# PULMONARY PATHOLOGY JOURNAL CLUB
(May 2014 articles)
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## Articles for Notation

### Original Articles

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Case Reports and Letters to the Editor


Hsieh et al. Pulmonary tuberculosis presenting as organizing pneumonia. Am J Respir Crit Care Med 2014;189:e63

I. Articles for Discussion


Purpose: To determine if the outcomes of patients with ground-glass lesions with radiographic and biopsy findings suspicious for early adenocarcinoma who are observed differ from those who are resected immediately.

Methods: The clinical outcomes of patients who had undergone CT-guided FNA of ground-glass lesions who were resected after abnormal cytology results were compared to those who opted for watchful waiting.

Results: This single-institution study included 63 patients, 47 of whom underwent immediate resection and 16 elected observation. Among the observation group, 6 (37.5%) ultimately had growth and/or development of a solid component in the ground-glass lesion, 5 of whom elected to proceed to definitive therapy. No distant metastases or lung cancer deaths occurred in the observation group. Outcomes for the immediate resection group were: 2 developed metastatic disease, 5 developed metachronous primaries, and 3 had progression in existing ground-glass nodules.

| TABLE 2. Inclusion and Exclusion Criteria Based on Cytologic, Radiographic, and Clinical Findings |
|---------------------------------|---------------------------------|---------------------------------|
| **Inclusion**                   | **Exclusion**                   |                                  |
| Cytology                        | Group 1                         | Necrotic debris                 |
|                                 | Atypical bronchioloalveolar proliferation | Benign “epithelial cells and histiocytes” |
|                                 | Atypical (glandular, epithelial, or bronchial) cells | Reactive (unless atypical) |
|                                 | Abnormal cells                  | Adenocarcinoma                  |
| Group 2                         | Adenocarcinoma with BAC features | Inflammation                    |
|                                 | Suspicious/favor/suspect BAC    | PCP/AFB+/fungal elements        |
| Radiology                       | Size <30 mm of largest nodule on CT scan | Cavitation                      |
|                                 | Pure ground-glass opacity or part-solid | Solid                           |
| Clinical                        | Must have follow-up records with outcome documented (repeat CT scans/physicians note) for at least 1 yr | Suspicion for infection based on clinical history |
|                                 |                                  | Treatment with chemotherapy     |
|                                 |                                  | History of lung adenocarcinoma or concurrent adenocarcinoma at the time of biopsy |

BAC, bronchioloalveolar adenocarcinoma; CT, computed tomography.
Discussion: Delayed resection of ground-glass lesions suspicious for adenocarcinoma does not appear to adversely affect outcome.

Take Home Message: For patients with suspicious ground-glass lesions who are poor surgical candidates, continued observation appears to be a reasonable practice.


Purpose: Categorizing atypical mesothelial proliferations along the pleural or peritoneal surface is diagnostically challenging. FISH detection of homozygous p16 deletions has been shown useful in discriminating malignant from benign mesothelial proliferations. This study correlates the p16 status of mesothelioma and separate surface mesothelial proliferations, which has not be previously studied.

Methods: p16 FISH was performed in 11 pleural and 7 peritoneal mesotheliomas in which there was both an invasive component and a separate surface proliferation.

Results: Homozygous p16 deletion was present in 5 of 11 pleural and 1 of 7 peritoneal invasive mesotheliomas and in all 6 positive cases, the separate surface proliferation also had p16 deletion. None of the cases in which the invasive component was p16 deletion-negative had a discordant p16 result in the surface proliferation.
FIGURE 3. Biopsy from a patient with clinical (thoracoscopic) and radiologic evidence of a mesothelioma, but the biopsy shows only a surface mesothelial proliferation (A and B) and no invasive tumor. C. The FISH image demonstrates loss of p16 in all of the surface cells. In the context of disease thought clinically (thoracoscopically or laparoscopically) and/or radiologically to be a mesothelioma, p16 deletion in the surface component, as demonstrated here, allows a diagnosis of mesothelioma without another biopsy.
**Discussion:** Surface mesothelial proliferations near invasive mesothelioma show the same p16 FISH pattern. Biopsies showing only a surface mesothelial proliferation that demonstrates homozygous p16 deletion by FISH can be diagnosed as mesothelioma if there is clinicoradiographic evidence of diffuse pleural or peritoneal tumor, but the absence of p16 deletion does not exclude underlying invasive mesothelioma.

