MAY PULMONARY PATHOLOGY JOURNAL CLUB

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I. ARTICLES FOR DISCUSSION

1. Morphologic Features of Fibrotic Hypersensitivity Pneumonitis in Transbronchial Cryobiopsies Versus Video-Assisted Thoracoscopic Biopsies- An In Silico Study. Churg and Wright. Arch Pathol Lab Med 2021; 145:448-52

Background

Transbronchial cryobiopsies (CBs) are more time efficient and less invasive than a VATS biopsy; thus, there is growing interest in using CBs for diagnosis of interstitial lung disease. However, we are already aware of the challenges of differentiating fibrotic hypersensitivity pneumonitis (FHP) from usual interstitial pneumonia/idiopathdic pulmonary fibrosis (UIP/IPF) in VATS biopsies.

Aim

This study investigated if histologic features that support a diagnosis of FHP in VATS biopsies are detectable and usable in CBs.

Method

This is a retrospective cross-sectional study using 15 VATS biopsy cases that were confidently diagnosed as FHP from a study published by Wright et al. From VAT biopsy slides at least 5 to 8 in silico circular "cryobiopsies" were created per case and analyzed for giant cells/granulomas or peribronchiolar metaplasia affecting ≥50% of bronchioles, features identified from the multidisciplinary discussion exercise that had supported a diagnosis of FHP.

Results

Cases /w giant cells/granulomas identified (10 original VATs contained giant cells/granulomas)	
2 "cryobiopsies"	10% (1 of 10)
4 "cryobiopsies"	40% (4 of 10)
5 "cryobiopsies"	50% (5 of 10)

Sensitivity/specificity for a positive diagnosis of FHP

	Peribronchiolar metaplasia affecting ≥50% of bronchioles	Peribronchiolar metaplasia affecting ≥50% of bronchioles + giant cells/granulomas
2 "cryobiopsies"	0.57/0.63	0.63/0.71
4 "cryobiopsies"	0.86/0.75	1.00/0.86
8 "cryobiopsies"	0.83/0.71	1.00/0.80

Conclusion

Giant cells/granulomas was an insensitive detector for identifying FHP in CBs. However, CBs are good at detecting peribronchiolar metaplasia, although an adequate number of samples is required. Four 21.6-mm^2 "cryobiopsies" was an adequate sample to provide a good reflection of the VATs biopsies if using the criteria of 50% or greater peribronchiolar metaplasia and giant cells/granulomas as indicators of FHP.

2. Accuracy and Reproducibility of Intraoperative Assessment on Tumor Spread Through Air Spaces in Stage 1 Lung Adenocarcinomas. Villalba et al. JTO 2021; 16:619-29

Background

- Sublobar resection considered acceptable for early-stage NSCLC
- Recent restrospective data suggests that sublobar resection in tumors with STAS has higher rate of local recurrence and worse outcome. Therefore, there is a possible need to assess for STAS on frozen section.
- Data on accuracy and reproducibility of STAS on FS is limited.

Aim

To assess interobserver and intra-observer agreement of STAS on FS

Material and methods

- Retrospective- 2010-2015 resected lung AD
- Panel of 3 pathologists, 100 (of 734) possible consecutive cases with the following inclusion criteria
    - FS performed intraoperatively
    - Slides from FS, FS paraffin and non FS paraffin available for review
    - Adequate adjacent non-neoplastic lung to assess for STAS
- Review by the panel as a consensus then 4 months later by 5 pathologists 2 of which had been on the panel. Round 1- STAS, no STAS Round 2- addition of equivocal STAS.
- STAS versus artefact - other usual pathologic variables recorded.

