MAY 2020 PULMONARY PATHOLOGY JOURNAL CLUB

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I. ARTICLES FOR DISCUSSION

1. Wright JL, et al. Pathologic separation of idiopathic pulmonary fibrosis from fibrotic hypersensitivity pneumonitis. Mod Pathol 2020;33:616-25.

OBJECTIVE: To identify pathologic variables that help separate IPF from chronic HP.

METHODS:

- Clinical, radiological, and pathologic data were re-reviewed for 23 patients with a fibrotic ILD and biopsy suggesting IPF or fibrotic HP.
- Clinical features, HRCT, and surgical lung biopsies were each examined independently using a prespecified approach.
- This was followed by a multidisciplinary discussion in which the likelihood of an IPF diagnosis was assigned by the clinician alone based only on clinical data, by the clinician and radiologist based on integrated clinical and radiologic data, and by the clinician, radiologist, and pathologist based on all three domains.

RESULTS:

- A higher MDD-based confidence of IPF was associated with older age at diagnosis, male sex, higher forced vital capacity, and absence of ground glass changes.
- Pathologic variables associated with a higher MDD-based confidence of IPF included increased number of fibroblast foci/cm2 and increased subpleural fibrosis.
- Pathologic variables associated with a higher MDD-based confidence of HP included an increased fraction of bronchioles with peribronchiolar metaplasia, increased foci of peribronchiolar metaplasia/cm2, and presence of giant cells/granulomas.

CONCLUSIONS:

- These results provide guidance in separating IPF from HP.
- A third of cases could not be confidently classified by MDD even when using these pathologic features combined with clinical and radiologic information.

TAKE-HOME MESSAGE: This is still a major problem in ILD diagnosis, and although this provides data to support what we're already doing (with a bit of circular reasoning), nothing has really changed from this study.

2. Fukihara J, et al. Probable usual interstitial pneumonia pattern on chest CT: is it sufficient for a diagnosis of idiopathic pulmonary fibrosis? Eur Respir J 2020;55:1802465.

OBJECTIVE: To determine whether a probable UIP pattern on chest CT is sufficient to diagnose IPF without histopathology in a patient presenting with an idiopathic ILD.

METHODS:

- The prognosis and time to first acute exacerbation (AE) were retrospectively compared in IIP patients with a UIP and a probable UIP pattern on initial chest CT.

RESULTS:

- 160 IIP patients with a UIP pattern and 242 with a probable UIP pattern were identified.
- Probable UIP pattern was independently associated with longer survival time (adjusted hazard ratio 0.713, 95% CI 0.536–0.950; p=0.021) and time to first AE (adjusted hazard ratio 0.580, 95% CI 0.389–0.866; p=0.008).
- In subjects with a probable UIP pattern who underwent surgical lung biopsy, the probability of a histologic UIP pattern was 83%.

- After multidisciplinary discussion and the inclusion of longitudinal behavior, a diagnosis of IPF was made in 66% of cases.
- In IPF patients, survival time and time to first AE were not associated with CT pattern.
- Among subjects with a probable UIP pattern, survival time and time to first AE were shorter in IPF patients than in non-IPF patients.

CONCLUSIONS:

- IIP patients with a probable UIP pattern on initial chest CT had a better prognosis and longer time to first AE than those with a UIP pattern.
- However, when baseline data and longitudinal behavior provided a final diagnosis of IPF, CT pattern was not associated with these outcomes.
- Diagnostic heterogeneity occurs among patients with a probable UIP pattern.

TAKE-HOME MESSAGE: Not surprisingly, imaging is not perfect and only 2/3rds of patients with probable UIP radiology were deemed to have IPF after MDD. Biopsies may still be worth considering in this setting, at least in some patients. *NOTE the excellent editorial accompanying this article in ERJ by Kolb et al. (listed below under articles for notation, non-neoplastic article #4).

3. Vivero M, et al. Metaplastic thymoma: a distinctive thymic neoplasm characterized by YAP1-MAML2 gene fusions. Mod Pathol 2020;33:560-5.

OBJECTIVE: To define the relationship of metaplastic thymoma to other thymic neoplasms and define their molecular characteristics.

METHODS:

- Paraffin-embedded material from 8 cases of metaplastic thymoma was subjected to targeted DNA-based hybrid capture NGS.
- Cases showing no somatic alterations subsequently underwent targeted RNA sequencing.
- Allele-specific real-time PCR was performed to detect GTF2I c.74146970T>A (p.L424H) mutations (common in type A and AB thymomas).

RESULTS:

- All cases showed characteristic histologic features of metaplastic thymoma and demonstrated no local recurrence or distant metastatic disease at 1–22 years of follow-up.
- 6 of 8 cases were successfully sequenced, all showing YAP1-MAML2 fusions; in four cases the fusions were detected by DNA sequencing and in two cases by RNA sequencing.
- Two distinct products were identified: 5′ YAP1 exon 1 fused to 3′ MAML2 exons 2–5 or 5′ YAP1 exons 1–5 fused to 3′ MAML2 exons 2–5.
- All cases underwent allele-specific real-time PCR and demonstrated no GTF2I L424H mutations.