**Take Home Message:** Although the caveats are clearly stated by the authors, a positive p16 deletion result has the potential to be taken out of context, resulting in an erroneous diagnosis of mesothelioma in superficial samples if not correlated with the clinical and radiographic findings adequately.

**Hwang et al.** Pulmonary large cell carcinoma lacking squamous differentiation is clinicopathologically indistinguishable from solid-subtype adenocarcinoma. Arch Pathol Lab Med 2014;138:626-635

**Purpose:** Although the WHO defines large cell carcinoma (LCC) without regard to immunohistochemistry (IHC), several prior studies have investigated IHC as a means to recategorize most, if not all cases of LCC as adenocarcinoma or squamous cell carcinoma. The current study compares the clinicopathologic and molecular characteristics of solid-type adenocarcinoma and LCC.

**Methods:** Surgical resections of NSCLC with solid growth pattern without overt squamous or neuroendocrine differentiation were included. There were 57 LCC and 42 solid adenocarcinomas, as defined by the WHO criterion of 5 intracellular mucin droplets in ≥2 HPFs. All cases were subjected to KRAS, EFGR, and ALK testing.
Results: Both LCC and solid adenocarcinoma frequently expressed TTF-1. The proportion of tumors harboring KRAS mutations was not significantly different (38% of solid adenocarcinomas; 43% of LCC). Both groups included one EGFR-mutated case and 1 case with an ALK rearrangement. No significant outcome or clinical differences between the LCC and solid adenocarcinoma groups were observed and in both groups the prevalence of smoking was > 95%.

<table>
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<th>Table 3. Morphologic and Immunohistochemical Characteristics of Solid Adenocarcinoma (ADC) and Large Cell Carcinoma (LCC)</th>
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<tr>
<td><strong>Morphology, No. (%)</strong></td>
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<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td><strong>Growth pattern</strong></td>
</tr>
<tr>
<td>Undifferentiated</td>
</tr>
<tr>
<td>With palisading (% of UD)</td>
</tr>
<tr>
<td>Basaloid</td>
</tr>
<tr>
<td>Combined undifferentiated/basaloid</td>
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<tr>
<td><strong>Clear cell features</strong></td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Focal</td>
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<tr>
<td>Extensive</td>
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<tr>
<td><strong>Immunohistochemistry, No. (%)</strong></td>
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<tr>
<td>TTF-1 +/- p63 -</td>
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<td>TTF-1 +/- p63 +</td>
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<tr>
<td>TTF-1 --/p63 --</td>
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<tr>
<td>TTF-1 --/p63 +/- p40 --</td>
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Abbreviations: TTF-1, thyroid transcription factor 1; UD, undifferentiated.

Discussion: Aside from not meeting WHO criteria for intracellular mucin, LCC lacking squamous or neuroendocrine differentiation is indistinguishable from solid adenocarcinoma.

Take Home Message: Is it time to abolish the LCC category all together? Based on the morphologic, immunohistochemical, molecular, and clinical similarity to solid adenocarcinoma, it appears that these tumors may best be reclassified as mucin-poor solid adenocarcinoma.

Kadota et al. The cribriform pattern identifies a subset of acinar predominant tumors with poor prognosis in patients with stage I lung adenocarcinoma: a conceptual proposal to classify cribriform predominant tumors as a distinct histologic subtype. Mod Pathol 2014;27:690-700

Purpose: Patients with acinar-predominant lung adenocarcinoma display a spectrum of clinical behavior. This study examines whether cribriform arrangements, which are regarded as a pattern of acinar adenocarcinoma according to the IASLC/ATS/ERS system, has prognostic importance.

Methods: In this single-institution study, slides from 1038 surgically resected stage I lung adenocarcinomas were retrospectively reviewed and the percentage of cribriform pattern was recorded.