Results

- 100 patients, 67 F, 57 wedge and 10 segmentectomy
- Panel of 3
    - STAS in 43 cases – associated with large overall and invasive tumor size, higher tumor grade, higher vasc inv, *k-ras* mutation
    - STAS in 19 (of 43) FS slides, 26 of FS paraffin, 5 of which had STAS only on the paraffin section
- 5 pathologists. High variability for presence of STAS in both rounds
    - 20-44% on FS, 23-48% on FS paraffin, 33-60% on non FS paraffin round 1
    - 28-41%, 22-46 and 35-58 % on round 2
- Overall sensitivity and specificity for FS 44.2% and 91.2%
- Sensitivity and specificity across all 5 35-77% and 77-91%
- Average intra-observer and interobserver concordance for STAS was moderate, and lower for artifacts. And didn't change significantly after consensus conference.
- The main reason for discordance (in multivariate) was the presence of artefactual clusters

Conclusion

- Low sensitivity to diagnose STAS – sampling being one reason, but high specificity
- Inter and intra-observer variability moderate – effect on clinical outcome and patient care would need to be studied. Other histologic factors that predict poorer outcome can be assessed on FS and shared at the time of FS. Not just STAS.

3. Pulmonary Pathology of COVID-19 Following 8 Weeks to 4 Months of Severe Disease. Aesif et al. AJCP 2021; 155:506-14

Background

- Data on pathology come from autopsies, usually within a month of onset of disease. Only 6 cases with death between 2-3 months after onset.
- Acutely, most common pattern is DAD.
- Little data on the pathology antemortem and after months of surviving COVID

Aim

Report antemortem pathologic findings in the lungs of 3 patients that survived severe disease, 8 weeks to 4 months after onset of disease

Results

- Patient 1- 46 yo Day 38 underwent debridement of a necrotic RML. Died on day 57
    - RML – infarct like necrosis. DAD. Presence *Candida albicans.*
    - Autopsy – Mostly DAD with extensive necrosis. No fibrosis.
- Patient 2 – 57 yo Day 74 surgical lung biopsy for possible fibrosis. Died on day 74
    - Surgical biopsy showed fibrosis in a pattern resembling NSIP with focal Hcbg. Focal superimposed ALI c/w org DAD. Patchy cellular pneumonia and fibrinous pleuritis. No OP. No thrombi.
- Patient 3 – 57 yo Day 126 bilateral lung transplantation – Day 202 alive requiring mechanical ventilation
    - Interstitial fibrosis and inflammation in a pattern resembling NSIP. Some peribronchiolar metaplasia. Foci of Hcbg. Hemosiderin laden macrophages. No ALI. No thrombi.

Conclusion

- Authors comment appropriately on limitations of their study including complications of ECMO, possibility of fibrotic lung disease prior to COVID (no pre-COVID imaging), or other causes of lung fibrosis.
- Nevertheless, fibrosis is a likely consequence of COVID infection, probably residual late phase of DAD.
- Still missing are studies looking at lung of patients who are out of the hospital, with residual symptoms so-called long haulers.

4. Preoperative Biopsy Diagnosis in Pulmonary Carcinoids, a Shot in the Dark. Moonen et al. JTO 2021; 16:610-8

Background

- Typically cannot distinguish TC from AC on small biopsy
- TC could be treated with sublobar resection versus AC
- Ki67 only used to distinguish carcinoid from high grade NEC on small biopsies, no data to suggest role for distinguishing TC from AC in the same context.

Aim

To assess the diagnostic accuracy of diagnosing carcinoid tumors on small biopsies

Material and methods

- Queried national databanks for cases with definitive pre-operative diagnosis of carcinoid tumors and who underwent resection (Stage I-III)
- Classified tumors as TC, AC, carcinoid NOS, HGNEC, Ca with NE features
- Correlated pre-op and post-op dx, post=op dx being the gold standard.
- Abstracted clinical data, staging, relapse, survival

