PULMONARY PATHOLOGY JOURNAL CLUB
(September 2010 articles)
October 25, 2010

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Non-neoplastic diseases


I. ARTICLES FOR DISCUSSION


- **Purpose:** To see if tumor budding correlates with outcomes, tumor subtype, or tumor immunohistochemical phenotype in lung adenocarcinoma.

- **Methods:** Retrospective study of 665 patients with small (30 mm or less in diameter) treated by surgical resection
  - Survival time calculated from date of surgery
  - Tumors stained with H&E, PAS-alcian blue, and VVG and examined for tumor budding (defined as single cancer cells and clusters of less than 5 cancer cells):
    - Classified based on WHO classification (including tumor subtype—BACs excluded from study)
    - Budding graded based on a field with the most budding and number of clusters per 20x field counted
    - Then 20 tumors with high budding were used to construct TMAs and stained with 14 antibodies looking at various tumor characteristics (cellular adhesion molecules, growth factor, differentiation, etc)

- **Results:** Tumor budding seen in 43.1% of cases
  - Statistically significant association between presence of budding and: lymph node metastases, pathologic stage, vascular invasion, lymphatic invasion, pleural invasion
    - Presence of predominant papillary and acinar subtypes associated with tumor budding
      - Also presence of a micropapillary component associated with budding
    - BAC predominant associated with NO tumor budding
  - Survival data: statistically significant difference in 5-year survival rates between groups with and without any tumor budding
    - NO outcome difference between no budding and “grade 1” budding
    - YES outcome difference between no budding and “grade 2-3” budding
IHC data: budding associated with changes in cellular adhesion molecule expression (B-catenin, E-cadherin, and laminin-5γ2) and one differentiation marker (surfactant apoprotein-A)
  - However, caveat being they did not stain TMAs on tumors without high budding to compare it to—would there be a statistically significant difference if compared to this group?

**Take home points:** They only looked at small tumors, but still found tumor budding—and it seems to be associated with other indicators of biologic behavior including nodal metastases, stage, vascular invasion, and pleural invasion. In this series, tumor budding was an independent prognostic factor for small sized adenocarcinomas. In some cases, following IHC, they found that tumor budding actually represented lymphatic invasion that just wasn’t obvious on H&E. Tumor budding also seems to be associated with several histologic subtypes of adenocarcinoma, perhaps indicating that there may be some biologic mechanism for the tumor budding that is particular to these tumor types, a finding which seemed to be confirmed by associations with a change in the expression profiles of cellular adhesion molecules and differentiation markers. Does this mean we will someday have to report tumor budding in our diagnostic reports?

- **Purpose:** To compare the accuracy of clinical staging compared to pathologic staging between adenocarcinoma and squamous cell carcinoma
- **Methods:** Retrospective study based on 1046 consecutive patients undergoing resection of primary lung carcinoma (excluding those with BAC and who had undergone pre-operative chemo/radiation therapy)
  - Clinical stage determined by CT scan (mediastinal or hilar lymph node >1.0 cm in shortest axis considered diagnostic of nodal metastasis)
  - Included some but not all patients who had undergone cytologic/histologic examination of suspicious nodes
    - If pt had pathologically dx’ed N2 disease then excluded
    - Otherwise cytologic/histologic diagnosis was ignored and pt staged clinically based on CT alone
- **Results:** Total 708 patients (483 adenocarcinoma and 225 squamous cell carcinoma)
  - Overall, distribution of N-status between clinical and pathologic was statistically different between SCC and adenocarcinoma:
  - Within individual cases, diagnostic accuracy of clinical staging higher for adenocarcinoma than SCC, but adenocarcinoma more likely to be upstaged

