Pulmonary Journal Club Mar (Articles from February 2025)

Dr. Margaret Kelly
Department of Pathology and Laboratory Medicine
University of Calgary, Calgary, AB, Canada

Table of Contents

Reviews

Case Reports

Articles for Discussion

Pavlisko EN et al. Diagnostic alignment to optimize inter-rater reliability among lung transplant pathologists. *J Heart Lung Transplant*. 2025;44(2):173–181; Editorial. Glanville AR. Lung transplant pathology: No longer through a glass darkly? J Heart Lung Transplant. 2025 Feb;44(2):183.

Background

- Chronic lung allograft dysfunction (CLAD) is the main limiting factor for long-term survival following lung transplantation (LTx).
- The gold standard to predict CLAD is histopathologic assessment of transbronchial biopsies (TBBX) including **acute rejection (AR)** and **lymphocytic bronchiolitis (LB)**, and more recently, **acute lung injury (ALI)** and **organizing pneumonia (OP)** are known predictors of CLAD.
- However, **inter-rater reliability (IRR)** among lung transplant pathologists for diagnosing these entities has historically been poor, especially for AR and LB.

Objective: To improve IRR among multiple pathologists across institutions so that CLAD-associated histopathologic patterns can be reliably identified, thus facilitating multicenter clinical trials and consistent clinical management

Hypothesis: **Prestudy diagnostic alignment** will result in good IRR amongst pathologists across multiple centres

Methods

- **Participants:** 9 expert LTx pathologists from 8 North American centers, participating in a clinical trial (CTOT-47). **Figure 1**
- **Diagnostic Alignment:** Each pathologist
  a. completed a survey on their practice habits - length of practice, quantity of slides prepared, stains utilized, utilization of digital pathology, and diagnostic criteria utilized for AR, LB, OP, and ALI, AND
  b. participated in **7 structured zoom-based alignment sessions** reviewing the diagnostic criteria for AR, LB, ALI, and OP, using ISHLT guidelines and how to handle confounding histologic features.
- **Slide Set:** 75 digitized TBBX slides (≤14 months post-transplant) from a previous clinical trial were selected so as to ensure rates for each histopathologic finding were between 20-35%, as documented in **Table 1**. The Duke pathologist reviewed each slide to confirm the pathology was representative.
- All 75 slides were reviewed by the 9 pathologists with **time from transplant** as the only clinical data provided.
- A **staggered starting slide number** was utilized to control for reviewer fatigue
- **Data Capture:** Standardized REDCap-based LASHA form **Figure S1**; diagnoses were graded per ISHLT guidelines.

- **Statistics:** IRR measured by **Fleiss' kappa** for:
- the presence or absence of **Any Finding** (defined as any A or B grade other than A0/B0, ALI or OP).
- the presence or absence of each individual finding (irrespective of grade/severity)
- the absence of all findings.

Results: Survey Findings

Table S1

- Median (25th, 75th percentile) number of **years in practice was 15** (between 5-30 y).
- Survey captured areas where the approach to biopsy assessment varied regarding criteria for diagnosing AX as well as histologic thresholds used to guide the diagnosis of AR and LB

Results: Diagnostic alignment sessions

- Greatest areas of **disagreement** involved **LB** including how to define small vs large airways, how to interpret squamous metaplasia, airways with mixed inflammation, including lymphocytes, plasma cells, neutrophils
- Decided to add categories: **AX-C and BX-C**- indicate that while perivascular or airway inflammation otherwise diagnostic of AR or LR are present, other findings in the biopsy, e.g. acute inflammation, OP, ALI, squamous metaplasia, raise concern for an alternate etiology such as infection or aspiration.
- **AX-inadequate** and **BX-inadequate**: inadequate sample quantity only in the absence of findings diagnostic of AR or LB.

Results: Digitized slide assessment results IRR

- For **all findings except ALI**, the Fleiss' kappa estimates and confidence bounds are in the good agreement range (≥0.58)
- **Landis and Koch scale**: the kappa estimates for Any Finding, AR, and ALI are in the moderate agreement range (between 0.41 and 0.60), with the upper confidence bound for Any Finding and AR falling in the substantial agreement range (between 0.61 and 0.80) and the lower confidence bound of ALI falling in the fair agreement range (between 0.21 and 0.40). The kappa estimates for **LB and OP are in the substantial agreement range**, with the lower confidence bound falling in the moderate agreement range.

- Heat map (**Figure 2**) to visualize agreement
- The group consensus - defined as the most common finding across the 9 pathologists.
- The agreement of each individual pathologist with the group consensus for each case was evaluated (**Figure 3**) and showed **3 outliers**: **2 for AR** (these pathologists (P7 and P9) did not complete all in-person training for AR) and **1 for ALI**.

