Pulmonary Pathology Journal Club

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Articles for Discussion

1. Chapel DB, Hornick JL, Barlow J, et al. Clinical and molecular validation of BAP1, MTAP, P53, and Merlin immunohistochemistry in diagnosis of pleural mesothelioma. Mod Pathol. 2022 Oct;35(10):1383-1397.

Background: BAP1 and MTAP immunostains play an important role in diagnosis of mesothelioma, but additional markers are needed to increase sensitivity.

Methods: The authors analyzed 84 pleural mesotheliomas (51 epithelioid, 27 biphasic, 6 sarcomatoid) by a hybrid-capture next-generation sequencing (NGS) panel including complete coverage of coding and splicing regions for BAP1, CDKN2A/MTAP, NF2, and TP53 and correlated molecular findings with diagnostic immunostains for BAP1, MTAP, Merlin, and p53, respectively. Fifty-seven reactive mesothelial proliferations served as benign comparators.

Results: Loss of BAP1, MTAP, and Merlin protein expression were, respectively, 54%, 46%, and 52% sensitive and 100% specific for mesothelioma. Two-marker immunopanels of BAP1 + MTAP, BAP1 + Merlin, and MTAP + Merlin were 79%, 85%, and 71% sensitive for mesothelioma, while a three-marker immunopanel of BAP1 + MTAP + Merlin was 90% sensitive. Diffuse (mutant-pattern) p53 immunostaining was seen in only 6 (7%) tumors but represented the only immunohistochemical abnormality in 2 cases. Null-pattern p53 was not specific for malignancy. An immunopanel of BAP1 + MTAP + Merlin + p53 was 93% sensitive for mesothelioma, and panel NGS detected a pathogenic alteration in BAP1, MTAP, NF2, and/or TP53 in 95%. Together, 83 (99%) of 84 tumors showed a diagnostic alteration by either immunohistochemistry or panel NGS.

Conclusion: Adding Merlin to the standard BAP1 + MTAP immunopanel increases sensitivity for mesothelioma without sacrificing specificity. p53 immunohistochemistry and panel NGS with complete coverage of BAP1, CDKN2A/MTAP, TP53, and NF2 may be useful in diagnostically challenging cases.

Take home message: Merlin might be worth adding to your toolset for mesothelioma and is roughly as good as BAP1 and MTAP for distinguishing benign from malignant proliferations. A panel-based approach is better (no surprise!).

2. Walsh SLF, Mackintosh JA, Calandriello L, et al. Deep learning-based outcome prediction in progressive fibrotic lung disease using high-resolution computed tomography. Am J Respir Crit Care Med. 2022 Oct;206(7):883-891.

Background: Reliable outcome prediction in patients with fibrotic lung disease using baseline high-resolution computed tomography (HRCT) data remains challenging.

Methods: The authors aimed to evaluate the prognostic accuracy of a deep learning algorithm (SOFIA [Systematic Objective Fibrotic Imaging Analysis Algorithm]), trained and validated in the identification of usual interstitial pneumonia (UIP)-like features on HRCT (UIP probability),

in a large cohort of well-characterized patients with progressive fibrotic lung disease drawn from a national registry. SOFIA and radiologist UIP probabilities were converted to Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED)-based UIP probability categories (UIP not included in the differential, 0-4%; low probability of UIP, 5-29%; intermediate probability of UIP, 30-69%; high probability of UIP, 70-94%; and pathognomonic for UIP, 95-100%), and their prognostic utility was assessed using Cox proportional hazards modeling.
Results: In multivariable analysis adjusting for age, sex, guideline-based radiologic diagnosis, and disease severity (using total interstitial lung disease [ILD] extent on HRCT, percent predicted FVC, DlCO, or the composite physiologic index), only SOFIA UIP probability PIOPED categories predicted survival. SOFIA-PIOPED UIP probability categories remained prognostically significant in patients considered indeterminate (n = 83) by expert radiologist consensus (hazard ratio, 1.73; P < 0.0001; 95% confidence interval, 1.40-2.14). In patients undergoing surgical lung biopsy (n = 86), after adjusting for guideline-based histologic pattern and total ILD extent on HRCT, only SOFIA-PIOPED probabilities were predictive of mortality (hazard ratio, 1.75; P < 0.0001; 95% confidence interval, 1.37-2.25).
Conclusion: Deep learning-based UIP probability on HRCT provides enhanced outcome prediction in patients with progressive fibrotic lung disease when compared with expert radiologist evaluation *or guideline-based histologic pattern*. In principle, this tool may be useful in multidisciplinary characterization of fibrotic lung disease. The utility of this technology as a decision support system when ILD expertise is unavailable requires further investigation.
Take home message: AI imaging tools are better than both radiologists and pathologists at predicting outcome in patients with progressive fibrotic lung disease. Welcome to the future. Unless pathologists can find a way to add more value to biopsies, they will continue to disappear from practice… which may or may not be the best thing for patients.