<table>
<thead>
<tr>
<th>Clinical N-status</th>
<th>Pathologic N-status</th>
<th>( p )-Value</th>
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</thead>
<tbody>
<tr>
<td>Adenocarcinoma (n = 483) (%)</td>
<td></td>
<td></td>
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<tr>
<td>N0 413(85.5)</td>
<td>358(74.1)</td>
<td>( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>N1 25(5.2)</td>
<td>39(8.1)</td>
<td></td>
</tr>
<tr>
<td>N2 45(9.3)</td>
<td>86(17.8)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma (n = 225) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 148(65.8)</td>
<td>151(67.1)</td>
<td>( p = 0.63 )</td>
</tr>
<tr>
<td>N1 38(16.9)</td>
<td>42(18.7)</td>
<td></td>
</tr>
<tr>
<td>N2 39(17.3)</td>
<td>32(14.2)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number clinically staged “correctly” (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma 355 (73%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma 147 (65%)</td>
</tr>
</tbody>
</table>

- Regarding outcome data:
  - Clinical N-status and pathologic N2 status not statistically significant for SCC
  - Clinical N0-1 had significantly better survival than clinical N2 for adenocarcinoma but NOT SCC
- **Take home points:** In this series, patients with adenocarcinoma were more likely to have clinically undetectable N2 disease than SCC; however, patients with the clinically undetectable N2 disease behaved the same as the rest of the clinical N0-1 patients. This was not the same for SCC, in which N0-1 disease had no survival advantage over N2 patients. Up to 25% of patients will have a change in N-stage following resection—a finding that could potentially impact the decision to undergo neoadjuvent therapy. Patients with adenocarcinoma are more likely to have clinically undetectable nodal metastasis—which begs the question, if it’s not detectable by imaging, how large of a met is it? And if it’s a micromet or ITCs, does it matter clinically (see next article…)
Marchevsky AM et al. The presence of isolated tumor cells and micrometastases in the intrathoracic lymph nodes of patients with lung cancer is not associated with decreased survival. Hum Pathol 2010; 41: 1536-1543.

- **Purpose:** To study whether the presence of isolated tumor cells or micrometastases have any impact on prognosis in non-small cell lung cancer.
- **Methods:** 266 consecutive resections of clinical stage I NSCLC (lobectomy with hilar/mediastinal lymph node dissection) with follow-up data available from tumor registry:
  - One H&E slide with three levels $\rightarrow$ N staged based on H&E alone
  - IHC cytokeratin AE1/3 $\rightarrow$ isolated tumor cell defined as $<0.2$ mm (pN0(i+)); micrometastasis defined as $0.2 - 2.0$ mm (pN1(mi) or pN2(mi) based on location)
  - Also performed meta-analysis of previously published data on outcomes
  - Did NOT have access to any adjuvant radiation/chemotherapy data
- **Results:**
  - Reviewed 4148 lymph nodes from 266 patients (75% adenocarcinomas, 14% squamous cell carcinomas, 7% adenosquamous carcinomas, 4% large cell neuroendocrine carcinomas)
  - With H&E only: 197 were pN0 and 69 were pN1
  - With IHC: ITCs in 8 N1 nodes (retrospectively could not be seen on H&E) and micromets in 67 nodes
    - A total of 55 patients upstaged following IHC
      - 8 pN0 $\rightarrow$ pN0(i+)
      - 27 pN0 $\rightarrow$ pN1(mi)
      - 3 pN0 $\rightarrow$ pN2(mi)
      - 25 pN1 $\rightarrow$ pN2(mi)
  - Statistically significant survival difference between patients who were pN0 and pN1 based on H&E alone
    - *NO survival difference* between: pN0 and pN0(i+), pN1(mi), or pN2(mi); pN1 and pN2(mi)
    - Meta-analysis also showed no prognostic difference between pN0 and either pN1(mi) or pN2(mi) disease; not enough information to compare pN0 against pN0(i+)

<table>
<thead>
<tr>
<th>Nodal Category</th>
<th># cases</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0 (H&amp;E)</td>
<td>197</td>
<td>70</td>
</tr>
<tr>
<td>N1 (H&amp;E)</td>
<td>69</td>
<td>39</td>
</tr>
<tr>
<td>N0 (IHC)</td>
<td>160</td>
<td>72</td>
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<tr>
<td>N0(i+) (IHC)</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>N1(mi) (IHC)</td>
<td>27</td>
<td>60</td>
</tr>
<tr>
<td>N1 (IHC)</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>N2(mi) (IHC)</td>
<td>28</td>
<td>47</td>
</tr>
</tbody>
</table>

- **Take home points:** Current data suggest that ITCs and micromets should NOT upstage lung cancer patients—though a lot more data need to be collected for a longer time to be sure. Comparison with adjuvant treatment should also be performed to see if these data contain a treatment bias.
Doxtader EE et al. Core needle biopsy in benign lung lesions: pathologic findings in 159 cases. *Hum Pathol* 2010; 41: 1530-1535.

