Pulmonary Pathology Journal Club

February 16, 2015 (Discussion of articles from January 2015)

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Lee et al. Reactive oxygen species modulator 1 (Romo1) expression is an independent predictor of poor survival in NSCLC patients who undergo surgical resection. Lung Cancer 2015; 87: 45-52.


Scarpino et al. EGFR mutation testing in pulmonary adenocarcinoma: Evaluation of tumor cell number and tumor percentage in paraffin sections of 120 small biopsies. Lung Cancer 2015; 87: 8-13.


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For discussion

Pleuropulmonary blastoma - A report of 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. Messinger et al, Cancer.

Background: PPB is the most common primary lung malignancy in childhood, which is associated with germline DICER1 mutations leading to a cancer predisposition syndrome in a subset. PPB seem to evolve in an orderly fashion through type I (purely cystic) to type II (solid and cystic) to type III (purely solid); however, not all type I tumors are destined to progress, and some cystic lesions regress (type Ir).

Methods: Cases were confirmed by central pathology review, collected from 1962-2012. Type I cases were characterized by cystic lesion composed of thin fibrous septa lined by attenuated epithelium. Within the septa is a population of primitive cells with or without rhabdomyoblastic differentiation, which often form a cambium layer. Microscopic thickening of the septa by sarcomatous elements is acceptable in type I. In the absence of any recognizable primitive cellular component, they are categorized as type Ir. Solid areas of type II and II tumors may contain areas resembling ERMS, spindle cell/fibrosarcoma, blastema, primitive/sarcomatous cartilaginous nodules, and anaplastic cells. DICER mutation testing was performed via Sanger sequencing from peripheral blood or saliva.

Results:

- 350 of 435 were confirmed to be PPB on central review (remaining 20% of cases were other entities)
- 33% were type 1, 35% were type II, and 32% were type III. 7 cases were diagnosed prenatally with lung cysts, and pneumothorax was common at presentation (type I and II>type III). Lesions were typically large (most type I>5 cm, most type II/III>10 cm).
- Mean age increased with tumor type: 8 mos, 35 mos and 41 mos for types I-III, respectively. Type Ir cases presented at an older age than type I tumors (8 vs. 46.5 mos)

![Figure 1. Age at diagnosis. Abbreviation: PPB, pleuropulmonary blastoma.](image)
• Type I PPB had a male predominance, and 5 year OS and DFS were 91% and 82%. Metastatic disease does not occur in pure type I tumors. Tumor progression to types II-III occurred in 10% of cases (median 23 mos after diagnosis; all deaths were from this group with tumor progression). Importantly, 2 cases of type Ir PPB progressed to type II-III. All cases were surgically resected, and adjuvant chemotherapy (received in 36% of type I and 12% of type Ir) had no effect on progression or survival.

• Genders were equally affected in type II/III tumors. OS and DFS were 71% and 59% for type II, and 53% and 37% for type III (p=0.0061 and p=0.0002). Adjuvant chemo is the standard of care, although regiments vary. Metastases can occur to brain, bone, and rarely liver.

**Figure 3.** Relapse/progression analysis. Abbreviation: Dx, diagnosis.

• Prognostic factors included tumor type and metastatic disease at presentation.

• 66% of patients had heterozygous germline mutations in DICER1, which was not related to outcome

**Discussion:**

• Accurate diagnosis and typing of PPB is important for prognostication

• Surveillance of known DICER mutation carriers may lead to earlier diagnosis and superior outcome; other tumors seen in this syndrome include cystic nephroma, ovarian Sertoli-Leydig tumors, ERMS, pituitary blastoma, pinealblastoma, and other rare tumors

**Take home message:** Typing of PPB correlates with survival, and tumors seem to progress from cystic to solid/sarcomatous lesions. Regressed PPBs need to be recognized and correctly diagnoses, since they have personal and familial risk for other tumors.
Thoracic epithelioid malignant vascular tumors: A clinicopathologic study of 52 cases with emphasis on pathologic grading and molecular studies of \textit{WWTR1-CAMTA1} fusions. Anderson et al, AJSP.

\textbf{Background}: Epithelioid vascular tumors encompass benign (epithelioid hemangioma), low to intermediate grade (epithelioid hemangioendothelioma, EHE) and high grade tumors (epithelioid angiosarcoma, EAS). Some morphologic overlap exists, and this distinction can be difficult on small biopsies. \textit{WWTR1-CAMTA1} fusion (t1;3) has been recently described in EHE but not in other vascular tumors, which has potential diagnostic utility. The soft tissue WHO proposes grading EHE into classic (low grade) and malignant (intermediate grade) types, which hasn’t been well validated at visceral sites.

\textbf{Methods}: Included cases were composed of 10 low grade EHE, 29 intermediate grade EHE, and 13 EAS, involving the lung, pleura, mediastinum, heart, and great vessels. Intermediate grade EHE had necrosis, moderate to marked nuclear pleomorphism, and >1 mitotic figure/2mm$^2$. 35 cases had exclusively thoracic disease (13 lung, 17 pleura, 5 mediastinum), with remaining 17 cases having multiorgan disease including thoracic involvement. Testing for \textit{WWTR1-CAMTA1} was performed by FISH for both genes.

\textbf{Results}:

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
& EHE & \\
& G1 (n = 10) & G2 (n = 29) & G3 (n = 13) \\
\hline
\textbf{Median age (range) (y)} & 57.6 (26-83) & 51 (22-80) & 67.8 (28-84) \\
\textbf{Sex (male/female)} & 2/8 & 24/5 & 10/3 \\
\textbf{Site} & & & \\
\textbf{Thoracic only} & 7 & 20 & 8 \\
\textbf{Multiorgan incl. thorax} & 3 & 9 & 5 \\
\textbf{Site of thoracic involvement} & & & \\
\textbf{Lung} & 5 & 11 & 7 \\
\textbf{Pleura} & 3 & 13 & 4 \\
\textbf{Mediastinum} & 1 & 5 & 1 \\
\textbf{Heart} & 0 & 0 & 1 \\
\textbf{Superior vena cava} & 1 & 0 & 0 \\
\textbf{Site of extrathoracic involvement} & & & \\
\textbf{Bone} & 0 & 5 & 0 \\
\textbf{Soft tissue} & 0 & 3 & 5 \\
\textbf{Liver} & 1 & 3 & 0 \\
\textbf{Lung} & 0 & 1 & 1 \\
\textbf{Brain} & 0 & 2 & 0 \\
\textbf{Retropertitoneum} & 0 & 1 & 1 \\
\textbf{Size of thoracic tumor (mean [range]) (cm)} & 5 (0.6-14) & 2.2 (0.5-15) & 5.3 (0.5-8) \\
\textbf{Follow-up} & & & \\
\textbf{Alive/dead} & 7/26 & 12/17 & 1/12 \\
\textbf{Mean follow-up time (range) (y)} & 1.52 (0.1-4.4) & 1.23 (0.06-6.7) & 0.94 (0.02-4.6) \\
\textbf{Pleural involvement} & 6/10 cases & 17/29 cases & 6/13 cases \\
\hline
\end{tabular}
\caption{Summary of Clinical Features and Pleural Involvement}
\end{table}

\textbullet Presenting symptoms included pleural effusion (39%), chest pain (29%), SOB (16%), hemoptysis (13%), and cough (12%). Two were incidentally discovered.
Average mitotic rates were 0 for low grade EHE, 2 (range 0-9) for malignant EHE, and 5 (range 1-12) for EAS - more useful for grading EHE than distinguishing EHE from EAS.

