December 2025 Pulmonary Pathology Journal Club (November Articles)

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Articles for Discussion

Adams M et al. *Whole Slide Image vs Microscope Glass Slide Performance for the Evaluation of Programmed Death-Ligand 1 (PD-L1) Expression in 14 Tumor Types Using PD-L1 IHC 22C3 pharmDx*. Mod Pathol

Background

Although whole slide imaging (WSI) has been validated for primary diagnosis in large multicenter studies, no comprehensive data exists comparing WSI vs light microscopy specifically for PD-L1 scoring across multiple tumor types using 22C3, a key companion diagnostic for immune checkpoint inhibitor therapy. PD-L1 scoring requires histologic recognition of tumor cells and immune cells, and assessment of staining completeness and intensity. Histologic heterogeneity and near-cutoff cases are frequent challenges, emphasizing the need for modality equivalence. This study evaluates whether WSI can reliably reproduce PD-L1 results obtained by traditional microscopy for 14 tumor types across CPS ≥1 and TPS ≥1% cutoffs.

Methods

726 surgical and biopsy specimens from 14 tumor types (breast/TNBC, BTC, cervical, colorectal, esophageal, endometrial, GEJ/gastric, HNSCC, ovarian, prostate, RCC, SCLC, urothelial, NSCLC) were utilized, and ≥100 viable tumor cells were required. Each specimen was scored by 3 readers on both MGS and WSI, with a ≥14-day washout, including 17 trained readers (14 board-certified pathologists + 3 Agilent-certified readers). Leica Aperio AT2 RUO scanner was used with Aperio ImageScope viewer on approved 14-27" monitors.

Results

- Across all tumor types, agreement between WSI and MGS was ≥89%
- Several tumor types showed 100% overall agreement, including ovarian carcinoma, RCC, and SCLC.
- Largest dataset was gastric/GEJ ADCA (n=133), with overall agreement 93.5%.
- NSCLC TPS ≥1% overall agreement 93.7%.
- 11 of 14 tumor types had concordance correlation coefficient ≥0.85, indicating low scoring variability.
- PC CPS ≥1, SCLC CPS ≥1, and UC CPS ≥1 showed lower CCC (0.80–0.81)

- Almost all discordances occurred in near-cutoffs (CPS 0–10, TPS 0–10%).
- A few outliers suggested reader-specific bias (e.g., certain readers tended to score some NCO cases slightly higher on WSI).
- Only 2 specimens (Endometrial, Gastric/GEJ) were discordant outside the NCO range.

Conclusions

WSI scoring of PD-L1 22C3 shows high concordance with traditional microscopy across a large, diverse set of tumors. Discordances largely arise in borderline cases—a known area of subjectivity. This supports expanded use of digital pathology for PD-L1 training, consultation, and diagnostic work (pending regulatory guidance).

Discussion / Comment: Authors state diagnostic use will require further regulatory-grade validation. We use this WSI for PDL1 today. Thoughts?

Carbone et al. *Clinical and Pathologic Phenotyping of Mesotheliomas Developing in Carriers of Germline BAP1 Mutations.* JTO

Background

Germline *BAP1* heterozygous inactivating mutations ($BAP1^{+/-}$) cause the BAP1 cancer syndrome, predisposing to mesothelioma, uveal melanoma, and clear cell renal cell carcinoma. This is transmitted in a Mendelian fashion (autosomal dominant). It is estimated that 8-16% of mesothelioma occur in patients with germline mutations in *BAP1* or other tumor suppressors. Prior work showed mesotheliomas in *BAP1* carriers have markedly prolonged survival (average 7 years) compared with sporadic mesotheliomas (average survival 6-18 months). This study aims to define the clinical course and distinctive histopathologic phenotype of mesotheliomas arising in germline *BAP1* carriers and to compare them with sporadic mesotheliomas.

Methods

This study analyzed 238 individuals with germline *BAP1*+/– mutations across 47 families (1999-2023) to characterize the distinct clinical and histologic features of *BAP1*-associated mesothelioma. 123 relatives without germline mutations were also included. 34 distinct pathogenic *BAP1* mutations were included (mostly truncating). Mesothelial

immunohistochemical markers included calretinin, WT1, keratin 8/18; carcinoma markers included Claudin-4, TTF1, MOC31, BerEP4, P40, and PAX8. BAP1 nuclear staining assessed carefully in invasive vs non-invasive areas.

