I. Discussion articles
Wong DWS, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115:1723-33.

II. Original work neoplasms

III. Original work non-neoplastic

IV. Reviews of note

V. Case reports


I. Articles for Discussion

Background: Several questions remain about MLN’s including incidence, significance, derivation and certain morphologic features. Most prior studies were autopsy based. This study was undertaken to evaluate MLNs in a wide variety of specimens to characterize incidence, distribution, relation to age, underlying disease, histogenesis, and to perform a large number of IHC.

Methods: 500 surgical bx, 25 extensively sampled lobectomies, 20 resections for pneumothoraces in patients less than 30 years, and 92 pediatric autopsies.

Results: 186 MLNs were identified in 81 cases, 69 of 500 (13.8%) of surgical lung biopsies, 12/25 (48%) of lobectomies. No MLNs found in patients less than 30 years of age from pneumothoraces or autopsies. Youngest patient overall was 22 years identified in a surgical lung biopsy.

<table>
<thead>
<tr>
<th>Associated Conditions</th>
<th>Cases With MLNs</th>
<th>Incidence (Cases With MLNs/Total (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic interstitial lung disease</td>
<td>36</td>
<td>239 15</td>
</tr>
<tr>
<td>UIP</td>
<td>12</td>
<td>112 11</td>
</tr>
<tr>
<td>Non-UlP</td>
<td>15</td>
<td>92 16</td>
</tr>
<tr>
<td>RBILD/DIP</td>
<td>9</td>
<td>35 26</td>
</tr>
<tr>
<td>Organizing pneumonia/BOOP</td>
<td>5</td>
<td>59 9</td>
</tr>
<tr>
<td>Diffuse alveolar damage/acute lung injury</td>
<td>1</td>
<td>26 4</td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
<td>5</td>
<td>30 17</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>2</td>
<td>25 8</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>9</td>
<td>29 31</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>4</td>
<td>17 24</td>
</tr>
<tr>
<td>Thromboembolic disease/infarcts</td>
<td>5</td>
<td>12 42</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>11</td>
<td>92 12</td>
</tr>
<tr>
<td>All conditions</td>
<td>69</td>
<td>500 13.8</td>
</tr>
</tbody>
</table>

BOOP indicates Bronchiolitis obliterans-organizing pneumonia; DIP, desquamative interstitial pneumonitis; MLNs, meningothelial-like nodules; RBILD, respiratory bronchiolitis-associated interstitial lung disease; UIP, usual interstitial pneumonia.

Most MLNs measured 1-2 mm, largest 4 mm. They were solitary in 59% and multiple in 41%. Eight cases had 5 or more nodules. There appeared to be no relationship of MLNs to blood vessels.

IHC: 100% positive for PR, CD56 (n=18) and EMA (n=11). Negative for other markers including CD31, TTF-1, keratin, ER, HMB-45.
Conclusions: The 13.8% incidence of MLNs in surgical lung biopsies is higher than 0.07% to 4.9% reported in previous autopsy series. Related to chronic lung disease, stretching, hypoxia, parenchymal destruction, etc.

MLNs in 48% of consecutive lobectomies also higher than reported incidence of 1.1 to 9.5% of lung resections for cancer. Related to concomitant chronic lung disease.

Highest incidence of MLNs in surgical biopsies was seen in cases with thromboembolic disease/infarcts and RBILD/DIP (42% and 26% respectively).

CD56 reactivity has not been previously reported but has been identified in meningiomas. Could occasionally cause confusion with carcinoid tumorlets.

Addendum: MLN found in biopsy from 10-year-old boy with a long history of severe chronic lung disease.

Comments:

See article in Human Pathology (Mizutani E, et al; Human Pathology, 2009; 40:678-82) which represents another large series of MLN’s.

**Introduction:** There have been few studies quantitating T-cell populations in lung allograft biopsies in acute rejection.

This study was undertaken to determine whether T-cell density differs among normal biopsies, those with AR and those with infection, and whether immunophenotyping aids in the identification of the cause of perivascular inflammation, the hallmark of AR in the lung.

**Methods:** Consecutive TX BX from 2004-2006 prospectively stained with antibodies to CD3 and CD4. All biopsies had at least 5 parenchymal pieces; ISHLT criteria

-- Surveillance biopsies performed at months 1, 3, 6 and 12.
-- Diagnostic biopsies conducted for new signs or symptoms of respiratory disease.