Results: The 5-year recurrence-free probability for the 46 patients with cribriform-predominant tumors of 70% was significantly lower than that for acinar-predominant tumors (87%) or papillary-predominant tumors (83%) and was comparable to micropapillary and solid-predominant tumors. By multivariate analysis, tumors with ≥ 10% cribriform pattern had a significantly higher risk of recurrence than those with < 10% cribriform pattern. Greater than or equal to 10% cribriform pattern was associated with smoking, higher stage, pleural invasion, and lymphatic-vascular invasion. Cribriform-predominant tumors were more frequently TTF-1-
negative (17%) than acinar-predominant tumors, but this difference was not statistically significant. The presence of a cribriform-predominant histology did not correlate with ALK rearrangements, KRAS mutations, or EGFR mutations.

Discussion: Cribriform pattern should be considered a distinct subtype of lung adenocarcinoma, as it has a high risk of recurrence.

Take Home Message: The authors again make a pitch for comprehensive histologic subtyping. Whether or not that practice is clinically relevant, what appears to be important from this study is to recognize cases in which there is ≥ 10% cribriform pattern.

Shekhel et al. Surgical pathology of pleural coccidioidomycosis: a clinicopathological study of 36 cases. Hum Pathol 2014;45:961-969

Purpose: Coccidioidal infections rarely involve the pleura. This study aims to better define the clinicopathologic characteristic of pleural coccidioidomycosis.
Methods: The clinicoradiographic and histologic features of biopsy, resection, or autopsy specimens from two institutions in Arizona in which coccidioidal spherules were present in pleural tissue were retrospectively reviewed.

Results: The median age among the 36 identified cases was 39 years and 69% of patients were male. Pleural involvement represented 7% of all pulmonary coccidioidal infections. There were 2 modes of presentation: ruptured cavitary infections and pleural-predominant disease with milder parenchymal involvement, both of which had similar histologic findings. Occupational exposure to soil, smoking, and immunodeficiency were risk factors. The most common symptoms were cough, chest pain, and dyspnea. Common imaging findings were effusions and adhesions. All cases were characterized by granulomatous pleuritis, but spherules were typically sparse (mean density, <1/10 HPF). All 3 deaths occurred in patients with ruptured cavities.

Discussion: Coccidioidomycosis should be considered in the differential of pleural effusions, ruptured cavities with decortication, and biopsy samples of presumed infectious pleuritis even in cases without significant pulmonary parenchymal disease.

Take Home Message: Generously sample granulomatous pleural samples as spherules may be sparsely distributed within the tissue.

II. Articles for Notation

Original Articles


Purpose: To investigate the utility of two new EGFR mutation-specific immunohistochemical antibodies in detecting EGFR mutations in lung adenocarcinoma.

Methods: EGFR mutational analysis was performed on 241 resected lung adenocarcinomas and an additional 6 cases that were post-neoadjuvant gefitinib-treated. Four antibodies (two novel clones SP125 and SP111; two previously reported clones 43B2 and 6B6) specific for L858R or 15-nucleotide exon 19 deletion EGFR mutations were tested on whole sections or TMAs.

Results: The sensitivity for the novels clones SP125 and SP111 was 76% and 83%, respectively, which is comparable to currently available antibodies, and was unaffected by gefitinib pretreatment.

Take Home Message: Although EGFR immunohistochemical antibodies are specific only to their target mutations, they can play a valuable role in low cellularity specimens. However, there are a number of caveats, including their relatively lower ability to detect point mutations than sequencing and nuances in interpretation of cases that exhibit low intensity staining.

**Purpose:** To evaluate the expression of TTF-1 in extrapulmonary adenoid cystic carcinoma (ACC).

**Methods:** Immunoeexpression of TTF-1 was evaluated in 40 ACCs, including 3 ACCs originating in the lung.

**Results:** While no primary ACCs, including those in the lung, showed TTF-1 staining, 41.7% of metastatic ACCs, all of which were only metastatic to the lung, were immunoreactive. Staining was focal and only seen in the cribriform subtype. TTF-1-positive cases also were immunoreactive for Napsin A.

**Take Home Message:** Although this paper was confusing to read, the authors appear to have demonstrated that TTF-1 and Napsin A immunoexpression are not in and of themselves evidence of primary pulmonary ACC.

**Ao et al. The utility of a novel triple marker (combination of TTF1, napsin A, and p40) in the subclassification of non–small cell lung cancer. Hum Pathol 2014;45:926-934**

**Purpose:** To compare the utility of a newly developed triple immunohistochemical marker that combines TTF-1, napsin A, and p40 with individual markers in subclassifying NSCLC.

