PULMONARY PATHOLOGY JOURNAL CLUB
(March 2026 articles)
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I. Articles for Discussion

Odintsov et al. The genomic landscape of NSCLC in systemic sclerosis reveals frequent *TP53* mutations and a paucity of actionable oncogenes. J Thorac Oncol 2026;21:103501

Purpose: To better understand the underlying molecular drivers of NSCLC in patients with systemic sclerosis (SSC) and other connective tissue diseases associated with ILD. Patients with SSC have a significantly elevated risk of NSCLC.

Methods: Among NSCLC patients who underwent tumor genomic profiling, patients with SSC (n=27) and other connective tissue disease associated with ILD (n=10) were retrospectively identified. Their clinical and genomic data were compared to a large cohort of NSCLC patients.

Results: ILD was relatively infrequent in SSc patients with a moderate/heavy smoking history, whereas all SSc patients with a never/light smoking history had ILD (mostly NSIP). Compared to non-SSc patients, there was a significant lack of canonical driver alterations typical of never-smokers (*EGFR*, *ERBB2* mutations and oncogenic fusions) in never/light smoking SSc patients (0/16 vs. 474/1255, $p = 0.004$). Instead, *TP53* mutations and APOBEC (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like)-attributable variants were disproportionately more frequent in this population (75% vs. 45.8%, $p = 0.038$). NSCLC patients with other inflammatory ILDs had similar genomic findings.

Discussion: The genomics of NSCLC arising in the setting of SSc and other inflammatory ILD, particularly in never/light smokers, is distinct – frequent *TP53* alterations, a paucity of targetable drivers, and APOBEC signature enrichment. It is postulated that chronic autoimmune inflammation might stimulate APOBEC activation, contributing to tumorigenesis.

Take Home Message: Understanding more about the genetic underpinnings of NSCLC arising in ILD may be the key to developing more effective, tailored therapies.

Chang et al. Primary pulmonary ameloblastoma: first case series with clinicopathologic and genomic analysis. Am J Surg Pathol 2026;50:283-291

Purpose: Describe the clinicopathologic features of 3 cases of primary pulmonary ameloblastoma (PPA), which heretofore has not been described as originating in this site.

Methods: The 3 cases were derived from the consultation practices of 3 academic institutions, including Mayo Clinic Scottsdale with 2 of the authors being members of this journal club.

Results: All 3 tumors were peripheral solitary lung masses (5.4-7.3 cm) that were removed with lobectomy from adult (40-68 years-old) never smokers. No gnathic primary tumor was identified

on clinical or radiographic examination. Histologically, the tumors showed a predominant stellate reticulum-like component with loosely arranged bland, p40-positive squamoid to spindle cells, intercellular bridges, and streaming to swirling architecture. The surrounding palisaded columnar cells exhibited focal reverse polarity at the interface with mast cell-rich myxoid stroma. There were also focal duct-like spaces containing dense basophilic material. BRAF V600E immunostaining was observed in all 3 tumors and *BRAF V600E* mutations were confirmed in 2. Complicating the diagnosis was the presence of floridly hyperplastic entrapped TTF-1-positive pneumocytes arranged in acinar structures that initially raised concern for a biphasic neoplasm. However, the lack of BRAF V600E staining in these cells aided in interpretation. There have been no recurrences or metastases in 2-36 months of follow-up.

Discussion: The differential diagnosis of PPA includes peculiar-appearing squamous cell carcinoma, myoepithelial tumors, and unusual salivary-type tumors. Prominent entrapped pneumocytes are a diagnostic pitfall that imparts a bronchiolar adenoma (BA)-like appearance. The distribution of p40-positive cells can aid in the distinction. PPA shows confluent expansile p40-positive tumor cells in contrast to a continuous basal layer in BA. Additionally, BRAF V600E staining is seen only in the tumor cells and not the entrapped pneumocytes in PPA, unlike BA, in which both the luminal and basal cells are BRAF V600E-positive.

Take Home Message: Consider BRAF V600E testing in a biphasic-appearing pulmonary neoplasm with a stellate reticulum-like component.

Wang et al. Deep learning-based virtual elastin staining improves visceral pleural invasion assessment in lung cancer. Mod Pathol 2026;39:100966

Purpose: To test a deep learning-based virtual elastin stain to assess visceral pleural invasion in lung cancer.

Methods: A conditional generative adversarial network was developed to translate standard H&E images into virtual representations of elastin. The intrinsic eosin fluorescence of H&E sections was used to create a co-registered ground truth for training. Visceral pleural invasion assessment by H&E alone was compared with virtual elastin staining. For reference validation, selected sections were subjected to traditional elastin staining with Victoria blue and evaluated by 3 experienced pulmonary pathologists.

Results: Virtual elastin staining significantly improved the diagnostic accuracy of pathologists in interpreting visceral pleural invasion as compared with H&E alone. Performance was best with thinner (1-3 micron) tissue sections.

Discussion: Virtual elastic staining has the potential to reduce costs and turnaround time associated with generating a separate elastin-stained slide for assessing visceral pleural invasion. Another advantage of this method is that it avoids the issue of tissue misalignment that inevitably occurs when a serial section is prepared.