3. Hambly N, Farooqi MM, Dvorkin-Gheva A, et al. Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry. Eur Respir J. 2022 Oct;60(4):2102571.
Background: Progressive fibrosing interstitial lung disease (PF-ILD) is characterized by progressive physiological, symptomatic, and/or radiographic worsening. The real-world prevalence and characteristics of PF-ILD remain uncertain.
Methods: Patients were enrolled from the Canadian Registry for Pulmonary Fibrosis between 2015 and 2020. PF-ILD was defined as a relative forced vital capacity (FVC) decline ≥10%, death, lung transplantation, or any two of: relative FVC decline ≥5% and <10%, worsening respiratory symptoms, or worsening fibrosis on computed tomography of the chest, all within 24 months of diagnosis. Time-to-event analysis compared progression between key diagnostic subgroups. Characteristics associated with progression were determined by multivariable regression.
Results: Of 2746 patients with fibrotic ILD (mean±sd age 65±12 years; 51% female), 1376 (50%) met PF-ILD criteria in the first 24 months of follow-up. PF-ILD occurred in 427 (59%) patients with idiopathic pulmonary fibrosis (IPF), 125 (58%) with fibrotic hypersensitivity pneumonitis (HP), 281 (51%) with unclassifiable ILD (U-ILD) and 402 (45%) with connective tissue disease-associated ILD (CTD-ILD). Compared with IPF, time to progression was similar in patients with HP (hazard ratio (HR) 0.96, 95% CI 0.79-1.17), but was delayed in patients with U-ILD (HR 0.82, 95% CI 0.71-0.96) and CTD-ILD (HR 0.65, 95% CI 0.56-0.74). Background

treatment varied across diagnostic subtypes, with 66% of IPF patients receiving antifibrotic therapy, while immunomodulatory therapy was utilized in 49%, 61%, and 37% of patients with CHP, CTD-ILD, and U-ILD, respectively. Increasing age, male sex, gastro-oesophageal reflux disease, and lower baseline pulmonary function were independently associated with progression.
Conclusion: Progression is common in patients with fibrotic ILD and is similarly prevalent in HP and IPF. Routinely collected variables help identify patients at risk for progression and may guide therapeutic strategies.
Take home message: The clinical trend to move away from traditional classification of fibrotic ILDs to a general clinical phenotypic designation as simply "progressive" or "non-progressive" continues. Binary lumping of patients into these 2 categories is convenient and pragmatic, but is this a step forward or backward in the field? Time will tell.

4. Malpica A, Euscher ED, Marques-Piubelli ML, et al. Localized malignant peritoneal mesothelioma (LMPeM) in women: a clinicopathologic study of 18 cases. Am J Surg Pathol. 2022 Oct;46(10):1352-1363.
Background: Localized malignant peritoneal mesothelioma is a rare tumor with limited information in the literature.
Methods: The authors present their experience with 18 cases seen in their hospital over a period of 43 years (1978 to 2021).
Results: Patients' median age was 55 years (y) (range: 33 to 79 y) and most of them were Caucasians. Patients presented with abdominal pain (11), ascites and right leg swelling (1), abdominal mass (1), and as incidental finding (1). Thirty percent of patients reported asbestos exposure, and all patients with available information had family history of tumors; a third had personal history of tumors. Seventy-seven percent had some form of abdominopelvic surgery and/or inflammatory process. Most cases had microscopic features typically seen in malignant mesothelioma; however, some cases had confounding features such as signet-ring cells, spindle cells, clear cell changes, and adenomatoid tumor-like appearance. BAP-1 by immunohistochemistry was lost in 1/3 cases. Only 1 patient underwent genetic testing and had an MSH2 germline mutation. Homozygous deletion of CDKN2A by FISH was not found in 1 tested case, although next-generation sequencing identified a CDKN2A pathogenic mutation. 16/18 (88%) had surgical treatment, and some also received adjuvant chemotherapy. The mean overall survival (OS) of their patients was 80.4 months (95% confidence interval: 54.3-106.52); the 3-year OS was 79%, while the 5-year OS was 52.6%. Fifty-three percent of patients had recurrences and 20% had tumor progression.
Conclusion: Although the limited sample precludes definitive conclusions, small tumor size, low-grade cytology, and low mitotic index appeared to be associated with indolent behavior.
Take home message: This is the largest cohort of localized malignant peritoneal mesothelioma in the literature. 30% had a reported exposure to asbestos, 77% had prior abdominopelvic surgery or abdominal inflammatory processes (diverticulitis, IBD, or endometriosis), and no patients had a reported talc exposure. 53% had recurrences and 20% had progression with disseminated disease.