Intranuclear inclusions, intracytoplasmic lumens and chondromyxoid/hyalinized stroma favored EHE, while blood lakes, slit-like vessels, papilla, marked nuclear atypia, and prominent nucleoli favored EAS.

WWTR1-CAMTA1 was found in 4/7 low grade EHE and 23/23 intermediate grade EHE, whereas EAS were negative (one case showed complex WWTR1 rearrangement).

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>EHE (n [%])</th>
<th>EAS (n [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD31</td>
<td>35/36 (97)</td>
<td>12/13 (92)</td>
</tr>
<tr>
<td>CD34</td>
<td>31/38 (82)</td>
<td>4/12 (33)</td>
</tr>
<tr>
<td>ERG</td>
<td>10/10 (100)</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>FLI1</td>
<td>73%</td>
<td>100%</td>
</tr>
<tr>
<td>Cytokeratin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pankeratin</td>
<td>7/33 (21)</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>CAM5.2</td>
<td>2/13 (15)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>CK7</td>
<td>3/15 (20)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>CK18</td>
<td>5/8 (63)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Any keratin marker</td>
<td>29%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Grade (p=0.026 for all tumors, p=0.010 for lung/pleural only tumors) was associated with poor prognosis: 4-year survival for the three tumor grades was 75%, 21% and 9%. Pleural invasion (p=0.042) and hemoptysis (p=0.001) were also poor prognostic factors.

Thoracic vs. multiorgan involvement was not associated with a survival difference in EHE, nor was tumor size, but multiorgan AS had a worse prognosis than those with disease limited to the thorax.

Discussion:

Grading into low grade EHE, intermediate grade EHE, and EAS is feasible and associated with significant survival differences. They hypothesize while WWTR1-CAMTA1 incites low and intermediate grade EHE, additional genetic abnormalities are likely present in intermediate grade tumors.

Keratin expression is common in these tumors, and is a diagnostic pitfall.

WWTR1-CAMTA1 fusion is present in most EHE but absent in EAS, and can be useful in diagnostically challenging cases.

Take home message: Grading seems worthwhile, especially if you have an excision specimen. Testing for WWTR1-CAMTA1 has great potential on small biopsy or ambiguous cases. Always remember this family of tumors in your differential of keratin positive neoplasms of the thorax.
INTERSTITIONAL PNEUMONIA RELATED TO UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE: PATHOLOGIC PATTERN AND PROGNOSIS. Kim et al, Chest.

BACKGROUND: Undifferentiated connective tissue disease (UCTD) involves conditions characterized by both having symptoms of connective tissue disease (CTD) and autoantibodies but not fulfilling the criteria of a specific CTD. The frequency or prognosis of the usual interstitial pneumonia (UIP) pattern in UCTD is unknown, which may be confused with idiopathic pulmonary fibrosis (IPF). This study aimed to investigate the frequency of the UIP pattern in interstitial pneumonia related to UCTD and compare its prognosis with that of IPF and UCTD-nonspecific interstitial pneumonia (UCTD-NSIP).

METHODS: 788 patients presumptive diagnosis of IIP, @ Asan Medical Center (01/05 - 12/12); Records reviewed retrospectively. Excluded: Patients with classic CTDs or exposure history in relation to the possible causes of ILD. Serology: ANA > 1:160 considered positive. Extractable nuclear Ag tests (SSA, SSB, Jo, Scl70, RNP) with ratio >1 were considered positive. Biopsy: Surgical biopsy in 363 patients; Trans-bronchial 11 patients. HRCT scan: performed at baseline in all patients and followed up annually or at a time of acute change in patient’s condition. HRCT scan was used for the diagnosis of UCTD-UIP. IPF diagnosis was reconfirmed according to new guidelines. UCTD was diagnosed according to the criteria by Corte & colleagues

RESULTS: 105 (13.3% vs 21% in literature) patients had UCTD (details in tables). Among all UIP-pattern pts. 8.1% had UCTD, from all NSIP, 26% had UCTD. Overall survival of UCTD-UIP group was shorter than that of UCTD-NSIP (p=0.021) but better than that of IPF-(p=0.042). No difference in survival between idiopathic & UCTD-NSIP.

<table>
<thead>
<tr>
<th>HRCT scan pattern (N=105)</th>
<th>UIP</th>
<th>NSIP</th>
<th>OP</th>
<th>Final pattern (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical UIP pattern</td>
<td>32 (30.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-UIP pattern</td>
<td>73 (69.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical lung biopsy (N=58)</td>
<td>24 (41.4)</td>
<td>29 (50.0)</td>
<td>5 (8.6)</td>
<td></td>
</tr>
<tr>
<td>UIP</td>
<td>44 (42 vs 73.1 non UCTD-UIP)</td>
<td>29 (28 vs 11.9 idiop)</td>
<td>9 (9 vs 8.6 idiop)</td>
<td></td>
</tr>
<tr>
<td>NSIP</td>
<td>29 (50.0)</td>
<td>5 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OP</td>
<td>5 (8.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UCTD-UIP (N=105)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>59.0 ± 10.4 (vs 65 non UCTD)</td>
</tr>
<tr>
<td>Sex: male</td>
<td>29 (27.6% vs 78% non UCTD)</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>30 (28.6)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>62 (59.0)</td>
</tr>
<tr>
<td>Sicca symptom</td>
<td>56 (53.3)</td>
</tr>
<tr>
<td>Raynaud</td>
<td>32 (30.5)</td>
</tr>
<tr>
<td>Morning stiff ness</td>
<td>11 (10.5)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Autoantibody</td>
<td></td>
</tr>
<tr>
<td>ANA (titer&gt;1:160)</td>
<td>54 (51.4)</td>
</tr>
<tr>
<td>SS-A (Ant-Ro)</td>
<td>40 (38.1)</td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>15 (14.3)</td>
</tr>
<tr>
<td>Scl-70</td>
<td>12 (11.4)</td>
</tr>
<tr>
<td>RF (titer &gt;1:160 IU)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>SS-B (Ant-La)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Positive two Ab</td>
<td>23 (21.9)</td>
</tr>
<tr>
<td>Positive three Ab</td>
<td>4 (3.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UCTD-</th>
<th>-UIP</th>
<th>-NSIP</th>
<th>P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>44 (41.9)</td>
<td>29 (27.6)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62.8 ± 8.0</td>
<td>52.5 ± 9.3</td>
<td>.005</td>
</tr>
<tr>
<td>Sex, male</td>
<td>15 (34.1)</td>
<td>6 (20.7)</td>
<td>.216</td>
</tr>
<tr>
<td>Smoking (ever smoker)</td>
<td>16 (36.4)</td>
<td>6 (20.7)</td>
<td>.153</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td></td>
<td>.695</td>
<td></td>
</tr>
<tr>
<td>Steroid only</td>
<td>17 (38.6)</td>
<td>13 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Steroid+IS</td>
<td>14 (31.8)</td>
<td>10 (34.5)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 (29.5)</td>
<td>6 (20.7)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UCTD-UIP: 31; NSIP: 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>Deterioration</td>
</tr>
</tbody>
</table>