Results

- 34 inactivating *BAP1* mutations were identified in 47 families; 10 families had the same mutation traced back to the same ancestor that immigrated to the us in 1717!
- The 238 carriers demonstrated a female predominance (about 1.5:1) that was not significant (p=0.09), but raises the possibility the mutation may be preferentially lethal to males during embryological development.
- 84 of 238 carriers (35%) developed mesothelioma, while none of the 123 BAP1–WT relatives did ($p < 0.0001$); 53% of carriers aged 30-49 had at least one malignancy, compared to 6.7% of WT relatives; by age 60-69 this was 93% vs 21%.
- 38 of 84 (45.2%) had additional malignancies (up to 4 other malignancies)
- Most cases occurred at a younger age (median 54, about 20 years younger than sporadic) and without asbestos exposure (only 1 exposed); age range 27-81 years
- Uveal melanoma was second most common (most common in 20-29 yo group, 22 cases overall, 8 also had meso), followed by clear cell RCC
- At surgery, multifocal 1–3 mm whitish serosal lesions were seen on pleura/peritoneum, often not visible on imaging (surgery most often done for effusion)
- 23 of these mesos had central pathologic review:
    - Background of diffuse mesothelial hyperplasia with foci showing tubulopapillary or trabecular epithelioid growth (BAP1 retained)
    - Mesos showed superficial invasion only, limited to submesothelial fat; deep invasion is rare; associated dense reactive fibrous tissue with inflammation
    - No sarcomatoid mesos observed
    - BAP1 IHC: invasive or in-situ neoplastic foci show loss of nuclear staining; hyperplasia retains BAP1.
    - Tumors are typically low-grade, with minimal atypia and rare mitoses.
- The authors propose new terminology—L-BAM (Low-grade BAP1-associated mesothelioma)—to distinguish these biologically indolent tumors from aggressive sporadic mesotheliomas.
- Most patients survive years to decades; median survival ~7 years. Aggressive behavior correlates with rare solid architecture, high nuclear grade, and deeply invasive growth (3 cases, all died within 1 year).

Conclusion

Mesotheliomas arising in germline *BAP1*$^{+}$/$^{-}$ carriers represent a biologically, histologically, and clinically distinct disease. Despite fulfilling current criteria for malignant mesothelioma (invasion + BAP1 loss), most are indolent, remain superficial for years, and probably do not warrant aggressive therapy at early stages.

Take Home Message: BAP1 loss ≠ aggressive mesothelioma in germline carriers, and multicavity superficial involvement should not automatically imply metastatic stage IV disease. Germline *BAP1* status is both a risk marker and a favorable prognostic biomarker. Multifocality and widespread hyperplasia should prompt consideration of a germline *BAP1* mutation and careful staging to prevent unnecessary aggressive therapy.

Sasahara Y et al. *Feasibility of histological grading system of small-sized pulmonary adenocarcinoma based on frozen section as a predictor for nodal metastasis*. Mod Pathol.

Background

Identifying lymph node metastasis in small (≤2 cm) clinically N0 lung adenocarcinomas is essential for determining whether lobectomy vs. sublobar resection (SLR) should be performed, since sublobar resections are often associated with a less complete nodal dissection. 11–18% of clinical N0 tumors harbor occult nodal disease on final pathology. The IASLC 2020 adenocarcinoma grading system (based on high-grade patterns: micropapillary, solid, complex glandular ≥20%) correlates strongly with lymph node metastasis and prognosis . However, the feasibility and clinical value of applying IASLC grading to frozen sections during intraoperative consultation remains poorly studied. This study evaluates whether frozen section IASLC grade can reliably match permanent section grading and predict occult lymph node metastasis intraoperatively.

Methods

This is a retrospective single-institution study (2015–2022) of 190 invasive lung ADCAs ≤2 cm on CT with consolidation: tumor ratio (CTR) on CT >0.5 (i.e. mostly solid, higher risk lesions), clinical staged as N0, with frozen section performed intraoperatively. Exclusion criteria included AIS/MIA, mucinous ADC, multiple lesions, or those with no LN sampling. Frozen sections obtained following Japanese Lung Cancer Society guidelines (peripheral

sampling, avoid necrotic/central areas and pleural invasion areas). 3 pathologists (resident, general pathologist, pulmonary pathology expert) independently graded slides using the IASLC grading system. Concordance with permanent sections measured as well as presence of pathologic lymph node metastasis (pN1–2).

Results

- Frozen section IASLC grading had substantial agreement, κ = 0.68 (95% CI 0.61–0.75), high-grade pattern recognition κ = 0.65
- After multiheaded scope consensus assignment of grade, frozen vs. permanent section overall concordance: 75.8% (144/190)
- Grade-specific concordance: Grade 1: 70.3%, grade 2: 64.4%, grade 3: 95.2%
- Frozen section sensitivity and specificity for grade 3: 69.8% (60/86) and 97.1% (101/104)
- Some grade 3 tumors were under called as grade 1 on FS due to sampling of lepidic edge (5 cases); none had LN mets
- pN1–2 in 12.1% (23/190), including 0 grade 1, 8 grade 2 (9%) and 15 grade 3 (24%)
- Pure-solid CT appearance also associated with metastasis, but less strongly
- Only IASLC grade 3 on frozen section was an independent predictor of LN mets: OR 4.34 (95% CI 1.54–12.2; P = .006)
- PET SUVmax showed similar OR but limited availability

Conclusions

IASLC grading applied to frozen sections is feasible, reproducible, and strongly predictive of lymph node metastasis in small (≤2 cm), CTR>0.5 pulmonary adenocarcinomas. Grade 3 on frozen section is a highly reliable indicator of biologic aggressiveness with high specificity (~97%), and the only independent predictor of occult nodal disease. This supports the notion that frozen section grading could be used to guide intraoperative lymph node dissection decisions.

