Pulmonary Pathology Journal Club – January 2025
Articles from December of 2024

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Articles for Discussion

Haghighi M et al. Digital Pathology in the Detection of Infectious Microorganisms: An Evaluation of Its Strengths and Weaknesses Across a Panel of Immunohistochemical and Histochemical Stains Routinely Used in Diagnostic Surgical Pathology. Arch Pathol Lab Med. 2024;148(12):1337-1343.

Purpose: Evaluate reliability of microorganism detection on histochemical and immunohistochemical-stained digitized slides; determine diagnostic statistics (sensitivity, etc) and interrater reliability

Methods:

- Broad case selection criteria: All cases for which one of the below IHC or histochemical ("special") stains were ordered from 2010-2021
- Collected cases/narrowed down cohort: 678 cases selected, with goals of selecting:
    - Equal number of positive vs negative cases
    - ≈ 100 cases for HSV, CMV, *H. pylori* (by IHC and Giemsa), spirochete, and fungi (GMS) and ≈ 20 cases of cryptococcus (mucicarmine) and acid-fast bacilli (Ziehl-Neelsen)

- Scanned at 40x magnification with no z-stacking (scanner: Philips ultra-fast scanner (UFS))
- All digital images were reviewed by 6 pathologists:
    - blinded to original diagnosis
    - all had limited digital pathology experience
    - all in practice (no trainees) - 2 hematopathologists, 1 oral pathologist, 1 cytopathologist, 1 gastrointestinal pathologist, and 1 neuropathologist
    - review order of the slides was randomized
    - *Sidenote: none of the slides were from cell blocks or other cytology samples*
- Pathologists could document their interpretation as positive, negative, or equivocal
- Reference standard was the original interpretation on review of the glass slides at the time of diagnostic evaluation
- Diagnostic statistics were calculated by pooling the results from all pathologists; equivocal results were not included
- Fleiss κ used to assess interobserver agreement (< 0.2 = poor, …etc. … , > 0.81 = excellent)
- Lastly, they also assessed color contrast ratio between the stained organism and the background tissue using an online tool (https://www.boia.org/blog/check-out-our-new-color-contrast-tool)

Results:

- Slides ultimately satisfactory for digital scanning: 620 slides / 678 total collected
    - 8.5% unsatisfactory
    - Scanning system failed to detect any tissue on 1 spirochete IHC stain and 3 mucicarmine stains despite multiple scanning attempts
- Diagnostic statistics:

Statistical Parameter	GMS	Mucicarmine	Ziehl-Neelsen
Accuracy	93%	64%	67%
Sensitivity	91%	62%	53%
Specificity	96%	100%	93%

PPV*	96%	100%	93%
NPV*	89%	12%	52%

**Caveat of PPV and NPV in this study is that this cohort was selected to have equal number of positive and negative cases, and therefore the cohort "prevalence" isn't reflective of the true prevalence in clinical practice*

- "Equivocal" rate across all stains: 4.7% (175 of 3696 total interpretations)
    - GMS: 6.8%
    - Mucicarmine: 2.6%
    - Ziehl-Neelsen: 4.1%
- 85% of the "equivocal" interpretations were from 3 of the pathologists (40, 51, and 57 "equivocal" calls, respectively)
- Interobserver Agreement:

Parameter	GMS	Mucicarmine	Ziehl-Neelsen
Fleiss κ	0.65	0.55	0.49
Strength of agreement	"Substantial"	"Moderate"	"Moderate"
P value*	< 0.001	< 0.001	< 0.001

**Statistically significant P values for Fleiss's Kappa just indicate the agree between raters is significantly better than would be expected by chance alone*

- Color Contrast Evaluation:

Take-Home Messages:

- There appears to be a high false negative rate (low SN) when evaluating digitized Ziehl-Neelsen and mucicarmine stains to identify AFB and *Cryptococcus spp.*
    - Reviewing the glass the old-fashioned way is likely the better approach for now
    - One limitation of this result is that they didn't have a direct comparison to how these 6 pathologists would do in identifying AFB or crypto when using a microscope + glass slides after a washout period (or a comparison using microscope + glass slides on a similar set of different cases)
- Assessing GMS for fungal elements digitally does not seem problematic
- Approximately 3-7% of results were deemed equivocal (unclear how that would compare to glass in a direct comparison)

Abe M et al. Evaluation of a Deep Learning Model for Metastatic Squamous Cell Carcinoma Prediction From Whole Slide Images. Arch Pathol Lab Med. 2024;148(12):1344-1351.

