Pulmonary Journal Club May 2025 (Articles from April 2025)

Presented by
Dr. Ying-Chun Lo, Assistant Professor of Laboratory Medicine and Pathology
Mayo Clinic, Rochester, MN

Articles for Discussion

(1) Identification of Defined Molecular Subgroups on the Basis of Immunohistochemical Analyses and Potential Therapeutic Vulnerabilities of Pulmonary Carcinoids
J Thorac Oncol. 2025 Apr;20(4):451-464.

Introduction:

- Multi-omic studies have identified three molecular separated pulmonary carcinoid (PC) subgroups (A1, A2, B) with distinctive mRNA expression profiles (e.g., OTP, ASCL1, and HNF1A).
- The authors aimed to establish an IHC biomarker panel that enables subgroup identification, and assessment of its potential clinical relevance.

Methods:

- All patients with resected pulmonary carcinoids (2003-2012) were identified from the Dutch Cancer/Pathology Registry, and tumors were revised.
- The IHC expression of OTP, ASCL1, and HNF1A was scored in a blinded fashion in a mRNA-profiled (n = 5 per subgroup) and national carcinoid cohort (N = 478).
- The expression of potential therapeutic targets (somatostatin receptor type 2a [SSTR2A] and delta-like canonical Notch ligand 3 [DLL3]) was assessed. Immunohistochemistry was assessed using H-scoring.

Results:

- OTP, ASCL1, and HNF1A reported similar IHC and mRNA expression patterns in the matched primary samples.
- In the national cohort, IHC separated PCs into subgroups A1 (n = 224 [53%], OTP^{high}-$ASCL1^{high}$-$HNF1A^{low}$), A2 (n = 161 [38%], OTP^{high}-$ASCL1^{low}$-$HNF1A^{high}$), and B (n = 37 [9%], OTP^{low}-$ASCL1^{low}$-$HNF1A^{high}$).
- In 12% of PCs, no distinct classification could be provided.
- Patients with A1 were enriched for older age (83% > 50 y), female individuals (83%), and peripheral location (55%) with low SSTR2A (median = 10) and high DLL3 (median = 52) expression.
- A2 included younger patients (34% < 40 y) and endobronchial/central (87%) tumors with high SSTR2A (median = 160), but low DLL3 (median 0) expression.
- Group B included more male individuals (59%) and recurrence was more frequent (19%) than in groups A1 (8%) and A2 (6%).
- Neuroendocrine cell hyperplasia was enriched in A1 (25%) compared with A2 (3%) and B (0%).

Conclusions:

- An OTP, ASCL1, and HNF1A IHC panel enables the identification of molecular-defined pulmonary carcinoid subgroups with distinct clinical phenotypes and diverging therapeutic vulnerabilities that require further prospective evaluation.

(2) Adverse Prognostic Impact of Transitional and Pleomorphic Patterns in Pleural Nonepithelioid Mesothelioma: Insights From Comprehensive Analysis and Reticulin Stain
Arch Pathol Lab Med. 2025 Apr 1;149(4):347-353.

Introduction:

- Mesothelioma subtyping into epithelioid and nonepithelioid categories plays a crucial role in prognosis and treatment selection, with emerging recognition of the impact of various histologic patterns.

Aim:

- To investigate the prognostic implications of transitional and pleomorphic patterns in sarcomatoid mesothelioma.

Design:

- A total of 132 mesothelioma cases (87 biphasic, 45 sarcomatoid) were analyzed.
- Histologic slides were assessed, treatment data collected, and cases categorized into predominant epithelioid or sarcomatoid patterns.
- The sarcomatoid mesotheliomas were classified into usual, pleomorphic, and transitional patterns, with reticulin staining for the latter. Statistical analysis included Cox regression and Kaplan-Meier methods.

Results:

- Younger age ($P = .02$) and receiving therapy ($P < .001$) correlated with improved survival for both histotypes.
- Advanced stage was associated with shorter survival in sarcomatoid cases ($P = .02$).
- Predominant epithelioid pattern in biphasic cases led to longer survival ($P < .001$).
- Transitional and pleomorphic patterns were indicative of worse prognosis, with significantly lower survival in cases with both patterns than in cases with the usual sarcomatoid pattern ($P = .046$).
- Multivariate analysis identified independent survival factors, including predominant epithelioid component in biphasic mesothelioma ($P = .001$) and chemotherapy ($P < .001$).

