Pulmonary Pathology Journal Club – February 24, 2025

(Articles January 2025)

Presented by
Yasmeen M. Butt, MD
Department of Laboratory Medicine and Pathology
Mayo Clinic Arizona

Table of Contents:

Articles for Discussion

Articles for Notation

Neoplastic Lung Disease

Page 9 Nakao M et al. Prognostic impact of the N2 subclassification and stage migration in the ninth edition of the TNM classification in surgically resected lung cancer. Lung Cancer. 2025 Jan:199:108073.

Page 10 Nanami H et al. Efficacy of cryobiopsy during medical thoracoscopy for diagnosing malignant pleural mesothelioma. Lung Cancer. 2025 Jan:199:108074.

Page 10 Sigalotti L et al. Proximal and Classic Epithelioid Sarcomas are Distinct Molecular Entities Defined by MYC/GATA3 and SOX17/Endothelial Markers, Respectively. Mod Pathol. 2025 Jan;38(1):100647.

Page 10 Sun Q et al. The Presence of Small-Size Circulating Tumor Cells Predicts Worse Prognosis in Non-Small Cell Lung Cancer Patients. Arch Pathol Lab Med. 2025 Feb 1;149(2):111.

Page 11 Suster D et al. Large-cell Basaloid Adenocarcinoma of the Lung: A Clinicopathologic Study of 12 Cases of a Distinctive Form of Lung Cancer Often Mistaken for Large-cell Neuroendocrine Carcinoma. Am J Surg Pathol. 2025 Jan 1;49(1):83-93.

Page 11 van Huizen. Rapid On-Site Histology of Lung and Pleural Biopsies Using Higher Harmonic Generation Microscopy and Artificial Intelligence Analysis. Mod Pathol. 2025 Jan;38(1):100633.

Page 11 Zhu Y et al. Molecular subtypes, predictive markers and prognosis in small-cell lung carcinoma. J Clin Pathol. 2024 Dec 18;78(1):42-50.

Non-Neoplastic Lung Disease

Page 12 Grant-Orser. BAL Fluid Cellular Analysis and Radiologic Patterns in Patients With Fibrotic Interstitial Lung Disease. Chest. 2025 Jan;167(1):172-182.

Page 12 Miyamoto Ei. Local intragraft humoral immune responses in chronic lung allograft dysfunction. J Heart Lung Transplant. 2025 Jan;44(1):105-117.

Reviews, Guidelines, and Consensus Statements

Page 12 Cipriani NA and Wolk RA. Update of newly-recognized salivary gland neoplasms: molecular and immunohistochemical findings and clinical importance. Histopathology. 2025 Jan;86(2):183-198.

Page 12 Odintsov I et al. Clear Cell Stromal Tumor of the Lung: Clinicopathologic, Immunohistochemical, and Molecular Characterization of Eight Cases. Mod Pathol. 2025 Jan;38(1):100632.

Page 12 Shields MD et al. Defining the needle in a haystack: A compendium of genomic, pathologic, and clinical characteristics of rare pulmonary tumors. Lung Cancer. 2025 Jan:199:108035

Case Reports

Page 13 Kaneko T. Exogenous Lipoid Pneumonia NEJM Images in Clinical Medicine.

Page 13 Kundu A. et al. A 23-Year-Old Man With Multilobar Consolidation Chest. 2025 Jan;167(1):e5-e8.

Page 13 Xi L et al. A 34-Year-Old Man With Fragile Vessels and Recurrent Hemoptysis. Chest. 2025 Jan;167(1):e19-e23.

Page 13 Zhou C et al. A 51-Year-Old Man With Dyspnea and a Pulmonary Nodule. Chest. 2025 Jan;167(1):e13-e17.

Correspondences/Editorials:

Page 13 Phillips WJ et al. Adjuvant Immunotherapy Should Not be Used in Patients With a Pathologic Complete Response to Neoadjuvant Chemoimmunotherapy. J Thorac Oncol. 2025 Jan;20(1):30-33.

Page 13 Aprety D et al. Adjuvant Immunotherapy Should Be Used in Patients With Non-Small Cell Carcinoma With a Pathologic Complete Response to Neoadjuvant Immunotherapy. J Thorac Oncol. 2025 Jan;20(1):34-38.

Articles for Discussion

Thunnissen E et al. A reproducibility study on invasion in small pulmonary adenocarcinoma according to the WHO and a modified classification, supported by biomarkers. Lung Cancer. 2025 Jan:199:108060.

