal reactions are seen in 4.3% of all patients with NSCLC. Metastatic involvement by NSCLC is not seen in lymph nodes exhibiting sarcoïdal granulomatous reactions.
  - Non-necrotizing granulomas revealed by EBUS-TBNA of lymph nodes during staging of NSCLC should serve to indicate the absence of lymph node metastases.

- **Purpose:** To understand the characteristics of peripheral small-sized lung cancers with positive mediastinal lymph nodes.
- **Methods:** The authors studied 360 patients with small-sized lung lesions with a maximum diameter of 2 cm or less.
- **Results:**

<table>
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<td>Comparison of patient characteristics according to pN status.</td>
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AD, adenocarcinoma; BAC, bronchioloalveolar carcinoma; CEA, carcinoembryonic antigen; LA, large-cell carcinoma; SD, standard deviation; and SQ, squamous-cell carcinoma.

- 21 patients (5.8%) had a positive mediastinal lymph node.
- Among them, 17 patients had lung lesions larger than 1.5 cm.
- No mediastinal nodal involvement was found in patients with squamous cell carcinomas.
In contrast, mediastinal nodal involvement was significantly common in patients with poorly differentiated carcinoma (P = 0.004) and high serum carcinoembryonic antigen levels detected during preoperative evaluation (P = 0.006).

None of the 14 patients with upper lobe tumor had a positive subcarinal lymph node.

Lower lobe tumors frequently developed extensive multiple-level involvement, which included the upper mediastinum.

Radiographic evaluation of pN2 patients using computed tomography revealed a total absence of ground-glass opacity, or the presence of a small area of ground-glass opacity.

**Conclusions:** Most small-sized non-small cell lung cancer cases with mediastinal lymph node metastasis were poorly differentiated adenocarcinoma without ground-glass opacity on CT.

- **Purpose:** The objective of the current study was to evaluate the risk of local failure (LF) after surgery for stage I to II nonsmall cell lung cancer (NSCLC) and assess surgical and pathologic factors affecting this risk.

- **Methods:** The records of all patients who underwent surgery for T1 to T2, N0 to N1 NSCLC at Duke University between 1995 and 2005 were reviewed.

- **Results:**
  - For all 975 consecutive patients, the 5-year actuarial risk of local and/or distant disease recurrence was 36%.
  - First sites of failure were local only (25%), local and distant (29%), and distant only (46%).
  - The 5-year actuarial risk of LF was 23%.
  - On multivariate analysis, squamous/ large cell histology and sublobar resections were found to be independently associated with a higher risk of LF.

- **Take-home message:**
  - Greater than half of disease recurrences after surgery for early stage NSCLC involved local sites.
  - Pathologic factors may help to distinguish those patients at highest risk.
II. ARTICLES FOR NOTATION ONLY

Non-neoplastic diseases


- **Purpose:** To evaluate the performance of acid-fast bacilli smear and mycobacterial culture on sputum and non-sputum specimens for TB diagnosis in a survey of HIV-infected patients.

- **Methods:** In Thailand and Vietnam, the authors enrolled people with HIV. Patients provided three sputum, one urine, one stool, one blood, and, for patients with palpable peripheral adenopathy, one lymph node aspirate specimen for acid-fast bacilli microscopy and mycobacterial culture on solid and broth-based media. Any patient with at least one specimen culture positive for Mycobacterium tuberculosis was classified as having TB.

- **Results:**
  - Of 1,060 patients enrolled, 147 (14%) had TB.
  - Of 126 with pulmonary TB, the incremental yield of performing a third sputum smear over two smears was 2%.
  - 90 (71%) patients were detected on broth-based culture of the first sputum specimen, and an additional 21 (17%) and 12 (10%) patients were diagnosed with the second and third specimens cultured.
  - Of 82 lymph nodes cultured, 34 (42%) grew M. tuberculosis.
  - In patients with two negative sputum smears, broth-based culture of three sputum specimens had the highest yield of any testing strategy.

- **Conclusions:**
  - In people with HIV living in settings where mycobacterial culture is not routinely available to all patients, a third sputum smear adds little to the diagnosis of TB.
  - Broth-based culture of three sputum specimens diagnoses most TB cases, and lymph node aspiration provides the highest incremental yield of any nonpulmonary specimen test for TB.