Conclusions:

- Histologic subtyping in mesothelioma plays a pivotal role in prognosis.
- Transitional and pleomorphic patterns, even in low percentages, indicate poorer outcomes.
- This study highlights the need for standardized diagnostic support and suggests the potential utility of histochemical staining in identifying more aggressive morphologic aspects.
- Recognizing the significance of these patterns can guide treatment decisions and patient care strategies.

(3) Insulinoma-associated protein-1 (INSM-1) is a useful diagnostic marker for the evaluation of primary thymic neuroendocrine neoplasms: an immunohistochemical study of 27 cases
Virchows Arch. 2025 Apr;486(4):721-727.

Introduction:

- Insulinoma-associated protein 1 (INSM1) immunohistochemistry has been established as a sensitive and reliable immunohistochemical marker for detecting neuroendocrine differentiation in tumors across various organ systems.
- However, this marker has not been adequately investigated in primary thymic neuroendocrine tumors.

Methods:

- The authors have studied a series of 27 cases of primary neuroendocrine carcinomas of the thymus, including 3 typical carcinoids, 18 atypical carcinoids, 4 large cell neuroendocrine carcinomas, and 2 small cell carcinomas.
- Immunostaining on whole tissue sections for INSM-1 was evaluated.
- Results of immunostaining for chromogranin and synaptophysin were also evaluated.

Results:

- 26/27 tumors (96%) demonstrated nuclear positivity for INSM1. 18 tumors (67%) showed strong and diffuse nuclear staining (3 +), 3 tumors (11%) moderate (2 +) nuclear staining, and 5 tumors (19%) showed weak (1 +) nuclear staining.
- The average percentage of tumor cells positive for INSM1 was 76%.
- Only one tumor, a small cell carcinoma, was negative.
- All tumors were positive for synaptophysin, and 26/27 (96%) were positive for chromogranin A.

Discussion:

- The nuclear staining with this marker offers the advantage of eliminating some of the ambiguity in the interpretation sometimes encountered with other markers.

Conclusions:

- This study confirms that INSM1 immunohistochemistry is a sensitive marker of neuroendocrine differentiation in primary thymic neuroendocrine neoplasms and demonstrates similar performance characteristics compared to other organ systems.
- An added advantage is the consistent staining across the entire spectrum of neuroendocrine tumors of this organ.

(4) Airway associated inflammation in post-transplant cystic fibrosis patients as a predictor of chronic lung allograft dysfunction (CLAD)
J Clin Pathol. 2025 Mar 19;78(4):251-258.

Background:

- In cystic fibrosis lung transplant recipients (LTRs), graft dysfunction due to acute infections, rejection or chronic lung allograft dysfunction (CLAD) is difficult to distinguish.
- Characterisation of the airway inflammatory milieu could help detect and prevent graft dysfunction.
- The authors speculated that an eosinophil or neutrophil-rich milieu is associated with higher risk of CLAD.

Methods:

- A retrospective, single-centre observational study of cystic fibrosis LTRs between 2002 and 2021 was performed.
- Data from biopsy slides, pulmonary function testing and bronchoalveolar lavage fluid microbiology tests were collected.
- The primary outcome was bronchiolitis obliterans syndrome (BOS) or death after transplant, with an 8-year follow-up period.

Results:

- 40 patients were identified with an average age of 35.3 at first transplantation, including 5 redo lung transplants.
- Fungal infections were correlated with higher rejection scores ($p<0.01$) and survival status ($p=0.027$).
- Fungal and bacterial infection rates were reduced in later transplants (2014-2021) compared with earlier (2002-2014).
- Fungal infections were associated with significantly worsened outcomes ($p\leq0.001$).
- Eosinophils in large airways was associated with worse BOS-free survival ($p=0.03$).

Conclusions:

- Subcategorisation of the inflammatory milieu (particularly noting eosinophils) in surveillance biopsies may help detect CLAD earlier and improve long-term outcomes in cystic fibrosis LTRs.

Articles for Notation – Neoplastic

EGFR mutation status affects intra-tumoural heterogeneity of PD-L1 expression but not agreement between assays in resectable non-small cell lung cancer

Lung Cancer. 2025 Apr:202:108463.

Background: The predictive value of PD-L1 to select patients for immunotherapy in resectable NSCLC remains imprecise, confounded by different assays used across trials and intra-tumoural heterogeneity (ITH). We sought to compare the concordance between 3 PD-L1 antibodies stratified by EGFR mutation status, evaluate ITH and implications on survival outcomes.