| Median follow-up, mo | 21 | 44 | ... |
| Survival (%) | .021 |
| 1 y | 97.7 | 96.6 |
| 3 y | 76.6 | 96.6 |

**Figure 1. Comparison of the Survival curves of patients with UCTD-UIP & UCTD-NSIP**

**Figure 2. Kaplan-Meier survival curves of the patients with UCTD-UIP and IPF.**

CONCLUSIONS: A UIP pattern, which seems to be frequent in UCTD, showed a poorer prognosis than that of UCTD-NSIP. However, the prognosis of UCTD-UIP was significantly better than that of IPF, highlighting the importance of searching for underlying UCTD in suspected IPF cases.
VALIDATION OF A SCORING SYSTEM TO PREDICT RECURRENTCE OF RESECTED SOLITARY FIBROUS TUMORS OF THE PLEURA. Tapias et al, Chest.

BACKGROUND: Solitary fibrous tumors of the pleura (SFTPs) are infrequent neoplasms with no standardized criteria to predict risk of recurrence after curative surgery. The aim of the present study is to validate a recently proposed recurrence score in a large European cohort of patients with SFTP.

METHODS: 113 patients who underwent complete resection of SFTPs. Patients were scored according to the pleural origin, morphology, size, hypercellularity, presence of necrosis or hemorrhage, and number of mitoses/10HPH. Receiver Operating Characteristic Curves were plotted for the score. Time to recurrence analysis was performed using the Kaplan-Meier and Cox proportional hazards methods.

RESULTS: Follow-up: 13.2 _ 7.3 years. There were 9 recurrences (8.0%). Score performance to predict recurrence was as follows: sensitivity 78%, specificity 74%, positive likelihood ratio 3.0, and negative likelihood ratio 0.3. A cutoff of 3 points was used to classify 79 patients at low risk and 34 patients at high risk for recurrence. High-risk classification was significantly associated with more recurrences (P.004), worse overall survival (P.0008), more extensive resections (P.001), and use of adjuvant therapies (P.009). The present score outperformed England’s criteria (P.049) and de Perrot classification (P.001).

### Time to Event Analysis of Factors Associated With Recurrence Included in the Scoring System

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio(95%CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural origin</td>
<td></td>
<td>.887</td>
</tr>
<tr>
<td>Visceral/ intrapulmonary</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>1.10 (0.30-4.10)</td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>.129</td>
<td></td>
</tr>
<tr>
<td>Pedunculated</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sessile</td>
<td>0.30 (0.06-1.42)</td>
<td></td>
</tr>
<tr>
<td>Size (longest axis)</td>
<td>.044</td>
<td></td>
</tr>
<tr>
<td>&lt;10 cm</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;=10 cm</td>
<td>4.17 (1.04-16.67)</td>
<td></td>
</tr>
<tr>
<td>Hypercellularity</td>
<td>.014</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.22 (1.49-34.85)</td>
<td></td>
</tr>
<tr>
<td>Necrosis or hemorrhage</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7.40 (1.85-29.71)</td>
<td></td>
</tr>
<tr>
<td>No. of mitoses/10 HPF</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&gt;=4</td>
<td>23.47 (4.84-113.92)</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS: The proposed scoring system, which combines common clinical and histologic features of resected SFTPs, remains predictive of recurrence in a separate patient population. The simple score may guide the postoperative surveillance of this uncommon tumor.
Articles for Notation

Neoplastic

Thymic carcinoma outcomes and prognosis: Results of an international analysis. Ahmad et al, J Thorac Cardiovasc Surg.

**Summary:** Multicenter retrospective collaborative study of 1042 cases of thymic carcinoma, collected by the International Thymic Malignancy Interest Group and European Society of Thoracic Surgeons. There was not central pathology review that I could see (Bill Travis is listed as an author). Most patients (78%) were Masaoka stage III or IV. Complete resection was able to be achieved in 61% of cases. 79% of tumors were squamous cell carcinoma. Median OS was 6.6 years. Multivariable analysis showed complete resection and adjuvant radiation therapy were associated with better survival.

**Take home message:** This is predominantly a clinical study with little pathologic information available, but it is a very large retrospective cohort. Complete resection and adjuvant radiation were independent predictors of better survival.

Validation of a molecular and pathologic model for five-year mortality risk in patients with early stage adenocarcinoma. Bueno et al, JTO.

**Summary:** They wanted to validate a cell cycle progression (CCP) score for risk stratification of adenocarcinoma patients treated with surgery only. They included 650 patients who were treated with surgery only (stage I and stage II). The expression signature they studied included 31 proliferation genes, studied by RT-PCR. The CCP score was an independent predictor of survival (HR 1.46) on multivariate analysis, and since pathologic stage also maintained significance in multivariate analysis, they combined the two into a prognosis score that was a stronger predictor (HR 2.01) and was a better predictor of survival than pathologic stage alone.

**Take home message:** They argue that high risk patients may benefit from adjuvant therapy to reduce cancer mortality. I wonder how this compares to other, cheaper, pathology-based risk stratification models, including overall grading and pattern-based grading- I did not see that they included any kind of grading system in the multivariate analysis.