Purpose: Evaluating invasion in non-mucinous adenocarcinoma (NMA) of the lung is crucial for accurate pT-staging. This study compares the World Health Organization (WHO) with a recently modified NMA classification.

Methods: A retrospective case-control study was conducted on small NMA pT1N0M0 cases with a 5-year follow-up. Seventy cases were reviewed by 42 pulmonary pathologists first according to the WHO classification and after tutorial according to a modified classification. A third round was conducted based on feedback from 41 peers of previous rounds. Additionally, orthogonal biomarker analysis was performed.

Results: In the first two rounds, 42 pathologists from 13 countries assessed all 70 cases, while 36 pathologists evaluated 41 non-unanimous cases in the third round. Kappa values for invasiveness increased in rounds 1, 2, and 3 to 0.27, 0.45 and 0.62, respectively. In contrast to low variation in total tumor size measurements (6 %), a marked increase in invasive tumor size variation was observed (42 %), which was associated with high uncertainty. In the third round 10 cases were non-invasive, all without recurrence. The modified classification showed in the 3rd round marked reduction of the variation in pT staging compared to the current WHO classification. Proliferation rate, tumor mutational burden, and transcriptomic profiles supported the distinction between invasive cases and non-invasive cases of the modified classification.

Fourteen out of the 70 cases recurred after surgical resection. Nine of the recurrences were recorded in the 25 cases with 100 % invasive judgements in round 1 and 2. Cases with a recurrence and a diagnosis of “no invasion” are considered discordant judgements. In the 1st round discordant scores occurred in 3 cases with 1, 1 and 6 judgements, respectively. In the 2nd round this occurred in 4 cases with 2, 3, 5 and 15 judgements, respectively (see also Supplementary Table 2). In the 3rd round this occurred in 2 cases with 1 and 3 judgements. In the third round > 21 pathologists scored “no invasion” in 10 cases, all of which were without a recurrence (mean follow-up time 69.5 months, range 11–132). Survival analysis (RFS and OS) for cases categorized if ≥ 21 pathologists scored invasion as ‘yes’ and else ‘no’ (a score of “not sure” is left out) is shown in Supplementary Table 5. Note an increase from 4 in the 1st round to 15 cases in the 2nd round, all with a 100 % RFS and OS for cases categorized

as “no invasion”. Thus, the consensus ability to identify cases which do not recur was improved following the first tutorial.

Take-home points: As per the paper “The modified adenocarcinoma classification has essentially higher reproducibility compared to the current WHO classification, with associated reduction of the variation in pT staging. Collapsed AIS is overdiagnosed as invasive adenocarcinoma when applying the criteria of the current WHO classification. Relapse free survival in patients with AIS at 5 years after resection is 100 %. Biomarker analysis strongly supports the modified classification.

Take a look at supplemental figure.

Volmonen et al. Evaluating tumour budding could improve the new grading system for lung adenocarcinoma. Lung Cancer. 2025 Jan:199:108067.

Objectives: To study the prognostic significance of tumour budding (TB) compared with the grading of lung adenocarcinoma (LAC).

Materials and methods: TB has been shown to be an indicator of a poor prognosis in many cancer types and is defined as a single tumour cell or small clusters of up to four cells within the myofibroblastic stromal tissue at the invasive margin of the tumour.

The postoperative haematoxylin and eosin-stained histological slices of 207 surgically treated LAC patients were retrospectively reviewed by a lung pathologist. Two groups were formed from the cohort: the high-grade TB group (≥10 buds) and low-grade TB group (0–9 buds). The prognostic significance of high-grade TB for the 5-year progression-free survival (PFS) and overall survival (OS) of patients was studied using the Kaplan–Meier method and Cox regression models. A novel four-tier grading system for LACs was developed by combining the World Health Organization (WHO) grading system and high-grade TB. The computed tomography (CT) imaging features of the tumours were assessed semiquantitatively by two chest radiologists.

Results: There were 166 patients with low-grade TB and 41 LAC patients with high-grade TB. Most of the tumours with high-grade TB were Grade 3 tumours. The median follow-up time was 60 months. The 5-year PFS was lower in the high-grade TB group than in the low-grade TB group (37.6 vs. 50.9 months, $p < 0.001$). High-grade TB remained an independent prognostic factor for poor PFS (clinical model: hazard ratio [HR] = 2.07, adj. $p = 0.012$, histopathological model: adj. HR = 2.09, adj. $p = 0.010$).