- **Purpose:** Determine types of non-neoplastic lung disease that can be diagnosed by core needle biopsy (CNB) and the factors that influence accuracy and specificity.

- **Methods:** 159 CNB with benign diagnoses from 155 patients were reviewed. Malignant or atypical diagnoses were excluded. Number of cores received was measured and added to obtain combined core length.

- **Results:** Biopsies with ≥ 3 cores more likely to yield specific diagnosis (82.5% vs. 54.5%, p = .002).

- Biopsies with combined length > 1 cm more likely to yield specific diagnosis (82.5% vs. 59%, p = 0.004).

- Overall, specific diagnosis made in 77% of cases. Necrotizing granulomatous inflammation most common (28%), organism detected in 1/3 of these cases.

- Next most common diagnoses: Scar, organizing pneumonia, benign neoplasm (hamartoma, SFT, schwannoma), non-necrotizing granulomatous inflammation.
  - Nonspecific diagnoses such as “interstitial fibrosis and chronic inflammation,” “acute and/or chronic inflammation,” “organizing hemorrhage” were 15% of total biopsies.
  - 8% of biopsies were nonrepresentative (fragments of normal lung or pleura)

- **Take-home message:** Specific diagnosis is more likely with more tissue (more cores or greater length of combined cores).
  - Granulomatous inflammation was most common finding; most presumed to be infectious even in the absence of confirmed organisms.
  - Some scars attributable to prior radiation or were apical cap. No scars were rebiopsied.
  - Only one false-negative biopsy where followup was malignant – diagnosis was chronic inflammation and fibrosis. A nonspecific finding on CNB should not be considered diagnostic.

CNB provides specific diagnoses in majority of cases.
II. ARTICLES FOR NOTATION ONLY

Neoplastic diseases

Trani L et al. Histology classification is not a predictor of clinical outcomes in advanced non-small cell lung cancer (NSCLC) treated with vinorelbine or gemcitabine combinations. Lung Cancer 2010; 70: 200-204.

- **Purpose:** To compare outcome data of patients treated with gemcitabine and/or vinorelbine (along or with platinum-based therapy) as a first-line chemotherapeutic agent between histologic subtypes of tumors.
- **Methods:** Retrospective study of 420 patients who received platinum/gemcitabine, platinum/vinorelbine, or single-agent gemcitabine or vinorelbine as first line chemotherapy and had clinicopathologic data and follow-up data available for review.
- **Results:**
  - Overall (regardless of histology)—no statistically significant difference in response rate or survival between pts on vinorelbine vs. gemcitabine or cisplatin vs. carboplatin
    - Adjusting for age, sex, performance status, and stage = marginally better progression-free survival with doublet chemo
  - Histologic type had no affect on likelihood of response to treatment
    - No statistically significant difference between adenocarcinoma vs. non-adenocarcinoma or squamous cell carcinoma vs. non-squamous cell carcinoma
- **Take home points:** Histologic subtype may impact response to some chemotherapy (pemetrexed with cisplatin) but not to all chemotherapy regimens.