Articles for Notation

Neoplastic

1. Ishii S, Takamatsu M, Ninomiya H, et al. Machine learning-based gene alteration prediction model for primary lung cancer using cytologic images. Cancer Cytopathol. 2022 Oct;130(10):812-823.

Summary: The authors developed an AI model that can predict gene alterations in ALK, EGFR, KRAS, or other genes in primary lung cancers using cytology specimens with reasonable accuracy.

Take home message: While using AI to predict the presence of mutations is interesting from an academic perspective, this AI model isn't perfect (no surprise!), only a few alterations were included in the AI model, and it's doubtful that AI will replace actual molecular testing any time soon.

2. Bossé Y, Gagné A, Althakfi W, et al. Prognostic value of complex glandular patterns in invasive pulmonary adenocarcinomas. Human Pathol. 2022 Oct;128:56-68.

Summary: A study of 2 complex glandular patterns, including cribriform and "fused gland" patterns, looking at their association with relapse-free survival and overall survival. In their cohort, the presence of cribriform pattern was associated with worse relapse-free survival, but not overall survival. The fused-gland pattern was not associated with either parameter.

Take home message: This adds to the growing literature on the significance of cribriform growth as a poor prognostic pattern, but also adds to inconsistencies in the literature, likely reflecting the problems with interobserver variability in distinguishing patterns of growth of adenocarcinoma in the lung, which should come as no surprise to this group.

3. Akhave N, Zhang J, Bayley E, et al. Immunogenomic profiling of lung adenocarcinoma reveals poorly differentiated tumor are associated with an immunogenic tumor microenvironment. Lung Cancer. 2022 Oct;172:19-28.

Summary: Resected stage I-III lung adenocarcinomas were classified by predominant pattern and grouped into well-differentiated, moderately differentiated, and poorly differentiated groups. Whole exome sequencing, gene expression profiling, IHC, and other molecular testing was performed and groups were compared for differences in genomic drivers, immune cell infiltrates, clonality, and survival. Poorly differentiated tumors were associated with a distinct immunogenic tumor microenvironment that predicts response to immune checkpoint inhibitors.

Take home message: The title of this paper basically says all you need to know.

4. Kawai T, Seki R, Miyajima K, et al. Malignant pleural mesothelioma with heterologous elements. J Clin Pathol. 2022;75:690-695.

Summary: Ten biphasic/sarcomatoid mesotheliomas with heterologous mesenchymal elements were compared with 2 cases of "pleural osteosarcoma". The latter 2 cases showed no distinct clinicopathological, IHC, or FISH testing differences from mesotheliomas with heterologous osteosarcomatous elements.

Take home message: Whether "pleural osteosarcoma" truly represents a distinct entity or simply sarcomatoid mesothelioma with overgrowth of a heterologous osteosarcomatous element remains to be determined… but this distinction doesn't seem to matter from a clinical standpoint as both are very aggressive with a poor prognosis.