Quantitation of lymphs was performed independently by two authors and divided into two compartments “alveolar septa and bronchial epithelium”. (? Bronchiolar). Biopsies were categorized into 6 groups: control, surveillance, suspected rejection, suspected infection, suspected OB and post-op graft failure.

**Results:**

Figure 5

![Graph A](image1)

**Alveolar Lymphs by bx indication**

![Graph B](image2)

**Alveolar lymphs by pathology dx**

![Graph C](image3)

**Alveolar lymphs by rejection grade**

Figure 6
There was an increase in T-cells in infection and rejection groups for all three markers without significant difference between infection and rejection. In contrast, in airways mucosa there was a significant increase in rejection B but only a mild increase in the infection group \((P < .0001)\).

In 55 cases with preliminary diagnoses rendered without IHC data there was a change in A grade diagnosis. In 4 cases (7%) perivascular infiltrates were noted on IHC and not seen on routine stains. One case was upgraded from A0BX to A1BX, one case upgraded from favor infection to A2B3 and two cases upgraded from nonspecific to A1B0. One case was downgraded from A1B0 to A0B0 and two cases were upgraded from BX to B1 as a result of airway epithelium appearing on deeper cuts. Two cases signed out as non specific inflammation were diagnosed as A0B1 and A0B2 with use of IHC.

**Conclusion:** IHC may help in identifying perivascular infiltrates and demonstrates increased intraepithelial T-cells even in low grade type B rejection. Type B rejection assessed quantitatively is more specific than type A rejection in comparison to infection.

**Comments:** The images in this manuscript are fine but the presentation of the data lacks simplicity and clarity. The graphs would be useful except the colors mentioned in the legend were not actually published in color (but are present if you print this handout in color or view it online!)

**Background:** The authors had two prime aims 1) to better evaluate the relationship between EGFR and K-ras mutational analysis and histologic features in a large group of reclassified lung neoplasms (418) according to WHO criteria; and 2) to test the predictive value of a scoring system for response to patients treated with EGFR-TKIs (tyrosine kinase inhibitors).

**Methods:** 418 cases of primary lung tumors were reviewed and reclassified. 313 were surgical resection cases, the remaining 99, large bx’s. Molecular analysis of EGFR exons 18, 19 and 21, and K-ras exon 2 performed by direct sequencing PCR. A scoring system was developed.

One point given for female sex, never smoker, adenocarcinoma type, Asian ethnicity, and presence of EGFR mutations. A point was subtracted for current smoking or K-ras mutation. Score zero given for male gender, ethnicity other than Asian, or wild type molecular workup. Final score, therefore, could range from -2 to +5. Scores were combined into three groups: low probability (-2 to -1), intermediate probability (0 to +1), and high probability (+2 to +4).

**Results:** Among the 418 patients, 154 were treated with EGFR-TKI.

**General observations:**
- Salivary gland, mucin rich, NE tumors do not harbor EGFR mutations. A subset of nonmucinous ADCA is related (not necessarily BACs) to EGFR mutations.
- Few K-ras mutations detected in high gr. NE tumors (3/20, 15%, LCNC, and 1/6, 17%, SCLCs) and none in carcinoids. K-ras mutations seem to characterize undifferentiated lung tumors such as LCC (3/6, 50%) & sarcomatoid ca’s (41%).
- 10-13 mucinous BACs, 4/9 colloid and signet-ring carcinomas, 3/9 solid adenocarcinomas, and 1 mixed adenocarcinoma) showed K-ras mutations.

**Main point:** The 3 probability groups significantly correlated with response to EGFR TKIs. Of note the addition of molecular results did not significantly change the predictive value of the scoring system.

**Conclusions:** Probably the most interesting conclusion is that the scoring system, although not perfect in predicting efficacy of EGFR-TKIs, may be a practical and satisfactory compromise when molecular testing is not available.

**Comments:** This is actually a well done study. The data is clearly presented and easy to follow. It is actually a very nice summary of the state of the art.

5. Wong DWS, Leung ELH, So KKT, Tam IYS, Sihoe ADL, Cheng LC, Ho KK, Au JSK, Chung LP, Wong MP, and University of Hong Kong Lung Cancer Study Group. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115:1723-33.

**Background:** Fusion genes are common on lymphoid and soft tissue malignancies, but apart from prostate carcinoma it is where in solid tumors. The echinoderm microtubule- associated protein like 4 gene (EML4) and the anaplastic lymphoma kinase gene (ALK) transforming fusion gene has just been identified in some lung cancers. It is formed by a small inversion within chromosome 2p and it results in constitutive dimerization of the kinase domain and thereby a consequent increase in the catalytic activity. The two studies summarized below both evaluated a large series of patients with lung carcinoma to determine what potential associations might exist between EML4-ALK positive tumors, with the ultimate goal of treating such patients with EML4-ALK specific inhibitors.