**Methods:** Immunoeexpression was scored semi-quantitatively on TMAs of resected lung cancers, including 77 each of adenocarcinoma and squamous cell carcinoma, and 46 metastatic lung adenocarcinoma.

**Results:** For adenocarcinoma, the triple marker was 93.5% sensitive and 77.5% specific, as compared to 85.7% and 75.0% for TTF-1 and 89.6% and 90.0% for napsin A. The triple marker was 88.3% sensitive and 92.5% specific for squamous cell carcinoma, while p40 was 80.5% and 90.0%, p63 was 93.5% and 80.0%, and CK5/6 was 89.6% and 80.0%. For metastatic lung adenocarcinoma, triple marker sensitivity and specificity was 71.7% and 73.5%.

**Take Home Message:** This novel triple marker demonstrates sensitivity and specificity comparable to individual markers in the subclassification of lung carcinoma with the added advantage of conserving tissue, which is critical in this era of molecular testing.

**Calio et al. ALK/EML4 fusion gene may be found in pure squamous carcinoma of the lung. J Thorac Onc 2014;9:729-732**

**Purpose:** To assess the prevalence of ALK rearrangements in squamous cell lung carcinoma.
**Methods:** ALK status was assessed in 40 consecutive resected pure squamous cell lung carcinomas by FISH. Squamous differentiation was confirmed by positive immunostaining for p40 and CK5/6 and negative immunoreactivity for TTF-1 and napsin A.

**Results:** An ALK rearrangement was identified in 1 (2.5%) of 40 cases.

**Take Home Message:** Although rare, ALK rearrangements can be found in squamous cell lung carcinoma, which offers a rationale for performing ALK testing in tumors other than adenocarcinoma.


**Purpose:** While the IASLC/ATS/ERS classification of lung adenocarcinoma has been validated in early stage disease, this study attempts to ascertain the relevance of this classification in advanced disease.

**Methods:** A variety of clinicopathologic features were evaluated in 313 lung adenocarcinoma patients who received platinum-based chemotherapy.

**Results:** Tumors were classified as follows: 44.7% acinar, 34.2% solid, 10.1% papillary, 7.4% lepidic, and 3.5% micropapillary. Response rates, as well as overall and progression-free survival were significantly better for high-grade adenocarcinomas as a group (combining micropapillary, papillary, and solid-predominant) than intermediate grade tumors (lepidic and acinar-predominant combined).

**Take Home Message:** The prognostic differences seen in early stage lung adenocarcinomas classified by the new system do not appear to hold for advanced disease. The longer overall survival seen in patients with advanced high-grade adenocarcinoma may reflect a better response to chemotherapy.


**Purpose:** To investigate the clinical relevance of pathologic subtypes in metastatic lung adenocarcinoma.

**Methods:** Major adenocarcinoma subtype according to the IASLC/ATS/ERS classification was assigned to 100 surgical biopsies of lung adenocarcinoma at a metastatic site. EGFR and KRAS mutation testing was also performed.

**Results:** There were 50 solid, 29 acinar, 20 micropapillary, and 1 papillary-predominant adenocarcinomas. No survival differences with respect to histologic subtype were observed in the 45 patients who did not receive systemic therapy. Of the 55 who did, worse survival was seen in solid-predominant adenocarcinoma, as compared to acinar and micropapillary-
predominant tumors. Solid-predominant tumors were also less likely to harbor EGFR mutations and were less frequent in never smokers.

Take Home Message: In patients with metastatic lung adenocarcinoma treated with systemic therapy, a solid-predominant histology at the metastatic site portends a poorer prognosis. Noting when a solid-predominant pattern is present in samples of metastatic lung adenocarcinoma would appear to be useful information to include in the pathology report.

De Cos Escuin et al. Tumor, node and metastasis classification of lung cancer – M1a versus M1b – Analysis of M descriptors and other prognostic factors. Lung Cancer 2014;84:182-189

Purpose: To assess the survival differences between M1a and M1b lung cancer patients and the prognostic impact of the different M descriptors.

