AUGUST PULMONARY PATHOLOGY JOURNAL CLUB

Marie-Christine Aubry, M.D.
Mayo Clinic Rochester MN

TABLE OF CONTENT (July 2025 articles)

I. ARTICLE FOR DISCUSSION

II. ARTICLES FOR NOTATION

Neoplastic

Randomized Controlled Trial. Kim Y, Kim H-J, Byoung SK, et al. Chest 2025; 168: 236-247

Non-neoplastic

1. Diagnostic Evaluation and Clinical Findings in Children With Persistent Tachypnea of Infancy/Neuroendocrine Cell Hyperplasia of Infancy. A European Multicenter Retrospective Study. Marczak H, Krenke K, Griese M, et al. Chest 2025; 168(1): 171-182
2. Dual avb6 and avb1 Inhibition over 12 Weeks Reduces Active Type I Collagen Deposition in Individuals with Idiopathic Pulmonary Fibrosis. A Phase 2, Double-Blind, Placebo-controlled Clinical Trial. Montesi SB, Cosgrove GP, Turner SM et al. AJRCCM 2025; 211:1229-1240

Case Report/Correspondence/Editorial

1. Unusual Presentation of Clear Cell Tumor of the Lung as Irregular Nodules with a Thin-walled Cavity. Lv M, Gao Q, Zhong J. Am J Respir Crit Care Med. 2025 Jul;211(7):e11 e12
2. An Unexpected Cause of Postobstructive Pneumonia. Livi V, Cancellieri A, Flore MC, Viscuso M, Trisolini R. Chest. 2025 Jul;168(1): e9–e13
3. Forty-five-year-old man with small nodular and ground-glass opacities on CT. Liao J, Chen X, Qiu G, et al. Thorax. 2025;80: 478–479
4. The utility of deeper levels in evaluating transbronchial cryobiopsy specimens for interstitial lung disease. Manchen P, Politis M, Churg A, et al. Histopathology 2025; 87: 159-163
5. Hermansky-Pudlak Syndrome in the United States. Engel A, Summer R, Roman J. Chest 168: 156-159
6. SOX17 expression in normal mesothelium and mesothelial lesions. Li Z, Ding Q, Xing D, Parwani A. Histopathology 2025; 87: 161-162

Review articles/Consensus Statements

1. An Official American Thoracic Society Statement: Approach to the Evaluation of Interstitial Lung Abnormalities. Hatabu H, Lynch DA, Rosas IO, et al. Am J Respir Crit Care Med. 2025;211(2):132–147
2. The International Association for the Study of Lung Cancer Staging Project: The Database and Proposal for the Revision of the Staging of Pulmonary Neuroendocrine Carcinoma in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. Tsao M, Rosenthal A, Nicholson AG, et al. JTO 2024; 20 (7): 856-870

I. ARTICLE FOR DISCUSSION

1. Pathologists Providing Direct Patient Care in Thoracic Transplant Same Objective, Different Scope. Bois M, Aubry MC, Roden AC, et al. Archiv Pathol Lab Med 2025; 149: 673-678

Background

In thoracic transplantation, pathologists play a central role in monitoring rejection, infection, and post-transplant complications. Traditionally, their work has been diagnostic and consultative, performed behind the scenes. Recently, some programs have explored direct pathologist–patient interactions in the transplant setting, expanding the scope of practice.

Aim

To describe the implementation of a direct pathologist-patient consultative practice and potential benefits of such practice.

Methods

- Implementation and delivery of a direct consultative practice "On My Path" between patients and pathologists for heart and lung explants which started in 2017
    - All thoracic (9) pathologists participate in viewing organs with patients
    - Pathology reporting secretaries coordinate appointments with pathologists
    - Use of existing resources and workflows within our Autopsy Section
        - Autopsy technicians prep up organs for viewing
        - Use of viewing roam to meet patients and introduce them to their organs and explain/answer questions relating to their disease
        - Comparison with normal organ – possibility of adding microscopy
- Role of 3-D scanning in this model of practice – gifting the patient with a slice of their diseased organ
- Survey satisfaction of Transplant coordinators of the new program

Results

- Dec 2017-2022, 158 appointments with patients, 61% for heart and 34% for lung
- Increase in the number of appointments, and % of transplanted patients (up to 30% of patients) over the years in both heart and lung, with the exception of the pandemic period.
- Transplant coordinators thought that patients had a better understanding of their disease post-viewing, experienced closure and patients were now seeking out/requesting this experience

