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Reviews, Case reports, and Editorials


Articles for Discussion

**FGFR1 Amplification in Squamous Cell Carcinoma of the Lung with Correlation of Primary and Metastatic Tumor Status.**
Monaco et al. Am J Clin Pathol

**Background and Purpose:** Fibroblast growth factor receptor 1 (FGFR1) gene is located in chromosomal region 8p11, which has emerged as an important oncogene in SqCC. FGFR1 is activated by a variety of mechanisms, including gene fusions and mutations, resulting in activation of downstream signaling pathways, leading to increased cell proliferation and survival in a variety of tumors. Recent studies have described amplification of FGFR1 in a subset of SqCCs. However, little is known about the correlation of FGFR1 amplification with clinicopathologic features and the findings in metastatic tumors, which may be helpful in characterizing these patients and guiding molecular testing in these cases. The aim of this study was to compare FGFR1 gene status with clinicopathologic variables and to look at the status in matched primary tumors and metastases.

**Methods:** Archived cases with a diagnosis of lung non–small cell carcinoma and SqCC tested for FGFR1 amplification by fluorescence in situ hybridization (FISH) were retrieved from UPMC from 2000 to 2013 and reviewed for FGFR1 amplification and clinicopathologic features. FGFR1 gene amplification was evaluated by FISH on formalin-fixed, paraffin embedded tissue sections from cytology cell blocks, tissue biopsy specimens, or surgical resections. FISH analysis of FGFR1 amplification was performed using a standard method with a three-color combined break-apart and amplification probe for FGFR1. FGFR1 (8p11.23-p11.22) appears as red and green signals, while the chromosome 8 centromere probe (blue signal) serves as a control probe. FGFR1 gene amplification was defined as a ratio between FGFR1 gene copy numbers and chromosome 8 greater than 2.

**Results:** Of the 336 cases tested by FGFR1 FISH, 52 (15%) were positive for amplification. Eight (13%) of 60 N0 cases and eight (17%) of 46 N1 or N2 cases were amplified, with no statistically significant difference. Of the 24 cases with matched primary and metastatic tumors, 22 (92%) were synchronous, 1 (4%) had discordant amplification, 3 (12.5%) demonstrate concordant amplification.

**Discussion:** The FGFR1-amplified tumors in current study tended to occur more often in slightly younger patients (p=0.04, 65 vs 69 year) with a trend toward tumor larger size (p=0.24, 2.8 vs 2.5 cm). Samples were largely from synchronous tumors diagnosed on the initial resection specimen prior to treatment, which may enrich for tumors that are genetically similar with minimal external factors selecting for different clones.
In studies looking at more metachronous tumors, or matched cases occurring before and after treatment, there may be more tumor heterogeneity, and subsequently, it is plausible that the discordance rate could be higher. Furthermore, other studies have shown that discordance may also be attributed to different tumors or other factors, particularly in the setting of a temporal lapse of more than 2.5 years, which is another argument to retest recurrences or metastases regardless of the primary tumor status.

**Take home message:**
1. Frequency of FGFR1 amplification is similar in SqCC with and without lymph node metastases.
2. But status in metastatic sites may be discordant from the primary in a small subset of cases. The case number is small: only 4 out 24 are tested positive for FGFR1 amplification, only 1 showed discordant status.
3. This may affect the decision to perform testing of metastatic SqCCs

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**Nuclear expression of CAMTA1 Distinguishes Epithelioid Hemangioendothelioma from Histologic Mimics**

**Doyle et al, AJSP**

**Background:** EHE is avascular neoplasm of intermediate malignancy, which shows recurrent t(1;3) leading to WWTR1-CAMTA1 fusion in most cases, (90%) with a minor subset showing YAP1-TFE3 fusion (<5%; focal well-formed vascular channels and voluminous eosinophilic cytoplasm). While WWTR1 is expressed in many tumor types, normal CAMTA1 expression is limited to the brain, making it potentially diagnostically useful. While prior studies have been conflicting, a recent study using a CAMTA1 antibody found expression in EHE (n=15) with expression in only 1 of the 276 non-EHE tumors (weak staining, ductal breast cancer). This study sought to test the antibody on EHE with special attention to “malignant” EHE, and compare expression to other epithelioid mesenchymal tumors.