5. Liu PP, Su YC, Niu Y, et al. Comparative clinicopathological and immunohistochemical study of micronodular thymoma and micronodular thymic carcinoma with lymphoid stroma. J Clin Pathol. 2022;75:702-705.
Summary: The clinical, pathologic, and IHC findings in 4 cases of micronodular thymoma with lymphoid stroma and 3 cases of micronodular thymic carcinoma with lymphoid hyperplasia were compared. Atypia and mitotic activity were the features used to distinguish one entity from the other. No patients had evidence of recurrence or died of their disease after surgical resection of either entity, though follow-up duration was limited in several cases.
Take home message: Micronodular thymic carcinoma with lymphoid hyperplasia has been added as a provisional entity or subtype of SqCC in the new WHO classification, but data on their clinical behavior remains limited. The 3 cases of this "entity" presented in this report suggest that the differences in their clinical behavior from micronodular thymoma with lymphoid stroma are minor and the prognosis is good, but more data from future studies is needed.

6. Zhu Y, Wang A, Allard GM, et al. Immunofluorescent and molecular characterization of effusion tumor cells reveal cancer site-of-origin and disease-driving mutations. Cancer Cytopathol. 2022 Oct;130(10):771-782.
Summary: The authors combined a previously developed immunofluorescence assay that can reliably separate tumor cells from non-tumor cells in pleural fluid with a novel method of TTF-1 multiplex immunofluorescence tagging, to specifically isolate cells of metastatic pulmonary adenocarcinoma from pleural fluid specimens. This enabled them to perform molecular testing for therapeutic targets successfully, even with very few malignant cells.
Take home message: Methods such as this may become more commonplace as more and more testing is required from small specimens.

7. Yao Q, Bai Q, Zhang X, et al. Assessment of ALK fusions in uncommon inflammatory myofibroblastic tumors with ALK IHC positivity but FISH-equivocal findings by targeted RNA sequencing. Arch Pathol Lab Med. 2022 Oct;146(10):1234-1242.
Summary: The authors studied cases of ALK-positive IMT (by IHC) that had equivocal or negative FISH results, to see if RNA sequencing could resolve the inconsistency. Most cases were resolved with RNA sequencing, though one case was confirmed as a misdiagnosis (spindle cell rhabdomyosarcoma with FUS-TFCP2 fusion), and alternate fusion partners were identified in several others, potentially explaining the discrepant FISH results.
Take home message: When you get a case suspected to be an IMT where the FISH is negative or inconsistent with the IHC, consider sequencing the tumor. You might be wrong, or there may be therapeutic implications as not all ALK fusions respond the same to crizotinib and ALK protein expression can be induced in the absence of a fusion by other mechanisms, which are often resistant to crizotinib.

Non-neoplastic
1. Bratt A, Williams JM, Liu G, et al. Predicting usual interstitial pneumonia histopathology from chest CT imaging with deep learning. Chest 2022 Oct;162(4):815-823.
Summary: The authors used 1239 patients with ILD, split them into 2 groups ("UIP" and "non-UIP" based on histopathology), and then used AI deep learning to create a model for predicting

histopathology from CT scans. They then compared the performance of the AI model with visual assessment by chest radiologists.
Take home message: The AI model evaluation of chest CT scans was better at predicting histopathology than traditional visual assessment of a CT scan by a radiologist.

2. Nandy S, Berigei SR, Keyes CM, et al. Polarization-sensitive endobronchial optical coherence tomography for microscopic imaging of fibrosis in interstitial lung disease. Am J Respir Crit Care Med. 2022 Oct;206(7):905-910.
Summary: The usefulness of adding polarization to endobronchial OCT imaging to quantify fibrosis was assessed in 15 patients.
Take home message: The polarization technique used by the authors during OCT imaging could distinguish destructive (i.e. architecture-effacing) from non-destructive (i.e. non-architecture-effacing) fibrosis and normal lung in vivo in patients with fibrotic ILDs, as fibrotic tissue displays birefringence and normal tissue does not when this technique is applied. The authors posit that this technique may have several potential clinical applications, including diagnostic support and guidance for more targeted tissue sampling of fibrotic or nonfibrotic areas.

3. Ravaglia C, Doglioni C, Chilosi M, et al. Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection. Eur Respir J. 2022 Oct;60(4):2102411.
Summary: The authors evaluated TBBx findings in 10 patients with suspected pulmonary sequelae after COVID-19, and correlated the findings with imaging and clinical parameters.
Take home message: Not surprisingly, a variety of findings were observed, ranging from fibrotic changes suggesting progression of preexisting ILD, persistent changes of acute lung injury and/or organization, and immunophenotypic changes.