CONCLUSIONS:

- Metaplastic thymoma is a distinct, clinically indolent thymic epithelial neoplasm characterized by YAP1-MAML2 fusion and lacking the GTF2I mutations found in Type A and AB thymomas.

TAKE-HOME MESSAGE: Metaplastic thymoma is distinctive with a characteristic YAP1-MAML2 fusion in all cases. Although not addressed in the manuscript, it raises the question whether MAML2 FISH might be useful in the small biopsy setting to support the diagnosis, depending on the FISH probes used.

4. Yagi Y, et al. Three-dimensional histologic, immunohistochemical, and multiplex immunofluorescence analyses of dynamic vessel co-option of spread through air spaces in lung adenocarcinoma. J Thorac Oncol 2020;15:589-600.

OBJECTIVE: To use 3D reconstruction of images from IHC and multiplex IF experiments to understand the spatial architecture of tumor cell clusters in the setting of STAS.

METHODS:

- Four lung adenocarcinomas, three micropapillary-predominant and one solid-predominant, were investigated.
- 350 serial sections were obtained from FFPE blocks.
- Serial H&E (100 slides), IHC (200 slides), and multiplex IF stains (50 slides) were made (CD31, collagen type IV, TTF-1, and E-cadherin).
- Whole slide images were reconstructed into 3D images for evaluation.

RESULTS:

- Micropapillary clusters and solid nests of STAS are focally attached to the alveolar walls, away from the main tumor.

CONCLUSIONS:

- STAS tumor cells can attach to the alveolar walls rather than just being free floating, as seen on the two-dimensional sections.
- This suggests that the tumor cells detach from the main tumor, migrate through air spaces, and reattach to the alveolar walls through vessel co-option, allowing them to survive and grow.
- This may explain the higher recurrence rate and worse survival of patients with STAS-positive tumors who undergo limited resection than those who undergo lobectomy.

TAKE-HOME MESSAGE: STAS is a real thing and not just an artifact, at least in some cases.

II. ARTICLES FOR NOTATION

Neoplastic

1. Le Stang N, et al. Differential diagnosis of epithelioid malignant mesothelioma with lung and breast pleural metastasis. Arch Pathol Lab Med 2020;144:446-56.

The authors performed a meta-analysis of articles on IHC in mesothelioma published between 1979 and 2017 and compared these data to results from the MESOPATH database, to determine the best markers to distinguish mesothelioma from metastatic lung adenocarcinoma and breast carcinoma. The pair with the best sensitivity and specificity for distinguishing lung adenocarcinoma from mesothelioma is calretinin/TTF-1, and the best pair for distinguishing breast carcinoma from mesothelioma is calretinin/ER. However, not surprisingly, neither pair is perfect and this study will probably not change practice from the current IHC panel-based approach using a greater number of markers.

TAKE-HOME MESSAGE: No changes are needed in your approach to diagnosing mesothelioma, unless you are practicing in a more resource-limited setting.

2. Rekhtman N. "Napoleon hat" sign: a distinctive cytologic clue to reactive pneumocytes. Arch Pathol Lab Med 2020;144:443-5.
Here, Natasha Rekhtman proposes a useful diagnostic feature (the "Napoleon hat" sign) that can be used in cytology specimens to aid recognition of reactive pneumocytes.
TAKE-HOME MESSAGE: For those who sign out cytology and need another clue to help distinguish reactive pneumocytes from malignant cells, this concept may help. They certainly look like Napoleon's hat!

3. Williams GH, et al. Interobserver reliability of programmed cell death ligand-1 scoring using the VENTANA PD-L1 (SP263) assay in NSCLC. J Thorac Oncol 2020;15:550-5.
This study provides data indicating that the SP263 PD-L1 assay from Ventana has excellent interobserver reliability in the hands of 6 European pulmonary pathologists, when performed on cases of NSCLC. For those other unlucky pathologists who also sign out PD-L1 assays, this should be reassuring to you!
TAKE-HOME MESSAGE: The SP263 PD-L1 assay has high interobserver reliability in the setting of NSCLC.

4. Lantuejoul S, et al. PD-L1 testing for lung cancer in 2019: perspective from the IASLC Pathology Committee. J Thorac Oncol 2020;15:499-519.
Because many articles have been published since the "IASLC Atlas of PD-L1 IHC Testing in Lung Cancer" was issued, his review from the IASLC Pathology Committee provides updates on the indications for immune checkpoint inhibitor therapy for lung cancer and discusses important considerations on preanalytical, analytical, and postanalytical aspects of PD-L1 testing. Those folks who sign out these tests or are involved in setting them up and validating them in their lab should be familiar with this document.
TAKE-HOME MESSAGE: Great update on most major aspects of PD-L1 IHC testing.