Tracking of viable circulating tumor cells (CTCs) in the peripheral blood of non-small cell lung cancer (NSCLC) patients undergoing definitive radiation therapy: Pilot study results. Dorsey et al, Cancer.

**Summary:** Pilot study of 30 patients looking at CTCs before, during and after definitive radiation. They were able to detect CTCs in 65% of patients. Median counts per mL were 9.1 (range 0-571 CTCs/mL) before therapy, compared to 0.6 (range 0-1.8 CTCs/mL) after therapy, which was a significant decline.
**Take home message:** Detectable CTCs seem to reflect response to radiation treatment, and they have started a clinical trial to look at this. The current study is limited by the small number of patients, which is even smaller when you consider the substantial number that did not have detectable CTCs.

**Outcome of primary neuroendocrine tumors of the thymus: A joint analysis of the International Thymic Malignancy Interest Group and the European Society of Thoracic Surgeons databases. Filosso et al, J Thorac Cardiovasc Surg.**

**Summary:** Retrospective multicenter trial of 205 patients with primary neuroendocrine tumors of the thymus. 77% of patients were men, median age was 54 (range 19-82) with a median size of 8 cm. Atypical carcinoid was most common (40%), followed by typical carcinoid (28%), and 28% of cases were celled either small cell or large cell neuroendocrine carcinoma. Remainder of cases did not have specific histologic subtype or was called carcinoid NOS. 69% of cases were Masaoka stage III or IV. Median overall survival was 7.5 years (five year OS 68%). Factors influencing OS on multivariate analysis included completeness of surgical resection and Masaoka stage, interestingly histologic subtype did NOT affect OS- while typical carcinoid seemed to trend above atypical on the survival curve, poorly differentiated tumors seemed to do about the same as atypical carcinoid, and the cumulative incidence of recurrence between all three groups was shocking similar.

**Take home message:** Neuroendocrine tumors of the thymus are rare, but seem to generally be bad actors, with presentation at high stage, regardless of histologic subtype. I’m not sure why all grades of NEC seemed to do the same at this location- they did not have centralized pathologic review that I saw (although Bill Travis was an author), but histologic subtype did not affect survival, and stage/completeness of resection were the most important prognostic factors.

**Micronodular thymoma with lymphoid stroma: an immunohistochemical study of the distribution of Langerhans cells and mature dendritic cells in 6 patients. Ishikawa et al, Histopathol.**

**Summary:** They sought to further understand the B-cell stroma observed in MNTLS. They looked at Langerhans cells (IHC for CD1a and Langerin) and mature dendritic cells (IHC for fascin) in 6 cases of MNTLS compared to type A and type AB thymomas (5 cases each). Langerhans cells were concentrated in the micronodules, with only rare cell in the stroma (about 75 vs 6 per HPF). Mature dendritic cells showed the reverse pattern (stroma > micronodules, 63 vs 6 per HPF), where they were located adjacent to the B-cell follicles admixed with T-cells.

**Take home message:** They propose an interesting hypothesis, that in MNTLS, tumor antigens are taken up by Langerhans cells in the micronodules, migrate into the stroma and mature to dendritic cells, where they present the antigen to T-cells which recruit the B-cell follicles- perhaps this immune response may lead to the observed good outcome.
**ROS1 gene rearrangement and copy number gain in non-small cell lung cancer.** Jin et al, Virchows Archives.

**Summary:** They tested 375 NSCLC patients (55% adenocarcinoma, 37% squamous cell carcinoma, remaining “other”), for ROS1 via FISH and IHC. Rearrangement was observed in 3 patients (0.8%), all women, non-smokers who had an adenocarcinoma component. ROS1 copy number gain (not amplification) was seen in 4.8% of cases, and was associated with worse survival on multivariate analysis. ROS1 IHC positivity was seen in 5% (18 cases, 2 of these 18 had ROS1 rearrangement, no significant association was observed with copy number gain and immunostain).

**Take home message:** They found even a lower incidence of ROS1 rearrangement than previously reported, especially considering this is an Asian cohort. The poor prognostic significance of copy number gain is interesting, but not sure what overall significance it has, since I am not aware that copy number gain predicts any kind of response to ALK inhibitors.

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**Reactive oxygen species modulator 1 (Romo1) expression is an independent predictor of poor survival in NSCLC patients who undergo surgical resection.** Lee et al, Lung Cancer.

**Summary:** Romo1 is a protein that plays a role in intracellular reactive oxygen species generation, which is overexpressed in most cancer cell lines related to invasiveness and chemoresistance. They studied Romo1 expression via IHC in 110 cases on NSCLC, and found high expression (seen in 14 patients, judged by H score, which is a combination of staining intensity and percentage of positive cells) to be associated with poor DFS and OS on multivariate analysis.

**Take home message:** Romo1 expression seems to be a poor prognostic factor in NSCLC, but is seen in the minority of cases (around 10%), and at this point has unknown clinical utility.

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**Risk stratification of patients undergoing pulmonary metastatectomy for soft tissue and bone sarcomas.** Lin et al, J Thorac Cardiovasc Surg.

**Summary:** Pulmonary mets occur in up to 50% of patients with sarcoma, and 19% may have the lung as the only site of metastasis- literature has shown that selected patients may have extended survival with complete resection of the metastases. They performed retrospective review of 155 patients (108 soft tissue sarcoma, 47 bone sarcoma) who underwent resection of pulmonary metastases. Multivariate analysis was used to find factors associated with poor prognosis. The following variables were identified: age > 45, disease-free interval of < 1 year, thoracotomy, synchronous disease, lobectomy, and site/type of sarcoma. Superior survival was seen in osteosarcoma and leiomyosarcoma, whereas liposarcoma and synovial sarcoma showed poor survival. Survival ranged from 65% for those with 2 poor prognostic factors to 3% for those with 5 factors.
Take home message: These poor prognostic factors could be used to preoperatively identify patients who will be expected to have a very poor outcome, in which medical therapy might be the better choice.


Summary: They studied 62 resected cases of pleomorphic carcinoma. 82% of patients were men, and overall survival was 68% at 5 years (seems high, but I guess they have a bias for low stage by looking at resected tumors). 24% were “pure” pleomorphic carcinomas, while the remainder had a recognizable NSCLC component. ZEB1 is a transcription factor apparently important in epithelial-mesenchymal transition, which has been associated with more invasive and mesenchymal properties, and they tested for expression via immunostaining (nuclear). They observed ZEB1 expression only in the pleomorphic component, and 12 cases were diffusely positive (>75%). Diffuse expression was an independent predictor of poor survival.