- **Purpose:** To examine clinical, epidemiological, and geographic factors associated with advanced pulmonary TB.

- **Methods:** Pulmonary tuberculosis cases in persons older than 15 years of age reported to the U.S. National Tuberculosis Surveillance System with advanced disease (cavitation on chest radiograph and acid-fast bacilli smear-positive sputum result) were compared with those without advanced disease.

- **Results:**
  - There were 35,584 cases of advanced pulmonary tuberculosis (APT) and 125,077 cases of non-APT reported from 1993 through 2006.
  - Proportions of pulmonary TB cases with APT increased from 18.5% in 1993 to 26.1% in 2006.
  - The association between APT and low TB incidence has grown incrementally since 2000.
  - The proportion of APT increased greatest among whites (65.4%), the employed (63.3%), and the U.S. born (59.2%).

- **Take-home message:**
  - This study highlights the need for TB diagnosis at early stages of the disease to minimize APT and decrease the risk of transmission.
  - Additional efforts should concentrate on reducing time to treatment initiation in low-incidence areas and among groups traditionally seen as being at low risk for TB disease.


- This is an introduction by Dan Visscher and Jeff Myers to a Special Section in the “Archives” edited by the same authors.


- This is a review article by Amir Lagstein and Jeff Myers in the “Archives” Special Section titled “New Frontiers in Pathology”.


- In this review, the authors discuss mechanisms for the pathogenesis of pulmonary fibrosis.
  - Initial hypothesis:
    - chronic inflammation is the cause of pulmonary fibrosis.
  - Subsequent hypothesis:
    - epithelial injury and impaired wound repair is the etiology of fibrosis without preceding inflammation.
  - Refinement of these hypotheses:
    - the alveolar-capillary barrier basement membrane (BM) plays an important role in conserving the architecture of the injured lung;
    - failure of reepithelialization and reendothelialization of the BM results in pathologic fibrosis;
    - transforming growth factor-beta is necessary but not sufficient to fibrosis of the lungs;
    - persistent antigens may play a role in the pathogenesis of usual interstitial pneumonia; and
    - epithelial-to-mesenchymal transformation and bone marrow-derived progenitor cells contribute to the pathogenesis of lung fibrosis.


- Findings of this review article include:
  - While the nonspecific interstitial pneumonia pattern predominates in most forms of connective tissue-associated ILD, studies in patients with RA-associated ILD (RA-ILD) suggest that the usual interstitial pneumonia (UIP) pattern is more common in this patient population.
  - High-resolution CT (HRCT) scans appear accurate in identifying UIP pattern in many patients with RA-ILD.
  - Although the data are limited, UIP pattern appears to predict worse survival in RA-ILD patients.

• **Background:** Lymphangiogenesis has been determined to play a role in structural remodeling in diffuse alveolar damage. However, the mechanism of lymphangiogenesis remains unclear.

• **Purpose:** The aim of this study is to investigate the cellular mechanisms of lymphangiogenesis in diffuse alveolar damage, focusing on the roles of macrophages.

• **Methods:**
  o Formalin-fixed and paraffin-embedded lung tissues from 13 autopsy cases with idiopathic diffuse alveolar damage were used.
  o D2-40 and CD68 antibodies were used as markers for lymphatics and macrophages.

• **Results:**
  o Immunohistochemistry showed the aggregation of numerous CD68+ macrophages around newly formed lymphatics in the intraalveolar fibrotic lesions in the proliferative stage, and some of the CD68+ macrophages were colocalized with the lymphatic endothelium. These macrophages were characterized by the expression of vascular endothelial growth factor-C.
  o The CD68+ macrophages around the newly formed lymphatics coexpressed CCR7. Dual immunostaining showed the coexpression of CCL19 - a ligand for CCR7 - on the lymphatic endothelium.

• **Take-home message:** Macrophages may participate in lymphangiogenesis in diffuse alveolar damage.

- **Purpose/Methods:**
  - The authors performed a clinicopathologic investigation of 26 autopsy cases of diffuse alveolar damage. Three of the cases were diagnosed as acute interstitial pneumonia.
  - Immunohistochemical staining for types I and IV collagen, α-smooth muscle actin, and Ki-67 was carried out.