Take Home Message: Frozen section IASLC grade 3 is a strong predictor of nodal metastasis risk. High-grade patterns can be detected with good interobserver reliability even on frozen tissue. Grade 1 FS tumors appear to have low risk of nodal metastasis.

Sadhu S et al. *ALK-rearranged malignant mesenchymal neoplasms of the thorax: therapeutically targetable 'ALKomas' beyond the spectrum of non-small cell lung carcinomas and thoracic inflammatory myofibroblastic tumors*. Virchows Arch.

Background

ALK fusions are well-established oncogenic drivers in various tumor types, including NSCLC, IMT, and epithelioid fibrous histiocytoma. Recently, a new family of *ALK*-rearranged mesenchymal neoplasms—distinct from IMT and EFH—has emerged. Prior reports (~29 cases) describe predominantly deep soft tissue tumors, often in children and young adults, and usually low-grade spindle cell neoplasms with CD34/S100 co-expression (similar to *NTRK*-rearranged tumors). These tumors respond well to ALK inhibitors, and therefore should be included in the diff dx of thoracic spindle cell malignancies in young, non-smoking patients, which are often diagnostically challenging. Early identification is critical because ALK-targeted therapy is highly effective and tissue-agnostic. This study provides the first series of primary thoracic *ALK*-rearranged mesenchymal tumors, expanding their clinicopathologic spectrum and highlighting recognition pitfalls.

Methods

This is a retrospective review (2019–2024) of primary thoracic masses with *ALK* rearrangements at a tertiary center. They excluded carcinomas, hematolymphoid neoplasms, IMT, and EFH by detailed histologic and IHC review. Architectural pattern, cytologic features, necrosis, mitoses, stromal quality, vascular pattern were assessed. Immunohistochemistry included ALK (D5F3, Ventana), broad cytokeratin, SMA, S100, CD34, desmin, MUC4, myogenic markers, SS18, STAT6, SOX10, NTRK. *ALK* rearrangement was confirmed using break-apart FISH in all cases. Clinical data collected included age, sex, presenting symptoms, metastatic status, therapy response.

Results

- 3 primary thoracic *ALK*-rearranged mesenchymal tumors were identified (25–33 years; all non-smokers; 2 men, 1 woman).
- 2 of 3 had metastases at presentation (brain, scalp, non-regional lymph nodes).
- 1 patient responded to crizotinib, 1 died within one week despite starting crizotinib.
- Histologic features included relatively monomorphic spindle-to-epithelioid morphology with variable stroma (myxoid, sclerotic, or collagenous), mild to absent inflammatory infiltrate; hemangiopericytoma-like vasculature, rhabdoid cells
- Necrosis present in 2/3, mitotic activity: 3–8/HPF in high-grade tumors; one low-grade lesion with low mitotic index.
- ALK diffuse strong cytoplasmic staining in all, keratin -, retained INI1 and H3K27me3.
- Contrary to literature describing CD34/S100 co-expression, thoracic ALKomas may lack both markers, risking misclassification (all CD34-, only 1 of 3 S100+).

Conclusions

Primary thoracic *ALK*-rearranged mesenchymal neoplasms are rare, aggressive, and occur in young, non-smoking patients. They may present with metastatic disease and lack distinctive morphologic or immunophenotypic features such as CD34/S100 positivity that are seen in soft tissue counterparts. ALK IHC should be included in the workup of any cytokeratin-negative spindle/epithelioid thoracic tumor in a young patient. Given their strong response potential, early identification allows access to ALK-targeted therapies, which may significantly impact prognosis.

Take Home Message: Include ALK IHC in the initial panel for young, non-smoking patients with spindle/epithelioid, keratin-negative thoracic tumors to identify potentially therapeutically targetable *ALK* mutated tumors.

Articles for Notation

Abele et al. *Distinct genomic profile of pediatric lung carcinoma: High frequency of ALK fusions and TP53 mutations compared to adults*. Lung Cancer.