Purpose: Design and validate a deep learning model to identify SqCC on whole slide images (WSIs) from lymph node dissection specimens

Methods:

- Training Set Cases:
    - 2,413 SqCC-positive slides from primary site SqCC resections and 4,174 "nonneoplastic lesion" slides
    - Derived from 5 hospitals in Japan, as well as some WSIs of cases from TCGA datasets

    - Primary sites of the SqCCs were esophagus, head and neck, lung, and skin
- Validation Set Cases: 30 SqCC-positive and 30 SqCC-negative slides (again - primary tumor)
- Test Set Cases: 41 SqCC-positive slides and 500 SqCC-negative slides, all of lymph node dissections done for SqCC of the esophagus, head and neck, and lung (no skin in test set)
- All scanned at 20x (scanner: Leica Aperio AT2 Digital Whole Slide Scanner)
- Deep learning: details are very complicated and I can't pretend to fully understand all the computational work they did, but basically they had the trained model evaluate small tiles from WSIs in the test set and assign a probability of having SqCC (probability from 0 to 1, where > 0.5 gets called positive and < 0.5 gets called negative)

Results:

- False positives: 63 cases; structures/cells falsely being called SqCC by the model as follows:
    - Crush artifact (46% of FPs)
    - Germinal centers (25%)
    - Histiocyte aggregates with anthracotic pigment (6%)
    - Vessels (5%)
    - Unexplained false positives (18%)
- False negatives: 3 cases of poorly-differentiated SqCC; example of foci that were missed:

Take-home points:

- Deep learning models could be effective screening tools for lymph nodes from SqCC resections (particularly because of the very low false negative rate, at least in this model)
- Overall accuracy of the model is limited by high false positive rates

Kaczorowski M et al. Immunohistochemical Evaluation of Schlafen 11 (SLFN11) Expression in Cancer in the Search of Biomarker-Informed Treatment Targets: A Study of 127 Entities Represented by 6658 Tumors. Am J Surg Pathol. 2024.

Background: Schlafen 11 (SLFN11) is a DNA/RNA helicase that regulates cellular response to replicative stress and irreversibly triggers cell death. Some preclinical in vitro studies and clinical trials have shown SLFN11 expression is associated with increased tumor sensitivity to DNA-damaging chemotherapeutic agents (and PARP inhibitors). In several ongoing clinical trials (all for small cell lung carcinoma), positive SLFN11 IHC defines one of the inclusion criteria.

Purpose: Evaluate SLFN11 IHC staining in a variety of epithelial, mesenchymal, and neuroectodermal tumors as well as a collection of normal tissue controls.

Methods:

- Cohort: 3,808 epithelial tumors and 2,850 mesenchymal and neuroectodermal tumors arranged in "multi-tissue paraffin blocks" (not specified whether they're tissue microarrays or larger samples of tissue)
- All tumors were treatment-naïve; was not specified whether all tumor tissue was from a primary site resection or whether metastatic tumor samples were included as well
- Antibody clone: anti-SLFN11 antibody (D-2, mouse monoclonal, Santa Cruz Biotechnology)

- SLFN11 staining review: estimated percentage of total tumor cells with nuclear staining of any intensity and categorized as having: “no SLFN11 staining”, “<10% of tumor cells” (low), “10-79% of tumor cells” (medium), and “ >80% of tumor cells” (diffuse).
    - Unclear whether this was done by one or multiple pathologists as it is not specified

Results:

		SLFN11-positive cases by category			
Tumor type	**Total cases**	**<10%, n**	**10-79%, n**	**> 80%, n**	**Total (+), n (%)**
Lung, adenocarcinoma	135	14	17	30	61 (45.2)
Lung, small cell carcinoma	62	3	7	37	47 (75.8)
Lung, SCC	73	5	16	11	32 (43.8)
Lung, carcinoid tumor	35	0	0	0	0
Malignant mesothelioma	118	3	9	97	109 (92.4)
Thymic carcinoma	12	3	2	0	5 (41.7)

- Normal epithelial cells throughout multiple anatomic sites/organs are mostly negative for SLFN11, although focal cells, including bronchial and alveolar epithelial cells, may have weak to moderate reactivity. Normal endothelial cells and a fraction of normal lymphoid cells tend to be positive (moderate to strong staining).

Take-home messages:
- Small cell carcinoma and mesothelioma had very high rates of SLFN11 expression (> 90% of cases, most cases with diffuse expression), while adenocarcinoma of the lung, squamous cell carcinoma of the lung, and thymic carcinoma had moderate rates of SLFN11 expression (40-50% of cases). All 35 carcinoid tumors of the lung were completely negative.
- Unclear at this time whether SLFN11 will have clinical utility, but it’s a biomarker to be aware of
- Future clinical trials will need to focus on determining appropriate cutoffs for positivity (percentage of positive tumor cells and degree of staining intensity to consider a cell positive)

Weissferdt A, Moran CA. Thoracic solitary fibrous tumors with small cell features: A clinicopathological and immunohistochemical analysis of 5 cases. Ann Diagn Pathol. 2024 Dec;73:152353. doi: 10.1016/j.anndiagpath.2024.152353. Epub 2024 Jun 8. PMID: 38878688.

Purpose: Describe the clinicopathologic and immunohistochemical features of five cases of SFT with “small cell morphology”

Methods:
- All fives cases were from the files of MD Anderson path department or personal files of one of the authors
- Stains performed on all cases: pancytokeratin, p40, STAT6, CD34, chromogranin A, synaptophysin, CD56, INSM1, TTF1, napsin A, desmin, myoD1, SMA

Results:
- Clinical: mean age = 55 (range: 43-74); 4 men/1woman; 3 pleural, 2 intrapulmonary (including 1 endobronchial); all presented with symptoms; tumor sizes: all between 4 and 6 cm
- Histopathology: small, uniform epithelioid to plasmacytoid cells with nested to solid growth pattern **see figures in paper*;*

    - 2 classified as intermediate risk by Deicco et al. criteria (increased mitotic activity and tumor necrosis both present), other 3 were low risk
    - Limited areas representing conventional growth patterns of SFT were seen in 1 case (i.e. bland spindle cells with patternless growth)
    - Dilated HPC-like/staghorn vessels were not prominent
    - No areas of "dedifferentiation" in any of the cases
- Immunohistochemistry: all STAT6 and CD34 positive; synaptophysin and CD56 focally positive in the two intrapulmonary cases, INSM1 focally positive in one of those two; all other markers negative

Take-home messages:

- SFT can morphologically mimic a neuroendocrine tumor or tumors in the "small round blue cell tumor" differential and can sometimes have focal expression of synaptophysin, CD56, and INSM1
- Areas with conventional SFT features can be helpful, but seem to be infrequent

Articles for Notation

Yu Z, Zou J, Xu F. The molecular subtypes of small cell lung cancer defined by key transcription factors and their clinical significance. Lung Cancer. 2024;198:108033

Purpose: Evaluate clinical characteristics, survival data, and treatment responses among the four "transcriptional regulator" subtypes (ASCL1, NEUROD1, POU2F3, and null) of small cell carcinoma in a retrospective cohort (N = 117)

Take-home message: Distribution of subtypes fairly similar to that seen in previous studies such as Baine *et al.*, 2020 paper from MKSCC: SCLC-A = 40%, SCLC-N = 33%, SCLC-P = 7%, SCLC-I = 20%. The subtypes showed no differences in baseline clinical characteristics (age, sex, smoking status, stage), survival, or response to etoposide + cisplatin (EP), irinotecan + cisplatin (IP), or one of these regimens + atezolizumab (immune checkpoint inhibitor). However, the study was almost certainly underpowered to detect differences in response to therapy given the small sizes of the subgroups.