- **Purpose:** To report the impact of histologic subtype on survival and toxicity outcomes in patients treated with either paclitaxel plus carboplatin (PC) or paclitaxel, carboplatin, and bevacizumab (PCB).
- **Methods:** Analysis of a previously defined set of patients who had histologically or cytologically confirmed stage IIIB or IV nonsquamous, non-small cell lung cancer who were then randomized into either PC vs. PCB.
  - Tumors categorized by predominant cell type
  - Primary endpoint of study = overall survival
- **Results:** Total of 878 patients with 68.8% adenocarcinoma, 18.9% “NOS”, 5.5% large cell carcinoma, 2.6% BAC, and 3.9% “other”.
  - There was a consistent improvement in progression-free survival over all histologic subtypes, but overall survival was improved only in the adenocarcinoma group (for all other histologic subtypes, data were inconclusive)
  - There was no increase in adverse affects associated with one specific histologic subtype.
Take home points: This study found an overall survival advantage for adenocarcinoma over other histologies with the addition of bevacizumab to other platinum-based chemotherapies. However, this study did not rereview the histologies of these tumors, and there certainly were a lot of “NOS” and “other” included in this tumor. And because of the contraindication of bevacizumab in patients with squamous cell carcinoma, we’ll never see a comparison with that tumor type.


Purpose: Somatic mutations in the EGFR kinase domain are associated with sensitivity to EGFR-tyrosine kinase inhibitors (EGFR-TKI) in patient with NSCLC. Different studies have reported very different mutation frequencies and clinical outcomes. This may be partially explained by technical differences in assessing EGFR mutations by PCR amplification from FFPE tissue and the limited reliability of various mutation detection approaches. This study evaluated whether denaturing HPLC is more sensitive and efficient than PCR.

Methods: All NSCLC patients with known EGFR mutations at the authors’ institution were identified. Cases included surgically resected specimens and bronchoscopic and needle biopsies. All samples were subjected to PCR and dHPLC for EGFR mutation detection.

Results: 373 patients with NSCLC were identified. 77% were adenocarcinomas or BACs. There was no direct comparison between sensitivity of HPLC and PCR. Overall, 88/373 (24%) had activating EGFR mutations. Clinical characteristics were consistent with previous studies – majority with mutations were female never-smokers with adenocarcinomas. They examined the relationship between the presence and type of EGFR mutations detected by HPLC and response to therapy with EGFR tyrosine kinase inhibitors. Patients with EGFR mutations detected by HPLC were statistically much more likely to respond to tyrosine kinase inhibitors.

Take-home message: HPLC may emerge as an alternative to PCR for EGFR mutation screening.


Purpose: To study the outcomes of bronchial carcinoids resected at a single medical center, focusing on outcomes and prognostic factors.

Methods: Retrospective chart review of 126 consecutive patients undergoing surgical resection of a bronchial carcinoid—did NOT review histology.
• **Results:** The only features that were statistically significant in predicting outcome were histology (typical vs. atypical) and stage:

![Graph](image1)

![Graph](image2)

- **Take home points:** Sort of reinforces what we already knew about carcinoids—histology and stage are the only things that predict outcome. In this series, resection provided “adequate” treatment without the need for adjuvant therapy. Also, subtotal resection, such as wedge or segment resections, don’t seem to negatively impact outcomes over larger resections.

Christensen JD et al. Correlation of [18F]-2-fluoro-deoxy-D-glucose positron emission tomography standard uptake values with the cellular composition of stage I non-small cell lung cancer 2010; 116: 4095-4102.

• **Purpose:** To determine whether there is a relation between FDG uptake activity on PET scan and the specific tumor cellular components of stage I non-small cell lung cancers.

• **Methods:** Retrospective review of early stage (T1a-T2a, N0, M0/stage I disease) patients who had an FDG-PET at time of initial staging, no prior therapy, and who subsequently underwent surgical resection—40 patients randomly selected from 235 who met study criteria. Both mean and max SUV were determined, and 5 random high-power fields of a single digitized slide from tumor were evaluated for % of tumor cells, stromal tissue, inflammation, necrosis, fibrosis, and “other” as well as histologic subtype, grade, and tumor dimension

• **Results:** There was no statistically significant correlation between mean/max SUV and specific cellular components. There was a significant correlation between mean SUV and mean necrotic material

• **Take home points:** We don’t really know why different lung tumors have different FDG uptake on PET scan; it does not seem to correlate with cellular composition. There is no direct correlation between SUV and number/% tumor cells in a tumor. There is potentially a positive correlation between mean SUV and tumor necrosis; however, a change in SUV does not necessarily correlate with a change in tumor burden, which may be important in following patients undergoing chemo/radiation. They did not correlate SUV value with histologic subtype in this study; that would have been interesting to see.