- **Sensitivity analysis** excluded the 2 pathologists who did not fully participate in alignment sessions. **Table 3**
    - **AR IRR improved to κ = 0.728**
    - Other values showed minor improvement

Conclusions

- **IRR and agreement** was **good** to **substantial** for most findings, particularly LB and OP.
- ALI agreement was poor, potentially due to artifact or limitations in digital slide review.
- **Historically**, IRR in lung rejection assessment ranges from 0.183 - 0.65 for AR and 0.035 - 0.465 for LB
- Removal of the 2 pathologists who did not fully participate in AR diagnostic alignment sessions, showed an improvement in IRR for AR, LB, and OP.
- Future studies utilizing a **control arm are needed to validate the useful of the survey and diagnostic alignment work** ***or assessment of the IRR prior to alignment***
- Study did not fully mimic the current standard workflow by **brightfield light microscopy** with **multiple slides** per TBBX, allowing for assessment of additional tissue levels and **special stains**
- Study **not optimally powered** for the evaluation of IRR for individual histologies (AR, LB, ALI, and OP)
- **Within rater repeatability** (Ed) would have been informative and complimentary
- Practical implications for both trial design and daily pathology workflow.
- The authors tackled an old problem — poor IRR in lung transplant pathology — with a structured, collaborative solution.
- It's reassuring to see that even with 9 raters (a large number in pathology studies), agreement held up well. The concept of AX-C and BX-C is particularly useful in real-world practice, where "rejection" might be present but confounded.

Take Home Message

- A well designed and written study, although the objective of the study, that is to demonstrate diagnostic alignment pre study can substantially improve IRR and agreement, could not be confirmed due to the lack of a control arm or assessment of IRR before diagnostic alignment.
- The lack of consensus on the survey despite the pathologists being relatively experienced and specialized is interesting and highlights the need for such diagnostic alignment before starting clinical trials.
- Findings reinforce the need for standardized criteria and possibly updating ISHLT guidelines to reflect nuanced interpretations (e.g., AX-C/BX-C for confounded cases).

Halloran K et al. The lung transplant endobronchial biopsy: A forgotten specimen comes of age. J Heart Lung Transplant. 2025;44(2):293–297.

Background

- EBB offers several advantages over transbronchial biopsy (TBB), such as reduced risk of pneumothorax and bleeding due to direct visualization as well as potentially better assessment of the small airways than TBB.
- EBBs can be safely obtained in patients with severe such as acute or chronic lung allograft dysfunction (ALAD/CLAD), when TBB is contraindicated.
- Endobronchial biopsies (EBBs) application in lung transplantation remains underutilized and somewhat controversial.

Objective: to provide a scientific rationale for incorporating EBB into ALAD and CLAD protocols

This is a **Perspective** article synthesizing prior research, clinical observations, and molecular data across multiple institutions, particularly the University of California San Francisco (UCSF).

- 269 subjects 1997-2011, > 1,000 EBB collected for early post-transplant surveillance. 2-3 EBB samples in third- or fourth-generation carinae, typically in the lower lobes; TBBX were performed as well.
- Lymphocytic bronchitis was assessed using ISHLT criteria for lymphocytic bronchiolitis (LB, B-grade rejection) and referred to as E grades.
- Overall, observed at least minimal perivascular lymphocytosis (A-score ≥ 1) in 18% of samples; small-airway LB (BR-score ≥ 1) in 15% of samples; and large-airway lymphocytic bronchitis (E-score ≥ 1) in 25% of samples.
- Lymphocytic bronchitis was strongly associated with LB and, to a lesser extent, with A-grade rejection.
- After excluding active infection, moderate to severe lymphocytic bronchitis was a rare finding but associated with CLAD over the subsequent 2 years
- In a follow up study of > 2,300 EBBs through 2015, lower grades of lymphocytic bronchitis were twice as common following the implementation of **routine azithromycin prophylaxis**; i*.e. higher grades therefore assumed to be less frequent;* although interestingly, no effect on the rates of CLAD was observed
- **Molecular Studies**: Gene expression analyses of EBBs reveal:
    - Distinct inflammatory/fibrotic signatures linked to rejection.
    - Reproducible molecular signals with strong prognostic value (e.g., c-index 0.76 for graft loss prediction).
    - Archetypes rich in T-cell-mediated rejection and interferon-gamma–inducible transcripts.
    - Molecular classifiers have been developed that predict outcomes when histology is equivocal.

Conclusion

The authors advocate for integrating EBB into post-transplant diagnostic workflows and surveillance protocols. EBBs provide a safe, repeatable source of biologically relevant tissue for both histologic and molecular analysis. They are especially valuable when TBB is not feasible. There is a call for multicenter studies, standardized scoring, and potential clinical trials targeting EBB-driven therapy.

Take Home Message

- Endobronchial biopsies offer underutilized but valuable insights into lung transplant pathology.
- They are safe, accessible, and informative
- There is strong potential for EBBs to supplement or replace TBBs in specific contexts when the latter is unsafe
- The data suggesting gene expression profiles in EBBs are more reproducible and predictive than histology is provocative and aligns with a broader shift toward molecular diagnostics.
- But more studies required.

Kojima N et al. Inflammatory spindle cell PEComa of the lung with YAP1::TFE3 fusion: a report of two cases and a potential relationship with clear cell stromal tumour. Histopathology. 2025 Feb;86(3):365–372.