This study reports whole-genome sequencing (WGS) of 14 primary lung carcinomas, including 13 pediatric patients, encompassing pulmonary mucoepidermoid carcinoma (PMEC), lung adenocarcinoma (LUAD n=6), and one adenosquamous carcinoma (ASC). *ALK::EML4* fusions were identified in 3 of 6 pediatric LUAD + the ASC case — representing 60%, far higher than adults (~5%). These fusions prompted targeted ALK therapy. ALK-inhibitor therapy (multiple generations sequentially) resulted in periods of disease stabilization, although progression occurred faster than in adults. MET inhibition (capmatinib) was clinically effective in the MET-amplified, ALK-positive case. *TP53* mutations occurred in 3 cases (42%), at a frequency similar to adult smokers but higher than adult never-smokers. All TP53-mutant cases were stage IV, suggesting association with advanced disease. Additional mutations typical of adult LUAD were seen: KRAS (G12D), EGFR (non-hotspot), NRAS, BRAF, RB1, and ATM. No smoking-related mutational signatures were detected; TMB was very low (median 0.17/Mb). One LUAD case showed homologous recombination deficiency (HRD), including MET amplification and the SBS3 signature. *MAML2* rearrangements were universal in the 7 MECs, with *CRTC1::MAML2* in 6 cases and *CRTC3::MAML2* in 1, matching the genetic profile of salivary-type mucoepidermoid carcinoma. MEC cases were uniformly low-grade (G1) and early stage (I–II), with excellent outcomes after resection (no recurrences); somatic variants occurred in CDKN2A, PIK3CA, and rare alterations such as ERCC1 and ROS1, but no actionable NSCLC-type driver mutations. TMB was extremely low (median 0.1/Mb). No pathogenic germline variants in cancer predisposition genes; polygenic risk scores also not elevated.

Take Home Message: In this cohort, ALK fusions were the dominant actionable driver in pediatric LUAD, occurring at far higher frequency than adults, often co-occurring with TP53 mutations, and associated with aggressive disease. Pediatric MEC is genetically defined by *MAML2* rearrangements and behaves as a classic salivary-type low-grade carcinoma with excellent outcomes.

Aldea et al. *Molecular Tumor Boards: A Consensus Statement from the IASLC*. JTO

This IASLC consensus outlines best practices for establishing and operating Molecular Tumor Boards (MTBs) to ensure consistent, accurate interpretation of complex biomarker data. MTBs should include at least a tumor-specific oncologist and a molecular pathologist

or molecular biologist, who collaboratively interpret NGS results, identify actionable alterations, recognize resistance mechanisms, and determine when findings suggest germline variants or CHIP. MTBs should prioritize complex or clinically impactful cases, use standardized reporting, and rank treatments by actionability scales such as ESCAT or OncoKB. Common pitfalls include low tumor content, RNA failure, fusion detection limitations, and misinterpretation of liquid biopsy results lacking sufficient ctDNA. The statement recommends structured workflows, pre-triage, and timely meetings (<14 days). It also offers solutions for resource-limited settings—regional hubs, virtual MTBs, and harmonized reporting templates. Future MTBs will incorporate transcriptomic/proteomic markers and AI-assisted data interpretation.

Take-Home Message: MTBs are essential for reliable, clinically meaningful interpretation of molecular data. Standardized workflows, multidisciplinary expertise, and evidence-based treatment prioritization improve patient management. Pathologists play a critical role by correlating histology with molecular findings and recognizing technical or biologic pitfalls. Regional or virtual MTB models can reduce global disparities in access to precision oncology.

Borm et al. *Liquid biopsy in BALF is now suitable for clinical practice in patients with suspected NSCLC*. Lung Cancer.

This study evaluates cell-free DNA (cfDNA) obtained from bronchoalveolar lavage fluid (BALF) as a minimally invasive means of improving molecular diagnosis in patients with suspected NSCLC. BALF was collected through a simple proximal bronchial flush during routine bronchoscopy/EBUS—an easily implementable technique requiring no advanced navigation tools. Among 77 patients with confirmed malignancy, BALF detected pathogenic variants in 75% of cases. Incorporating BALF reduced the proportion of patients lacking a molecular diagnosis before treatment from 39% to 12% (a 50% reduction). Tumor-positive BALF was more likely at higher T-stages (96% in T4 vs 55% in T1). Median BALF VAF was 5%, higher than typical plasma ctDNA yields. In 68 evaluable cases, BALF showed 78% sensitivity, 67% specificity, 94% PPV, and 32% NPV versus tissue NGS. About 54% were fully concordant, another 18% partially concordant. Discordant findings were mostly due to multiple primaries, subclonality, or low tumor content in tissue. BALF rarely produced false positives—only one benign case, explained by a hematologic disorder.