4. Calabrese F, Roden AC, Pavlisko E, et al. Lung allograft standardized histological analysis (LASHA) template: a research consensus proposal. J Heart Lung Transplant. 2022 Oct;41(10):1487-1500.
Summary: An international group of expert lung transplant pathologists in the ISLHT developed a very comprehensive template to standardize pathologic reporting in lung transplant specimens.
Take home message: Hopefully the use of standardized terminology and reporting will reduce misinterpretation of lung transplant complications and bias in clinical trials. A useful reference for those who interpret lung transplant specimens.

5. Villalba JA, Hilburn CF, Garlin MA, et al. Vasculopathy and increased vascular congestion in fatal COVID-19 and acute respiratory distress syndrome. Am J Respir Crit Care Med. 2022 Oct;206(7):857-873.
Summary: The authors compared lung parenchymal and vascular changes between patients with fatal COVID-19 pneumonia and patients with fatal ARDS from other viral and non-viral causes. Machine learning was used to analyze the microvasculature, and clinical parameters were also assessed.
Take home message: In fatal COVID-19 pneumonia, vasculopathic changes were more common than in fatal cases of ARDS or other viral or non-viral pneumonias with DAD.

Case Reports, Reviews, and Editorials

1. Choi B, Ash SY. Deep learning-based classification of fibrotic lung disease: Can computer vision see the future? Am J Respir Crit Care Med. 2022 Oct;206(7):812-814.
Summary: A nice editorial accompanying the discussion article from Walsh et al., highlighting the promise but also the ongoing challenges with AI-based tools for classifying disease using image analysis of CT scans. We certainly face the same challenges with AI tools in pathology!

2. Jesudasen SJ, Montesi SB. Beyond what meets the eye: Artificial intelligence in the diagnosis of idiopathic pulmonary fibrosis. Chest. 2022 Oct;162(4):734-735.
Summary: Another nice editorial accompanying the other paper this month investigating AI and machine learning to classify fibrotic ILD by HRCT.

3. Spagnolo P, Bonniaud P, Rossi G, et al. Drug-induced interstitial lung disease. Eur Respir J. 2022 Oct;60(4):2102776.
Summary: A nice contemporary clinical review of drug-induced ILD that includes some of the newer biologic agents and immune checkpoint inhibitors, and current treatment algorithms.

4. McLaughlin J, Martin D, Safi J, et al. Endotracheal xanthoma disseminatum. Am J Respir Crit Care Med. 2022 Oct;206(7):901-902.
Summary: Great case report of a rare entity that includes dramatic clinical images and some histology images from the tracheal biopsy. Worth a quick glance!

5. Kasajima A, Klöppel G. Neuroendocrine tumor G3 of bronchopulmonary origin and its classification. Pathol Int. 2022;72:488-495.
Summary: Nice review and discussion of the ongoing problem of terminology in neuroendocrine tumors and clash between the pulmonary world and GI world. Could we finally all agree that a grade 3 WDNET also occurs in the lung, get rid of carcinoid and atypical carcinoid designations, and standardize terminology across specialties for well-differentiated neuroendocrine tumors? Maybe the next iteration of the WHO classification will get there…

6. Cottin V, Valenzuela C. Progressive pulmonary fibrosis: all roads lead to Rome (but not all at the same speed). Eur Respir J. 2022 Oct;60(4):2201449.
Summary: Interesting editorial accompanying the discussion article from Hambly et al., highlighting many of the clinical implications of their findings and similarities between PPF and IPF.

7. Kerchberger VE, Bastarache JA. Pulmonary vasculopathy in COVID-19 acute respiratory distress syndrome: a step closer to the full picture. Am J Respir Crit Care Med. 2022 Oct;206(7):809-810.
Summary: Editorial accompanying the study by Villalba et al. characterizing microvascular changes in cases of fatal COVID-19 and ARDS from other causes.

8. Churg A, Galateau-Salle F. Well differentiated papillary mesothelial tumor: a new name and new problems. Mod Pathol. 2022 Oct:35(10):1327-1333.

Summary: Nice review and perspective piece on WDPMT from Andy and Francoise, highlighting some of the new problems associated with the term and practical testing advice when faced with something that looks like WDMPT. In their opinion, we should consider BAP1 and MTAP stains and CDKN2A FISH in such cases to evaluate for "WDMPT-like" mesothelioma in situ that may have potential for malignant behavior down the road… a potential pitfall.