Background

- PEComas are a group of mesenchymal neoplasms defined by spindle or epithelioid cells with dual myogenic and melanocytic differentiation.
- Most pulmonary PEComas have **TSC1/2 alterations**, while ~20% harbor **TFE3 fusions**, but **YAP1::TFE3 fusion** has **not** previously been reported in PEComas.
- **Clear cell stromal tumour of the lung (CCST-L)** is a newly recognized entity with overlapping morphology but **no myomelanocytic differentiation** and frequent **YAP1::TFE3 fusions**.
- This study reports **two lung tumours** with **myomelanocytic features** and **YAP1::TFE3 fusion**, exploring their potential link to CCST-L.

Methods

- **Histology & IHC:** Broad panel- markers for melanocytic, myogenic, and epithelial differentiation.
- **Molecular Studies:**
  - **FISH** for TFE3 and YAP1 rearrangements.
  - **RNA sequencing** using TruSight Pan-Cancer panel in one case to confirm the fusion.

Results

- **Case 1:** 61M, 3.1 cm hilar mass, SUVmax 4.62, no recurrence at 32 months; **Case 2:** 68M, 2.8 cm hilar mass, SUVmax 7.74, no recurrence at 7 months.
- Both tumours: **Spindle cell proliferation** (storiform/fascicular), minor epithelioid clear cell component, **prominent inflammatory background**, **dilated vessels**.
- **Case 1:** Focal necrosis, up to 9 mitoses/50 HPF; **Case 2:** No necrosis, 3 mitoses/50 HPF, focal melanin.
- **Both cases:** Positive for **HMB45, Melan A, h-caldesmon** (Case 1: diffuse HMB45; Case 2: focal expression).
- **FISH:** YAP1 and TFE3 rearrangements in both cases.
- **RNA-seq (Case 1):** YAP1 exon 7 – TFE3 exon 7 fusion detected; preserves TEAD and WW domains of YAP1 and bHLH of TFE3.

Conclusion: These cases represent a **novel subset of PEComas** with:

- Inflammatory spindle cell-rich morphology,
- Myomelanocytic differentiation,
- **YAP1::TFE3 fusion**, previously unreported in PEComa.

Their clinicopathologic and genetic similarity to **CCST-L** raises the hypothesis of a **biological relationship** between these two tumour types.

Take Home Message

- The authors only describe 2 cases, but another (first description of such a tumor) article described a similar tumor in the pancreas - **Tsukita H et al. A case of pancreatic**

PEComa with prominent inflammatory cell infiltration: the inflammatory subtype is a distinct histologic group of PEComa. Diagn Pathol. 2024 Apr 15;19(1):59.

- YAP1::TFE3 fusion defines **2 cases** the authors describe as **pulmonary PEComas** with inflammatory spindle cell histology
- Not sure where these tumors fit in classifications but they may be on a **spectrum** of YAP1::TFE3-rearranged lung neoplasms, ranging from CCST-L (no melanocytic differentiation) to PEComa (evident myomelanocytic differentiation).

Articles for Notation

Neoplastic Disease

Wan, Y et al. (2025). Multiple Pulmonary Sclerosing Pneumocytomas (PSPs): A Comprehensive Analysis of Clinicopathological Characteristics and Whole-Exome Sequencing (WES) Results. American Journal of Surgical Pathology, 49(2), 138-149.

Summary

- This study explores the clinicopathological characteristics and genetic mutations associated with multiple pulmonary sclerosing pneumocytomas (PSPs).
- PSP is a rare benign lung neoplasm that typically presents as a solitary nodule, with only a few cases of multiple nodules reported.
- The authors identified 11 patients with multiple PSPs and performed whole-exome sequencing (WES) on six patients to investigate the genetic underpinnings.
- Of the 11, 9 only had 2 PSPs, one had 3 and another 1 had multiple bilateral PSPs
- AKT1 mutations were found in 50% of PSP nodules, with a predominant p.E17K alteration. In addition, novel ARID1A mutations co-occurred with AKT1 mutations.
- **PSPs involving multiple nodules often have independent origins, as evidenced by limited overlap in mutation spectra across different nodules from the same patient**.
- Interestingly, no AKT1 mutations were found in the case of diffuse multiple nodules, but shared non-driver mutations were observed.

Take Home Message

- Largest series to date, but still very small sample size, so more work is needed.
- AKT1 mutations are a common driver in cases involving two or three nodules but different molecular signatures indicating they arose independently
- In the case of multiple bilateral tumors, AKT1 mutations were not found; likely independent tumors but possibility of metastases in some cases couldn't be entirely excluded.
- Targeted therapies, such as mTOR inhibitors may be considered in the future for multiple cases

Suster et al. (2025). Insulinoma-Associated Protein-1 Expression in Lymphoepithelial Carcinoma of the Thymus: A Potential Pitfall for Diagnosis with Neuroendocrine Carcinomas of the Thymus. Arch Pathol Lab Med, 149, e31–e35.