Tan K et al. Mesothelin (MSLN) promoter is hypomethylated in malignant mesothelioma but its expression is not associated with methylation status of the promoter. Hum Pathol 2010; 41: 1330-1338.
• **Purpose:** Gene methylation leads to malignant progression in some tumors. Mesothelin is restricted to the epithelioid type and epithelioid component of biphasic type of malignant mesothelioma (MM). Purpose was to clarify regulatory mechanisms of expression.

• **Methods:** Mesothelin expression was assessed by IHC on 39 cases of pleural MM, 41 of lung carcinoma, 26 of nonneoplastic lung, and 12 of normal lung. Tissue was microdissected and methylation-sensitive single nucleotide primer extension was used for methylation analysis.

• **Results:** Mesothelin was expressed in epithelioid MM and adenocarcinoma, but not in sarcomatoid mesothelioma. There was no statistically significant difference between methylation status of the *MSLN* promoter between epithelioid and sarcomatoid MM, but the *MSLN* promoter was significantly hypomethylated in the MM cases regardless of its subtype.

• **Take-home message:** Mesothelin is expressed in epithelioid mesotheliomas but not in sarcomatoid mesotheliomas. There is no significant difference in *MSLN* promoter methylation between these groups, but hypomethylation of the *MSLN* promoter is a characteristic feature of all MM. Mesothelin at the protein level may be lost post-transcriptionally in sarcomatoid mesotheliomas.


• **Purpose:** To evaluate whether immunohistochemical expression of ribonucleotide reductase subunit M1 (RRM1) predicts tumor response to gemcitabine and correlates with outcomes.

• **Methods:** Retrospective study of patients with locally advanced or metastatic non-small cell lung carcinoma who received gemcitabine as first or second line chemotherapy and stained available tissue for RRM1, then scored five 400x fields for both % positive cells and staining intensity.

• **Results:** 40 tumors eligible for study:
  o 26 (65%) negative for RRM1; 14 (35%) positive for RRM1
  o Did have a statistically significant median survival rate between two groups (12.9 mos in RRM1-negative compared to 5.1 mos in RRM1-negative)
  o No statistically significant difference in response rate between the two groups but did show a lower disease control rate (including partial response and stable disease) in RRM1-positive group.

• **Take home points:** RRM1 function is essential for DNA synthesis and is interrupted by the active metabolite of gemcitabine, difluorodesycytidine 5’-diphosphate; RRM1 overexpression can deplete gemcitabine levels and lead to tumor survival. This study would indicate overexpression of RRM1 correlates with poor prognosis in patients receiving gemcitabine chemotherapy. Therefore IHC for this marker may have use in evaluating patients who may receive this drug.

• **Purpose:** To try to establish markers which may provide a “relevant prognostic grouping” for lung tumors.

• **Methods:** Study of 405 lung cancers selected solely on the basis of tissue availability, which were subsequently typed based on WHO classification, constructed into TMAs, and stained for a panel of markers that play various roles in the EGFR cyclin within the cell
  o Also performed FISH for both EGFR and cyclin D1 gene

• **Results:**
  o In univariate analysis: e-cadherin, nuclear p27, cyclin D3 expressing tumors had significantly worse survival.
    ▪ Positivity for EGFR staining correlated with significantly decreased overall survival time
    ▪ Although all histologic subtypes trended towards worse overall survival for all of the above four markers, this was only statistically significant for adenocarcinoma
    ▪ When stratified to reflect stage—none of them was statistically significant
  o When analyzed with respect to stage, the combo of e-cadherin positivity and EGFR expression showed reduced overall survival
  o In multivariate analysis: only cyclin D1 was an independent predictor of poor overall survival time.

• **Take home points:** This group looked at various immunohistochemical markers for a group of intertwined molecular factors that represent EGFR signaling, G1 mitotic phase, and epithelial-mesenchymal transition. They were able to show that cyclin D1 IHC was an independent prognostic factor (similar to next paper). How clinically useful these data are remains to be seen.