Take-Home Message: BALF liquid biopsy is feasible, reliable, and ready for routine practice in suspected NSCLC. It substantially increases molecular diagnostic yield, especially when tissue is limited or inaccessible. Proximal bronchial lavage provides higher local tumor

DNA than plasma ctDNA and requires no advanced bronchoscopy equipment. BALF is complementary, not a replacement, for tissue—particularly since PD-L1 and histology still require cells. This test is ideal for early-stage or hard-to-biopsy lesions and may become especially relevant in the context of lung cancer screening.

Briggs et al. *Noncoding DNA Variants Increase the Genetic Diagnostic Yield in Primary Ciliary Dyskinesia*. Am J Respir Crit Care Med.

Primary ciliary dyskinesia (PCD) often remains genetically unresolved when testing is limited to coding regions. In a cohort of 496 clinically suspected PCD patients, standard coding-region sequencing yielded a complete genetic diagnosis in 46.8%. Among the 86 patients with incomplete diagnoses, 42 underwent end-to-end sequencing covering intronic, UTR, and coding regions of 17 PCD genes. Previously undetected variants—mostly deep intronic, splice-altering mutations—were identified in 16 of 42 patients (38.1%), including three recurrent variants (e.g., *CCDC40 c.1441-919G>A; DNAH11 c.6547-963G>A; ODAD1 c.11291+1403G>A*). RNA studies from nasal epithelium confirmed pseudoexon inclusion, cryptic splice-site activation, or exon skipping in several cases. Three exon-level CNVs were also newly detected. Incorporating these findings improved diagnostic yield from 46.8% to 50%, with a projected potential rise to 53.4% if applied to all incomplete cases. For pathologists, this work underscores that many "single-hit" PCD cases actually harbor second intronic pathogenic variants, often invisible to routine exon-based NGS. *HYDIN* and *DNAH11*—genes already diagnostically challenging—had multiple newly validated noncoding pathogenic variants.

Take-Home Message: Noncoding intronic variants are a significant and recurrent cause of PCD, often producing splice disruption and pseudoexons. End-to-end gene sequencing materially increases diagnostic yield beyond standard exon-only NGS. Pathologists should be aware that negative or incomplete genetic results do not exclude PCD—especially in HYDIN and DNAH11. RNA confirmation from nasal epithelium is crucial when evaluating predicted splice variants. Better genetic resolution is increasingly important as PCD-targeted therapies (including mRNA treatments) move toward clinical trials.

Cho et al. *Genomic Profiles of Pathogenic and Moderate-Penetrance Germline Variants Associated With Risk of Early-Onset Lung Adenocarcinoma*. JTO

This large Japanese multicenter study evaluated germline cancer-predisposition variants in early-onset lung adenocarcinoma (LADC; ≤40 years) compared with later-onset disease. Whole-exome/genome sequencing of 348 early-onset and 1425 later-onset cases revealed

significantly higher rates of *TP53* (2.9%) and *BRCA2* (1.7%) germline pathogenic variants (GPVs) in early-onset cases. Somatic profiling showed that *BRCA2* GPVs frequently demonstrated loss of heterozygosity and homologous recombination deficiency, whereas *BRCA1* GPVs did not, indicating biologic differences in tumorigenesis. The study also identified a novel *ALKBH2* loss-of-function germline variant (Glu35fs) associated with increased early-onset LADC risk (OR 2.57). Tumors from *ALKBH2* carriers demonstrated a stronger correlation between smoking exposure and *SBS4* mutational signature.

Take Home Message: *TP53* and *BRCA2* germline variants are more frequent in early-onset LADC, especially in never-smokers. *BRCA2*—but not *BRCA1*—carriers show biallelic inactivation and HRD, with potential implications for PARP inhibitor sensitivity. A novel *ALKBH2* frameshift variant increases susceptibility to early-onset LADC and is enriched in East Asian populations.

Dagogo-Jack I., et al. *Mesotheliomas with BAP1, CDKN2A, MTAP, NF2 alterations*. JTO

This study analyzes the genomic and clinicopathologic characteristics of mesotheliomas harboring key tumor suppressor alterations—*BAP1, CDKN2A, MTAP*, and *NF2*—genes central to mesothelioma biology. The authors focus on how combinations of these alterations correlate with distinct molecular phenotypes, histology, and outcomes. Inactivation of *BAP1, CDKN2A, MTAP,* and *NF2* represents the core set of recurrent mesothelioma alterations. *CDKN2A* loss was significantly enriched in non-epithelioid tumors, aligning with more aggressive subtypes. *NF2* alterations, either alone or combined with *BAP1* loss, defined a subset with distinct transcriptional profiles. *MTAP* loss frequently co-occurred with *CDKN2A* deletions, reflecting their chromosomal proximity, and is highlighted as a potential therapeutic vulnerability (e.g., PRMT5-directed strategies). Histologically, alteration patterns showed correlation with epithelioid vs. biphasic/sarcomatoid differentiation, supporting the utility of integrated genomics in diagnostic stratification. The work underscores that mesothelioma behavior is heavily shaped by the combination—not just the presence—of these tumor suppressor alterations.