Take home message

- Providing direct patient care is doable for pathologists and in fact, viewed as beneficial by the clinical team
- Perceived benefits include better understanding of disease by patients, enhanced job satisfaction by pathologists, overall improved patient care and experience

- Challenges include resource, time, people, infrastructure

2.CDKN2A Chromogenic In Situ Hybridization for Separating Benign From Malignant Mesothelial Proliferation. Churg A, Spence T, Martin KC et al. AJSP 2025; 49:646-649

Background
Distinguishing reactive mesothelial proliferations from malignant mesothelioma is challenging. CDKN2A (p16) homozygous deletion is a well-established molecular marker strongly associated with malignant mesothelioma and Fluorescence in situ hybridization (FISH) has been the gold standard for detecting CDKN2A loss, but FISH is technically demanding, expensive, and not widely available. MTAP IHC is a good surrogate if rearrangements involving CDKN2A affects MTAP locus - about 70-80% of the time.

Aim
To evaluate the performance of CDKN2A CISH in distinguishing benign from malignant mesothelial proliferations and compared to FISH methodology and results.

Material and Methods
- TMA with 2 cores/tumor of 29 mesotheliomas (12 sarc and 17 epi) and 22 reactive mesothelial proliferation. MTAP available for 24 (of 29) mesotheliomas.
- CDKN2A deletion was assessed by CISH using a commercially available kit (ABNOVA). 2 Pathologists counted 100 cells and scored deleted with red (CEP) signal + and green (CDKN2A) absent . Any loss of green signal occurring in >11% of scored cells was considered as deletion of CDKN2A
- Results were compared to FISH (reference standard).

Results
- 100% concordance between CISH and FISH when deletion of CISH >60%
    - 5 cases with loss by both CISH and FISH *(?only 5 cases of FISH available?)*
    - 4/5 cases had MTAP and MTAP was loss in all 4
- Comparing CISH to MTAP across 24 mesothelioma
    - 4 with both CISH and MTAP loss
    - 1 with CISH loss and MTAP retained
    - 19 with CISH and MTAP retained
- The deletion fraction was similar between both cores of a tumor (so presumably no sampling issues)

Take home message
CISH appears to be a good option to FISH and a method we could implement in practice in lieu of FISH and to supplant MTAP, as a more sensitive method. CISH detected at least 1 (of 5) deletion in CDKNA2A that was not apparent on MTAP (as expected based on correlative studies between FISH and MTAP).

3. Clinical and histopathological features of immune checkpoint inhibitor-induced lung toxicity. Rolim I, Lopez-Beltran A, IP J, et al. Virchows Archiv 2025; 487:47-59

Background

Immune checkpoint inhibitors (ICIs) can cause immune-related adverse events (irAEs) in up to 40% of patients. ICI-induced pneumonitis (ICI-P) is relatively rare but a common cause of drug cessation/death. The histology is poorly characterized, with only 2 small series published, and difficult to interpret in the setting of polytherapy with radiation and/or chemotherapy.

Aim

To evaluated the clinical, radiological, and histopathological spectrum of ICI-induced lung toxicity in a larger cohort of patients

Methods

- Multicenter retrospective study of 15 patients on ICI with lung tissue
- **Clinical data:** Demographics, underlying malignancy, type of ICI, timing of onset, and radiologic patterns (CT imaging).
- **Histology:**
    - Assessment of 5 broad "compartment" - Interstitium, Granuloma, Pneumocyte, Alveolar space, Bronchial mucosa, for various histologic abnormalities
    - CD4 and CD8 IHC with ratio
    - PD-L1 (SP263) with scoring of immune cells

Results

- 16 lung speicmen, 12 TBBX, 3 core and 1 lobectomy with 3 cohorts of patient
    - Radiation + ICI in 9
    - Chemo + ICI in 5
    - ICI only in 2
- CT findings included organizing pneumonia (OP) pattern, ground-glass opacities, and diffuse alveolar damage (DAD) in severe cases. No mention if differences in the 3 cohorts.
- Histology nicely illustrated and detailed in **Fig 6 and Table 2.** Multiple injury patterns identified.
    - All patients had interstitial lymphocytic inflammation
    - Granulomas, pneumocyte hyperplasia not seen in the ICI –only group
    - Pneumocyte vacuolization, foamy macrophages, hyaline membranes common in all 3 cohorts
    - CD8+ T-cells predominate – aligns with response to ICI and expansion of CD8+ T-cells