**Methods:** Immunostaining was performed manually using anti-CAMTA1 rabbit polyclonal antibody (Novus Biologicals). 15 pulmonary EHE were included, and 5 were from mediastinum or pleura. 11 of the cases were “malignant” EHE.
Results:

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Total Cases</th>
<th>CAMTA1 Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHE</td>
<td>59</td>
<td>51 (86)*</td>
</tr>
<tr>
<td>Epithelioid hemangioma</td>
<td>20</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Epithelioid angiomatous nodule</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Epithelioid angiosarcoma</td>
<td>25</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Composite hemangioendothelioma</td>
<td>5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pseudomyogenic hemangioendothelioma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>25</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sclerosing epithelioid fibrosarcoma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myxoid epithelial neoplasms of soft tissue</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PEComa</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Osifying fibromyxoid tumor</td>
<td>10</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Of the 8 CAMTA1-negative tumors, 6 were positive for TFE3. CAMTA1 was positive in 44 of 48 (92%) cases with conventional histology and 7 of 11 (64%) cases with “malignant” histology.

- Diffuse nuclear CAMTA1 staining was seen in 44 of 48 conventional EHE (92%) and 7 of 11 malignant EHE (64%).
- 6 of the 8 CAMTA1 negative tumors showed nuclear TFE1 expression.
- CAMTA1 staining was seen in only 1 other tumor, core biopsy of a lung mass originally called epithelioid angiosarcoma, which is retrospect was probably EHE with solid growth.
- 5 cases showed focal weak cytoplasmic staining which should be ignored.

Discussion:
Nuclear CAMTA1 expression is specific and sensitive marker of EHE, which is helpful in distinguishing from morphologic mimics including epithelioid angiosarcoma. Prior study including carcinomas (n=169) also showed good specificity. If anyone is interested in bringing it on, make sure you pay attention to the specific antibodies, as other antibodies are not useful.

Banff study of pathologic changes in lung allograft biopsy specimens with donor-specific antibodies.
Wallace et al, JHLT

Background: Pathologic characteristics of AMR in the lung remain poorly understood, and the role of C4d staining remains unclear.

Methods: Digital slide analysis of 161 cases was performed by 9 experienced lung transplant pathologists from different institutions. All patients had complete serologic DSA data available from within 30 days of the biopsy, and had a negative infectious work-up. 55 patients had denovo DSAs (34%), 32 had non-DSAs (20%), and 74 (46%) had no antibodies. The pathologists were asked to assess for
Results
• No association was found with the presence of ACR, airway inflammation, or BO and the presence of DSAs.
• Acute lung injury (17%, pneumocyte hyperplasia and interstitial edema) +/- DAD (4%, hyaline membranes) had a significant association with DSAs vs. patients with no antibodies (p=0.0008). There was no association with non-DSAs vs. patients with no antibodies (p=0.91).
• There was a significant difference in endotheliitis (6%) in patients with DSA vs. those with no antibodies (p<0.0155), but no difference between those with DSA and non-DSA.
• Capillary inflammation (21%) was significantly more common in patients with DSAs vs. patients with no antibodies (p=0.0014). There was no association of non-DSAs vs. patients with no antibodies (p=0.99).
• More than average margination of PMNs grade 1 (17%), at least 2 PMNs back to back grade 2, frank capillaritis grade 3 (combined grades 2-3 7%).
• 14% of cases had focal (<50%) C4d, and 7% had diffuse via IHC. No significant difference was seen for focal C4d among the 3 groups. Diffuse IHC staining was more common in patients with DSA than those with no antibodies (0.0322). 1 of 67 IF was diffusely positive for C4d, and that patient had non-DSA.
• Agreement was fair for adequacy, airway inflammation, ALI, and endotheliitis. Agreement was slight for BO, aspiration, and capillary inflammation. Agreement moderate for ACR, hemosiderosis, and C4d. Agreement was less than chance for suspected infection.
• 33% of all interpretations were considered suboptimal or inadequate, and 38% did not have small airways.
Discussion
Capillary inflammation is associated with DSAs, but agreement is weak. ALI and endotheliitis also associate with DSAs with fair agreement, but ALI is not specific and endotheliitis is not very common (6%). They argue that C4d is not very helpful in detecting DSAs, and encourage use of clinical findings, DSA testing and biopsy results as a “triple test” for AMR.