Summary

- Insulinoma-associated protein-1 (INSM1) was touted as specific for neuroendocrine cells but has been detected in various sarcomas and carcinomas (including SFT) and in a squamous cell carcinoma of the thymus

- This study evaluates the expression of insulinoma-associated protein-1 (INSM1) in 34 cases of lymphoepithelial carcinoma (LEC) of the thymus – because they morphologically can resemble NECs.
- Immunohistochemical staining showed moderate to strong positivity of the tumor cells for INSM1 in 65% of cases, focal weak positivity in 20%.
- Chromogranin and synaptophysin staining were mostly negative although a 1 and 12 cases had focal and weak positive staining respectively.
- Could pose a diagnostic challenge, especially in small biopsies, although p40/p63 positivity should solve this problem.
- The areas of positivity for INSM1 and for either chromogranin or synaptophysin did not overlap and the latter were seen to be distributed at random, unlike the distinctive pattern of staining for INSM1, which showed a predilection for a peripheral distribution in the tumor cell cords and islands and doesn't signify neuroendocrine differentiation but may suggest an unknown role in tumor growth regulation.

Take Home Message

Pathologists should be aware of this potential pitfall (INSM-1 positve LECs)

Parrack PH, Sholl LM. OTP Expression in Pulmonary and Thymic Neuroendocrine Neoplasms. Am J Surg Pathol. 2025;49(2):188.

Summary

- This letter investigates the diagnostic utility of Orthopedia Homeobox protein (OTP) in distinguishing pulmonary from thymic neuroendocrine neoplasms.
- OTP expression in 15 lung and 9 thymic neuroendocrine tumors (typical and atypical carcinoids, large cell neuroendocrine carcinoma).
- All thymic neuroendocrine tumors were negative for OTP, consistent with earlier findings by Nonaka et al. Am J Surg Pathol. 2016;40:738–744 who had studied 5 thymic carcinoids
- Most pulmonary carcinoids (13/15, 87%) expressed OTP. Expression was stronger in typical carcinoids (average H-score: 231) than atypical carcinoids (average H-score: 82).

Take Home Message

OTP IHC is a helpful tool to distinguish pulmonary carcinoid tumors from thymic neuroendocrine neoplasms, with strong and consistent nuclear expression in pulmonary typical carcinoids and no expression in thymic tumors. Since two atypical pulmonary carcinoids were negative, this stain is most reliable for typical carcinoids

Non-Neoplastic Disease

Fortarezza F et al. Giant cell interstitial pneumonia: case series with comprehensive ultrastructural analyses of "not only" hard metal pneumoconiosis. Histopathology. 2025 Feb;86(3):450–459

Summary

- This study presents five cases of **giant cell interstitial pneumonia (GIP)**, a rare fibrosing lung disease characterized by **DIP-like reaction, numerous septal and alveolar giant cells**, **cannibalistic multinucleated giant cells** and **centrilobular fibrosis**, traditionally linked to **hard metal exposure**, particularly tungsten and cobalt.
- Although only one case had confirmed occupational exposure to hard metals, **ultrastructural analyses (SEM and EDX)** revealed tungsten in three cases (in trace amounts in two), and **asbestos fibres** in three patients. Notably, **no cobalt** was detected in any sample.
- One case involved **recurrence of GIP in transplanted lungs**, supporting theories of an **immune-mediated component** in GIP's pathogenesis.
- Several other metal particles (e.g., aluminium, antimony, molybdenum) were identified across all cases, indicating **a broader environmental or occupational exposure profile**.
- Asbestos levels in some cases were elevated but below diagnostic thresholds for asbestosis. Histologic features typical of asbestos-related disease were absent.

Comments

- The use of BAL and TBB to diagnose GIP is questionable in light of the absence of interstitial fibrosis in these two cases
- Findings in keeping with 3 explants examined in Khoor A, Roden AC, Colby TV et ak. Giant cell interstitial pneumonia in patients without hard metal exposure: analysis of 3 cases and review of the literature. Hum Pathol. 2016 Apr;50:176-82: one of their patients also recurred after transplantation

Take Home Message

- GIP may arise from **exposures beyond traditional hard metals**, including **asbestos and various trace elements** as well as an **immune-mediated pathogenesis**.

Garg S, Reinhart K, Couture A, et al. Highly Pathogenic Avian Influenza A(H5N1) Virus Infections in Humans. N Engl J Med. 2025;392(9):843–854.

Summary

- This report from the CDC describes 46 laboratory-confirmed human cases of highly pathogenic avian influenza A(H5N1) virus infection in the United States from March through October 2024. These cases emerged amid outbreaks in dairy cows and poultry.
- **Exposure:**

    - 20 patients had exposure to infected poultry (all involved in depopulation activities).
    - 25 had exposure to infected or presumed-infected dairy cows (most also had contact with raw milk).
    - 1 case had no known exposure.
- **Clinical Features:**
    - All 45 patients with known exposures had **mild illness**, with **no hospitalizations or deaths**.
    - **Conjunctivitis** was the most common symptom (93%), followed by fever (49%) and respiratory symptoms (36%).
    - About a third had conjunctivitis only.
- **Treatment and Outcomes:**
    - **87%** of patients received **oseltamivir**, typically within 2 days of symptom onset.
    - Median illness duration was 4 days.
    - No secondary transmission was detected among 97 household contacts.
- **Diagnostics:**
    - **Conjunctival swabs** were highly sensitive for detection, positive in 90% of symptomatic patients.
    - RT-PCR and genetic sequencing confirmed **H5 clade 2.3.4.4b** viruses in all cases.
- **Public Health Implications:**
    - Suboptimal **PPE use** was reported, especially among dairy workers (only 48% reported using eye protection).
    - There is no current evidence of human-to-human transmission in the U.S., but vigilance is needed given the virus's known potential for severe disease in global contexts.