5. Medina MA, et al. Preoperative bronchial cytology for the assessment of tumor spread through air spaces in lung adenocarcinoma resection specimens. Cancer Cytopathol 2020;128:278-86.
BAL fluid would seem to be an attractive specimen for potentially identifying STAS preoperatively and potentially stratifying patients into those needing lobectomies and those for whom a sublobar resection may be more appropriate. Unfortunately, this study indicates that BAL fluid cytology cannot adequately predict the presence of STAS in the subsequent resection specimen.
TAKE-HOME MESSAGE:
STAS cannot be reliably detected preoperatively by BAL fluid cytology.

<u>Non-neoplastic</u>
1. Liu N, et al. Lung transplantation for bronchopulmonary dysplasia in adults: a clinical and pathologic study of 3 cases. Am J Surg Pathol 2020;44:509-15.
Pathologic findings in lung explants from 3 adults with BPD are described. All showed a mixed pattern of changes including those associated with "old BPD" and also elements of "new BPD" including of alveolar simplification with fibrosis, chronically remodeled and narrowed small airways, and chronic venous changes / muscular hypertrophy, potentially explaining the disease phenotype in these patients (COPD, pulm HTN).

TAKE-HOME MESSAGE: Features of BPD can also be seen in adults if they undergo lung transplantation.

2. Maldonado F, et al. Transbronchial cryobiopsy for the diagnosis of interstitial lung diseases: CHEST guideline and expert panel report. Chest 2020;157:1030-42.
An excellent review and critical analysis of the current literature on cryobiopsies. Two weak evidence-based recommendations were made based on low or very low quality evidence, and four additional consensus-based statements were made. These recommendations and statements primarily relate to issues faced by clinicians (e.g. number of sites to sample, distance from pleura, use of fluoroscopy, size of cryoprobe to use), although they also reiterate that the applicability of these recommendations depends on the availability of pathologists with expertise in ILD diagnosis.

3. Shoemark A, et al. International consensus guideline for reporting transmission electron microscopy results in the diagnosis of primary ciliary dyskinesia (BEAT PCD TEM Criteria). Eur Respir J 2020;55:1900725.
This document represents an international effort to develop consensus diagnostic and reporting guidelines for TEM evaluation of PCD, from experts representing 18 centers in 14 countries. The document includes beautiful TEM images illustrating Class1 and Class 2 defects and provides guidance on interpretation and reporting. This may not be applicable to everyone, but this is an essential document for those few of us who report TEM findings in ciliary biopsies.

4. Kolb M, et al. Prognostic impact of typical and probable usual interstitial pneumonia pattern in idiopathic pulmonary fibrosis: is the debate about biopsy a Star Wars saga? Eur Respir J 2020;55:2000590.
An insightful editorial accompanying the paper by Fukihara et al., included above for more extensive discussion. It also touches on the findings in the recent INBUILD trial and highlights elements of the ongoing debate about "probable UIP", "progressive fibrosing ILD", the limitations of these concepts, and how these terms should be viewed in our current treatment era. Although these issues are primarily clinical, they will directly impact pathology practice and the types of biopsies we will (or won't) be receiving in the future, and provide further rationale for discovering a better gold standard or better biomarkers of etiology.

5. Butnor KJ, et al. Impact of histopathologic changes induced by polyethylene glycol hydrogel pleural sealants used during transthoracic biopsy on lung cancer resection specimen staging. Am J Surg Pathol 2020;44:490-4.
This is a beautifully written article on PEG hydrogel sealants in lung cancer resections. Cautions are included for potential artifacts from PEG hydrogel that could have an impact on interpretation of the tumor or staging. For those who haven't encountered PEG hydrogel before in your practice (myself included), you should view the nice photos at the very least.
TAKE-HOME MESSAGE: Although no major impact on tumor evaluation or staging occurred in the study cases from PEG hydrogel instillation, we should still remain alert to this possibility, particularly artifacts from prior disruption of the visceral pleura that could mimic pleural invasion.

6. Cottin V, et al. Prolidase deficiency: a new genetic cause of combined pulmonary fibrosis and emphysema syndrome in the adult. Eur Respir J 2020;55:1901952.
This is an interesting case report of an accelerated form of ILD that developed in a 22-year-old Portuguese man who had prolidase deficiency. This ILD shared some imaging features with CPFE, but he was also a smoker and had a number of clinical findings suggestive of underlying autoimmune disease. Whether this is simply a peculiar case of CTD-ILD occurring in a heavy smoker or something truly related to prolidase deficiency remains unclear. Regardless, it might be something to remember, just in case you encounter something similar.

7. Dermawan JK, et al. Expanding the spectrum of chronic necrotizing (semi-invasive) aspergillosis: a series of eight cases presenting as radiologically solid lung nodules mimicking malignancy. Histopathology 2020;76:685-97.
This is an interesting series of cases of aspergillus in the lung that did not fit neatly into recognized categories of pulmonary aspergillosis. Rather, all cases presented as lung nodules, usually solitary, in a manner closely mimicking lung cancer and prompting surgical resection. This suspicion was enhanced by the fact that all patients were smokers. At resection, all showed a necrotic granuloma with fungal hyphae.
TAKE-HOME MESSAGE: Aspergillus can present as a solitary lung mass mimicking lung cancer.