Kozono D et al. Lung-MAP Next-Generation Sequencing Analysis of Advanced Squamous Cell Lung Cancers (SWOG S1400). J Thorac Oncol. 2024;19(12):1618-1629

Purpose:

- Perform NGS on a large cohort of patients with previously treated stage IV or recurrent SqCC to evaluate for molecular alterations with potential therapeutic or prognostic implications (but also for clinical trial sub-study assignment for several different novel targeted therapies under investigation – either a *PIK3CA*, *CDK4/6*, *FGFR*, or *PARP* inhibitor)
- Compare results to mutation profiles of primary SqCCs from the TCGA LUSC dataset

Take-home message:

- The prevalence of SNVs and small indels in particular genes known to be commonly altered in SqCC (*TP53, LRP1B, MLL2, CDKN2A, FAT3*, etc) is similar between this dataset and the TCGA dataset, although overall prevalence of these mutations are higher in the S1400 (advanced disease) cohort ($p = 7.95 \times 10^{-18}$)
- 1325 (79%) of patients had tumor molecular alterations that would qualify for enrollment in one of the four sub-studies (and therefore randomization in an investigational targeted therapy trial)
- No significant difference in survival among four groups of patients stratified by their sub-study qualifying mutations (all had poor survival)

- *PARP4* point mutations were more frequent in this high stage/recurrent dataset (14.8%) compared to TCGA (3.0%). *PARP4* and it's protein product are not particularly well-characterized, but the enzyme is thought to function as a tumor suppressor.

Obaid Q et al. Comparison of antigenicity between frozen section vs non-frozen section tissue blocks: An immunohistochemical study of antibodies commonly used in gynecologic pathology. Am J Clin Pathol. 2024

Purpose: Evaluate differences in tissue antigenicity induced by rapid freezing in a variety of gynecologic tumor samples using immunostains frequently used in gynecologic pathology (N = 177 frozen blocks and 177 non-frozen blocks)

Take-home message: Overall concordance between frozen vs non-frozen was 87%. Only 2.3% were deemed major qualitative differences that could impact management. Avoid using sections from block that were frozen for HER2, p53, and PMS2 when possible.

Zhu W, Han H, Ma Z, Cao H, Yan Y, Zhao Y, Deng C, Xu H, Fu F, Fan F, Zhang Y, Chen H. Prognostic value of KRAS G12V mutation in lung adenocarcinoma stratified by stages and radiological features. J Thorac Cardiovasc Surg. 2024;168(6):1525-1537

Purpose: Evaluate the prognostic value of KRAS G12V in a retrospective cohort (N = 3,829) who underwent resection of adenocarcinoma of the lung; analyses stratified by state and radiologic features

Take-home message: 275 (7.7%) of the patients had a KRAS mutation, 60 with G12V (22% of all KRAS mutations) and 215 (78%) with other KRAS mutations. For patients with pT1 tumors and patients with part-solid tumors (radiographically), both KRAS G12V mutations and KRAS non-G12V mutation were associated with worse recurrence free survival in multivariate models controlling from other factors. Recurrence almost always occurred within less than 2 years in KRAS G12V-postive tumors.

Sainz PV et al. Improving Cancer Probability Estimation in Nondiagnostic Bronchoscopies: A Meta-Analysis. Chest. 2024;166(6):1557-1572

Purpose: Approaches to estimating the probability of cancer following a nondiagnostic bronchoscopy biopsy of a peripheral pulmonary lesion (PPL) conventionally have relied on dichotomous test assumptions calculating negative predictive value (NPV) and false omission rate (FOR) using prevalence, sensitivity, and specificity. The authors describe an alternative method of estimating the probability of disease that they term the *multidisease test approach using Bayes' theorem*, arguing that oversimplified conventional methods underestimate the risk of malignancy in the setting of a nondiagnostic bronchoscopic biopsy.