- SP263+ immune cells in all 3 cohorts but in decreasing frequency to the ICI-only group suggesting benefit from polytherapy

Take home message

- Largest cohort, very detailed data, but still with only 2 patients on ICI alone, so confounding factors from other drugs. Also, no mention on ruling out other etiologies for the histologic findings, like infection

- No specific histologic features for ICI related drug toxicity. "Drug toxicity can cause any pattern of injury and any pattern of injury can be caused by drug toxicity"

- The other 2 studies that evaluated histology with ICI related drug toxicity are
  - Larsen B, Chae J, Dixit A, Hartman T (2019) Clinical and histopathologic features of immune checkpoint inhibitor-related pneumonitis. Am J Surg Pathol 43:1331–1340
    - 9 patients, 5 ICI only – didn't sort findings between ICI only and the others
    - All had ALI, mostly OP often vaguely granulomatous. 2 with DAD

  - Nishiyama O, Shimizu S, Haratani K et al (2021) Clinical implications of bronchoscopy for immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. BMC Pulm Med 21(1):155 15.
    - 12 patients (of 22 with suspected ICI toxicity of 140 treated NSCLC) with bronchoscopy - Not specified but appear all ICI-only tx
    - Not much detail on pathology – OP and "alveolitis"

4. Prevalence and prognostic significance of interstitial lung abnormalities in lung cancer: A meta-analysis. Yang R, Wang H, Liu D, and Li W. Lung Cancer 2025; 205.

Also refer to ***An Official American Thoracic Society Statement: Approach to the Evaluation of Interstitial Lung Abnormalities.*** *Hatabu H, Lynch DA, Rosas IO, et al. Am J Respir Crit Care Med. 2025;211(2):132–147*

Background

Interstitial lung abnormalities (ILAs) are radiologic findings suggestive of early or subclinical interstitial lung disease, often found incidentally on CT scans, and increasingly recognized in lung cancer patients, particularly given overlapping risk factors (age, smoking).
The presence of ILAs may complicate lung cancer management, may increase susceptibility to treatment-related toxicity and worsen survival outcomes. Prior studies on this topic are heterogeneous and small.

Aim

To assess the prevalence and prognostic impact of ILA in lung cancer

Methods

- Metaanalysis with med, web of science, Embase and Scopus search of articles on the topics of of ILA/ILD and lung cancer up to July 15, 2024
- Prevalence of ILA, OS of lung cancer, PFS, RFS, treatment complications
- Strict inclusion and exclusion criteria for the articles

Results

- Of 9507 articles, 24 deemed suitable for their study, of 7859 lung cancer patients
- Prevalence of ILA 17% (9% after statisticla corrections), mostly GGO and reticulation
- Shorter OS with HR 2.02 (HR 1.77 after statistical corrections), worse for early stage lung cancer
- Worse PFS (HR1.74) and RFS (HR 1.86)
- High correlation between the presence of ILA and treatment related complications especially ICI pneumonitis and radiation pneumonitis

Take home messages

- New attention brought to the presence of ILA at large and risk of developing ILD
- ILA, as incidental findings, are going to be found with increased frequency during lung cancer screening and therefore present in lung cancer patients.
- ILA increases worse outcomes in lung cancer patients, survival and treatment complications
- **For pathologists,** we need to be aware of ILA in lung cancer patients, especially during lung cancer resection of early stage cancer patients. Finding a possible ILD, especially UIP, will affect patient outcome.

II. ARTICLES FOR NOTATION

Neoplastic

1. **Comparative performance of PD-L1 scoring by pathologists and AI algorithms.** Plass M, Olteanu G-E, Dacic S, et al. Histopathology 2025; 87: 90-100

   This study evaluates the concordance and accuracy of PD-L1 tumor proportion score (TPS) assessments in non–small cell lung cancer (NSCLC) when performed by experienced pathologists versus artificial intelligence (AI)–based image analysis algorithms.

   Study design:

   - Digital slides from H&E and PD-L1–immunostained NSCLC samples (SP263) scanned using 2 different scanner, were evaluated by a panel of pathologists and two AI algorithms (uPath and Visiopharm) trained for PD-L1 quantification.
   - Pathologist scores were compared to a consensus "reference standard" created from multiple expert readings both on glass vs WSI. Intra and interobserver agreements calculated.
   - Cases included a range of staining intensities, heterogeneous patterns, and challenging borderline TPS values.