Take Home Message

- While human infections with H5N1 in the U.S. have so far been **mild and self-limited**, almost all occurred in occupational settings with exposure to infected animals, particularly **poultry and dairy cows**.
- **Conjunctivitis** was the predominant symptom -**PPE adherence** critical to mitigate risk.
- No evidence of **human-to-human transmission** has been observed to date.

Editorial Summary: The Emerging Threat of H5N1 to Human Health. Ison et al. N Engl J Med. 2025;392(9):916–918.

- Human cases are increasing due to greater exposure, especially among agricultural workers.
- Most recent U.S. infections were mild and linked to exposure to poultry or cows.
- A notable severe case in Canada involved a 13-year-old girl who required intensive care and ECMO; sequencing revealed mutations (E627K, E186D, Q222H) possibly enhancing virulence and human adaptation.
- H5N1 remains a critical zoonotic threat with increasing crossover into humans. Although most human cases are currently mild, the virus's potential for mutation and adaptation—especially in mammalian hosts—warrants aggressive surveillance, interagency collaboration, and preparedness for broader transmission

Reviews

Hofman et al. Artificial intelligence for diagnosis and predictive biomarkers in non-small cell lung cancer patients: New promises but also new hurdles for the pathologist. Lung Cancer. 2025 Jan;200:108110.

Summary

- Non-small cell lung cancer (NSCLC) represents a significant global health burden and remains the leading cause of cancer-related mortality.
- Predictive biomarkers in pathology have increased complexity and workload, especially in thoracic pathology.
- Artificial intelligence (AI), especially deep learning (DL) and machine learning (ML), has emerged as a promising tool to support pathologists in diagnosis, biomarker assessment, and treatment decision-making.
- Despite significant interest, AI integration into routine pathology practice has faced several technological, regulatory, and practical hurdles.
- The authors synthesized published literature and integrated expert opinion to discuss:
  - The current and potential applications of AI in thoracic pathology.
  - Technical capabilities of AI (including DL and foundation models).
  - Examples of diagnostic, prognostic, and predictive AI tools in NSCLC.
  - Challenges in implementation, including regulatory, technical, and ethical concerns.
- **Diagnostic Applications:**
  - Excellent performance in classifying LUAD vs. LUSC from H&E slides (AUC ~0.97).
  - Tools like ConvPath and QuPath-based pipelines can estimate tumor cell content with >90% accuracy.
  - AI aids in detecting rare subtypes (e.g., neuroendocrine tumors), NOS tumors, and STAS.
  - New AI tools like ANORAK predict histologic grading with prognostic implications.
- **Predictive Applications:**
  - AI enhances PD-L1 IHC scoring, overcoming interobserver variability.
  - Deep learning models can infer PD-L1 status and immunotherapy response from H&E slides.
  - Tumor mutational burden (TMB) estimation from H&E is being explored but not yet clinically adopted
  - AI assists in analyzing the tumor microenvironment, especially tertiary lymphoid structures (TLS), correlating with immunotherapy response.
- **Mutation Prediction:**
  - AI tools have predicted mutations like EGFR, KRAS, TP53 with AUCs of 0.73–0.87.
  - Rare fusions (e.g., NTRK) remain a challenge due to lack of sufficient training data.

Limitations and Challenges:

- Model generalizability, explainability, and the "Clever Hans" phenomenon are concerns.
- Technical limitations include scanner variability, staining differences (HES vs. H&E), and slide quality.

- Regulatory issues include accreditation, reimbursement, ethical concerns, and data privacy.

Take Home Message

- AI has the potential to transform thoracic pathology—especially in NSCLC
- Pathologists must play a central role in validating, implementing, and governing AI tools to ensure safe and meaningful integration into practice.

Franciosi AN et al. Diffuse Cystic Lung Disease: A Clinical Guide to Recognition and Management. CHEST. 2025 Feb;167(2):529–547.

Summary

- Diffuse cystic lung diseases (DCLDs) are a heterogeneous group of disorders united by the radiologic finding of multiple thin-walled lung cysts.
- These diseases differ markedly from fibroinflammatory interstitial lung diseases (ILDs) in terms of etiology, clinical features, prognosis, and therapeutic options.
- Importantly, DCLDs may be underrecognized despite their potential frequency in clinical practice.
- Comprehensive clinical review based on literature from PubMed (1980–2023), the authors' personal archives, and additional scholarly sources.
- Synthesize data on classification, imaging, histopathology, clinical features, and management of DCLDs, offering an updated and practical diagnostic algorithm and clinical guidance.