Methods: The survival and various other prognostic factors of all lung cancer patients with M1 disease that were registered in a Spanish cooperative group during a 21-month period were analyzed.

Results: Among 195 M1a and 445 M1b NSCLC patients, those with M1b had significantly worse survival than those with M1a disease. Survival was significantly worse in M1b patients with metastatic disease at multiple locations as compared to metastatic disease at only one site. Of M1b patients with metastatic disease at only one site, those who had multiple lesions had significantly poorer survival than those who a single lesion, particularly in the CNS.

Take Home Message: Not only does separating M disease into M1a and M1b have prognostic value, so too does quantifying the number of sites and lesions.

Hamanaka et al. A subset of small cell lung cancer with low neuroendocrine expression and good prognosis: a comparison study of surgical and inoperable cases with biopsy. Hum Pathol 2014;45:1045–1056

Purpose: To better understand the pathologic characteristics of a subset of SCLC that has good prognosis.

Methods: A total of 96 cases (45 resections and 51 biopsy samples) were studied by gene expression profiling and immunostaining for chromogranin, synaptophysin, CD56, p63, and keratin 34betaE12.

Results: Patients negative for neuroendocrine markers had significantly better prognosis than those that showed neuroendocrine staining. There was no survival difference between patients that showed or lacked immunoexpression of basaloid markers.

Take Home Message: Hmm… how is it that tumors with immunohistochemical expression of basaloid markers are classified as SCLC?
**Kim et al. Impact of cigarette smoking on response to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors in lung adenocarcinoma with activating EGFR mutations. Lung Cancer 2014;84:196-202**

**Purpose:** To assess the impact of smoking on TKI response in patients with activating EGFR-mutated lung adenocarcinoma.

**Methods:** Detailed smoking histories and clinical outcomes were assessed in 222 Korean patients with lung adenocarcinomas with activating EGFR mutations treated with TKIs.

**Results:** There were 65.3% never-smokers, 19.8% < 30 pack-year smokers, and 14.9% > 30 pack-year smokers. Heavy smokers had significantly shorter survival than never-smokers. No difference in survival was observed between never and light smokers. In multivariate analysis, smoking ≥ 30 pack-years was an independent predictive factor for disease progression.

**Take Home Message:** Heavy smokers with activating EGFR-mutated lung adenocarcinomas do not fare as well as patients with lighter smoking histories in response to EGFR TKIs.


**Purpose:** To confirm that pirfenidone, an oral antifibrotic agent, reduces disease progression in IPF.

**Methods:** In this phase 3 trial, 555 patients were randomly assigned to the study drug or placebo for 52 weeks with a primary end point of change in forced vital capacity (FVC).

**Results:** Pirfenidone significantly improved progression-free survival. The proportion of patients with no decline in FVC was significant as compared to placebo. There was also a relative reduction in the proportion of patients who had an absolute decline of ≥10 percentage points in the percentage of the predicted FVC or who died.

**Take Home Message:** This drug, along with another presented in a subsequent article in this month’s journal club, appears to be a breakthrough in slowing the relentless progression of IPF.


**Purpose:** RET fusion has been identified as a driver mutation in the development of lung adenocarcinoma, but the underlying molecular mechanisms are not well understood. This study attempts to better elucidate these mechanisms.

**Methods:** Genomic segments from 18 cases containing RET breakpoint junctions were cloned and analyzed by PCR using next-generation sequencing.
Results: Breakpoints in RET were identified in a 2.0-kb region in all but 1 case, 56% of which were caused by simple reciprocal inversion.

Take Home Message: As in papillary thyroid carcinoma, RET fusion is a driver mutation in lung adenocarcinoma, but occurs through multiple pathways and are different than those observed in papillary thyroid carcinoma, which is important in guiding the development of targeted therapies.

Pan et al. ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. Lung Cancer 2014;84:121-126

Purpose: To better understand the clinicopathologic features of fusion-positive lung adenocarcinomas.

Methods: PCR was performed to identify ALK, ROS1, and RET fusions in resected specimens from 1139 Chinese lung adenocarcinoma patients. The clinicopathologic characteristics of fusion-positive tumors were assessed.