Methods: Tissue microarrays were constructed from stage IA-IIIA NSCLC with 3 tumour cores per patient. Tumour proportion score (TPS) was evaluated by 3 pathologists for SP263, SP142, 22C3 and analysed in tertiles of < 1 %, 1-49 % and ≥ 50 %. ITH was defined as discordant TPS in ≥ 2/3 tumour cores. Cohen's kappa test was used to assess agreement. Survival outcomes were estimated using Kaplan-Meier.

Results: A total of 561 patients were included, 59.5% (334/561) were EGFR-mutant. Stage IA comprised 45.5%(255/561), IB 24.1%(135/561), IIA 12.7%(71/561), IIB 4.5%(25/561) and IIIA 13.4%(75/561). Across 1683 tumour cores, SP263 and 22C3 had the highest concordance (Kappa = 0.689), followed by 22C3 and SP142 (Kappa = 0.354), then SP263 and SP142 (Kappa = 0.284), similar between EGFR-mutant and EGFR-wildtype. Agreement between pathologists was almost perfect. ITH by SP263 was observed in 14.1 % of EGFR-mutant versus 24.2 % in

EGFR-wildtype(p = 0.002). Discordance was highest among TPS 1-49 % at 92.6 % (88/95) followed by ≥ 50 % at 37.8 % (14/37) and least among < 1 % at 0 % (0/429) (p < 0.001). For tumour cores scored 1-49 %, 63 %/70 % of adjacent cores were scored < 1 % for EGFR-wildtype/mutant respectively. Histological grade was the only independent predictor of PD-L1 ITH on multivariable analysis. PD-L1 ITH was not associated with survival on multivariable analysis.

Conclusion: PD-L1 scoring by SP263 and 22C3 are interchangeable but not SP142 regardless of EGFR status. PD-L1 ITH was more common in EGFR-wildtype versus EGFR-mutant tumours. Extra care should be taken to select the most representative tumour core for tumours with high histological grade or TPS 1-49% as this may influence peri-operative treatment decisions.

Pathological & radiological variables in the diagnosis of bronchopulmonary carcinoids (BPCs) with a focus on Antigen Kiel 67 (Ki-67) proliferation index

Lung Cancer. 2025 Apr:202:108493.

Background: Bronchopulmonary carcinoids (BPCs) are classified into typical carcinoids (TC) and atypical carcinoids (AC), based on the mitotic count and absence/presence of necrosis on pathology specimens. There are limitations to accurate measurement of these criteria. It important to study other markers like Ki-67, to enhance the diagnostic accuracy of lung carcinoids.

Objective and methodology: Retrospective analysis of BPCs treated with surgery between 2012-2022, to examine the accuracy of Ki-67 on the diagnostic specimen, concordance of diagnostic and resection specimens, diagnostic accuracy of Positron Emission Tomography (PET) and concordance of clinical and pathological staging.

Results: 205 patients were included in the analysis (final diagnosis TC 180, AC 25). Mean age 60.5 years and 68 % female. Ki-67 (<5% vs. 5-30 %) on diagnostic biopsy, available in 64 % (n = 131) of the cohort, had specificity (diagnose TC correctly) of 89.4 % (95 %CI 80.4 %-94.7 %) and sensitivity (diagnose AC correctly) of 77.8 % (40.2 %-96.1 %). This compared to 97.5 % (90.3 %-99.6 %) and 36.4 % (12.4 %-68.4 %) for mitotic count (<2mitoses/2mm^2 vs. 2-10mitoses/2mm^2) and 100 % (94.4 %-100 %) and 21.4 % (5.7 %-51.2 %) for necrosis (absence vs. presence). A pre-resection diagnosis of TC (including surgical biopsy) shows better concordance with final diagnosis on resection specimen (94.9 %, 95 %CI 88.7 %-97.9 %, n = 117) as compared to the diagnosis of AC 83.3 % (95 %CI 50.9 %-97.1 %, n = 12). Concordance for AC appears higher with image guided lung biopsy 80 % (95 % CI, 29.9 %-98.9 %) than bronchoscopy 50 % (9.5 %-90.5 %). SUVmax on 18FDG-PET was a modest predictor of BPC sub-type with an AUC of 0.684 (95 % CI: 0.545,0.823). The clinical and pathological staging were concordant in 46 % (85/184) cases. However, 27 % (50/184) were upstaged and 13 % (23/172) found to have occult nodal metastases on pathology review of the surgical specimens.