Take home message: The ZEB1 data is kind of interesting, and I wonder if it is a marker of true mesenchymal transition more than anything. But at this point, I’m not sure if it has any practical implications.


Summary: They reviewed preop PET on 255 patients and correlated with adenocarcinoma subtype at resection. Most patients (230) were stage I. Subtypes were determined by two pathologists, with consensus by double scoping in cases with disagreement, and they were blinded to PET results. Their pattern breakdown was 34% papillary, 32% acinar, 12% lepidic, 8% solid, 5% MIA, 5% AIS, 2% micropapillary, and 1% mucinous. Highest SUVmax was observed in micropapillary predominant, followed by solid, mucinous, acinar, papillary, lepidic, MIA and AIS. They divided the patterns into three groups: low risk (lepidic predominant, AIS and MIA), intermediate risk (acinar, papillary and mucinous), and high risk (solid and micropapillary), and the three groups showed significant differences in SUVmax (averages 1.21, 2.68, 5.76, respectively) as well as recurrence. Multivariate analysis showed PET avidity to be an independent risk factor for overall survival.

Take home message: As you might expect, PET avidity correlates with invasive pattern, with the more “high grade” patterns showing increased avidity compared to the low risk tumors (AIS, MIA and lepidic growth). Not sure this is entirely new, but I thought it was a good read.
Diagnostic significance of cell kinetic parameters in World Health Organization Type A and B3 thymomas and thymic carcinomas. Roden et al (Anja Roden first author, MC Aubry senior author, Joanne Yi coauthor), Human Pathol.

Summary: The WHO classification of thymomas is of questionable prognostic significance, and has reproducibility issues. The authors sought to study whether cell kinetic variables (mitotic count, Ki67, bcl2 staining) could aid in the classification of type A, B3 thymomas and thymic carcinomas, which can be difficult to distinguish and have prognostic differences. 80 cases of type A and B3 thymomas and thymic carcinomas were classified by 2 thoracic pathologists. Agreement was seen in 83% of cases: 31 cases agreed as type A, 21 agreed as type B3, and 14 agreed as thymic carcinoma. Median mitotic activity was 6 times higher in thymic carcinoma than thymoma, but some overlap was observed. Bcl2 expression was more common in thymic carcinoma than thymoma, but again, overlap was observed. There was a significant difference in Ki67 labeling index between types A1 and B, as well as between both types of thymoma and thymic carcinoma. Rpart analysis showed Ki67 over 14% was observed only in thymic carcinoma, and less than 5.1% was only seen in thymoma. Ad hoc analysis showed that Ki67 >13.5% was thymic carcinoma, and <2% was only seen in type A thymoma. There were 14 cases in which the pathologists disagreed (mostly between B3 and thymic carcinoma), and the Rpart method was able to classify 11 of 14, with the ad hoc method able to classify 7 of 14.

Take home message: Ki67 labeling index may be helpful in classifying difficult cases of thymic epithelial neoplasms, particularly between thymic carcinoma and thymoma.


Summary: Retrospective study of 1,763 patients who underwent resection of NSC lung cancer and had a clinical diagnosis of ILD: 74% had UIP, and 26% had “non-UIP” pattern radiographically that was not broken down further. 90% of patients were men and 94% were smokers (!). Five year survival was 40%. Interestingly, they saw a much worse 5-year survival in patients who underwent wedge (33%) vs. those who underwent lobectomy or segmentectomy (<60%)- I wonder if this is because patients who underwent wedge had much more severe background lung disease and could not tolerate anatomic resection. Another interesting finding was that patients with stage IA lung cancer who had a preop %VC of less than 80% had a 5 year survival of only 20%. 50% died from cancer recurrence, and 27% died from respiratory failure. Multivariable analysis showed type of surgical procedure, predicted %VC, and tumor location (lower lobe) to be independent predictors of poor survival.

Take home message: Interesting study describing what they call “competing risks of death” in patients who develop lung cancer in a background of ILD (mostly UIP patients). Seems that patients with poor lung function and clinical low stage disease may benefit from non-surgical therapy such as SBRT.
**EGFR mutation testing in pulmonary adenocarcinoma: Evaluation of tumor cell number and tumor percentage in paraffin sections of 120 small biopsies.** Scarpino et al, Lung Cancer.

**Summary:** They sought to better define the minimal number of tumor cells that need to be present to successfully perform EGFR testing. They tested progressively smaller number of tumor cells removed from 12 surgically resected specimens, captured by laser microdissection, then validated this on 120 small biopsies. They found that 140 tumor cells (0.12 mm²) allowed detection of EGFR mutations in 11 of 12 cases. If there was EGFR polysomy or amplification, they observed a 2-4 fold increase in assay sensitivity. They detected EGFR mutations in 26 of their 120 small biopsies. Only a single small biopsy actually had <200 tumor cells. The EGFR positive case with the lowest number of tumor cells had 364 (0.12 mm²). 42% of the EGFR mutated cases had tumor cells comprising <20% of the tissue.

**Take home message:** Generally they thought if you had enough cells to make a confident diagnosis, you probably had enough to perform EGFR mutation testing using current techniques (I guess this generally depends on the boldness of your diagnoses- seems like calls are possible with less cells than this). They were successful with 140 tumor cells (0.12 mm²), and when the tumor cells represented <20% of the tissue.

**Characteristics and outcomes of second nodules identified on initial computed tomography scan for patients undergoing resection for primary non-small cell lung cancer.** Stiles et al, J Thorac Cardiovasc Surg.

**Summary:** 88 of 155 patients (57%) were found to have additional pulmonary nodules on initial CT for primary NSCLC, with a total of 137 nodules detected (some patients had more than one). 32 were resected at the same time as the primary cancer: 61% were benign, 39% were malignant (second primaries or lobar mets). The 105 nodules that were not resected were followed by CT: 30% resolved, 19% shrunk, 27% were stable, 13% grew, and remaining were lost to follow-up. 5 of 14 growing nodules followed by CT were malignant (new primaries). Five year OS was the same for patients with and without second nodules.

**Take home message:** Second nodules are common, and most are benign. They seem more likely to be malignant if located in the same lobe as the NSCLC. The outcome is the same as those without a second nodule, so authors assert that these patients should not be denied surgical treatment.

**Her2 gene mutations in non-small cell lung carcinomas: Concurrence with her2 gene amplification and her 2 protein expression and phosphorylation.** Suzuki et al, Lung Cancer.