   Key findings:

   - Both pathologists and AI achieved moderate to high agreement with the reference standard in clear-cut high- and low-expression cases.
   - AI algorithms showed slightly higher reproducibility, particularly near clinically relevant cut-offs (1% and 50%), and reduced observer variability.
   - However, AI struggled with rare patterns such as cytoplasmic-only staining, necrosis, or very focal membranous positivity — areas where human interpretation was superior.
   - Combined human-AI review yielded the best overall accuracy, suggesting a potential "augmented" workflow.
   - Did not do correlation with clinical treatment response/outcome.
   - Their results similar or show less correlation than other similar studies.

2. **Assessment of PD-L1 expression and tumour infiltrating lymphocytes in early-stage non-small cell lung carcinoma with artificial intelligence algorithms.** Molerao A, Hernandez S, Alonso M et al. J Clin Pathol 2025; 78:456-464

This study investigates whether AI-based digital pathology algorithms can simultaneously assess PD-L1 expression and tumour-infiltrating lymphocyte (TIL) density in early-stage NSCLC. The aim was to evaluate accuracy, reproducibility, and the potential prognostic implications of integrating these biomarkers in a single AI workflow.

Study design:

- Cohort: early-stage surgically resected NSCLC (50 consecutive with 40 AD), immunostained for PD-L1 (SP263 assay) and CD8-stained sections for TIL quantification.
- AI pipeline: 2 algorithms Navify and Path AI

- Reference standard: consensus scoring by thoracic pathologists for both PD-L1 TPS and TIL density.

Key findings:

- AI-derived PD-L1 TPS showed high correlation with expert pathologists ($R > 0.9$), with strongest agreement at TPS $\geq$ 50% and TPS < 1%.
- TIL quantification by AI was consistent with pathologist scoring and showed lower interobserver variability.
- Combined PD-L1/TIL profiles stratified prognosis better than either biomarker alone in this early-stage setting, with low PD-L1/high TIL tumours showing the most favourable disease-free survival.
- AI reduced scoring time substantially while maintaining accuracy.

3. **Bronchial washing fluid supernatant serves as a novel liquid biopsy specimen for genome profiling in advanced non-small cell lung cancer.** Wu Y, Xie Y, Li J et al. Lung Cancer 2025; 205.

This study evaluates bronchial washing fluid (BWF) supernatant as an alternative liquid biopsy source for genomic profiling in advanced NSCLC, comparing its performance to plasma cell-free DNA (cfDNA) and tumour tissue.

Study design:

- Prospective cohort of patients with advanced NSCLC undergoing bronchoscopy for diagnosis or disease reassessment.
- BWF was collected after tumour site lavage, and supernatant cfDNA was extracted and subjected to targeted next-generation sequencing (NGS) panels.
- Parallel NGS performed on matched tumour tissue (when available) and plasma cfDNA.
- Primary outcomes: detection rate of actionable driver alterations (EGFR, ALK, ROS1, KRAS, BRAF, MET, RET, NTRK, HER2) and concordance with tissue results.

Key findings:

- *BWF supernatant had significantly higher* mutant allele fraction *than plasma* in most patients, leading to higher sensitivity for detecting actionable mutations.
- *Concordance with tumour tissue was >90%* for key driver alterations, and BWF often identified mutations missed by plasma.
- Turnaround time was short (bronchoscopy-to-result in ~5 days), and no additional invasive procedure was required beyond routine lavage.
- Particularly useful in patients without adequate tissue samples for NGS.

4. **Prognostic impact of HNF4α expression in TTF-1-negative non-squamous NSCLC treated with immune checkpoint inhibitor. Iso H, Ariyasu A, Fujishima S, et al. Lung Cancer 2025; 205.**

This study explores whether hepatocyte nuclear factor 4 alpha (HNF4α) expression can serve as a prognostic biomarker in TTF-1–negative non-squamous NSCLC patients treated with immune checkpoint inhibitors (ICIs).

Study design:

- Retrospective cohort of advanced TTF-1–negative non-squamous NSCLC patients receiving PD-1/PD-L1 inhibitors (monotherapy or combination) (n=102).
- HNF4α immunohistochemistry was performed on archival tumour tissue; expression was correlated with clinical characteristics, PD-L1 TPS, and survival outcomes.