Segura-Rivera, R., & Pina-Oviedo, S. (2024). Marginal zone lymphoma of extranodal sites: A review with an emphasis on diagnostic pitfalls and differential diagnosis with reactive conditions. Human Pathology, 156, 105683.

Summary

- Marginal zone lymphoma (MZL), particularly mucosa-associated lymphoid tissue (MALT) lymphoma, is a common form of B-cell lymphoma that arises primarily at extranodal sites, including the lungs.
- MALT lymphoma is often associated with chronic inflammatory conditions, which can make histologic distinction from reactive processes challenging.
- The review outlines the diagnostic pitfalls and provides guidance on recognizing MALT lymphoma in extranodal locations
- especially relevant for pathologists dealing with pulmonary MALT lymphoma, as it can be difficult to differentiate from reactive pulmonary conditions.
- For lung MALT lymphoma, the gold standard remains histopathologic evaluation with IHC markers such as CD20 and PAX5.; the presence of monocytoid cells, plasma cells with Dutcher bodies, and disrupted lung architecture can be highly suggestive of lymphoma rather than a reactive process.
- Molecular techniques like immunoglobulin gene rearrangement (IGH) testing can sometimes be inconclusive, making careful histologic assessment crucial.
- The differential diagnosis can be complex, and therefore, close follow-up and repeat biopsies may sometimes be necessary.

Fakhruddin N et al. Primary mediastinal large B-cell lymphoma from the clinic to genomics: Insights for pathologists. Human Pathology. 2025;156:105705.

Summary

- This comprehensive review provides an in-depth look at **primary mediastinal large B-cell lymphoma (PMBL)**, a distinct subtype of aggressive B-cell lymphoma, with emphasis on its clinicopathologic, molecular, and therapeutic aspects.
- It aims to aid pathologists—especially thoracic and hematopathologists—in differentiating PMBL from histologically and immunophenotypically overlapping entities like **classic Hodgkin lymphoma (cHL)** and **mediastinal grey zone lymphoma (MGZL)**.
    - Dense **fibrosclerotic stroma** with **alveolar compartmentalization** of large lymphoma cells is characteristic.
    - Cytologic features range from **centroblastic to immunoblastic**, with some cases showing **clear cytoplasm** or even **lipoblast-like** morphology.
    - **CD30** is usually weak and heterogeneous (contrast with strong, uniform staining in cHL and MGZL).
    - Positive markers supporting PMBL: **CD23, MAL, CD200, PD-L1/PD-L2, c-REL**.
    - **CD15** is usually negative or dot-like if present; **EBV** is generally absent.
- **Differential Diagnosis in Mediastinal Biopsies:**
    - PMBL vs. **cHL (nodular sclerosis variant)**: overlapping age, location, fibrosis, and cytology.
    - PMBL vs. **MGZL**: MGZL has stronger CD30, retains pan-B markers.
    - PMBL may be misdiagnosed on **core biopsies** due to fibrosis or HRS-like cells.
    - Use of an extended IHC panel (e.g., CD23, MAL, CD200, p63, absence of GATA3) is essential for accurate classification.

Take Home Message

- PMBL should be a prime diagnostic consideration in **young patients with a mediastinal mass** showing **fibrosclerosis** and **large B-cell morphology**, especially in core biopsies.
- Proper recognition hinges on appreciating subtle **histologic clues**, using a **targeted IHC panel**, and understanding its **molecular distinctiveness**.
- Given its overlap with cHL and MGZL, **diagnostic precision** directly impacts **treatment decisions** and **prognosis**.

Case Reports

Li et al. Renal Angiomyolipoma with Inferior Vena Cava and Cardiac Extension: An Unusual Cause of Exertional Dyspnea. Am J Respir Crit Care Med. 2025 Feb;211(2):261–262

Summary

A 55-year-old woman presented with **progressive exertional dyspnea** over 6 months. Imaging (echocardiography and CT) revealed **a hypodense, fatty mass extending from the left kidney through the left renal vein and inferior vena cava (IVC) into the right atrium**

Histopathologic examination - **renal angiomyolipoma (AML)**.
Vascular extension of AML into the IVC and right atrium is **extremely rare**. This extension caused functional obstruction, leading to the patient's dyspnea.

Take Home Message

- Renal AML can rarely extend into **large veins and cardiac chambers**, causing significant cardiopulmonary symptoms.

Lv M-L et al. Fruits Hanging on the Branches of the Lung: Pulmonary Epithelioid Hemangioendothelioma. Am J Respir Crit Care Med. 2025;211(2):e3–e4.

Summary

- 50-year-old male who presented with a two-week history of cough and dyspnea. Chest CT showed a 3.8-cm dominant mass in the left lower lobe with pleural involvement and numerous well-defined, slightly enhanced nodules in both lungs. The nodules had internal calcifications and followed a perivascular and peribronchial distribution—described evocatively as "fruits hanging on the branches of the lung."
- Histologically, PEH—a rare vascular tumor of endothelial origin.