Compared with the WHO Grade 3 group, the Novel Grade 4 group had a shorter mean PFS (36.7 vs. 45.3 months), and according to the PFS analysis, the novel four-tier grading system was superior to the WHO grading system (AIC = 591.9 vs. AIC = 596.6, ΔAIC > 2). On CT, tumours with higher TBs are usually smooth or spiculated.

Conclusion: This is the first study to show that high-grade TB (>9 buds) is associated with a higher LAC grade. The The incorporation of TB into the WHO grading scheme may improve the prognostic significance of LAC grading.

Take-home points: Tumor budding may be added in the future to morphologic features assessed for lung adenocarcinomas.

Pogoriler J and Vargas SO. Cystic masses of the pediatric lung: update on congenital pulmonary airway malformation and its differential diagnosis. Virchows Arch. 2025 Jan;486(1):177-188.

Purpose: This review is intended to summarize the current state of knowledge regarding lesions that have been historically classified as CPAM or that enter its differential diagnosis, with the added aim of assessing current classification schemes and providing proposed modifications.

Take-Home Messages: Cystic masses of the pediatric lung have been generally termed “CPAM,” although they represent a diverse array of conditions with very disparate etiologies and molecular underpinnings. The recent advances in histologic and genotypic correlation summarized herein can help pathologists render more refined diagnoses that provide more specific information about etiopathogenesis and in turn better inform management. Entities are proposed to be grouped into the following: Supernumerary airway/lung tissue, DICER1-associated cystic lung disease (pleuropulmonary blastoma types I and Ir), Bronchial atresia–associated congenital cystic lung disease, and KRAS mosaic mutation-associated congenital pulmonary airway malformations. Fetal lung interstitial tumor and congenital peribronchial myofibroblastic tumor are also discussed.

Churg et al. Pathological features of connective tissue disease-associated interstitial lung disease in transbronchial cryobiopsies. Histopathology. 2025 Jan;86(2):260-267.

Aim: Attempted to provide pathological guidelines for separating usual interstitial pneumonia (UIP) of idiopathic pulmonary fibrosis (IPF), fibrotic hypersensitivity pneumonitis (FHP) and connective tissue diseaseassociated ILD (CTD–ILD) in cryobiopsies.

Results: non-specific interstitial pneumonia (NSIP) pattern alone was seen in 36 of 120 (30%) CTD–ILD, three of 83 (3.6%) FHP and two of 38 (5.2%) IPF cases, statistically favouring a diagnosis of CTD–ILD. The combination of NSIP + OP was present in 29 of 120 (24%) CTD–ILD, two of 83 (2.4%) FHP and none of 38 (0%) IPF cases, favouring a diagnosis of CTD–ILD. A UIP pattern, defined as fibroblast foci plus any of patchy old fibrosis/fibrosis with architectural distortion/honeycombing, was identified in 28 of 120 (23%) CTD–ILD, 45 of 83 (54%) FHP and 27 of 38 (71%) IPF cases and supported a diagnosis of FHP or IPF. The number of lymphoid aggregates/mm2 and fibroblast foci/mm2 was not different in IPF, CTD–ILD or FHP cases with a UIP pattern. Interstitial giant cells supported a diagnosis of FHP or CTD–ILD over IPF, but were infrequent.

Methods: 120 cyrobiopsies were reviewed with MDD established CTD-ILD compared with prior MMD established IPF or FHP.

Take Home Points: In the correct clinical/radiological context the pathological findings of NSIP, and particularly NSIP plus OP, favour a diagnosis of CTD–ILD in a cryobiopsy, but CTD–ILD with a UIP pattern, FHP with a UIP pattern and IPF generally cannot be distinguished.

Articles for Notation

Kaczorowski M et al. Expression of POU2F3 Transcription Factor and POU2AF2, POU2F3 Coactivator, in Tuft Cell-like Carcinoma and Other Tumors. Am J Surg Pathol. 2025 Jan 1;49(1):62-72.

Purpose: Expression of the POU2F3 transcription factor is a marker of tuft cell lineage. However, tuft cell development, differentiation, and proliferation are controlled by the expression of the complex formed by POU2F3 and POU2AF2 or POU2AF3 transcriptional coactivators.