Results: ALK, ROS1, and RET fusions were identified in 5.1%, 1.0%, and 1.3% of patients, respectively. Tumors with ROS1 fusions were significantly larger than ROS1 fusion-negative tumors. All tumors with RET fusions were ≤ 3 cm. The three fusion genes were more prevalent in solid-predominant adenocarcinoma. Fusion-positive tumors had a significantly higher prevalence of extracellular mucin, cribriform pattern, signet ring cells, and hepatoid cytology. Survival did not differ from fusion-negative tumors.

Take Home Message: Given the tendency for fusion-positive carcinomas to show abundant extracellular mucin and solid, cribriform, hepatoid, signet ring cell morphologies, when tumors with these features are encountered, testing to identify these fusions should be considered.


Purpose: To determine whether nintedanib, an intracellular inhibitor of multiple tyrosine kinases, is effective in reducing lung-function decline and acute exacerbations in patients with IPF.

Methods: Randomized, double-blind, 52-week phase 3 trials were conducted with a primary end point of the annual rate of decline in forced vital capacity (FVC).

Results: There were 1066 patients who received the study drug or placebo in a 3:2 ratio. The study drug significantly reduced adjusted annual rate of change in FVC, as compared to placebo. No significant difference was observed with respect to time to first acute exacerbation.

Take Home Message: Finally, a pharmacologic agent that appears to slow the progression of IPF, at least as measured by a reduction in the decline in FVC.

**Purpose:** To assess the potential of CISH to detect ALK-rearranged lung cancers.

**Methods:** Both CISH using a break apart probe for the ALK gene and RT-PCR for EML4-ALK were performed on 181 samples. Sanger sequencing was also performed on all samples that were positive by RT-PCR to confirm the results.

**Results:** CISH was successful in 96% of samples, detecting 7 positive cases with 100% concordance with RT-PCR. There were 10 samples in which RT-PCR failed, all but one of which was able to be successful assayed with CISH.

**Take Home Message:** CISH is a reliable, convenient, and inexpensive alternative to sequencing to detect ALK-rearranged lung cancers, especially in limited and/or poor quality samples.

Wang et al. Classification of thymic epithelial neoplasms is still a challenge to thoracic pathologists - a reproducibility study using digital microscopy. Arch Pathol Lab Med 2014;138:658-663

**Purpose:** To assess the reproducibility of the diagnosis of thymic epithelial tumors using digital imaging.

**Methods:** Experts at 6 institutions classified 20 cases of thymoma or thymic carcinoma and assessed for the presence of invasion using digital microscopy initially and after discussion of discordant cases evaluated an additional 10 cases.

**Results:** Diagnostic agreement was achieved in 70% of cases with an overall kappa of 0.39. The kappa for invasion assessment was 0.45. Following discussion of diagnostic criteria, the additional 10 cases were evaluated and kappa values for classification and invasion improved to 0.67 and 0.57, respectively.

**Take Home Message:** Digital imaging appears to be a modality that experts can reliably evaluate tumors that are relatively uncommon in general practice, such as thymic tumors.

Wynes et al. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. J Thorac Onc 2014;9:631-638

**Purpose:** To date, the only approved modality for determining whether lung carcinoma patients are eligible for ALK inhibitor therapy is the break-apart FISH assay. Immunohistochemical (IHC) detection of ALK protein expression would appear to be a cost-effective, readily available alternative. This study is an international collaborative effort to evaluate a new automated standardized ALK IHC assay.
Methods: Archival NSCLC specimens, 48 of which were ALK FISH-positive and included 5 cytology, 14 biopsy, and 37 resection specimens, were provided to international collaborators for staining with the anti-ALK D5F3 primary antibody and the OptiView amplification detection system. IHC scoring was binary with strong granular cytoplasmic staining considered positive.

Results: There were 100 evaluable cases. The ALK IHC assay had a sensitivity of 90%, specificity of 95%, and accuracy of 93% relative to ALK FISH results. Agreement on the IHC score by 7 of 7 and 6 of 7 readers was achieved in 88% and 96% of cases, respectively on initial review. Following discussion of discrepantly scored cases, agreement rose to 95% and 97%, respectively.

Discussion: ALK IHC is sensitive, specific, and accurate with excellent inter-reader agreement.

Take Home Message: This study adds to the burgeoning literature that IHC is an acceptable alternative to FISH to identify patients who may benefit from crizotinib therapy.