**Summary:** They investigated 1275 NSCLC occurring in Asian patients (mostly adenocarcinomas, 1055) for mutations in Her2, Her2 amplification (via CISH), as well as immunostaining for Her2 and phosphorylated Her2. Mutations were observed in 3.6% of all cases, and were only seen in adenocarcinomas (4.3%) - and about half of tumors with mutations also had amplification. The
mutations occurred in isolation (no other driver mutations detected in KRAS, EGFR, BRAF or ALK), and were more common in younger patients, non-smokers, and those with smaller tumors. *Her2* mutation was a predictor of poor outcome in invasive adenocarcinomas, and of those with *Her2* mutations, *Her2* amplification was further poorly prognostic, while phosphorylation was favorable.

**Take home message:** *Her2* mutations are found in 4.3% of adenocarcinomas in Asian patients, and tended to occur in non-smokers and at a younger age. Tumors were smaller, and specifically in invasive adenocarcinoma, it seemed to be a poor prognostic factor. They did not really discuss therapeutic implications or lack thereof.

**In the hunt for therapeutic targets:** *Mimicking the growth, metastasis, and stromal associations of early-stage lung cancer using a novel orthotopic animal model.* Weiss et al, JTO.

**Summary:** They describe an animal model whereby they inject small numbers of GFP-labeled human or mouse lung cancer cells into the left lung of a mouse, and were able to generate solitary pulmonary nodules that grew and spread distantly with time. They were then able to use the GFP-labeling, immunofluorescence and IHC to look at the tumor local microenvironment, and found that leukocytes and fibroblasts were recruited to the tumor margins, and that a myeloid attracting and CCR-2 binding chemokines were produced in the tumor microenvironment.

**Take home message:** Direct injection of a small number of tumor cells into mouse lungs seems to induce an animal model that is promising for studying early stage lung cancer and lung cancer progression. They have pretty cool pictures of mouse lung tumors and mouse PET-CTs 😊.

**Non-neoplastic**

**Heterologous gene expression signatures correspond to distinct lung pathologies and biomarkers of disease severity in idiopathic pulmonary fibrosis.** DiPianto et al, Thorax.

**Summary:** They sought to better understand if the spatial and temporal heterogeneity seen in UIP pattern corresponded to expression of genes that may mediate the disease. They looked at a gene expression microarray containing 40 cases of IPF, and looked for genes differentially expressed between IPF and controls, as well as looking for groups of genes that showed heterogeneous expression among different IPF patients. 2,940 genes were differentially expressed between IPF and control cases. Two clusters of genes were identified that showed marked heterogeneity in the IPF population, those involved in bronchiolization, and those involved in lymphoid aggregation, which corresponded to histologic bronchiolization and number of lymphoid aggregates (evaluated with H&E, and also immunostains for CK5, trichrome, PAS, and keratin 14 to aid in recognition of areas of bronchiolization, and CD3/CD20 to look at lymphoid aggregates). These histologic features were scored 0-3 by a pathologist blinded to the expression array results, and correlated with the gene expression data.
MMP3 was encoded in the bronchial cluster, and CXCL13 was encoded in the lymphoid cluster, and elevated levels of these markers in the serum corresponded to disease severity and shortened survival.

**Take home message:** This is a complicated study, but seems fairly elegant. The bronchiolization and lymphoid aggregate signatures seem essentially to correspond to honeycomb change, and the serum biomarkers (MMP3 and CXCL13) they found seem to correlate with poor survival and disease severity (around one quarter of patients in the biomarker group were receiving immunosuppression, so this result needs to be validated in larger independent cohorts).

**Pulmonary vascular hypertensive changes in lungs of patients with sudden unexpected death.**

**Summary:** Study of 44 asymptomatic (symptoms <24 hours before death)/untreated patients with sudden death that were found to have changes of pulmonary hypertension at autopsy, which they characterized as widespread and severe. 64% of patients were women, mean age was 24 years (range 4 days to 93 years). 41% of patients died at rest, while 16% died following cardiac surgery and 16% died during pregnancy/post-partum (6 of these 7 pregnant/post-partum patients had congenital heart disease). All patients had right ventricular hypertrophy at autopsy, and the lungs were typically otherwise grossly normal. The underlying cause of pulmonary hypertension was found to be congenital heart disease in 27 patients (61%): 14 had a simple defect (4 ASD, 4 VSD, 4 PDA, 1 AVSD, 1 aortic atresia; 7 had been corrected and 7 were uncorrected due to Eisenmengers syndrome) and 13 had a complex defect with associated ASD or VSD, all of which had been surgically corrected without complications, but all of which had plexiform arteriopathy in the lungs at autopsy. The remaining 17 patients had plexiform arteriopathy (7), PVOD (6), chronic thromboembolic disease (1), pulmonary arteriovenous malformation (1), and localized pulmonary giant cell vasculitis (1).

**Take home message:** Post-cardiac surgery and pregnancy seem to be risky times for patients with occult pulmonary hypertension, with risk of sudden death. Congenital heart disease is an important cause of pulmonary hypertension in these patients. Pulmonary hypertension should be included in the differential diagnosis of sudden death, especially when right ventricular hypertrophy is observed at autopsy, and the pulmonary parenchyma should be well sampled to look for characteristic histologic changes (they recommend 2 sections per lobe in patients with RVH, along with VVG stains as needed).


**Summary:** Report of 5 cases of PPFE (3 autopsy, one surgical biopsy, one explant), average age 73 years (4 women, 1 man) with pulmonary symptoms ranging from 14 months to 9 years. Two patients had medication exposure (dapsone and daptomycin), and one had eosinophilic pneumonia during their disease course (they use this evidence to suggest that it may be a non-specific pattern of chronic lung
injury rather than a specific idiopathic ILD). Four patients had clinically apparent fibrosis. They found changes of PPFE in both upper and lower lobes (prior reports have stressed upper lobe predominance). They propose diagnostic criteria including: multilobar subpleural and/or centrilobular fibrous interstitial pneumonia characterized by extensive (>80%) proliferation of elastic fibers in non-atelectatic lung, along with absent to mild chronic inflammation, and absent to rare granulomas.

**Take home message:** This small series of PPFE stresses that fibrosis is present in multiple lobes and may not have as much of an upper lobe predominance as previously thought, and propose that it may be a non-specific pattern of chronic lung injury given that it has been described secondary to numerous conditions, including adverse drug reaction, infection, autoimmune disease, genetic ILD, post-bone marrow transplant, or may be seen concurrently with other patterns of ILD (UIP and HP).