Lymph node dissection in thymic malignancies: Implication of the ITMIG lymph node map, TNM stage classification, and recommendations.
Hwang et al, JTO.

Background: Lymph node dissection is currently not standard practice for thymic malignancies. Therefore, little is known about the typical pattern of lymphatic spread when it occurs in these tumors, or about how a full LN dissection might impact prognosis. The ITMIG and IASLC have developed and LN map and TNM staging system for the 8th edition of AJCC, which they set out to validate.

Methods: To investigate patterns of LN metastases in these tumors, they undertook a retrospective review of 131 resected thymic malignancies (99 thymoma, 32 thymic carcinoma including thymic neuroendocrine tumors) with lymph node dissection. They classified nodal mets according to the node map proposed by the ITMIG/IASLC, designating anterior nodes as N1 (lower anterior cervical, perithymic, prevascular, paraaortic, ascending aortic, superior phrenic, supradiaphragmatic, inferior phrenic, and pericardial) and deep nodes as N2 (deep cervical, supraclavicular, upper and lower paratracheal, subaortic, subcarinal, hilar, and internal mammary). Any nodes outside of these regions were designated as M1 disease.
Results

• They found 13 patients with LN mets (6 N1, 7 N2).
• 86% of the N2 disease was right paratracheal LN mets.
• Using the new proposed TNM staging system, risk of LN mets was 1% for stage 1 and 37.5% for stage 2/3.
• Nodal metastases were present in 8% of M0 patients and 43% of M1 patients.
• The rate of LN mets was 25% for thymic carcinoma and only 5.1% for thymoma (p<0.001).
• There were no nodal mets in types A, AB, or B1 thymomas.
• Freedom from recurrence rate was 87.9% for N0 patients vs. 38.5% for N1/N2 patients (p<0.001).

Take home point: The new proposed staging system does a good job predicting patients at risk for LN metastases. The right paratracheal area seems to be a particular hotbed for LN mets in thymic tumors. Thymic carcinomas had the most nodal disease, which is unsurprising, and types A, AB and B1 thymomas did not have any nodal disease in this study.

Neoplastic Articles for Notation

MMP-7 is a highly specific negative marker for benign and malignant mesothelial cells in serous effusions.

Davidson et al, Human Pathology.

Summary: This group had previously found MMP-7 to be overexpressed in ovarian serous carcinomas compared to peritoneal malignant mesotheliomas, and thought IHC for this marker may have some diagnostic utility. They looked at cell blocks from 307 effusions containing metastatic carcinoma (184 ovarian, 55 breast, 32 lung, 36 other), and 49 containing malignant mesothelioma, and did IHC for matrix metalloproteinase-7 on all. MMP-7 was positive (cytoplasmic staining) in 40% of carcinomas and negative in all mesotheliomas and reactive mesothelial cells. However, staining was usually only focal (most cases showed positivity in <50% of tumor cells). Expression was most common in GYN type carcinomas. Sensitivity and specificity to differentiated high grade serous from mesothelioma were 46% and 100%, respectively.

Take home point: Doesn’t seem to be a very diagnostically useful marker for this purpose, because it lacks sensitivity for carcinoma, but it is a specific negative marker of mesothelial cells.

The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (8th) edition of the TNM classification of lung cancer. Goldstraw et al, JTO.
Summary: The 8th edition of AJCC staging is scheduled to be published late this year, and implemented in early 2017. The IASLC database was used to provide evidence for the changes in the 7th edition, and a new database was constructed to propose changes for the upcoming 8th edition. They have 94,708 cases in their database from 16 countries, which have been statistically analyzed.
Take home message: I have to say, this is a complicated read, and it is hard to distill than changes down to key points even after reading it. The main differences I see is that T1 tumors are being broken down into 3 subcategories (< 1cm T1a, 1-2 T1b, 2-3 cm T1c). T2 now only spans tumors up to 5 cm (T2a 3-4 cm, T2b 4-5 cm). Tumors 5-7 cm are now T3, along with the tumors invading current “T3 structures” as defined by the 7th edition. Tumors greater than 7 cm are now T4, and diaphragm invasion is added to the list of “T4 structures” (it was a T3 structure in 7th edition). Endobronchial tumors that are located <2 cm from carina or with atelectasis/obstructive pneumonia were T3, are now moved down to T2. Whew! 😊

Utility of BAP1 Immunohistochemistry and p16 (CDKN2A) FISH in the diagnosis of malignant mesothelioma in effusion cytology specimens. Hwang et al, AJSP.