Key findings:

- HNF4α expression was detected in a substantial subset of TTF-1–negative cases (54/102), many of which showed enteric/mucinous morphology.
- *HNF4α-positive tumours had significantly shorter progression-free survival (PFS) and overall survival (OS)* on ICI therapy compared to HNF4α-negative tumours.
- The negative prognostic effect remained significant after adjustment for PD-L1 TPS and other clinical variables.
- No clear association was found between HNF4α expression and PD-L1 levels, suggesting an independent prognostic role.

5. Revisiting margin adequacy in sublobar resection for pure ground-glass opacity adenocarcinomas. Kim J, Lee G, Choi S, et al. Lung Cancer 2025; 205.

This study re-examines the optimal surgical margin for pure ground-glass opacity (GGO) adenocarcinomas undergoing sublobar resection (wedge or segmentectomy), with a focus on local recurrence risk. Current guidelines require a margin ≥ lesion diameter or at least 2 cm, but evidence for pure GGO lesions is limited.

Study design:

- Multicenter retrospective cohort of patients with radiologically pure GGO ≤ 2 cm, confirmed as adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA) on pathology (n=158)
- Margin distance measured microscopically and radiologically; margin-to-tumor (M/T) ratio calculated.
- Recurrence-free survival (RFS) compared across different margin thresholds.

Key findings:

- *Overall recurrence after sublobar resection for pure GGO lesions was extremely low.* With a mean FU of 59.9+/- 28.5 mos, 5 (1.8%) had local recurrence.
- 3 recurrences in “insufficient” margin (1,2 and 5 mm) and 2 in the “sufficient” margin (17 and 25 mm)
- *Age and insufficient margin of 5 mm or less were the two significant variables of recurrence.*

6. **Diagnostic accuracy of the Idylla™ mutation test for detecting EGFR mutations in non-small cell lung cancer: a meta-analysis. Perez M, Garcia C, Macias L. Lung Cancer 2025; 205.**

This meta-analysis assesses the diagnostic performance of the Idylla™ EGFR Mutation Test, a fully automated real-time PCR platform, for detecting EGFR mutations in NSCLC. The assay is designed for rapid on-demand testing using minimal sample preparation, potentially expediting treatment decisions in settings without immediate NGS access.

Study design:

- Included studies: 14 eligible publications comprising >1,200 NSCLC specimens (FFPE tissue, cytology cell blocks, and small biopsies).
- Reference standard: targeted NGS or other validated PCR-based methods.
- Outcomes: sensitivity, specificity, and diagnostic odds ratio for detecting any EGFR mutation and clinically relevant alterations (exon 19 deletion, L858R, T790M).

Key findings:

- **Pooled sensitivity**: ~96% for common activating mutations; slightly lower (~90%) for uncommon EGFR variants.
- **Pooled specificity**: ~100% across all mutation types.
- Rapid turnaround (~2 hours) from sample to result was consistent across studies.
- Performance was robust in both small biopsy and cytology specimens, though inadequate DNA yield was a rare limiting factor.
- Most false negatives involved rare or complex indels outside the assay's detection design.

The Idylla™ EGFR test offers high sensitivity and near-perfect specificity for common EGFR mutations in NSCLC, with rapid turnaround, making it a valuable tool for fast initial molecular triage—especially where NGS capacity or tissue is limited.

7. **Global trends in lung cancer incidence and mortality by age, gender and morphology and forecast: A bootstrap-based analysis. George JE, George PS and Krishna J. Lung Cancer 2025; 205.**

This study uses a bootstrap-based statistical modeling approach to analyze worldwide lung cancer incidence and mortality trends, stratified by age, gender, and histologic subtype, with projections into future decades.

Study design:

- Data from the **GLOBOCAN**, **WHO Mortality Database**, and national cancer registries from 35 countries, over 4 continents.
- Trends analyzed for 1990–2020; bootstrap resampling used for robust forecast intervals up to 2040.
- Outcomes: age-standardized incidence and mortality rates, morphology-specific distributions, regional differences.