Take Home Message: It would be helpful to compare the accuracy of virtual elastic staining to traditional elastic staining rather than just H&E alone, factoring in the time needed to train

pathologists on this method. It is problematic that non-standard thickness sections are required for optimal performance.

Myers et al. Bronchiolocentric interstitial pneumonia is a more accurate interstitial lung disease classification than hypersensitivity pneumonia: con. Am J Respir Crit Care Med 2026;212:564-567 and rebuttal 568

A journal club member emeritus is the first author of an opinion piece asserting that idiopathic bronchiolocentric interstitial pneumonia (iBIP), a term proposed in a 2025 update of the international multidisciplinary classification of the interstitial pneumonias (see Eur Respir J 2025;66:2500158) is a less accurate designation than hypersensitivity pneumonitis (MDD-HP) in patients who, following multidisciplinary discussion, satisfy morphologic criteria for a HP diagnosis in whom no causative exposure has been identified. The argument is made that reporting a morphologic HP pattern in patients without an identified cause is a powerful motivator for identifying occult antigenic exposures and that changing diagnostic language risks devaluing the importance of seeking such exposures for which avoidance is a key therapeutic tenet.

Ryerson et al. Bronchiolocentric interstitial pneumonia is a more accurate interstitial lung disease classification than hypersensitivity pneumonia: pro. Am J Respir Crit Care Med 2026;212:561-563 and rebuttal 569-570

The authors contend that BIP is a sound diagnostic term and that HP be reserved for patients who have undergone multidisciplinary discussion and a causative environmental exposure has been identified. They assert that many patients with BIP either have a cause other than HP, such as collagen vascular disease-associated ILD, or no identifiable cause. To label a patient as having HP without an identified cause can be problematic, they argue, as data have shown that such patients have an elevated likelihood of developing features of autoimmune disease on follow-up.

II. Articles for Notation

Original Articles - Neoplastic

Hung et al. Transcription factor-based subtype assignment in pulmonary large cell neuroendocrine carcinoma. Histopathology 2026;88:81-830

Purpose: Evaluate the clinicopathological significance of transcription factor-based IHC subtyping in pulmonary large cell neuroendocrine carcinoma (LCNEC).

Methods: 117 pulmonary high-grade neuroendocrine carcinomas, including 70 LCNEC and 47 tumors with combined or intermediate morphology between prototypical SCLC and LCNEC were stained for ASCL1, NeuroD1, POU2F3, YAP1, and HNF4A and compared to next-generation sequencing data in 19 cases.

Results: The majority of cases (62%) were ASCL1-dominant. YAP1 and HNF4A correlated with large cell morphology. NeuroD1 dominance was more common in tumors with

combined/intermediate morphology, but some tumors with morphology straddling LCNEC and SCLC had POU2F3 dominance.

Take Home Message: Transcription factor-based IHC has the potential to be helpful in distinguishing LCNEC from SCLC in morphologically ambiguous cases with YAP1 and HNF4A correlating with large cell morphology.

Williams et al. Spatial molecular plasticity underpins lethal morphologies in lung adenocarcinoma. Mod Pathol. 2026;39:100960

Purpose: To discover the molecular underpinnings of two high-risk growth patterns (solid and micropapillary) in lung adenocarcinoma in order to better understand mechanisms that contribute to their lethality.

Methods: 160 pure epithelial growth regions of interest were identified in 51 resected lung adenocarcinomas and characterized using the NanoString GeoMx digital spatial profiler. Results were validated in 27 cases at the protein level using Akoya PhenoImager multiplex immunofluorescence, in 432 cases at the RNA level with TempO-Seq, and in 30 cases with an independent GeoMx spatial profiler.

Results: Gene expression analysis demonstrated fundamentally divergent evolutionary trajectories leading to solid and micropapillary growth and intratumoral plasticity in both patterns.

Take Home Message: Divergent molecular trajectories in solid and micropapillary pattern lung adenocarcinomas have potential implications for systemic therapy. Whereas cytotoxic therapies targeting proliferative cells may be effective in areas of solid growth, they may be ineffective in micropapillae, which are relatively metabolically inactive.

Davidson et al. The specificity of HEG1 as mesothelioma marker depends on the differential diagnosis. Virchows Archiv 2026;488:617-626

Purpose: Assess the diagnostic role of HEG1 in malignancies affecting the serosal cavities.

Methods: HEG1 immunoexpression (SKM9-2 monoclonal antibody) was evaluated in 534 specimens (341 effusions and 193 surgical specimens) that included mesothelioma and carcinomas of tubo-ovarian, breast, lung, uterine, cervical, GI, and GU origin.

Results: 98% of mesothelioma effusions and 93% of surgical mesothelioma specimens expressed HEG1 (95% overall sensitivity). HEG1 expression was infrequent (≤10%) in breast, lung, uterine/cervical carcinomas, but stained most tubo-ovarian carcinoma effusions (53%) and surgical specimens (71%). Consistent HEG1 expression was seen in reactive mesothelial cells in effusions and endothelial cells in surgical specimens. While the specificity of HEG1 in the distinction from non-tubo-ovarian carcinomas was 93%, specificity was only 38% when the differential diagnosis was tubo-ovarian carcinoma. Nearly all HEG1-positive carcinomas also expressed claudin-4.