Summary: Whether one can (or should) definitively diagnose malignant mesothelioma on effusion cytology specimens is an area of controversy, since mesotheliomas can be very bland, and reactive mesothelial proliferations can show pretty impressive atypia. This group seeks ancillary tests that could make the diagnosis more definitive on cytology material, since invasion, the gold standard of mesothelioma diagnosis, cannot be assessed on cytology. They studied 15 cases of malignant meso and 3 cases of reactive mesothelial proliferations (I really wish they had more cases, but they cite other prior larger series that looked at reactive cases), in which they had both cell block and definitive biopsy. Four cases did not have enough cytology material for p16 FISH. 11 of 11 cases of mesothelioma had deletion of p16 and/or loss of BAP1 expression. BAP1 loss alone was seen in 67% of cases, and matched in biopsy in cytology material. Homozygous p16 deletion was found in 80% of biopsies and 73% of evaluable cytology material. 47% of biopsies and 43% of cytology specimens showed loss of both. The reactive processes had normal results for p16 and BAP1 (no loss of either).

Take home message: These markers show promise, but I feel larger studies are definitely needed, especially to make sure that false positives will not occur. In the end, I think we need to ask if we are comfortable definitively diagnosing meso on the grounds of these tests? Hopefully larger studies are in the works.

Lung cancer survival in Norway, 1997-2011: From nihilism to optimism Nilssen et al, ERJ.

Summary: Population based study of 34,157 Norwegian patients with lung cancer. Molecular genetic testing increased from 0% to 26%, and IHC evaluation increased from 8% to 26% over that time period. One year survival for unresectable patients increased from 22% to 34%, and for resectable patients (18% of cohort) increased from 75% to 92%. Improved survival persisted after multivariable analysis. The largest improvement in survival was observed in resected adenocarcinomas, while
patients >80 years saw the smallest increase. Even small cell carcinoma patients had an increase in survival.

**Take home point:** Seems we are making good progress in survival for patients with lung cancer, probably due to a number of contributing factors, although some of this may be due to increasing numbers of incidentally discovered lepidic tumors which may introduce some survival bias.

**Aggressive tumor microenvironment of solid predominant lung adenocarcinoma subtype harboring with epidermal growth factor receptor mutations.**
Sarawutari et al, Lung Cancer.

**Summary:** They studied 214 lung adenocarcinomas with EGFR mutations, and separated them into predominant growth pattern groups (lepidic, papillary, acinar and solid). In a subset of cases, they looked at expression of various proteins associated with tumor invasiveness (ezrin, laminin5), epithelial mesenchymal transition (E-cadherin), immune evasion (PDL1), and tumor stem-cell like phenotype (ALDH1). They also looked at “tumor supporting” protein expression on stromal cells in a subset of cases (D2-40, CD34, CD204, and FOXP3). Not surprisingly, they found solid predominant tumors to have a worse prognosis and more LN metastases and LVI. They also found that solid predominant tumors had higher expression of ezrin, laminin5, and PDL1, with more podoplanin positive fibroblasts and more CD204 positive macrophages than the other types. They propose the poor behavior of solid predominant tumors may be due to increased invasion and immune evasion phenotypes, along with expression of tumor promoting proteins by the stromal cells.

**Take home message:** The poor prognosis of solid predominant tumors may be in part due to tumor microenvironmental factors, including promotion of invasion, immune evasion, and stromal tumor promotion.