Take-home message: via an exhausting amount probability and statistics, the authors demonstrate that conventional dichotomous estimations of probability of malignancy following a nondiagnostic bronchoscopic biopsy underestimate risk by a median underestimate of 12% using their multidisease test method as a reference, which they argue is more accurate.

Salisbury ML *et al.* Progressive Early Interstitial Lung Abnormalities in Persons at Risk for Familial Pulmonary Fibrosis: A Prospective Cohort Study. Am J Respir Crit Care Med. 2024;210:1441-1452.

Purpose: Quantify risk of clinically and/or radiographically progressive familial pulmonary fibrosis (FPF) in a cohort of first-degree relatives of IPF patients based on the quantity and quality of interstitial lung abnormalities (ILAs) on HRCT at time of enrollment (all patients lacked clinical or radiographic ILD at time of enrollment).

Take-home message: In those who have a first-degree relative with IPF, even very subtle or focal bilateral ILAs on their initial HRCT were likely to have progressive FPF during the study period (average follow-up time: 6.2 years) compared to those with no ILAs at all (OR = 9.2 for mild ILAs on initial CT, 17.1 for moderate ILAs on initial CT ($p < 0.0001$ for both)).

De Lorenzis E et al. Concordance and Prognostic Relevance of Different Definitions of Systemic Sclerosis Interstitial Lung Disease Progression. Am J Respir Crit Care Med. 2024;210(11):1348-1357

Purpose: Compare four clinical definitions of disease progression in systemic sclerosis-related ILD (SSc-ILD) and assess their ability to predict survival in a longitudinal retrospective cohort of patients with SSc-ILD (N = 245). These different definitions have criteria that primarily involve percent change in FVC or DLCO from the patient's baseline, but some incorporate worsening symptoms or increased fibrosis on HRCT.

Take-home message: OMERACT and Erice definitions (see Table 1 for definitions) of progression were both fairly strong predictors of mortality when analyzing the full cohort (HR = 2.9, $p = 0.011$ and HR = 2.7, $p = 0.014$, respectively), although this correlation with mortality varied by patient subgroup. In patients with disease duration > 3 years, nonsevere FVC impairment, and PASP > 40 mm Hg, none of the four sets of criteria to define progression were reliable.

Rose JA et al. Development, Progression, and Mortality of Suspected Interstitial Lung Disease in COPDGene. Am J Respir Crit Care Med. 2024;210(12):1453-1460.

Purpose: Determine the prevalence, rate of progression, and incidence of ILD and its relationship with mortality in a large cohort of patients with COPD (COPDGene; participants are current and former smokers aged 45–80 years with at least a 10 pack-year smoking history recruited from 21 centers nationwide (USA)). ILD was defined as interstitial lung abnormalities (ILA) and fibrosis and/or FVC < 80% predicted.

Take-home message: 268 of 9,588 participants (2.8%) had "prevalent ILD", i.e. ILD at the time of enrollment. Those with ILD at enrollment had higher mortality over a median of 10.6 years follow-up compared to those who *only* had ILA (without fibrosis and with FVC > 80%): mortality = 51% vs 33% (HR = 2.0, $p < 0.001$). 67% of those with prevalent ILD had progression based on either CT or FVC decline (and progression was associated with decreased survival). At 5-year follow-up point, incident ILD (i.e. new cases of ILD) occurred in 148 of 4,842 participants (3%), corresponding to 5.5 cases/1,000 person-years. While ILD only co-occurs alongside COPD in a subset of patients, it is associated with higher mortality and often has a progressive clinical course.

Wohlgemuth K et al. Pathogenic variants in CFAP46, CFAP54, CFAP74 and CFAP221 cause primary ciliary dyskinesia with a defective C1d projection of the central apparatus. Eur Respir J. 2024;64(6):2400790

Purpose: Characterize primary ciliary dyskinesia (PCD) - specifically cases (N = 9) associated with a defective C1d projection of the ciliary central apparatus, and evaluate the applicability of the European Respiratory Society diagnostic guideline to this subtype of PCD.