Conclusion: The diagnosis and sub-typing of BPCs on diagnostic specimens is challenging. Our data suggest Ki-67 could increase diagnostic accuracy, but further research is needed to confirm this.

Absence of orthopaedia homeobox protein (OTP) expression is associated with disease spread and adverse outcome in pulmonary carcinoid tumour patients

Virchows Arch. 2025 Apr;486(4):675-685.

Introduction: Pulmonary carcinoid (PC) tumours typically have a good prognosis, although metastases occur, and the disease may progress after a long period of time. Expression of orthopaedia homeobox protein (OTP) has been recognized as a possible independent prognostic marker in PCs. Immunohistochemical (IHC) OTP expression has been associated with better prognosis, but the staining has yet to be implemented in routine clinical diagnostics.
Methods: In response to this, two new monoclonal OTP antibodies were recently developed.This retrospective study included 164 PC patients operated on at Helsinki University Hospital between 1990 and 2020. Tissue microarray slides, prepared from formalin-fixed and paraffin-embedded primary tumour samples, were stained with OTP IHC using one polyclonal and two novel monoclonal antibodies.
Results: Absence of OTP expression was associated with a shorter disease-specific survival (DSS) and disease progression ($p < 0.001$). Patients without OTP expression had a 5-year DSS of 73-79%, whereas 5-year DSS was 91-94% with OTP expression, depending on the primary antibody. In a univariable Cox regression model, absence of OTP expression was associated with adverse outcome along with atypical histological subtype, metastatic disease, Ki-67 proliferation index > 1%, and larger tumour size. In a multivariable Cox regression model, only absence of OTP expression and lymph node involvement at the time of diagnosis were associated with risk of worse prognosis.
Conclusions: All three antibodies showed good concordance with each other.Our findings support the role of OTP as an independent prognostic marker in PCs and applicability of IHC staining in routine clinical use with novel monoclonal antibodies.

Prognostic implications, genomic and immune characteristics of lung adenocarcinoma with lepidic growth pattern

J Clin Pathol. 2025 Mar 19;78(4):277-284.

Aims: Conflicting data were provided regarding the prognostic impact and genomic features of lung adenocarcinoma (LUAD) with lepidic growth pattern (LP+A). Delineation of the genomic and immune characteristics of LP+A could provide deeper insights into its prognostic implications and treatment determination.

Methods: We conducted a search of articles in PubMed, EMBASE and the Cochrane Library from inception to January 2024. A domestic cohort consisting of 52 LUAD samples was subjected to whole-exome sequencing as internal validation. Data from The Cancer Genomic Atlas and the Gene Expression Omnibus datasets were obtained to characterise the genomic and immune profiles of LP+A. Pooled HRs and rates were calculated.

Results: The pooled results indicated that lepidic growth pattern was either predominant (0.35, 95% CI 0.22 to 0.56, p<0.01) or minor (HR 0.50, 95% CI 0.36 to 0.70, p<0.01) histological subtype was associated with favourable disease-free survival. Pooled gene mutation rates suggested higher EGFR mutation (0.55, 95% CI 0.46 to 0.64, p<0.01) and lower KRAS mutation (0.14, 95% CI 0.02 to 0.25, p=0.02) in lepidic-predominant LUAD. Lepidic-predominant LUAD had lower tumour mutation burden and pooled positive rate of PD-L1 expression compared with other subtypes. LP+A was characterised by abundance in resting CD4+memory T cells, monocytes and γδ T cells, as well as scarcity of cancer-associated fibroblasts.

Conclusions: LP+A was a unique histological subtype with a higher EGFR mutation rate, lower tumour mutation burden and immune checkpoint expression levels. Our findings suggested potential benefits from targeted therapy over immunotherapy in LP+A.

Articles for Notation - Non-Neoplastic

The Dawn of Precision Medicine in Fibrotic Interstitial Lung Disease
Chest. 2025 Apr;167(4):1120-1132.

Topic importance: Interstitial lung diseases (ILDs) represent a broad group of heterogeneous parenchymal lung diseases. Some ILDs progress, causing architectural distortion and pulmonary fibrosis, and thus are called fibrotic ILDs. Recent studies have shown a beneficial effect of antifibrotic therapy in fibrotic ILDs other than idiopathic pulmonary fibrosis (IPF) that manifest progressive pulmonary fibrosis (PPF). However, it remains challenging to predict which patients with fibrotic ILDs will demonstrate PPF. Precision medicine approaches could identify patients at risk for progression and guide treatment in patients with IPF or PPF.