Take Home Message: Mesothelioma genomic profiling reveals recurring, biologically meaningful patterns centered on *BAP1, CDKN2A/MTAP*, and *NF2* loss. These alterations correlate with histologic subtype and may guide both diagnostic precision and therapeutic targeting, especially where *MTAP* or *CDKN2A* loss suggests emerging targeted options.

Hamada et al. *Association of lung silica deposition with epidermal growth factor receptor–mutant lung cancer.* Lung Cancer.

This retrospective cross-sectional study of 174 surgically resected lung adenocarcinomas quantitatively evaluated silica particle deposition in lung tissue using polarized light microscopy. Patients with EGFR-mutant tumors had significantly higher silica counts than wild-type cases (median 26 vs 9 particles, $P < 0.001$). ROC-derived threshold (≥18 particles) identified a high-silica group, in which 66.7% of tumors were *EGFR*-mutant versus 30.4% in the low-silica group. High silica deposition remained independently associated with EGFR mutations (adjusted OR 3.20, 95% CI 1.49–6.88). Only three patients had occupational exposure, and silica accumulation correlated with age, indicating non-occupational environmental inhalation (e.g., $PM_{2.5}$, Asian dust) as the likely source. The authors propose that silica-induced IL-1β–mediated inflammation may promote *EGFR*-mutant tumorigenesis.

Take Home Message: Higher lung silica deposition is strongly associated with *EGFR*-mutant lung adenocarcinoma, even in patients without occupational exposure. Silica accumulation likely reflects chronic environmental exposure and may drive carcinogenesis via IL-1β–mediated inflammatory pathways.

Khalid A et al. *Pleural Endosalpingiosis: A Novel Entity.* CHEST.

This report describes a case of pleural endosalpingiosis, discovered in a 46-year-old woman with a lymphocyte-predominant exudative pleural effusion and pleural nodularity. Thoracoscopic biopsies showed ciliated glandular epithelium with CK7+, PAX8+, WT1+, calretinin–, consistent with Müllerian origin. Other infectious and malignant causes were excluded. Follow-up imaging showed complete resolution of the effusion and nodules.

Take Home Message: Pleural endosalpingiosis, though extremely rare, should be considered when pleural biopsies show tubal-type ciliated glands with a Müllerian immunophenotype. Histology remains essential for diagnosis.

Le X, Kim TM, Loong HH, et al. Sevabertinib in Previously Treated and Untreated HER2-Mutant Non–Small-Cell Lung Cancer. *NEJM*

Sevabertinib, a selective HER2/EGFR inhibitor designed to spare wild-type EGFR, was evaluated in three cohorts of HER2-mutant NSCLC (treatment-naïve, previously treated, and post-HER2 ADC). Across 209 patients, the drug showed meaningful antitumor activity, with ORR 64% in previously treated patients, 71% in treatment-naïve, and 38% after HER2

ADC therapy. Responses were durable (median DoR 8.5–11 months), and PFS was longest in the treatment-naïve cohort. Toxicity was dominated by diarrhea (84–91%), mostly low grade; grade ≥3 occurred in up to 23% depending on cohort. Treatment discontinuation due to AEs was low (3%), and no ILD attributable to drug was reported.

Take Home Message: Sevabertinib shows high response rates and manageable toxicity in HER2-mutant NSCLC, including patients previously exposed to HER2 ADCs. It represents a promising targeted therapy option with particularly strong performance in treatment-naïve disease.

Major et al. ***Implementation of a next-generation sequencing and PD-L1 immunohistochemistry reflex testing protocol for non–small cell lung cancers improves turnaround time.*** **Am J Clin Pathol.**

The authors implemented a reflex testing protocol for NSCLC stage IB and above, automatically sending specimens for NGS (DNA/RNA panel) and PD-L1 IHC without waiting for oncologist orders. This operational change aimed to address common delays that prevent timely biomarker-driven treatment. In an analysis of 492 cases, reflex testing resulted in a significant reduction in turnaround time (TAT) from procedure to NGS sign-out, from 22 days → 20 days overall ($P < .000103$). In cytology-only samples TAT decreased from 22 days → 19 days ($P < .00000283$). Additionally, TAT from pathology sign-out to NGS report and from molecular lab receipt to NGS sign-out also shortened significantly. Reflex testing was efficient across surgical and cytology specimens, with cytology often moving more quickly into the testing pipeline.

Take Home Message: Automatic reflex biomarker testing for NSCLC accelerates NGS and PD-L1 results, reducing operational delays and supporting earlier initiation of targeted or immunotherapy-based treatments.