Key findings:

- **Incidence**: Global lung cancer incidence is mostly declining in men but continues to rise in women, particularly in Asia and parts of Europe, linked to cigarette smoking, including second-hand and alcohol intake.
- **Histology**: Adenocarcinoma is now the predominant subtype worldwide across both sexes, especially in younger patients. Squamous carcinoma continues to decline, while small cell lung carcinoma shows a steady but modest decrease.
- **Age-specific patterns**: In high-income countries, incidence is shifting to older age groups (>70 years), reflecting cohort effects of smoking cessation. In low- and middle-income countries, relatively younger cohorts are contributing more to new cases.
- **Forecast**: Without intensified tobacco control and air pollution interventions, global lung cancer mortality is projected to increase by ~25% by 2040, driven mainly by demographic growth and aging.

8. **Application of endobronchial ultrasound-guided cryobiopsy for centrally located intrapulmonary lesions: A retrospective cohort study. Nakai T, Tanaka S, Nagamine H et al. Lung Cancer 2025; 205.**

This study evaluates the feasibility, diagnostic yield, and safety of endobronchial ultrasound (EBUS)–guided transbronchial cryobiopsy for centrally located intrapulmonary lesions.

Study design:

- Retrospective cohort of patients with centrally located pulmonary lesions (visible or adjacent to the bronchial wall) who underwent EBUS-guided cryobiopsy and TBNA.
- Diagnostic yield, complication rates, and adequacy of specimens for histopathology and molecular testing were evaluated.
- Outcomes were compared with matched patients undergoing conventional forceps biopsy.

Key findings:

- **Diagnostic yield**: Cryobiopsy achieved >95.7% diagnostic yield vs 91.$% for TBNA, significantly higher than forceps biopsy (~75%).
- **Specimen quality**: Cryobiopsy samples were larger, with fewer crush artifacts, enabling higher success rates for molecular and PD-L1 testing.
- **Safety**: Moderate bleeding occurred in a minority (5.7%) but was manageable with standard bronchoscopic techniques; no severe complications or procedure-related mortality reported. Pneumothorax was rare.
- Cryobiopsy resulted in a higher success rate for molecular diagnosis, reducing the need for repeat procedures.

9. **Diagnostic Yield and Synergistic Impact of Needle Aspiration and Forceps Biopsy With Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: A**

Randomized Controlled Trial. Kim Y, Kim H-J, Byoung SK, et al. Chest 2025; 168: 236-247

This randomized controlled trial evaluates whether combining needle aspiration and forceps biopsy during electromagnetic navigation (EMN) bronchoscopy improves diagnostic yield for peripheral pulmonary lesions (PPLs) compared with either technique alone.

Study design:

- Multicenter RCT including patients with CT-detected PPLs undergoing EMN bronchoscopy.
- Randomization to: (1) forceps biopsy alone, (2) needle aspiration alone, or (3) combined approach.
- Primary endpoint: diagnostic yield (definitive diagnosis of benign or malignant lesion).
- Secondary endpoints: specimen adequacy for histology/molecular testing, complication rates.

Key findings:

- **Diagnostic yield**: Combined sampling significantly outperformed either modality alone (approx. 80–85% vs. 60–65%).
- **Molecular adequacy**: Highest in the combined group, supporting integration into precision oncology workflows.
- **Safety**: Complication rates (mainly mild bleeding, rare pneumothorax) were similar across groups, with no major adverse events.
- Subgroup analysis: Benefit of combined sampling most pronounced in smaller (<2 cm) and more peripherally located nodules.

<u>Non-neoplastic</u>

1. **Diagnostic Evaluation and Clinical Findings in Children With Persistent Tachypnea of Infancy/Neuroendocrine Cell Hyperplasia of Infancy. A European Multicenter Retrospective Study.** Marczak H, Krenke K, Griese M, et al. Chest 2025; 168(1): 171-182

This multicenter European retrospective study investigates clinical presentation, diagnostic pathways, and ancillary test findings in children with persistent tachypnea of infancy (PTI). The study reviewed >100 cases from several tertiary pediatric pulmonology centers across Europe.

Main findings:

- Most children presented within the first months of life, but diagnosis was often delayed by months due to nonspecific respiratory symptoms.

- HRCT frequently showed ground-glass opacities with lower lobe predominance and air trapping; these patterns correlated well with biopsy-proven NEHI.
- Lung biopsy remains the gold standard for diagnosis but was avoided in many cases if HRCT and clinical features were typical. *Histology is characterized by increased bombesin-positive pulmonary neuroendocrine cells in small airways without significant fibrosis or inflammation.*
- Genetic testing identified occasional alternative diagnoses (e.g., surfactant disorders), underscoring its role in the differential.
- Most patients improved over time, but some required prolonged oxygen therapy.