### EML4-ALK Lung Cancers

<table>
<thead>
<tr>
<th>Tumor Types</th>
<th>Inamura</th>
<th>Wong</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>363</td>
<td>266</td>
</tr>
<tr>
<td>ADCA</td>
<td>253</td>
<td>209</td>
</tr>
<tr>
<td>ADSQ</td>
<td>7</td>
<td>Other/ADSQ/MEC 12</td>
</tr>
<tr>
<td>SQ</td>
<td>72</td>
<td>34</td>
</tr>
<tr>
<td>LCC</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>SCC</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>EMLR-ALK (+)</td>
<td>3%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Pap ADCA</td>
<td>5%</td>
<td>ADCA 11%</td>
</tr>
<tr>
<td>Acinar ADCA</td>
<td>6%</td>
<td>MEC 1%</td>
</tr>
<tr>
<td>ALK-1 ⊕ IHC</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Age</td>
<td>Younger (&lt;50)</td>
<td>Younger</td>
</tr>
<tr>
<td>Gender</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Light/none</td>
<td>Light/none</td>
</tr>
<tr>
<td>Inamura</td>
<td>Wong</td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td>EGFR mutations</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>KRAS mutations</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>TP53 mutations</td>
<td>Rare</td>
<td>None</td>
</tr>
<tr>
<td>TTF-1 immunoreactivity</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** EML4-ALK fusion gene was present in various histologic types of non-small cell lung cancer (mostly ADCA) and occurred mutually exclusive of EGFR and KRAS mutation. It was also associated with young age and light or non smoking.

**Comment:** I actually found both of these papers well-written, and, despite the fact that I was initially put off by a gene about which I knew nothing, they succeeded in helping educate me.
II. Original Work Neoplasms


**Background:** GATA transcription factor family has a potential role in carcinogenesis. It consists of six conserved zinc finger transcriptional factors binding to consensus DNA sequence (A/T) GATA (A/G) in their target gene promoters and enhancers. GATA6 regulates gene transcription within respiratory epithelium. Expression of GATA6 and TTF1 is subject to precise cell specific and developmental regulation during lung morphogenesis. The close cooperation between transcription GATA6 and TTF1 has not been investigated in pleural tumors or in their prognosis and differential diagnosis.

**Methods:** Normal pleura and lung and sixty-three mesotheliomas were studied immunohistochemically with antibodies to GATA6 and TTF1.

**Results:** Nuclear immunoreactivity for GATA6 was stronger and more frequent in MM than metastatic pleural adenocarcinoma. Prognosis was better for patients with GATA6 expression when compared to those with no GATA6 expression (P=0.002). In subgroup analysis the difference was significant in epithelial and sarcomatous mesotheliomas.

TTF expression was not correlated with GATA6 expression in metastatic pulmonary adenocarcinoma samples and was negative in all pleural mesotheliomas.

**Conclusions:** These results suggest that GATA6 plays a role in pleural malignancies, predicting longer survival in subgroups of MM.

**Comment:** This is probably the first study showing that there is a prognostic marker which may be useful in mesothelioma.

Among 2770 patients with non-small cell lung carcinoma that underwent resection between 1995 – 2005 a gender difference in survival was demonstrated for women over men. There was no survival advantage in “propensity matched gender pairs” but a gender difference was observed for adenocarcinoma subsets suggesting that pathobiology of adenocarcinoma in women is different from that of men.

Comment: I’m not sure how applicable this is to the general group of patients with lung carcinoma since only surgical resection specimens were considered.

This is a clinical radiologic study comprising a group of 40 patients with ground-glass opacities.

The authors used a stepwise approach using oral antibiotics and follow-up CT scan 40-60 days later with CT guided core biopsies of residual lesions. They thought that their approach increased the diagnostic specificity and reduced time to definitive diagnosis in this group of patients.

As I think we all know anyway, their conclusions were that “malignant ground-glass opacities have a fairly typical appearance, but some benign lesions closely mimic their malignant counterparts”.

This study analyzed the usefulness of 2 newly described markers, X-linked inhibitor of apoptosis protein (XIAP) and an isoform of the glucose transporter, GLUT-1, in comparison to epithelial membrane antigen in the distinction between benign and malignant mesothelial processes.