Mamdani et al. ***A Phase II study of GT103 in combination with pembrolizumab in refractory, metastatic NSCLC.*** **Cancer.**

This Phase II single-arm study evaluated GT103, an anti–complement factor H monoclonal antibody, combined with pembrolizumab in patients with advanced NSCLC previously treated with PD-1/PD-L1 therapy. Twenty-one patients were treated. The combination was well tolerated, with fatigue and lymphopenia being the most common adverse events, and only one case of grade 3 immune pneumonitis. Efficacy was modest: ORR 10% (1 CR, 1 PR), disease control rate 67%, and median PFS 2.6 months. However, a subset showed

durable benefit, including the complete responder who remained on therapy for >21 months. No strong correlation with PD-L1 status was observed.

Take Home Message: The regimen is safe and shows signals of durable benefit in a minority of patients. ORR alone may underestimate activity due to the immune-modulating mechanism of GT103. Further study will require biomarker-selected populations and survival- or immune-response–oriented endpoints.

Ng et al. *Small bowel metastatic SWI/SNF-deficient undifferentiated carcinoma may be predictive of lung primary—a rare presentation with novel SMARCA2 mutation findings in a study of three cases*. Virchows Archiv.

This study reports 3 cases of small bowel (SB) metastatic undifferentiated carcinoma (UDC) showing SMARCA4 and/or SMARCA2 deficiency, all ultimately determined to originate from primary non-small cell lung carcinoma (NSCLC). GI metastases from lung cancer are uncommon, but SB is the most frequent GI site when they occur. All 3 patients were older heavy male smokers, presenting with large lung tumors and synchronous or metachronous SB masses. SB and lung tumors were primarily undifferentiated carcinomas, many with prominent rhabdoid tumor cell (RTC) morphology (10–50%). Epithelial markers were variably positive (AE1/AE3, CK7, EMA). SMARCA4 deficiency was present in 2 cases, with SMARCA2 deficiency in all 3 SB tumors and 2 lung tumors. MMR proteins and SMARCB1 were retained. “Stemness” markers (SOX2, SALL4, CD34) were variably weak/focal, favoring NSCLC over thoracic SMARCA4-DUTs. *SMARCA2* frameshift/nonsense mutations identified in 2 lung tumors—unusual because SMARCA2 deficiency is classically epigenetically driven. *SMARCA4* abrogating mutations in 2 cases correlated with IHC loss. Frequent missense passenger mutations *in EGFR, ALK, ROS1,* and smoking-associated genes *KRAS, KEAP1, STK11,* consistent with heavy smoking histories. Tumor mutation burden ranged from low to high. Mutational signatures included signature 4, a hallmark of tobacco carcinogenesis.

Take Home Message: Small bowel undifferentiated carcinomas with SMARCA4/A2 loss—especially with rhabdoid morphology—strongly suggest metastatic NSCLC, even when lung involvement is occult or recent.

Shimamura et al. *Comparative analysis of the tumor immune microenvironment between thymoma and thymic carcinoma*. Lung Cancer.

This study examined the tumor immune microenvironment (TIME) of 157 thymic epithelial tumors (TETs)—including 145 thymomas and 12 thymic carcinomas (TCs)—using multiplex fluorescence immunohistochemistry (mFIHC) to characterize immune cell populations within tumor vs stromal regions. Thymoma subtypes B1 and B2 displayed high CD4+ and CD8+ T-cell infiltration, consistent with their role in supporting thymic T-cell maturation. TCs showed markedly reduced T-cell infiltration, increased Foxp3+ T-regulatory cells, and a more immunosuppressive microenvironment. CD4+CD8+ double-positive T cells, reflecting immature thymocytes, were most abundant in B2 > B1 > AB thymomas and nearly absent in type A and TC, aligning with preserved thymopoietic function in B-type tumors. Myasthenia gravis-associated thymomas had higher stromal B-cell density (CD20+CD79a–) ($p = 0.0165$),and higher anti-AChR antibody levels. In MG cases, serum anti-AChR titers correlated with increased Foxp3+ T-reg density in stroma, suggesting immune dysregulation related to autoimmunity. Favorable prognostic markers included high infiltration of CD4+ T cells ($p = 0.0310$), high CD8+ T cells ($p = 0.0215$), and high CD68+ macrophages ($p = 0.0432$). Multivariate analysis confirmed CD4+ and CD8+ densities as independent prognostic factors. Unfavorable prognostic marker (stroma) included increased CD20+CD79a– B-cell density ($p = 0.0088$).