**The pulmonary histopathology of Anti-KS transfer RNA synthetase syndrome. Schneider et al, Arch Pathol Lab Med.**

**Summary:** Antisynthetase syndromes are a subset of connective tissue disease, usually dermatomyositis and polymyositis, with specific auto-antibodies. Anti-KS autoantibodies occur in only 1-5% of myositis patients, but often present with pulmonary disease without other systemic manifestations of connective tissue disease. They present the pulmonary findings in surgical biopsies of 5 patients with anti-KS antibodies and interstitial lung disease. Four patients were women, and presented with dyspnea. Most patients did not have myositis or skin rash, but 3 had Mechanics hands and 2 had Reynaud’s phenomenon. Four patients had UIP pattern, and one had organizing pneumonia.

**Take home message:** While the current literature stresses the commonness of interstitial lung disease in patient with anti-KS (>80% of patients), it emphasizes NSIP pattern, when UIP pattern is what they most commonly observed in this study. Although this antibody is uncommon, it is associated with a high prevalence of lung disease, and thus testing could be considered in the work up of UIP before connective tissue disease is considered excluded.

**Severity and outcome of cystic lung disease in women with tuberous sclerosis complex. Taveira-DaSilva et al, Eur Resp J.**

**Summary:** Comparison on 94 women with TS/LAM to 460 women with sporadic LAM, including 40 cases from each group which were matched for age and lung function. Patients with TS/LAM seemed to present at a younger age but generally had less respiratory symptoms, and presented more often with pneumothorax. The presence of renal AMLs increased the chance the patient had TS/LAM rather than sporadic LAM. TS/LAM patients had better lung function than sporadic LAM patients, as judged by the proportion of patients with abnormal lung function and rate of FEV1 decline. There were some young TS/LAM patients that displayed abrupt rapid progression of lung disease.
Take home message: Sporadic LAM patients seem to have worse overall lung function than patients with TS/LAM, but some TS/LAM patients will experience rapid and abrupt progression of lung disease—thus the authors advocate periodic PFT and imaging screening of these patients.

Editorials and Reviews

Non-coding RNA: A new tool for the diagnosis, prognosis and therapy of small cell lung cancer. Huang et al, JTO.

Take home message: It has become clear that ncRNAs have important cellular functions, including gene silencing, as well as transcriptional, post-transcriptional and epigenetic regulation. Dysregulation of non-coding RNAs is important in the pathogenesis of small cell lung cancer, including microRNAs which have a role in tumorigenesis via pathways of cell proliferation, apoptosis, migration and invasion. Paper includes complete discussion of the roles of ncRNAs as oncogenes and tumor suppressors in small cell, as well as musings on the possible clinical applications (diagnosis, prognosis, therapy). Quite a detailed resource on this complicated topic.


Take home message: FGFR1 may be a promising therapeutic target, and has been shown to be amplified in pulmonary squamous cell carcinomas. 13 studies were included in their meta-analysis. About 19% of pulmonary squamous cell carcinomas have FGFR1 amplification. FGFR1 amplification was associated with smoking, lymph node metastasis, and no differences in survival are observed.

Mucins in lung cancer- Diagnostic, prognostic, and therapeutic implications. Lakshmanan et al, JTO.

Take home message: Mucins seem to be overexpressed in NSCLC and may be biomarkers of disease progression. This review includes a discussion of normal mucin expression profiles in the lung, along with detailed discussion of role of MUC1, MUC4, and secretory mucins and their role in lung cancer carcinogenesis. They also discuss possible future role of mucins in diagnosis, and particularly the possible development of anti-MUC1 targeted therapy.

Helping smokers quit- Opportunities created by the affordable care act. McAfee et al, NEJM.

Take home message: Lack of coverage of smoking cessation methods/medications is a barrier to quitting, and the affordable care act essentially requires coverage of these services/meds. The ACA also allows insurance companies to charge smokers higher premiums, which they cannot do if the smoker enrolls in an approved cessation program.

**Take home message:** Discussion of the difficulties in studying thymic carcinoma as a rare “orphan” disease, which only retrospective studies and often incomplete data.


**Take home message:** Ubiquitin positive cytoplasmic inclusions have been associated with pneumocyte injury and seem to increase with the extent of DAD-related injury. The detection of such inclusion can be enhanced by immunostaining. Many inclusions are observed in DAD and UIP, with less seen in OP and airspace enlargement with fibrosis. Therefore they argue these inclusions are a marker of pneumocyte injury that may reflect the severity and prognosis.

**Case Reports and Letters to the Editor**


**Summary:** During resection of bronchogenic cyst, hard lesions incidentally palpated in lung of a 51 year old woman. Wedge biopsy showed calcified nodules corresponding to dendritiform pulmonary ossification with interstitial fibrosis and inflammation, presumed secondary to patient’s underlying scleroderma. 58 year old man incidentally found to have diffuse bilateral minute interstitial opacities. Wedge biopsy showed diffuse dendritiform ossification without inflammation. They seemed to be arising from scattered tendinous-like fibrous nodules resembling those seen in Ehlers-Danlos (clinical investigation for this syndrome was negative, deemed to be idiopathic in this case).

**Take home message:** DPO can occur outside the most usual setting of UIP, including in collagen vascular disease-associated interstitial lung disease (scleroderma in this example) as well as in the idiopathic setting. Includes complete discussion of literature on this topic.

Pulmonary fibrosis in dyskeratosis congenita: Report of 2 cases. Dvorak et al (Joanne Yi senior author, Tom Colby, Henry Tazelaar, Kevin Leslie Co-Authors), Human Pathol.

**Summary:** DC is an inheritable disease frequently showing muco-cutaneous manifestations, bone marrow failure/cytopenias, as well as pulmonary fibrosis, caused by mutations leading to poor telomere maintenance leading to shortening. The first patient is a 24 year old man who presented
with cough and dyspnea, found to have upper and middle lobe predominant fibrotic interstitial lung disease with septal thickening. Wedge biopsy shoed histologic UIP pattern with foci of proliferating lymphatics in the interlobular septa and BVBs, focally resembling lymphangiomatosis. He also had cytopenias and was subsequently found to have X-linked DC. The second patient is a 46 year old woman who presented with dyspnea, which progressed over several years from non-specific interstitial changes to radiographic UIP pattern. She experienced a somewhat abrupt worsening. Wedge biopsy showed histologic UIP. She died of pulmonary disease. She had been diagnosed as DC, probably recessive, largely due to compelling family history.

**Take home message:** Patients with DC can experience significant interstitial fibrosis, overall with a histologic UIP-pattern often showing prominent fibroblast foci, although some unusual characteristics (upper lobe predominance, lymphatic proliferation) may be noted- and some may be unclassifiable.

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**Pulmonary artery sarcoma:** Not every filling defect is a pulmonary thromboembolism. Khawar et al, JTO.