Take-home message: POU2F3 expression is a highly sensitive but nonspecific indicator of tuft cell differentiation. Co-expression of POU2F3 and POU2AF2 appears to be a more specific marker, although it may not pinpoint tumors driven by the POU2F3-POU2AF3 complex.

McColl KS et al. Identification of HEPACAM2 as a novel and specific marker of small cell carcinoma. Cancer. 2025 Jan 1;131(1):e35557

Purpose: This study investigated HEPACAM2 expression in patients with SCLC via RNA sequencing and evaluated its relationship to progression-free survival (PFS) and overall survival (OS).

Take-home message: With its remarkable specificity, high expression, presence in early disease, and extracellular secretion, HEPACAM2 could be a potential diagnostic cell surface biomarker for early SCLC detection. These findings warrant further investigation into its role in the pathobiology of SCLC.

Nakao M et al. Prognostic impact of the N2 subclassification and stage migration in the ninth edition of the TNM classification in surgically resected lung cancer. Lung Cancer. 2025 Jan:199:108073.

Purpose: In the ninth edition of the TNM classification of lung cancer, N2 is subdivided into single-station (N2a) and multiple-station involvement (N2b), and some stage changes are made to stage II–III. This study aimed to validate the new classification and determine the effect of stage migration and vice versa on the prognosis of each pathological stage due to these changes.

Take-home message: Although the N2 subclassification had some impact on survival stratification, it was difficult to predict the subdivided pN2 status, preoperatively. The overall survival difference in stage III was smaller in the ninth edition than in the eighth edition, due to the complex effects of stage migration and vice versa.

Nanami H et al. Efficacy of cryobiopsy during medical thoracoscopy for diagnosing malignant pleural mesothelioma. Lung Cancer. 2025 Jan:199:108074.

Purpose: Although medical thoracoscopy is an established diagnostic procedure

for pleural diseases, there is no consensus on whether it guarantees a high diagnostic yield for MPM. Cryobiopsy has been shown to have the potential to improve tissue sampling in other diseases; therefore, they aimed to investigate its efficacy in diagnosing MPM.

Take-home message: Cryobiopsy is effective in improving the subtype confirmation rate as well as MPM diagnostic yield compared to conventional biopsy.

Sigalotti L et al. Proximal and Classic Epithelioid Sarcomas are Distinct Molecular Entities Defined by MYC/GATA3 and SOX17/Endothelial Markers, Respectively. Mod Pathol. 2025 Jan;38(1):100647.

Purpose: Epithelioid sarcoma (ES) is a rare tumor hallmarked by the loss of INI1/SMARCB1 expression. Apart from this alteration, little is known about the biology of ES. This paper sought to identifiy the molecular nature of these tumor types, which can be seen rarely in the lung.

Take-home message: Proximal-ES and Classic-ES represent distinct molecular entities defined by MYC/GATA3 and SOX17/endothelial molecular traits, respectively. Besides providing insights into the biology of ES, our study pinpoints subtype-specific biomarkers and potential therapeutic vulnerabilities.

Sun Q et al. The Presence of Small-Size Circulating Tumor Cells Predicts Worse Prognosis in Non-Small Cell Lung Cancer Patients. Arch Pathol Lab Med. 2025 Feb 1;149(2):111.

Purpose: To identify indicators that can predict the prognosis of lung cancer patients.

Take-Home Message: Small-size circulating tumor cells (CTCs) are a reliable prognostic indicator and a probable predictor of the severity of disease in NSCLC patients.

Suster D et al. Large-cell Basaloid Adenocarcinoma of the Lung: A Clinicopathologic Study of 12 Cases of a Distinctive Form of Lung Cancer Often Mistaken for Large-cell Neuroendocrine Carcinoma. Am J Surg Pathol. 2025 Jan 1;49(1):83-93.

Purpose: A distinctive form of lung adenocarcinoma that closely mimics large-cell neuroendocrine carcinoma is described.

Take-Home Message: Large-cell basaloid adenocarcinoma is an unusual variant of lung cancer that is easily confused with large-cell neuroendocrine carcinoma. Awareness of this unusual variant of lung adenocarcinoma is important for treatment and prognosis and for avoiding misdiagnosis.

van Huizen. Rapid On-Site Histology of Lung and Pleural Biopsies Using Higher Harmonic Generation Microscopy and Artificial Intelligence Analysis. Mod Pathol. 2025 Jan;38(1):100633.