**The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma.**
Singhi et al, Mod Pathol.

**Summary:** They looked at 86 peritoneal mesotheliomas using dual color fish for NF2 and CDKN2A, and IHC for BAP1. They found homozygous CDKN2A deletions in 25 cases (29%), hemizygous NF2 loss in 30 cases (35%), and loss of BAP1 expression in 49 cases (57%). 79% of peritoneal mesotheliomas had at least one of these abnormalities. CDKN2A deletion or NF2 loss correlated with shorter progression free survival (p<0.02) and poorer overall survival (p<0.03), and the effect appeared to be cumulative and significance persisted on multivariate analysis. BAP1 loss was not associated with clinical outcome.
**Take home message:** Loss of CDKN2A and NF2 seems to be a poor prognostic factor in peritoneal mesothelioma.

**Respiratory cytology- Current trends including endobronchial ultrasound-guided biopsy and electromagnetic navigational bronchoscopy.**

*Sturgis et al, Archives.*

**Summary:** They analyzed the responses to the 2013 CAP supplemental survey from the interlaboratory comparison program in bronchopulmonary cytology. This included 788 laboratories. Two thirds of labs used cytotechs to screen their bronchopulmonary cytology material. 40-50% of labs performed touch preps from the biopsy material, and of those, about half issued separate cytology and biopsy reports, while the other half issued an integrated report. >95% of labs interpreted bronchial washings and brushings, while only 43% read EUS-FNA material. 14% were receiving material obtained by electromagnetic navigational bronchoscopy. Intra-procedural adequacy assessment was most often performed for transcutaneous CT guided biopsies (74%). Cytology material was increasingly used for IHC and molecular studies.

**Take home point:** Snapshot of bronchopulmonary cytology practices across the country at this time shows widespread use, rising rates of imaging guided material, and increasing utilization for IHC and molecular testing.

**Non-neoplastic articles for Notation**

**Pirfenidone for idiopathic pulmonary fibrosis: Analysis of pooled data from three multinational phase 3 trials**

*Noble et al, ERJ*

**Summary:** Pirfenidone is an oral antifibrotic agent recently approved to treat patients with IPF. Prior studies had showed some conflicting efficacy results, so this study looked at pooled data of pirfenidone vs. placebo, using data from CAPACITY and ASCEND trials. 1,247 IPF patients were included (623 treatment, 624 placebo; 90% completed 12 months of treatment): patients receiving pirfenidone experienced “clinically meaningful reductions in disease progression”, measured as a 44% reduction in the proportions of patients with >10% decline in FVC or death, and a 59% increase in patients with no decline (<0.001). Treatment effect was noticeable as early as 3 months. Treatment was also associated with better progression-free survival (HR 0.62, p<0.001), 6 minute walk distances, and dyspnea scores. Adverse effects of the drug included mild to moderate GI complaints and rash, which infrequently led to discontinuation of drug.
**Take home point:** Pirfenidone seems to have a clinically meaningful treatment benefit for patients with IPF, and an acceptable safety profile.

**Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT.**
*Walsh et al, Thorax.*

**Summary:** They used 150 cases of interstitial lung disease on CT, which were interpreted by 112 radiologists (96 were specialized thoracic radiologists), using the categories of UIP, possible UIP, and inconsistent with UIP. They also asked them to score traction bronchiectasis, emphysema and honeycombing as definitely present, possibly present, or absent. The diagnoses of the patients assigned by a multidisciplinary team included 34 IPF, 21 NSIP, 51 connective tissue disease associated ILD, and 44 chronic HP (only 22 of the patients had biopsy confirmation of their diagnosis). Interobserver agreement was moderate and was not different between general radiologists (0.48) vs experienced thoracic radiologists (0.52). Agreement was best for honeycombing (0.59), followed by traction bronchiectasis (0.42) and emphysema (0.43). Stratifying the CTs by multidisciplinary team diagnosis or patient age did not improve agreement.

**Take home point:** Agreement on the diagnosis of UIP pattern on CT is only moderate, even for experienced thoracic radiologists.

**Reviews, case reports and editorials**

**Mucinous cystic tumor with CK20 and CDX2 coexpression of the thymus: Is this a benign counterpart of adenocarcinoma of the thymus, enteric type?**  
*Akiba et al, Pathol International.*

**Take home point:** They describe a case of an 8 cm unilocular cystic thymus mass filled with mucin in a 55 year old man. The cyst was lined by bland goblet cells, with only focal papilla formation. Patient alive and well at 10 years. Is this a distinct entity, or an under sampled teratoma, unusual bronchogenic or thymic cyst?