Results

- 1003 patient with final diagnosis of carcinoid
- 330 with paired pre-op and post-op specimens
    - TC in 48.5%, AC in 26.7% and NOS (? On resected) in 24.8%
    - Pre-op dx was TC in 36.6%, AC in 4.5%, NOS in 47.9%, HGNEC in 1.8%, other in 9.1%
    - In 57% the pre-op and post-op dx didn't match
- Surgery performed
    - 92% underwent (bi) lobectomy or pneumonectomy.
    - Wedge done in 15 cases dx as TC or carcinoid NOS pre-op
        - Post-op dx was AC in 2 and carcinoid NOS in 4
    - No difference in surgery performed based on pre-op dx
- Outcome
    - 25 with progression and 55 with death
    - Relapse free survival better for pre-op dx of TC and NOS vs atypical
    - For post op dx same but even more so as presumably more accurate dx of AC

Conclusion

- The authors conclude that we can't dx as TC or AC on a small biopsy. Which is probably what most practices have known and done for years I suspect.
- The authors suggest looking at KI67 along with other biomarkers such as OTP, CD44 and MEN1 to see if can predict TC vs AC on biopsy.

II. Articles for notation

Neoplastic

1. Use of a Commercially Available Deep Learning Algorithm to Measure the Solid Portions of Lung Cancer Manifesting as Subsolid Lesions at CT: Comparisons with Radiologists and Invasive Component Size at Pathologic Examination. Ahn et al. Radiology 2021; 299: 202-10

Interesting study comparing measurements of solid components in sub-solid Ads between computer, radiologists (5) and pathologists. The computer was not always able (89%) to identify and measure a solid component (too small, cystic changes…). Measurements between computer and radiologists were mostly concordant and both always less than size of invasion as measured by pathologists.

Interestingly, their premise is that there is interobsever variability between radiologists and thus the need for automated measurement yet used measurements performed by radiologists as gold standard. But more importantly, is that the computer can do the job as well as a radiologist, probably more consistently and facilitate the workflow with automation. A similar pathology study should be attempted.

2. Expression of the immunoproteasome subunit β5i in non-small cell lung carcinomas. Kiuchi et al. J Clin Pathol 2021; 74:300-6

Immunoproteosome (Beta 1i, 2i and 5i subunits) are inducible proteosome and play a role in the production of antigens presented by MHC class I molecules that elicit T-cell mediated immune cell response. There are currently drugs being developed targeting immunoproteosome. The study looked at expression of IP β5i in NSCLC by IHC which was present in 20% of all NSCLC, including 40% of AD, and associated with better survival in stage I and II patients. And in their cell line experiments, there was enhanced cell death in NSCLC cell lines that expressed β5i when exposed to both specific immunoproteosome inhibitor and a proteosome inhibitor. So possibly a new therapeutic target.

3. The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC. Mino-Knudson et al. JTO 2021; 16:686-96

The IASLC Pathology Committee conducted a survey of pathologists to assess the practice of PDL1 testing. There was a response of 344 pathologists across Europe, North America and Asia. Results of the survey showed difference across regions and laboratories in the use of some specimen types like cell blocks or smears, use of antibodies although 22C3 was the most commonly used, TAT, LDT versus not and not insignificantly (up to 18%) with no formal QA, training for scoring, or standardized reporting. The Committee concluded that this meant there were opportunities to provide additional QA measure and training.

4. Tumor cell proliferation (Ki-67) expression and its prognostic significance in histological subtypes of lung adenocarcinoma. Li et al. Lung Cancer 2021; 154:69-75

The authors looked at Ki-67 LI across 1028 Ads and compared LI between the predominant histologic subtype. Not surprisingly, higher LI was seen in AD solid and MP compared to Pap, Acinar and then LPA. More interestingly tumors that had any component of solid or MP had a higher LI than those without and comparable to predominant solid and MP. So Ki67 LI would be more predictive of prognosis than predominant subtype alone.