Review findings: Multiple biomarkers able to highlight disease susceptibility risk, to provide an accurate diagnosis, and to prognosticate or assess treatment response have been identified. Advances in precision medicine led to the identification of endotypes that could discriminate patients with different fibrotic ILDs or patients with different disease courses. Importantly, recent studies have shown that particular compounds were efficacious only in particular endotypes. The aforementioned findings are promising. However, implementation in clinical practice remains an unmet need.

Summary: Substantial progress has been observed in the context of precision medicine approaches in fibrotic ILDs in recent years. Nonetheless, infrastructure, financial, regulatory, and ethical challenges remain before precision medicine can be implemented in clinical practice. Overcoming such barriers and moving from a one-size-fits-all approach to patient-centered care could improve patient quality of life and survival substantially.

High-dimensional tissue profiling of immune cell responses in chronic lung allograft dysfunction

J Heart Lung Transplant. 2025 Apr;44(4):645-658.

Purpose: The immunological drivers of chronic lung allograft dysfunction (CLAD), the major barrier to long-term survival after lung transplantation, are poorly understood at a tissue level. Tissue imaging using mass spectrometry with laser ablation of regions of interest offers single-cell resolution of distinct immune cell populations and their spatial relationships and may improve our understanding of CLAD pathophysiology.

Methods: Lung tissue from 23 lung transplant recipients, 20 with and 3 without CLAD, was sectioned and stained with a 40-plex antibody panel before 81 regions of interest from airways, blood vessels and lung parenchyma were laser ablated.

Results: 190,851 individual segmented cells across 41 mm^2 tissue were captured before 26 distinct immune and structural cell populations were identified and interrogated across CLAD phenotypes. CLAD was associated with expansion of cytotoxic T cells, γδ T cells and plasma cells and M2 macrophage polarization compared with non-CLAD. Within CLAD, bronchiolitis obliterans syndrome was characterized by more γδ T cells and fewer Th1 cells than restrictive allograft syndrome. Both adaptive and innate immune cells were involved in the temporal evolution of fibrotic remodeling. Although fibrosis seemed to be partially associated with different factors in restrictive allograft syndrome (M2 macrophages, Th1 cells) and in bronchiolitis obliterans syndrome (γδ T cells).

Conclusion: Imaging mass cytometry enables in-depth analyses of immune cell phenotypes in their local microenvironment. Using this approach, we identified major differences in cell populations in CLAD versus non-CLAD and in BOS versus RAS, with novel insights into the fibrotic progression of CLAD.

Letters, Brief Communications, Case Reports

(1) A Novel Case of Pulmonary Sclerosing Diffuse PEComatosis With Neuroendocrine Cell Hyperplasia
Am J Surg Pathol. 2025 Apr 1;49(4):411-415.

(2) Pulmonary Arterial Inflammatory Myofibroblastic Tumor in an Adult
Am J Respir Crit Care Med. 2025 Apr;211(4):640-641.

(3) Is Tissue the Issue When It Comes to Severe Asthma?
Chest. 2025 Apr;167(4):911-913.

(4) A 57-Year-Old Man With Persistent Miliary Pattern Pulmonary Nodules and New Lung Masses on Chest CT Scan
Chest. 2025 Apr;167(4):e113-e117.

(5) A New Pulmonary Nodule in a Patient With a History of Lymphoma
Chest. 2025 Apr;167(4):e133-e139.

Reviews

(1) Data set for the reporting of lung cancer: recommendations from the International Collaboration on Cancer Reporting (ICCR)
Histopathology. 2025 Apr;86(5):665-680.

(2) Neoadjuvant Therapy and Lung Cancer: Role of Pathologists
Arch Pathol Lab Med. 2025 Apr 1;149(4):e78-e81.

(3) Pulmonary Adenocarcinoma Updates: Histology, Cytology, and Grading
Arch Pathol Lab Med. 2025 Apr 1;149(4):e82-e86.

(4) Thoracic Frozen Section Pitfalls: Lung Adenocarcinoma Versus Selected Mimics
Arch Pathol Lab Med. 2025 Apr 1;149(4):e93-e99.

(5) Uncommon Tumors of the Lung: Recently Described and Rediscovered Tumors
Arch Pathol Lab Med. 2025 Apr 1;149(4):e87-e92.