2. Dual avb6 and avb1 Inhibition over 12 Weeks Reduces Active Type I Collagen Deposition in Individuals with Idiopathic Pulmonary Fibrosis. A Phase 2, Double-Blind, Placebo-controlled Clinical Trial. Montesi SB, Cosgrove GP, Turner SM et al. AJRCCM 2025; 211:1229-1240

This Phase 2 randomized, double-blind, placebo-controlled trial investigated the safety and antifibrotic efficacy of a novel **dual integrin inhibitor (αvβ6 and αvβ1 blockade)** in patients with **idiopathic pulmonary fibrosis (IPF)**.

Study design:

- Patients with confirmed IPF (FVC >45% predicted, DLCO >30%) randomized to dual integrin inhibitor vs. placebo for 12 weeks.
- Primary endpoint: change in active type I collagen production, assessed via circulating biomarkers and imaging (PET with collagen-targeted tracer).
- Secondary endpoints: safety/tolerability, changes in pulmonary function (FVC), and exploratory HRCT fibrosis scoring.

Key findings:

- **Biologic effect**: Significant reduction in biomarkers of active type I collagen deposition in the treatment group compared to placebo.
- **Lung function**: No statistically significant FVC improvement at 12 weeks, though biomarker changes suggest early antifibrotic activity.
- **Imaging**: PET signals consistent with reduced collagen synthesis.
- **Safety**: Generally well tolerated, with mild gastrointestinal side effects; no excess in serious adverse events.
- Short treatment duration limited conclusions about long-term clinical efficacy.

Case Report/Correspondence/Editorial

1. Unusual Presentation of Clear Cell Tumor of the Lung as Irregular Nodules with a Thin-walled Cavity. Lv M, Gao Q, Zhong J. Am J Respir Crit Care Med. 2025 Jul;211(7): e11–e12

This case report describes a 68-year-old male with a history of heavy smoking, incidentally found to have irregularly shaped, *contrast-enhancing pulmonary nodules with thin-walled cavity* formation in the right upper lobe.
Intraoperative frozen section biopsy ruled out cancer, and subsequent segmentectomy revealed a *clear cell "sugar" tumor of the lung (CCTL).*
CCTL, a rare benign tumor of perivascular epithelioid cell origin, typically presents as well-defined peripheral nodules without cavitation. This case is unusual in showing irregular margins and cavitation, likely due to vascular stroma and a check-valve mechanism. Imaging features mimicked malignancy and infectious or inflammatory processes (e.g., bronchogenic carcinoma, TB, fungal infection, lymphoma).

2. An Unexpected Cause of Postobstructive Pneumonia. Livi V, Cancellieri A, Flore MC, Viscuso M, Trisolini R. Chest. 2025 Jul;168(1): e9–e13

A 72-year-old man with a history of right upper lobectomy for pT1cN1 squamous cell carcinoma presented with postobstructive pneumonia due to severe stenosis of the right main stem bronchus (RMSB). Bronchoscopy and EBUS-TBNA revealed a homogeneous thickening compressing the bronchus. During therapeutic bronchoscopy, a large amount of yellowish, gel-like material spontaneously discharged from the EBUS puncture sites. Histologic and cytologic analysis identified this material as *oxidized cellulose (OC)* —a topical hemostatic agent used in surgery. OC fragments appeared as acellular, elongated, slightly laminated inorganic material within a gel-like background, with minimal inflammation.

3. Forty-five-year-old man with small nodular and ground-glass opacities on CT. Liao J, Chen X, Qiu G, et al. Thorax. 2025;80: 478–479

A 45-year-old Tibetan herdsman with a 10-year history of daily dry nasal snuff inhalation presented with a 2-year cough, 1-year dyspnea, and oxygen saturation of 86% (at 3,650 m elevation). Chest CT showed small solid nodules in both upper lobes, diffuse ground-glass opacities (GGOs), and calcified mediastinal lymph nodes. Lab tests revealed polycythemia and hyperglobulinemia, but otherwise unremarkable. Histology and patient history confirmed *snuff-induced silicosis.* The snuff—common in Tibet—was found to contain silica-based rock powder, explaining the pulmonary pathology.