Take Home Message

- Should be included in differential diagnosis of multiple calcified nodules distributed along bronchi and vessels.
- Definitive diagnosis relies on histology and immunohistochemistry (CD31, CD34, FLI-1, ERG); Molecular identification of *WWTR1–CAMTA1* or *YAP1–TFE3* fusions can aid in diagnosis.

Shi X et al. An Immunocompetent 56-Year-Old Woman With Multiple Enlarged Lymph Nodes and Recurrent Fevers. Chest. 2025;167(2):e41–e45.

Summary

- A 56-year-old immunocompetent woman presented with a 2-month history of recurrent fevers and multifocal lymphadenopathy, notably in the mediastinum and bilateral supraclavicular regions.
- Excisional biopsy of a right supraclavicular lymph node revealed granulomatous inflammation with extensive necrosis and sparse fungal hyphae, along with elevated IgG4 (serum level: 20 g/L; IgG4/IgG ~70%).
- FNAB followed by high-throughput sequencing and fungal culture confirmed **Rhizopus microsporus**, consistent with **mucormycosis confined to lymph nodes**, a presentation previously undocumented in immunocompetent hosts.
- The patient was successfully treated with combined antifungal therapy—IV amphotericin B cholesteryl sulfate complex and oral isavuconazole—resulting in significant clinical and radiologic improvement without hepatotoxicity or nephrotoxicity.

Take Home Message

- Mucormycosis should be in the differential for multifocal lymphadenopathy—even in immunocompetent patients.
- Elevated IgG4 may be secondary to infection

Naiditch H et al. A 40-Year-Old With Prior Stem Cell Transplant for Chronic Myeloid Leukemia Presents With Dyspnea and Respiratory Failure. CHEST. 2025;167(2):e47-e51.

Summary

- 40-year-old male with a history of chronic myeloid leukemia (CML) and prior haploidentical stem cell transplant who presented with recurrent hypoxemic respiratory failure.
- The patient's extensive medical history included persistent leukemia, recurrent pulmonary emboli, invasive fungal infection, and esophageal nocardiosis.
- Initial workup including BAL and imaging was unrevealing for infection.
- Surgical lung biopsy - **pulmonary alveolar proteinosis (PAP)**. This diagnosis was notable for being **secondary to hematologic malignancy**, rather than the more common autoimmune form.
- Potentially due to dysfunctional alveolar macrophages - GM-CSF antibodies were not detected, further supporting the secondary nature.
- Despite treatment with GM-CSF and whole lung lavage, the patient's respiratory status deteriorated. He transitioned to comfort care and died shortly after.
- From a clinical standpoint, despite maximal supportive care, the prognosis in secondary PAP associated with refractory hematologic malignancy remains poor.
- It raises the question of whether earlier recognition and intervention might impact outcomes in similar cases.

Take Home Message

- **Secondary PAP** is a rare but important diagnosis in post-transplant or hematologic malignancy patients with respiratory failure.

Wade MA et al. A 21-Year-Old Man With Unilateral Chest Pain, Lobar Consolidation, and Pleural Effusion. Chest. 2025;167(2):e53–e56.

Summary

- 21-year-old man presented with acute, atraumatic left-sided chest and abdominal pain. Initially misdiagnosed as a viral syndrome, he was later found to have worsening lobar consolidation and a large pleural effusion. Thoracentesis yielded gross blood consistent with hemothorax. Further imaging revealed an abrupt cutoff of an anomalous arterial branch from the descending thoracic aorta, raising suspicion for **extralobar pulmonary sequestration (ELS) with torsion**.
- **ELS** is a rare congenital malformation of nonfunctional lung tissue **not connected to the tracheobronchial tree**, encased in its own pleura, and typically supplied by **a systemic artery** from the thoracic aorta.
- In this case, the lesion was located in the **left posterior costodiaphragmatic sulcus**, a classic location for ELS.
- Radiologic red flags: dense, homogenous consolidation, associated pleural effusion, and abnormal vasculature with abrupt cutoff—suggestive of **torsion and infarction**.
- The patient underwent **emergent thoracotomy**, revealing necrotic lung tissue with a single vascular pedicle—hallmark of ELS. Surgical resection led to full recovery.

Take Home Message

- Extralobar pulmonary sequestration should be considered in **young patients** with unexplained unilateral thoracic symptoms, especially if imaging reveals consolidation with systemic arterial supply.
- **Torsion of ELS**, though rare, can lead to hemothorax and infarction, necessitating urgent surgical intervention.
- Radiologic review and **contrast-enhanced CT with vascular reconstruction** are critical in identifying the feeding vessel and confirming diagnosis.
- Highlights how congenital anomalies like ELS can present later in life and mimic more common conditions such as pneumonia or pulmonary embolism.
- For pulmonary pathologists, it's a reminder to maintain a broad differential when faced with mass-like consolidations and to consider the vascular supply—especially in necrotic, hemorrhagic, or atypical lesions.

Rahaman T et al. Consolidation with pseudocavitation. Thorax. 2025;80:119.