• **Purpose:** To use immunohistochemical analysis of TMAs constructed from stage IIIA pN2 non-small cell lung carcinomas to try and immunophenotype the diverse array of N2 disease.

• **Methods:** Study of patients with resected stage IIIA pN2 disease who had survived 4 weeks after surgery, with no neoadjuvant chemo/radiation, with negative margins, and with available tissue to stain
  o I’m unsure whether they constructed TMAs from the tumor or the nodal metastasis
  o Stained for EGFR, ErbB-2, c-kit, COX-2, surviving, bcl-2, cyclin D1, cyclin B1, and MMP-2 and -9.
  o Tumors were analyzed with regard to survival data and were clustered based on IHC results

• **Results:**
  o Within histologic subtypes: bcl-2 and cyclin D1 were associated with squamous cell; MMP-2 and -9 and surviving were increased in all other subtypes
  o Multivariant analysis showed cyclin D1 positivity was an independent positive prognostic factor; EGFR trended towards better survival and surviving trended towards worse (unfortunate naming I suppose…)
In SCC, cyclin D1 was the only significant prognostic factor; in non-SCC, female gender and COX-2 were the only independent positive prognostic factors and MMP-2 and increasing number of node stations were poor prognostic factors.

There were 5 well-defined clusters that shook out; clusters 1 and 2 had statistically significant longer survival.

**Take home points:** There are a lot of studies out there looking at various IHC studies, some of which have conflicting outcomes. This study seems to show that depending on histologic subtype, IHC can be used to stratify risk in patients. This group makes the point that IHC could be used to determine whether a patient may need more intensive adjuvant therapy, though to my knowledge they did not correlate their outcome results with any chemo/radiation therapies.


**Purpose:** To investigate the prognostic impact of immunohistochemical evidence of angiogenic factors (vascular endothelial growth factor and its receptors—VEGF-A/VEGFR-2) and T-lymphocyte immune response (CD4/CD8).

**Methods:** Retrospective study looking at all resected stage I-IIIA tumors without prior therapy (n=335) with follow-up data available.

- TMA constructed using viable tumor and central tumor stroma and stained for VEGF-A, VEGFR-2 (scored semi quantitatively 0 – 3), CD4, and CD8 (expressed as % nucleated cells)

**Results:** Statistically significant difference in 5-yr survival rates between three groups:

- High VEGF-A/VEGFR-2 and low CD4/CD8 = 27%
- Low VEGF-A/VEGFR-2 and high CD4/CD8 = 87%
- All other combinations = 58%

**Take home points:** VEGF-A/VEGFR-2 and co expression of CD4/CD8 are strong prognostic indicators, independent of other clinicopathologic variables. This may serve as a jumping off point for further research into therapeutic strategies targeting either angiogenic blockade or increasing CD4/CD8 lymphocyte infiltration.


**Purpose:** To look at chromosomal alterations of a single inflammatory myofibroblastic tumor in detail using microarray-based comparative genomic hybridization (array CGH), which enables looks at the genome with higher resolution than other methods.

**Methods:** An IMT resected from a 15-year-old girl was examined histologically, immunohistochemically, and then genomic DNA was extracted and examined using array-CGH.

**Results:** A number of various copy number alterations were observed across several chromosomes, including those which contain both known and potential oncogenes and tumor suppressor genes. RNA expression of several tumor suppressor genes was repressed and levels of oncogenes were elevated.
**Take home points:** IMT’s share some chromosomal alterations seen in other lung neoplasms; this may, eventually, help us figure out the pathogenesis of IMT.