Take-home message: Pathogenic variants were identified in two novel PCD genes- *CFAP46* and *CFAP54*, as well as in genes previously found in to be altered in PCD patients - *CFAP74* and *CFAP221* genes. Importantly, these patients with C1d-defective PCD lack many of the classic clinical characteristics of PCD as they tended to have normal situs composition, normal nasal NO production rates, normally ciliary ultrastructure by TEM, and normal ciliary beating by high-speed videomicroscopy analysis (although all patients did have chronic respiratory disease & bronchiectasis/mucus plugging). Aside from the variants identified on sequencing, *in vitro* ciliary transport assay was the only other form of testing that demonstrated an abnormality (significantly reduced mean transport velocities). In young patients with unexplained chronic respiratory disease including bronchiectasis and mucus plugging, genetic testing for PCD should include sequencing of these four genes of the C1d projection regardless of whether more classic clinical features of PCD are present.

Reviews, Guidelines, and Consensus Statements

Roy-Chowdhuri S et al. The American Cancer Society National Lung Cancer Roundtable strategic plan: methods for improving turnaround time of comprehensive biomarker testing in non–small cell lung cancer. Cancer. 2024;130(24): 4200-4212

Purpose: Many patients with metastatic NSCLC do not receive comprehensive and/or timely biomarker testing (molecular and PD-L1). This “strategic plan” discusses the extent of the problem, highlight key factors that prolong biomarker testing turnaround time (TAT), propose strategies to reduce it, and present a process map to help physicians and organizations improve testing efficiency.

Take-home message: This is a broad and brief overview of the preanalytical and analytical problems that result in delayed or less than comprehensive biomarker testing. They note some possible strategies to optimize NSCLC biomarker testing TAT, but refrain from making any explicit recommendations to address specific barriers. See their Table 1 for strategies, challenges, and limitations related to each factor affecting TAT.

Fox AH et al. The American Cancer Society National Lung Cancer Roundtable strategic plan: advancing comprehensive biomarker testing in non–small cell lung cancer. Cancer. 2024;130(24): 4188-4199

Purpose: Outline ACS NLCRT’s strategic plan to achieve comprehensive NSCLC biomarker testing for all appropriate patients.

Take-home message: The strategic plan includes five broad recommendations to address five corresponding challenges in providing comprehensive NSCLC biomarker testing, which they discuss in further detail throughout the plan. To me, these recommendations read more as “priorities”, but are as follows:
Recommendation 1: Disseminate clear and consistent educational materials for biomarker testing to physicians and patients.

Recommendation 2: Provide education to proceduralists performing tissue sampling for potential lung cancer and guide the development of institutional policies promoting adequate tissue collection.
Recommendation 3: Promote the use of guideline-driven biomarker panel testing through testing algorithms and implementation of reflex testing.
Recommendation 4: Encourage standardized biomarker test reports and develop algorithms that aid in directing treatment.
Recommendation 5: Remove the disconnect between payer policies and evidence-based guidelines for comprehensive biomarker testing to increase coverage and avoid delays.

Wang JM et al. Quantitative Imaging Methods in Combined Pulmonary Fibrosis and Emphysema. Chest. 2024;166(6):1463-1472

Purpose: Summarize the findings of numerous clinicoradiologic studies (40 in total, most published 2010-2024) that have attempted to describe and quantify the findings in patients with combined pulmonary fibrosis and emphysema (CPFE), discuss the use of quantitative imaging modalities in large population studies and single-center cohorts to predict CPFE patient outcomes, and highlight how clinicians and researchers should tailor future research efforts regarding imaging of this entity.

Take-home message: Methods employed to estimate the extent of emphysema and fibrosis on HRCT in CPFE patients had included direct radiologist estimation via conventional visual assessment, automated CT algorithms (crude; without machine learning), and more recently machine learning algorithms. While there has been significant variation in the methodologies and cohorts used to investigate the extent of emphysema and fibrosis in CPFE, the majority of studies have indicated that the quantity of both emphysema and fibrosis (and metrics that combine them into a single value) are associated with reduced DLCO, worse respiratory symptoms/quality of life, and/or decreased survival. Moving forward, there is a pressing need to develop a standardized and quantitative radiographic definition of CPFE.