Yoshida et al. Immunohistochemical detection of ROS1 is useful for identifying ROS1 rearrangements in lung cancers. Mod Pathol 2014;27:711-720

Purpose: To determine the utility of immunohistochemistry for identifying ROS1-rearranged lung cancers.

Methods: Using an anit-ROS1-specific rabbit monoclonal antibody (D4D6), immunoeexpression was evaluated in TMAs containing 17 rearranged and 253 non-rearranged lung carcinomas.

Results: Staining was observed in all 17 rearranged cases, mostly in a diffuse pattern that was of moderate to strong intensity. Weak or focal ROS1 staining was seen in 31% of non-rearranged cases and the remaining cases were non-immunoreactive. Optimal discrimination was seen with an H-score (calculated based on percentages of cells stained and staining intensity) cutoff of ≥ 150.

Take Home Message: If appropriate cutoff values are used, ROS1 immunohistochemistry is an accurate modality for identifying patients who have ROS1-rearranged tumors and in turn may benefit from ALK inhibitors.
Review Articles, Consensus Statements, and Editorials


A very nice and comprehensive review with the high quality images and clinical correlation one would expect from this journal.


This editorial accompanies the two articles on phase 3 drug trials showing reduced disease progression in IPF. It provides a historical perspective upon which to gauge the relative importance of these pharmacologic agents in the management of IPF.


A very nice backdrop for an article in the same journal by Wynes et al. on ALK immunohistochemistry that details ALK testing up to now, as well as current concepts and controversies.


Yet another consensus statement, this time on the histological classification of thymic neoplasms. A new type A thymoma variant, “atypical type A thymoma”, is proposed and criteria for separating other thymic neoplasms are refined.

Selman et al. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis an integral model. Am J Respir Crit Care Med 2014;189:1161-1172

A rather heady article in which a model of genetically-induced loss of epithelial integrity in the aging lung resulting in a failure to adequately respond to mechanical stretch and subsequent overproduction/accumulation of extracellular matrix is proposed. There is a nice figure depicting the proposed model of IPF pathogenesis.

Case Reports and Letters to the Editor


Case Summary: A 38-year-old women with ROS1-rearranged papillary lung adenocarcinoma initially treated with pemetrexed and cisplatin, followed by crizotinib after disease progression on which she developed military dissemination to the brain.
Take Home Message: The CNS is known to be a sanctuary site for ALK-rearranged lung adenocarcinoma in patients treated with crizotinib, likely due to low drug penetration through the blood-brain barrier. It appears from this report that a similar situation exists for ROS1-rearranged lung cancer.


Case Summary: A 56-year-old male with an exon 19 EGFR deleted NSCLC had a poor response to erlotinib. Additional testing disclosed a coexisting KIF5B/RET fusion gene, which can successfully be treated with RET inhibitors.

Take Home Message: This case further challenges the theory of mutually exclusive driver mutations in NSCLC and highlights a previously unrecognized mechanism of EGFR TKI resistance, making a case for next generation sequencing as a modality for testing.

Hsieh et al. Pulmonary tuberculosis presenting as organizing pneumonia. Am J Respir Crit Care Med 2014;189:e63

Case Summary: An 80-year-old male with fever, dyspnea, productive cough, and bilateral consolidation underwent thoracoscopic biopsy, which disclosed organizing pneumonia. Ziehl-Neelsen staining was positive for acid-fast bacilli and culture grew MTB.

Take Home Message: Wonder if anyone else has encountered TB presenting with this pattern and if staining for AFB should be part of the work-up for any biopsy showing organizing pneumonia?


Case Summary: A 64-year-old male with presumptive IPF who had been exposed to Corian dust for 16 years was found to have UIP on surgical lung biopsy, but the specimen also featured abundant polarizable material within the fibrotic regions and along lymphatics. Energy dispersive x-ray spectroscopy confirmed the presence of aluminum trihydroxide, suggesting a potential causal relationship between Corian dust exposure and pulmonary fibrosis. An accompanying rebuttal letter by a DuPont company physician takes aim at the fibrogenic potential of aluminum compounds.

Take Home Message: Stay out of the kitchen and just order takeout (or at least don’t remodel it yourself).