**Summary:** 76 yo man presents with a PA filling defect and presumed PE. No DVT or risk factors for DVT were discovered. H continues to do poorly (dyspnea, weight loss) for around a year on anticoagulation, when follow-up imaging revealed a 16 cm PA mass. Biopsy compatible with PA sarcoma.

**Take home message:** The histology pictures are nothing special, but the CT images of the progression from a filling defect to a huge mass are quite impressive.

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**Spontaneous regression of non-small cell lung cancer in AIDS after immune reconstitution.** Menon et al, JTO.

**Summary:** 44 yo man (cigarette smoker) with 20 year history of AIDS (CD4 count=77), with neurosyphillis and toxo, presents with severe headache and 1.8 cm ring enhancing brain mass. Toxo treatment does not improve his symptoms; craniotomy revealed poorly differentiated non-small cell carcinoma. Staging showed a 1.7 cm RUL nodule, 4.7 cm right adrenal mass, and a 2.4 cm mass anterior to the pancreas. Lung and adrenal biopsies showed TTF1 positive NSCLC. The patient received whole brain irradiation and HAART was reinstituted (he had been non-compliant). The patient has received no other therapy, and serial imaging over 5 years has shown decreasing size of all lesions- at five years, the adrenal and peripancreatic lesions were no longer visible, lung lesion measured 1.1 cm. His CD4 counts during this time have been persistently >200.

**Take home message:** Remarkable case of near-total regression of stage IV non-small cell lung cancer after institution of anti-retroviral therapy in an AIDS patient. Gives more hope to all those working on immune-stimulating therapies for lung cancer.
A case of amiodarone-induced acute fibrinous and organizing pneumonia mimicking mesothelioma. Picicucci et al, ARCCM.

Summary: 79 year old man with known asbestos-related pleural plaques and round atelectasis. He had taken amiodarone for 8 months for a-fib. Admitted with dyspnea, low grade fever and cough. CT showed unilateral circumferential right sided pleural effusion, pleural thickening, volume reduction, RUL GGOs, mediastinal adenopathy, RLL and LLL consolidation. Foamy macrophages were seen on BAL. Transbronchial biopsy showed AFOP. Patient was treated with steroids, amiodarone was discontinued, and CT findings resolved at 3 months.

Take home message: Amiodarone can cause AFOP pattern, and lung injury pattern can mimic mesothelioma on imaging, especially in patients with prior asbestos-related pleuroparechymal disease. It is a little unclear how the AFOP pattern explains all CT findings, as only a transbronchial biopsy was performed (no pleural biopsies or peripheral sampling).

Diffuse pulmonary ossification in permanent vegetative state. Porzionato et al, Pathol International.

Summary: A 21 year old woman entered a permanent vegetative state after a car accident, and died 17 years after the accident. She breathed spontaneously for the vast majority of this period. Autopsy revealed diffuse dendritiform and nodular pulmonary ossification, with a lower lobe and posterior accentuation. MicroCT analysis confirmed distribution and showed the 3D branching nature of the calcifications.

Take home message: Persistent/permanent vegetative state may be associated with DPO, possibly related to frequent infections or respiratory imbalance.


Summary: 55 year old non-smoking man with known Li-Fraumeni developed stage IV lung cancer, which was found to be an adenocarcinoma with an EGFR exon 19 deletion as well as a exon 20 T790M mutation (known resistance mutation). He died of progressive lung cancer. A 57 year old non-smoking woman with a history of breast cancer presented with stage IV lung cancer, and was subsequently found to have Li-Fraumeni. She had prolonged response to erlotinib, and her tumor was found to harbor EGFR L858R after clinical progression was noted. She died of progressive lung cancer.

Take home message: There appears to be some propensity to develop EGFR-mutated lung adenocarcinomas in Li-Fraumeni syndrome. Most tumors arise before age 55, and there is a female predominance.

**Summary:** Sporadic mutations in BRCA-associated protein 1 (BAP1) have been found in 23% of mesotheliomas. Germline mutations in BAP1 have been reported, and are associated with high risk of mesothelioma and melanoma, among other tumor types. They screened 78 patients with mesothelioma for germline BAP1 mutations, which they found in one patient, which was a synonymous mutation and thus did not impact protein sequence (silent mutation, minor allele).

**Take home message:** They found no significant germline mutations in 78 cases of mesothelioma. Thus, germline mutations in BAP1 can be estimated to be present in 1-2% of mesothelioma cases, suggesting a minor role in overall pathogenesis.

Letter to the Editor: Sarcoidosis and subsequent cancer risk: A Danish nationwide cohort study. Sogaared et al, Eur Resp J.

**Summary:** Large epidemiologic cohort study of cancer risk after the diagnosis of sarcoid (patients with cancer diagnosis before the diagnosis of sarcoid were excluded). 12,890 cases of sarcoid were included, and they observed a standardized incidence ratio of cancer diagnosis of 1.3 (95% CI 1.3-1.4). The risk was especially high in the first 3 months (excess risk of lung cancer, tonsillar cancer, and lymphoma; absolute 3 month cancer risk 1.2%). Risk was moderately increased from 3 months-3 years (risk of lung, tonsil, brain, and hematologic malignancies), with a 3 year absolute cancer rate of 3.2%. There was a 20% increased risk of cancer at 3-10 years after diagnosis (lymphoma, tonsil, hepatobiliary, and non-melanoma skin cancers), and 10% increased risk >10 years (hepatobiliary and non-melanoma skin cancer).

**Take home message:** Interesting study. Early risk seems to be result of increased surveillance, as well as tumors know to be associated with “sarcoid-like reaction” at diagnosis or during treatment. Some long term risk could be due to immunosuppression (HPV-related tonsil cancer, non-melanoma skin cancer), but there may be some true increased risk of some cancer types (hepatobiliary, lymphoma).


**Summary:** 70 year old man with asbestos exposure presents with effusion and pleural mass encasing the right lung with extensive calcification. Biopsy called extraskeletal osteosarcoma. Treated as mesothelioma on clinical grounds, died 5 months later. Autopsy showed sarcomatous elements with focal keratin and EMA expression, along with foci of osteosarcomatous and chondrosarcomatous differentiation. They called focal rhabdomyoblastic differentiation, although desmin was positive and myogenin/myoD1 negative (maybe more rhabdoid than truly rhabdomyoblastic).
Take home message: I think many of us have seen osteosarcomatous differentiation in a mesothelioma, but his case also had chondrosarcomatous and rhabdoid differentiation. Important to remember meso can show various heterologous elements, which are often keratin negative (especially on a small biopsy), which is why knowing the clinical and radiographic information can be so important.