Case Reports

Nakagaki N et al. Multiple lung cyst formation caused by metastatic bladder cancer. Thorax. 2024;79(12):1160-1161

Case Summary: 90-year-old man who presented with hemoptysis and had a past medical history of bladder cancer s/p transurethral resection (diagnosed 10 years prior to this presentation). Chest and abdominal CT demonstrated a large cystic lesion with thin walls surrounded by infiltration and ground-glass opacities in the left lower lobe of the lung; follow-up CT one year later showed multiple cysts with surrounding ground-glass opacities; some cysts contained fluid. The patient's condition worsened and he died approximately 1.5 years after his initial presentation with hemoptysis. Autopsy showed cystic lesions identifiable grossly and microscopically surrounded by metastatic high-grade papillary urothelial carcinoma; evidence of bronchial obstruction was observed around the cystic lesions.

Chapman R et al. Pneumothorax Secondary to Cavitating Pulmonary Kaposi Sarcoma in an Immunocompetent Adult. Am J Respir Crit Care Med. 2024;210(12):e18-e19.

Case Summary: 52-year-old man presented with progressive dyspnea over the past 2 weeks and worsening left-sided pleuritic chest pain and had a past medical history of endemic (immunocompetent) Kaposi sarcoma of the left leg diagnosed more than 20 years prior to this

presentation, s/p chemotherapy and radiotherapy. He recently had been diagnosed with relapsed Kaposi sarcoma in the form of progressive, cavitating lung lesions via PET scan. In the ED, chest imaging showed left-sided pneumothorax and multiple cavitating pulmonary nodules bilaterally. After radiology review, the cause of pneumothorax was deemed to be secondary to rupture of a peripheral cavitating lesion. He was managed conservatively and was discharged from the hospital in stable condition.

Correspondences/Editorials
Paired correspondence regarding mesothelioma in situ and follow-up time:
Nabeshima K. Recommendation on the minimum time for follow-up in diagnosing mesothelioma in situ. Histopathology. 2024;85(6):962-963

Summary/my interpretation: Dr. Nabeshima argues that cases that meet histopathologic criteria for mesothelioma in situ (MIS) at the time of tissue sampling (and are therefore diagnosed as such), but progress to form pleural lesions diagnostic of mesothelioma within a short timeframe (< 1 year), were likely radiographically occult and/or undersampled invasive mesotheliomas to begin with. He suggests that pathologists and clinicians should both be aware of this possibility of what he suspects is undersampled invasive mesothelioma and that a diagnosis of MIS merits close clinical follow-up for at least 1 year before the "in situ" portion of that diagnosis should be accepted as the ground truth (i.e. histologic diagnosis of MIS + 1 year of follow-up without developing invasive mesothelioma = bona fide MIS diagnosis). His two concluding suggestions are:

1) Pathology reports with a diagnosis of MIS should discuss the caveat that a histologic diagnosis of MIS does not necessarily correspond to a prolonged course before the development of invasive/clinically-apparent mesothelioma and that continued follow-up is needed (at least 1 year)
2) A retrospective study to examine the median time required for MIS to progress to an invasive tumor would be helpful, specifically in cases that have not progressed for at least 1 year after the diagnosis of MIS

Churg A. Time requirements for diagnosing mesothelioma in situ. Histopathology. 2024;85(6):963

Summary/my interpretation: Dr. Churg responds that he doesn't believe a time delay is necessary before making a formal diagnosis of MIS, but rather it's important to convey to clinicians in these cases that "this process has a very high likelihood of progression to invasion and that additional workup/therapy is required". Basically, there is agreement that these patients need to be followed closely due to the high risk of disease progression, whether that occurs in the short term or long term, but there is disagreement on whether a follow-up time requirement is needed before establishing a formal diagnosis of MIS (and this disagreement seems be more about diagnostic philosophy than practical clinical medicine).