Take Home Message: Context matters when using HEG1. This marker is highly sensitive for mesothelioma and is useful in the distinction from breast and lung carcinoma, but has rather low specificity when tubo-ovarian carcinoma is in the differential. Note that HEG1 also stains reactive mesothelium and endothelial cells.

Kassem et al. Orthogonal validation of anaplastic lymphoma kinase (ALK) immunohistochemistry with molecular analysis for *ALK* gene rearrangement is required to finetune staining protocols with the D5F3 clone and can impact external quality assessment. Virchows Archiv 2026 Mar;488:511-522

Purpose: To validate laboratory-developed ALK IHC protocols for the effective screening of tumors for *ALK* gene rearrangements.

Methods: After receiving feedback from external quality assessments regarding the weak intensity of a laboratory-developed test for ALK IHC, the authors retrospectively compared 3 protocols for ALK IHC with different staining intensities and sensitivities to molecular data on *ALK* fusions in 462 tumors, a subset of which were lung adenocarcinomas.

Results: Two protocols resulted in diffuse, weak cytoplasmic staining in most non-ALK-rearranged tumors, leading to equivocal or false-positive ALK IHC results. A third less sensitive protocol was more specific, showing good concordance with molecular data (97% sensitivity; 85% specificity). Despite this, external quality assessment considered the third protocol to be insufficiently sensitive.

Take Home Message: For laboratories that use ALK IHC as a screening method, overly sensitive protocols result in false positives that have the potential to lead to overuse of confirmatory molecular tests. To avoid this, laboratories should consider fine-tuning their ALK IHC protocol by comparing the diagnostic performance of ALK IHC with molecular data.

Oskarsdottir et al. Cyclin D1 overexpression with cytoplasmic localization distinguishes Erdheim-Chester disease from reactive histiocytic infiltrates. Am J Surg Pathol 2026;50:273-282

Purpose: Examine the diagnostic utility of cyclin D1 and pERK as IHC markers of MAPK pathway activation in Erdheim-Chester Disease (ECD) and its histopathologic mimics.

Methods: 41 confirmed cases of ECD (including 1 pleural and 1 lung) along with 59 histologic mimics (xanthogranuloma, reactive xanthogranulomatous inflammation, fat necrosis, retroperitoneal fibrosis, IgG4-related disease, and several other entities) were tested.

Results: 90% of ECD cases demonstrated cyclin D1 overexpression, often both nuclear and cytoplasmic. Of the histologic mimics, 83% of xanthogranulomas showed diffuse cyclin D1 expression, weak patchy staining was seen in 62% of cases of fat necrosis, and the remainder were cyclin D1-negative.

Take Home Message: In the proper clinicoradiographic context, strong nuclear and cytoplasmic cyclin D1 staining can help support a diagnosis of ECD. However, it should be noted that this marker is not entirely specific for ECD and negative staining does not exclude ECD.

Review and State-of-the-Art Articles

Lo et al. What is new for 2026: challenges & updates in pulmonary pathology

A nice review of need-to-know developments and challenges in pulmonary pathology with one of our journal club members as the first author. Topics discussed include the integration of histologic and molecular assessment in the staging of multiple non-small cell tumors. While nearly all tumor pairs can be confidently classified as either related or unrelated by broad-panel next-generation sequencing (NGS), important caveats are highlighted. These include the concepts that intrapulmonary metastases frequently show histologic progression from low grade to high grade patterns and conversely, some synchronous primary lung carcinomas can appear deceptively similar architecturally. MET and HER2 as emerging actionable biomarkers in non-small cell lung carcinoma is also discussed. For both MET and HER2, 3+ IHC is now recognized as an actionable result independent of genetic mutations. As a result, targeted IHC for MET and HER2 alongside NGS is being increasingly implemented in routine practice. Lastly, the molecular subtypes of small cell lung carcinomas are discussed.

Mor et al. Clinical utility of lung biopsy in fibrotic interstitial lung disease. Am J Respir Crit Care Med 2026;212:571-590

Article detailing recommended methods of lung biopsy for the diagnosis of fibrosing ILD, relative indications and contraindications of biopsy, and factors related to the decision to proceed with biopsy. Contains some potentially useful figures if you are tasked with preparing a presentation on the role of lung biopsy in fibrosing ILD for a clinical audience.

Case Reports

Wang et al. Mycelial growth in the bronchial lumen of a patient with acute promyelocytic leukaemia. Thorax 2026;81:292-293

Case Summary: Striking photo montage of bronchial occlusion by *Rhizopus* in a patient with acute leukemia.

Take Home Message: Up to two-thirds of patients with pulmonary mucormycosis have endobronchial abnormalities, such as endobronchial growth with adherent mucus plugs. The authors cite a reference that indicates adherent mucus plugs are seen exclusively with mucormycosis, a finding that can aid in the distinction from invasive aspergillosis bronchoscopically.