Summary

- A 48-year-old man (non-smoker) presented with 6-week history of shortness of breath, mucoid cough, appetite and weight loss.
- **CT** thorax: Right lower lobe consolidation with ground-glass opacities and pseudocavitation. Similar pseudocavitated nodules in contralateral lung.
- CT-guided biopsy: Neoplastic cells with lepidic architecture and glandular formation. **CK7:** Positive; **TTF-1, Napsin A, CK20, CDX2:** Negative
- **Mucinous adenocarcinoma of the lung** with **lepidic pattern**, presenting radiographically as **consolidation with pseudocavitation**.
- **Pseudocavitation**: areas of low attenuation resembling air bubbles within a consolidation or nodule, representing spared alveoli, ectatic bronchi, or emphysema—not true necrotic cavitation.
- Proposed mechanisms include bronchiolar obstruction leading to distal air trapping and mucus retention.
- Diagnostic significance:
    - **Prevalence in lung cancer:** ~15.3%
    - **Specificity for adenocarcinoma:** 92.4%
    - **Specificity for lepidic pattern:** 77–85%

Take Home Message

- Recognizing pseudocavitation can help pathologists and clinicians consider adenocarcinoma earlier in the differential for persistent consolidation.

Wang L et al. Pleural Paragonimiasis. N Engl J Med. 2025 Feb 13;392(7):e19.

Summary

- A **17-year-old boy** from **El Salvador**, asymptomatic at presentation, was found to have a **pleural effusion** on chest radiograph during a **routine immigration screening**. Further

CT imaging confirmed the effusion and revealed a **4-mm peripheral lung nodule** on the same side.
- **Pleural fluid cytology** showed **eosinophilia** (13% eosinophils) and **parasite eggs**.
- **Targeted 28S rRNA sequencing** identified **Paragonimus mexicanus**.
- **Pleural paragonimiasis** due to *Paragonimus mexicanus*.
- Paragonimiasis, a lung fluke infection, is typically acquired through consumption of **undercooked freshwater crustaceans**. This patient had consumed such foods **two years prior to emigration**. While *P. westermani* is more common in Asia, *P. mexicanus* is endemic to **Central and South America**.
- Treatment with **praziquantel** is effective, though resolution may be slow.

Take Home Message
- Pleural eosinophilia in immigrants from endemic regions should raise suspicion for **parasitic infections**, including **paragonimiasis**.

Ufuk F. Lymphoid Interstitial Pneumonia. Images in Clinical Medicine. N Engl J Med. 2025;392(8):806.

Summary
- 37-year-old man with a 10-month history of dry cough, fatigue, and dry mouth. On physical examination, crackles were present bilaterally at the lung bases, and signs of xerostomia were evident, including dry oral mucosa, conjunctivae, and dental caries.
- Imaging revealed **reticular opacities and cystic lucencies** in both lungs on chest X-ray. **High-resolution CT (HRCT)** demonstrated **thin-walled, peribronchovascular cysts** mainly in the lower lobes, with **mild ground-glass opacities and subpleural reticulation**.
- Laboratory findings included a **positive autoantibody profile for Sjögren's syndrome**, which was confirmed with a minor salivary gland biopsy. Importantly, **HIV testing was negative**, and **immunoglobulin levels were normal**.
- Histologically, a **surgical lung biopsy** revealed **dense interstitial lymphocytic infiltration** with **marked alveolar septal thickening**.
- The final diagnosis was **lymphoid interstitial pneumonia (LIP)** associated with **Sjögren's syndrome**.

Take Home Message
- **LIP is a rare, benign lymphoproliferative disorder** often associated with autoimmune diseases such as **Sjögren's syndrome**.
- **HRCT findings of peribronchovascular cysts and interstitial changes** are key radiologic clues.
- **Histologic confirmation** is critical to exclude mimics like Langerhans cell histiocytosis.

Leaf RK, Messick BH, Meador CB, Loneman D. Case 7-2025: A 65-Year-Old Woman with Weakness, Back Pain, and Pancytopenia. N Engl J Med. 2025;392(9):903–914.

Summary

- 65-year-old woman presenting with weakness, back pain, and pancytopenia.
- Labs showed profound thrombocytopenia, anemia, leukopenia, elevated LDH, and extremely high ferritin.
- Imaging revealed pulmonary nodules and hepatic lesions. The differential diagnosis considered TTP, nutritional deficiencies, infections, autoimmune disorders, and marrow infiltration by malignancy.
- Bone marrow biopsy revealed **extensive infiltration by small-cell neuroendocrine carcinoma**, confirmed by positive immunostains for CD56, synaptophysin, and chromogranin. Due to severe cytopenias and poor performance status, cytotoxic chemotherapy was not pursued. The patient transitioned to comfort care and died on hospital day 6.
- Imaging and autopsy findings supported a diagnosis of **metastatic small-cell lung carcinoma** with myelophthisis and cancer-associated thrombotic microangiopathy (TMA).

Take Home Message

- **Small-cell lung carcinoma (SCLC)** can rarely present with isolated **bone marrow infiltration**, mimicking hematologic diseases like TTP or aplastic anemia.
- Profound pancytopenia, leukoerythroblastic blood smear, and constitutional symptoms should raise suspicion for **myelophthisic marrow involvement by metastatic cancer**.