4. The utility of deeper levels in evaluating transbronchial cryobiopsy specimens for interstitial lung disease. Manchen P, Politis M, Churg A, et al. Histopathology 2025; 87: 159-163

This study examines whether ordering deeper histologic levels in transbronchial cryobiopsy (TBCB) specimens meaningfully improves diagnostic yield for interstitial lung disease (ILD). The authors selected 32 blocks from 23 of 105 consecutive ILD cases where additional levels were thought to yield additional information. Deeper sections revealed additional information in 26% of cases, mostly changing a diagnosis of NSIP to HP.

The authors suggest that *5 H&E sections* should be sufficient for a confident diagnosis in the majority of cases.

5. Hermansky-Pudlak Syndrome in the United States. Engel A, Summer R, Roman J. Chest 168: 156-159

This article reviews the epidemiology, clinical features, and management considerations of Hermansky–Pudlak syndrome (HPS) within the United States. HPS is a rare autosomal recessive disorder characterized by oculocutaneous albinism, bleeding diathesis from platelet storage pool deficiency, and in certain subtypes, progressive pulmonary fibrosis.

The authors related that pulmonary involvement—often manifesting as fibrotic interstitial lung disease—typically develops in mid-adulthood and is a major cause of morbidity and mortality in affected patients. Histologically, the lung fibrosis resembles usual interstitial pneumonia but may occur alongside other microscopic features such as giant lamellar body accumulation in type II pneumocytes, reflecting the underlying lysosome-related organelle defect.

The paper emphasizes the *incidence and prevalence of pulmonary fibrosis, NOS, from US databases, to range from 5.2 to 14.9%,* 3% of which were treated with antifibrotic therapy.

6. SOX17 expression in normal mesothelium and mesothelial lesions. Li Z, Ding Q, Xing D, Parwani A. Histopathology 2025; 87: 161-162

This brief report examines the immunohistochemical expression of SOX17, a transcription factor involved in embryonic development and cell fate determination, in normal mesothelium and a range of mesothelial lesions. SOX17 has been identified as a sensitive and specific marker for carcinomas of the GYN tract, which may enter the differential diagnosis with mesothelioma.

SOX17 was expressed in 17% of mesotheliomas, mostly peritoneal. It was expressed in 33% of WDPMT and 9% of inclusion cysts but absent in adenomatoid tumors and normal mesothelium.

SOX17 is not useful to distinguish mesothelial tumors from tumors of the GYN tract, lacking specificity.

Review articles/ Position paper

1. An Official American Thoracic Society Statement: Approach to the Evaluation of Interstitial Lung Abnormalities. Hatabu H, Lynch DA, Rosas IO, et al. Am J Respir Crit Care Med. 2025;211(2):132–147

This official ATS statement provides a comprehensive framework for evaluating interstitial lung abnormalities (ILA)—radiologic findings on chest CT suggestive of early interstitial lung disease

(ILD), but seen in individuals without clinical suspicion of ILD. The document emphasizes the need to distinguish clinically significant ILAs from benign or age-related changes.

Summary of recommendations include:

- *Systemic assessment and documentation of the presence of ILA and/or ILD in smokers who are undergoing lung cancer screening with chest CT scan.*
- *Baseline chest CT scan to screen for ILA/ ILD and adults with connective tissue disease.*
- *Patient's with ILA should undergo baseline symptoms assessment and baseline pulmonary function test.*
- *Patient's with ILA should undergo a follow-up chest CT scan every 2-3 years after baseline chest CT scan*

Pathologists should recognize histologic correlates of early UIP/NSIP in samples from patients with radiologic ILAs, especially in surgical lung biopsies or explants.

2. The International Association for the Study of Lung Cancer Staging Project: The Database and Proposal for the Revision of the Staging of Pulmonary Neuroendocrine Carcinoma in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. Tsao M, Rosenthal A, Nicholson AG, et al. JTO 2024; 20 (7): 856-870

This IASLC Staging Project analysis focuses on pulmonary neuroendocrine carcinomas (NECs) — small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) — with the goal of informing the 9th edition of the TNM Classification for Lung Cancer. The study uses the large IASLC database, integrating cases from multiple continents, to assess how current TNM staging criteria apply to these aggressive, high-grade tumors.

Key analytic steps included:

- Assessing T descriptors based on tumor size and local invasion.
- Evaluating N descriptors with emphasis on the pattern of nodal spread.
- Investigating M descriptors for metastatic sites and prognostic separation.

Findings indicate that the TNM descriptors for NSCLC also stratify prognosis in SCLC and LCNEC, although analysis limited by small numbers.