Take Home Message: Thymoma subtypes B1–B2 maintain a T-cell–rich microenvironment, including immature and mature T-cell populations. Thymic carcinoma exhibits an immunosuppressive TIME with higher Foxp3+ T-regs and fewer effector T cells. MG-associated thymomas show increased stromal B-cells, supporting the role of B-cell–mediated autoimmunity in MG pathogenesis. Tumor-infiltrating CD4+ and CD8+ T cells predict good prognosis, while stromal B-cells predict poor outcome in thymomas. The divergent TIME signatures between thymoma and TC have implications for predicting ICI toxicity and therapeutic response, given the known high rate of adverse events in thymoma.

Wu et al. Prospective Analysis of Mesotheliomas in Subjects With BAP1 Cancer Syndrome: Clinical Characteristics and Epigenetic Correlates of Disease. *JTO*

This prospective study evaluated 50 adults with germline BAP1 mutations to determine the prevalence, histopathology, detectability, and epigenetic characteristics of mesotheliomas in BAP1 cancer syndrome (BCS). Median follow-up was 21.8 months. Of 45 surgically evaluated patients, 39 (87%) had previously unrecognized mesothelioma. Across body cavities, 78% of hemi-thoraces and 84% of abdominal cavities had mesothelioma. Most

were multicompartmental, often involving 2–3 serosal surfaces. CT sensitivity was only 37% (higher for chest), specificity 70%, and PET/CT was rarely helpful (FDG avidity in only ~5%). Histological features included low-volume, diffuse, plaque-like mesothelioma involving parietal pleura/peritoneum; arcades or strings of flattened epithelioid mesothelial cells within dense collagenous stroma often with residual but sometimes obliterated fat; typically 0.5–1 mm thick, sometimes extending into fascia but not muscle; low nuclear grade (1–2) with minimal pleomorphism; frequent lymphoid infiltrates. There was loss of nuclear BAP1 in tumor cells and occasionally in overlying atypical mesothelium. Progression is slow: repeat VATS/DL at 1–2 years showed minimal evolution, though some patients expanded from single- to multi-compartment disease. Therefore, no immediate therapy was recommended for subclinical disease, and surveillance is advised. Germline BAP1 mutations create characteristic, mutation-specific DNA methylation patterns, including reproducible hyper/hypomethylated hotspots across the genome (e.g., HOXA, ZIC, HLA region). Differences between two major mutation clusters (e.g., 1717del vs 1938mut) correlated with distinct chromatin signatures. A panel of 10 methylation probes predicted tumor burden with ~90% accuracy, suggesting potential for future noninvasive biomarkers.

Take Home Message: Assuming you believe these are actually mesotheliomas and not some pre-invasive or more indolent condition, subclinical mesotheliomas are extraordinarily common in BAP1 cancer syndrome, present in nearly 90% of adults with germline BAP1 mutations. These lesions are diffuse, low-volume, low-grade, with highly characteristic histology and BAP1 loss. Disease progression is slow, and immediate oncologic therapy is usually not indicated.

Yang et al. The clinicopathological characteristics and prognosis of mucin-laden nonmucinous lung adenocarcinoma. JTCVS

This retrospective study evaluated 529 patients with mucin-laden nonmucinous lung adenocarcinoma (MNLA) to define their clinicopathologic features and prognostic factors. MNLA was defined as nonmucinous adenocarcinoma with either intra-cytoplasmic or extracellular mucin, excluding invasive mucinous adenocarcinoma and colloid adenocarcinoma. Acinar component was very common (95.7%), as were papillary (58%) and micropapillary (52%) components. Most tumors were intermediate (56.9%) or high grade (42.5%) by IASLC grading. Three mucin-distribution patterns were recognized: extracellular mucin (59.5%), intracytoplasmic mucin (signet-ring–like) (18.2%), mixed intra- and extracellular mucin (22.3%). *EGFR* mutations were most prevalent in tumors with extracellular mucin (47.8%). *ALK* rearrangements were highly enriched in mixed mucin-

distribution tumors (37.5%) and present in 26% of intracytoplasmic mucin tumors. *KRAS* mutation rate was low (3%), consistent with this East Asian cohort. Extracellular mucin distribution was associated with worse DFS (aHR 1.87 vs intracytoplasmic), worst OS (aHR 4.24 vs intracytoplasmic), high cumulative incidence of distant recurrence independent of stage and grade (aHR 2.82), large size and papillary/micropapillary components. Mixed mucin distribution showed intermediate outcomes. Intracytoplasmic mucin had the best prognosis among the three groups. STAS was more common in extracellular mucin tumors (though not statistically significant). Almost 90% of tumors were radiologically purely solid. Nomograms incorporating mucin pattern, age, T/N stage, LVPI, and grade showed good discrimination (C-index ≈0.75–0.83).

Take Home Message: Extracellular mucin correlates with more aggressive histology (papillary/micropapillary),larger tumor size, higher *EGFR* mutation rate, and significantly poorer DFS, OS, and increased distant metastases. Reporting presence and pattern of mucin in nonmucinous adenocarcinomas may provide prognostic stratification.