- **Results:**
  - Diffuse alveolar damage due to severe infection:
    - all 7 patients showed multiple organ dysfunction;
    - 2 of 7 patients showed interstitial myofibroblast proliferation.
  - Diffuse alveolar damage due to drug toxicity:
    - 3 of 16 patients showed multiple organ dysfunction;
    - 15 of 16 showed interstitial myofibroblast proliferation.
  - Acute interstitial pneumonia:
    - 3 of 3 patients showed no multiple organ dysfunction;
    - 3 of 3 patients showed marked interstitial myofibroblast proliferation.

- **Take home message:**
  - The authors conclude: “These results suggest that the pathophysiologic mechanism of diffuse alveolar damage caused by severe infection is one of systemic circulation disturbance, although the mechanism underlying diffuse alveolar damage due to tumor with chemotherapy or drug toxicity appears to involve interstitial pneumonia-like lesions that are similar to acute interstitial pneumonia”.
  - To me, this article does not make much sense.
Neoplastic diseases

• **Background/Purpose/Methods:**
  - Two randomized controlled trials of lung cancer screening initiated in the 1970s, the Johns Hopkins Lung Project and the Memorial Sloan-Kettering Lung Study, compared 1 arm that received annual chest X-ray and 4-monthly sputum cytology (dual-screen) to a second arm that received annual chest X-ray only.
  - The authors estimated the efficacy of lung cancer screening with sputum cytology, using combined data from these trials (n = 20,426).

• **Results:**
  - Over 1/2 of squamous cell lung cancers diagnosed in the dual-screen group were identified by cytology; these cancers tended to be more localized than squamous cancers diagnosed in the X-ray only arm.
  - After 9 years of follow-up, lung cancer mortality was slightly lower in the dual-screen than in the X-ray only arm.

• **Take-home message:** These data are suggestive of a modest benefit of sputum cytology screening.


• This is a review article, discussing key technical issues and standardized reading strategies for the EGFR FISH assay of non-small cell lung cancer.


• Review article.

- **Purpose:** To explore the role of two angiogenic factors (VEGF and BMP-2) in carcinogenesis.

- **Results:**
  - Expressions of VEGF, BMP-2 and BMP-4 mRNAs were significantly higher (7.1-fold, 25.6-fold and 2.3-fold, respectively) in lung cancer samples than in adjacent normal lung tissues (real-time RT-PCR).
  - Analysis based on the Pearson’s correlation coefficient indicated positive correlation between VEGF and BMP-2 gene expression; no significant correlation between VEGF and BMP-4 gene expression was found.
  - Significant differences in the serum levels of VEGF between patients with T1 tumors and patients with T2, T3 or T4 tumors were observed; patients with T2, T3 and T4 tumors, respectively, had 1.6-fold, 1.8-fold and 2.3-fold greater serum levels of VEGF than their peers with T1 tumors.

- **Take-home message:**
  - The authors emphasize the importance VEGF and BMP-2 in the evaluation of lung cancer patients.
  - The article is poorly written.

- **Background:** Vascular endothelial growth factor (VEGF) and its receptor vascular endothelial growth factor receptor 2 (VEGFR2) seem to play key roles in tumor-induced angiogenesis.
- **Purpose:** The purpose of this study was to correlate immunohistochemical expression of VEGF-A and VEGFR2 with patient characteristics and survival.
- **Methods:**
  - Paraffin-embedded histological material from 102 patients operated for NSCLC was included in the study.
  - Sections were incubated with primary monoclonal antibodies to VEGF-A and VEGFR2.
  - Immunohistochemical staining was assessed semi-quantitatively by estimating the percentage and intensity of tumor cells stained.
  - Kaplan–Meier survival curves were generated to evaluate the significance of VEGF-A and VEGFR2 expression for the prognosis.
- **Results:**
  - VEGF-A and VEGFR2 expression was observed in the majority of NSCLC patients.
  - VEGF-A expression showed a correlation to histological type with increased expression in adenocarcinomas as compared to squamous cell carcinomas.
  - There was no statistically significant correlation between VEGF-A and VEGFR2 expression and age, gender or stage at diagnosis.
  - There was no relation between expression of VEGF-A and VEGFR2.
  - There was no relation between VEGF-A and VEGFR2 expression and survival.
- **Conclusion:** VEGF-A and VEGFR2 are expressed in NSCLC, but the immunohistochemical expression of VEGF-A and VEGFR2 has no prognostic significance in NSCLC.


- **Case report.**