**Methods**: The performance of each marker was compared using receiver operator characteristic curve analysis.

EMA demonstrated the best accuracy with an area under the curve of 0.91 as compared to XIAP (0.67), GLUT-1 monoclonal (0.74), and GLUT-1 polyclonal (0.80). Based on these findings the EMA is a better marker for the diagnosis of mesothelioma.

**Comment**: For those of you brave enough to diagnose mesothelioma on fluids alone, you should keep using EMA.
III. Original Work Non-neoplastic


The disintegrin and metalloprotease (ADAM) molecules appear to play a central role in normal and abnormal biologic processes, including asthma, interstitial lung disease, eosinophilic pneumonia and lung cancer. This study was undertaken to assess the expression and localization of various ADAMs with metalloprotease activity (ADAM8, ADAM9, ADAM10, ADAM17, ADAM19, ADAM33) in human lung tissue.

Lung tissue was obtained from 9 individuals who underwent surgery for lung cancer or lung transplantation for emphysema. For those interested, table 1 shows the localization of expression of ADAMs in human lung tissue.

Comment: I suspect that this is just the beginning of ADAM (pun intended).

The aim of the present study was to clarify the characteristics of lymphangiogenesis in pulmonary fibrosis associated with idiopathic diffuse alveolar damage.

In the exudative stage greater numbers of capillaries were observed in the alveolar wall than in normal lung. Lymphatics were observed around large blood vessels and in the lobular septa. In the proliferative phase collapsed capillaries and lymphatics were observed in the interstitium.

Using morphometric techniques and 3-dimensional reconstruction, some new lymphatics appear to lack connection to existing lymphatics. Lymphangiogenesis occurs independent of capillary angiogenesis.

Fibrocytes are circulating mesenchymal cell progenitors involved in tissue repair and fibrosis.

Fibrocytes were defined as cells positive for CD45 and collagen-1 by flow cytometry and quantified in patients with stable IPF and during acute exacerbation. Controls consisted of healthy age-matched volunteers and patients with ARDS.

Fibrocytes were significantly elevated in patients with stable IPF with a further increase during acute exacerbation (P < 0.001 vs controls). Patients with ARDS were not different from healthy control subjects.

The mean survival of patients with fibrocytes higher than 5% of total blood leukocytes was 7.5 months compared with 27 months for patients with less than 5% (P <0.001).

Comment: An interesting study with potential predictive value.

This represents an editorial to the prior paper and asks several pertinent questions. It puts the above study into context.

Fifty-one autopsy cases of patients with SIDS were analyzed. In 47% of cases pulmonary hypoplasia was associated with brainstem hypodevelopment.

Pulmonary hypoplasia was more frequent in the SIDS group compared to controls (P <0.05).
IV. Reviews of Note


An outline of the topics covered includes:

I. Host Defense Against Aspergillus
   A. Innate Immunity
   B. Cellular Immunity
II. Spectrum of Human Disease in Aspergillosis
III. Invasive Aspergillosis
   A. Epidemiology
   B. Clinical Manifestations and Diagnosis
   C. Therapy for Invasive Aspergillosis
   D. Prevention of Invasive Aspergillosis
IV. Future Perspectives

Comment: This is largely review of invasive aspergillosis. There is at least 1 worthwhile figure dealing with pathogenesis.

This review focuses on recent research using genomics to examine lung carcinogenesis, histologic differentiation, and progression. It’s a great overview and has some very nice images which could be useful for lecture purposes.

PEComas: the name says it all.
V. Case Reports


This case highlights the fact that pulmonary alveolar microlithiasis is an autosomal recessive disease with a mutation of SLC34A2.

Comment: A nicely done study that highlighted new information (at least for this old dog).

Just thought you would want to know about this article in case you decided to go into dermatopathology but didn’t want to completely give up being a pulmonary pathologist.

A nice review with beautiful images representing the third case of primary follicular dendritic cell tumor in the lung. The discussion and differential diagnosis are excellent.

Diagnosis: diffuse alveolar damage secondary to leflunomide.

Just one more drug to remember!

A case of Erdheim-Chester disease. We all know about pulmonary involvement but myocardial involvement is usually constituted as an effusion or pericardial thickening. This patient presented with a mass in the right atrium thought to represent Erdheim-Chester.

**Diagnosis**: bacterial pneumonia with abscess likely due to group A beta-hemolytic strep with toxic shock.

**Diagnosis:** Diffuse malignant mesothelioma with extensive osseous differentiation.

A nice case of granulomatous Pneumocystis in a patient on chemotherapy for multiple myeloma.