- **Purpose:** To exhaustively search for any evidence that human adenocarcinomas may be etiologically related to betaretroviral infection.
- **Methods:** Multiple methodologies (including immunohistochemistry, immunoblotting, RT-PCR, southern blotting) were performed on fresh tissue to find any evidence of the presence of proteins related to, RNA of, or antibodies directed against the Jaagsiekte sheep retrovirus (JSRV), which is the cause of a contagious form of lung cancer found in sheep (ovine pulmonary adenocarcinoma or OPA).
- **Results:** Of 28 samples collected:
  - 9 adenocarcinomas and 1 squamous cell reacted positively through IHC
  - None reacted to immunoblot analysis for JSRV
  - Retroviral RNA specific to the lung tumors was NOT found (it was present in both tumor and normal if it was present at all)
  - By screening cDNA libraries, they couldn’t find what antigen was reacting with IHC
- **Take home message:** Although retroviruses may be to blame in certain sheep pulmonary adenocarcinomas, there is no evidence that this is the case in humans…yet.

**Non-neoplastic diseases**


- **Purpose:** To describe a case of hypersensitivity pneumonia likely related to antigens from molds growing within a saxophone.
- **Methods:** A case is described of a 48-year-old man presenting with a 5 month history of dyspnea. He subsequently underwent CT scans and a wedge biopsy.
- **Results:** The wedge lung biopsy showed NSIP; CT scan showed bilateral poorly-defined nodules with ground-glass infiltrates. Subsequently, in testing the patient’s environment, *Ulocladium botrytis* and *Phoma* species were isolated from the mouthpiece of the patient’s saxophone; the patient did have antibodies directed against these two fungi. Further saxophone research found fungal colonization in 13 of 15 saxophones tested, though no additional cases of HP were found.
- **Take home points:** Add this exposure to the already long list of potential exposures to look for in suspected cases of HP. And I never imagined I would ever use the word “saxophone” so much in journal club.


- **Purpose:** To describe a case of hypersensitivity pneumonia likely related to antigens from organisms growing within a trombone.
• **Methods:** A case is described of a 35-year-old professional trombone player with a chronic cough for the past 15 years. He subsequently underwent an HRCT; no biopsies were performed.

• **Results:** CT showed a mosaic pattern which was pronounced on expiratory views. Bronchoscopy was normal. However, he noticed that symptoms resolved when he was not playing his trombone and were worse when he was playing more than normal. Subsequent culture of a biofilm found inside the trombone revealed *Mycobacterium chelonae/abscessus*, *Fusarium* species, *Stenotrophomonas maltophilia*, and *E. coli*. After regularly cleaning the trombone with isopropyl alcohol, symptoms resolved until he forgot to clean it, when they resumed again. Additional testing of other brass instruments (7 trombones and 4 trumpets) showed contamination with various mycobacterial and fungal species, though none of their owners were symptomatic.

• **Take home points:** Same as the last article.


• **Purpose:** Commentary on the previous two case reports of so-called “wind-instruments lung”.

• **Take home points:** It seems with the addition of these two cases, there are now three reported cases in the literature of apparent hypersensitivity pneumonia caused by wind instrument use. It is interesting to note that although most of the instruments sampled had a variety of mycobacterial organisms, bacteria, and molds growing, very few musicians seem to be affected by breathing problems. The authors surmise this may be due to exposure duration and concentration or the breathing patterns of the musicians. This interesting association needs to be kept in mind by clinician, pathologists, and musicians alike when evaluating a suspected case of hypersensitivity pneumonia. In the second report, a thorough cleaning in isopropyl alcohol was able to disperse the biofilm. However, some instruments are unable to undergo this isopropyl alcohol treatment without ruining the instrument itself—if clinicians can’t get people to give up their birds, giving up their instruments may prove equally as difficult.


• **Purpose:** To describe several cases of pulmonary Langerhans’ cell histiocytosis that were diagnosed on CT-guided, transthoracic core needle biopsy

• **Methods:** Three cases are presented in which patients (all smokers) were found to have multiple pulmonary nodules on chest CT scans. Subsequently, image guided core needle biopsies were performed.

• **Results:** Classic findings of PLCH were found in all three cases. Lesions were CD1a and S100 positive. All cores also demonstrated respiratory bronchiolitis. Also presented were two patients clinically and radiographically suspected to have PLCH who only had respiratory bronchiolitis on core biopsy but did have PLCH on subsequent wedge biopsies.

• **Take home message:** Sometimes you can diagnose PLCH on a transthoracic biopsy. Sometimes you can’t.