**Patient with slow-growing mediastinal mass presents with chest pain and dyspnea.**  
*Biswas et al, Chest.*

**Take home point:** Presentation of a patient with a 22 cm mass in her hemithroax with areas of fat on preop imaging. FISH was negative for MDM2, DDIT3, EWSR1, and FUS. They called it a liposarcoma anyway 😊. It has areas of myxoid change and lipoblasts with some areas they say resemble well-diff liposarc, but I wonder if it is a “myxoid pleomorphic liposarcoma” given the mediastinal location and myxoid areas
along with the lack of any specific genetic abnormalities typical of WDL/DL or myxoid liposarcoma.

**Primary pulmonary salivary gland-type tumors: A review and update**  

**Take home point:** Nice review complete with some nice tables, photomicrographs, and charts, including IHC and molecular features of different salivary type tumors found in the lung. They have a nice pie chart that shows the relative frequency of different types of tumors in the lungs vs. in the salivary glands.

**Primary salivary duct carcinoma of the lung, mucin rich variant.**  
Fishbein et al, Human Pathol

**Take home point:** They report a large lung tumor in a smoker that showed peculiar “in situ” involvement of the bronchial seromucinous glands with central necrosis, resembling DCIS. Immunostains showed expression of mammoglobin, GCDFP, GATA3 and focal/weak AR. No clinical evidence of breast cancer in this lady. Lots of mucin. I think may people would have just called this tumor a poorly diff adeno, or if they had done immunostains postulated breast cancer, but they propose this represents the entity in the title. It showed a \textit{BRAF G464V} mutation, which has been described in the literature in breast and lung cancer but never in salivary type cancers. I appreciate the unique immunophenotype here, but not sure there would be any harm to the patient to just call this a poorly differentiated non-small cell carcinoma or adenocarcinoma.

**A new staging system for thymomas- Will it improve outcome?**  
Huang, JTCVS

**Take home message:** Editorial on the issues surrounding the new proposed staging of thymic tumors, if you want to read some commentary about the strength and weaknesses of the data used to generate the new proposed system.

**Tumor islands and spread through alveolar spaces: Distinct patterns of invasion in lung adenocarcinoma**  
Morales-Oyarvede et al, Pathology International

**Take home point:** Well written review discussing mechanisms of airway spread, including tumor islands (nests of tumor discontinuous from main tumor nodules, but connected based on 3D modeling) and spread through alveolar spaces (STAS), both of which have been associated with poorer outcome in resected lung cancer, as
well as increased risk of recurrence for patients undergoing wedge resection (vs. lobectomy).

**Spontaneous pneumothoraces due to metastatic endometrial stromal sarcoma in a woman infected with HIV**
Shah et al. AJRCCM

**Take home point:** Case of numerous solid and cystic lung nodules, biopsied and found to be metastatic ESS, despite the fact that most HIV patients with pneumothoraces have opportunistic infection. Nice CT images.

**Resentitization to crizotinib by the loratinib resistance mutation L1198F**
Shaw et al. NEJM

**Take home point:** Report of a case, patient treated with crizotinib and developed resistance via a C1156Y mutation in the ALK kinase domain after 18 months. She responded to the third generation ALK inhibitor loratinib. When she relapsed, after 8 months, sequencing showed L1198F mutation in addition to the previously detected C1156Y. This mutation causes steric interference and inhibits loratinib binding, but causes paradoxical increased affinity for crizotinib. Therefore she was re-challenged with crizotinib and had response for an additional 6 months.

**ALK-rearranged squamous cell lung carcinoma responding to crizotinib: A missing link in the field of non-small cell lung cancer?**
Vergne et al, Lung Cancer.

**Take home point:** They report a case of CK5/6, p40 and p63 positive, TTF negative lung squamous cell carcinoma with ALK rearrangement that responded to crizotinib. So this can occur. Makes you wonder about under sampled adenosquam, as the diagnosis was made on bronchial biopsy. Interesting that she was also a never smoker, which would be very unusual for run-of-the-mill squam, and that is why she was tested (3+ ALK stain by IHC).