Purpose: Currently, there is no method for the on-site rapid histologic feedback on biopsies taken in diagnostic, endoscopic, or surgical procedures. Higher harmonic generation (HHG) microscopy is a laser-based technique that provides images of unprocessed tissue. In this study, we report the feasibility of an HHG portable microscope in the clinical workflow in terms of acquisition time, image quality, and diagnostic accuracy in suspected pulmonary and pleural malignancy.

Take-Home Message: The assessment by pathologists and an artificial intelligence algorithm showed that image quality was sufficient for a malignancy or nonmalignancy diagnosis in 97% of the biopsies, and 87% of the HHG images were correctly scored by the pathologists. HHG is therefore an excellent candidate to provide a rapid pathology outcome on biopsy samples, enabling immediate diagnosis and (local) treatment.

Zhu Y et al. Molecular subtypes, predictive markers and prognosis in small-cell lung carcinoma. J Clin Pathol. 2024 Dec 18;78(1):42-50.

Purpose: Their results validated the feasibility of lung biopsy samples for identifying SCLC molecular subtypes, and revealed that combined SCLCs were significantly enriched in the subtype of POU2F3-dominant SCLC (SCLC-P)
and for the non-SCLC components of combined SCLCs, adenocarcinoma was more prevalent in ASCL1-dominant SCLC, while large-cell neuroendocrine carcinoma was more commonly seen in SCLC-P.

Take-Home Message: This study describes the diagnosis, prognosis
and predictive significance of SCLC molecular subtype classifications, which would aid in the development of personalised treatments and subtype-specific treatment of SCLC.

Grant-Orser. BAL Fluid Cellular Analysis and Radiologic Patterns in Patients With Fibrotic Interstitial Lung Disease. Chest. 2025 Jan;167(1):172-182.

Background: BAL cellular analysis is often recommended during the initial diagnostic evaluation of fibrotic interstitial lung disease (ILD). Despite recommendation for its use, betweencenter heterogeneity exists and supportive data concerning the clinical utility and correlation of BAL findings with radiologic features or patterns remain sparse.

Take-Home Message: BAL cellular analyses did not significantly correlate with radiologic features, guideline patterns, or MDD-based diagnoses. Ground glass opacities are often interpreted to represent pulmonary inflammation, but were not associated with BAL lymphocytosis in this cohort.

Miyamoto Ei. Local intragraft humoral immune responses in chronic lung allograft dysfunction. J Heart Lung Transplant. 2025 Jan;44(1):105-117.

Purpose: Donor human leukocyte antigen (HLA)-specific antibodies (DSA) and non-HLA antibodies can cause allograft injury, possibly leading to chronic lung allograft dysfunction (CLAD) after lung transplantation. It remains unclear whether these antibodies are produced locally in the graft or derived solely from circulation.

Take-Home Message: DSA and non-HLA antibodies can be produced within activated B cell- rich lung allografts.

Case Reports

Kaneko T. Exogenous Lipoid Pneumonia NEJM Images in Clinical Medicine.

Diagnosis: Exogenous Lipoid Pneumonia due to induced vomiting of large amounts of oil salad dressing.

Kundu A. et al. A 23-Year-Old Man With Multilobar Consolidation Chest. 2025 Jan;167(1):e5-e8.

Diagnosis: Primary myeloproliferative hypereosinophilic syndrome

Xi L et al. A 34-Year-Old Man With Fragile Vessels and Recurrent Hemoptysis. Chest. 2025 Jan;167(1):e19-e23.

Diagnosis: Vascular Ehlers-Danlos.

Zhou C et al. A 51-Year-Old Man With Dyspnea and a Pulmonary Nodule. Chest. 2025 Jan;167(1):e13-e17.

Diagnosis: Isolated pulmonary vasculitis.

Correspondences/Editorials:

Phillips WJ et al. Adjuvant Immunotherapy Should Not be Used in Patients With a Pathologic Complete Response to Neoadjuvant Chemoimmunotherapy. J Thorac Oncol. 2025 Jan;20(1):30-33.

Aprety D et al. Adjuvant Immunotherapy Should Be Used in Patients With Non-Small Cell Carcinoma With a Pathologic Complete Response to Neoadjuvant Immunotherapy. J Thorac Oncol. 2025 Jan;20(1):34-38.

Take-Home Points: Dueling articles highlight the clinical importants of pathologic complete response and whether or not this should be treated.