5. Challenges in Ki-67 assessments in pulmonary large-cell neuroendocrine carcinomas. Walts et al. Histopathol 2021; 78:699-709
The background for this study is the reported large interobserver variability for the diagnosis of LCNEC and distinction from atypical carcinoid and SCLC, with consequently reported 5-year OS that range from 13-57% and for Stage I 18-88%. The author looked at the role of KI-67 to assist with the diagnosis. They looked at 77 of their cases of LCNEC and did a literature review on the topic. Assuming we would all agree with their dx of LCNEC the range of Ki67 was 1-64%, mean and median 26%. And the Ki67 did not correlate with OS or DFS while stage did. And mitosis (cut-off of 25/2mm^2) did for OS although not for DFS. The review of the literature showed similar results with ranges of mean Ki-67 from 25.6 to 75%. So based on these results, caution around use of Ki67 for the diagnosis especially for distinction with carcinoid tumor.

6. *KRAS* G12C-mutated advanced non-small cell lung cancer: A real-world cohort from the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). Sebastian et al. Lung Cancer 2021; 154:51-61
With the promising results of KRAS inhibitors, the authors analyzed their national registry of NSCLC. Of 4,032 patients, over a fourth (1,434) were tested for *KRAS* and 160 (11%) had *KRAS G12C* mutation (versus 251 with other *KRAS* mutation and 628 wild type). 33.8% of those with *KRAS G12C* mutation also had PDL1 expression (TPS>50%) [more than other mutation or wild type]. No significant differences in outcome in the 3 groups….at this point. Too early to analyze data for treatment with checkpoint inhibitors.

7. Diffuse expression of MUC6 defines a distinct clinicopathological subset of pulmonary invasive mucinous adenocarcinoma. Kishikawa et al. Mod Pathol 2021; 34:786-97
The authors studied 70 invasive mucinous AD, assessing expression of 5 different MUC, various transcription factors including TTF1, and gene expression. Diffuse (90% of TC) MUC6 expression was present in 19 tumors, associated with smaller tumor size, women, *KRAS* wild type and better clinical outcome (but doesn't seem that a multivariate was done).

8. Pulmonary Adenocarcinomas of Low Malignant Potential Proposed Criteria to Expand the Spectrum Beyond Adenocarcinoma In Situ and Minimally Invasive Adenocarcinoma. Yambayev et al. Am J Surg Pathol 2021; 45:567-76
The authors identified a set of criteria which would allow, beyond AIS and MIA, to identify AD with 100% disease free survival. In AD 3 cm or less, non mucinous, these criteria include 15 and greater % of lepidic growth and lacking high grade patterns [10 or >% cribriform, 5 MP, 5 solid], >1 mitosis/2mm^2, angiolymphatic or visceral pleural invasion, STAS or necrosis. This was done in a small cohort of 328 cases but very promising data.

9. High expression of Ras-specific guanine nucleotide-releasing factor 2 (RasGRF2) in lung adenocarcinoma is associated with tumor invasion and poor prognosis. Nakagawa et al. Pathol International 2021; 71:255-60
Authors studied a small cohort of NSCLC for expression of RasGRF2 by IHC and suggested high expression was associated with poor prognosis but not so significant in multivariate.

<u>Non-neoplastic</u>

1. Clinical Significance and Histologic Characterization of *Histoplasma* Granulomas. Demkowicz and Procop. AJCP 2021; 155:581-87
This study reviewed the pathology of Histoplasma granuloma in 62 patients. They devised a grading scheme by which grade 1 were deemed active and characterized by the absence of rim of fibrosis, grade 2 with rim of fibrosis and ongoing granulomatous inflammation and grade 3 no granulomatous inflammation and well defined rim of fibrosis. More than 90% were grade 2 and 3. Over 60% were not treated. Cases that were treated were either immunocompromised host post transplant or had positive microbiologic studies. More importantly, in either scenario, none developed progressive or disseminated Histoplasmosis.

2. Genetic variations in the human severe acute respiratory syndrome coronavirus receptor *ACE2* and serine protease *TMPRSS2.* Fujikura and Uesaka. J Clin Pathol 2021; 74:307-13
Interesting study looking at genetic variations in the human *ACE2* and *TMPRSS2*. Genetic variations were rare, specific to a population (population studied included US, UK, Japan and Africa) and considered deleterious which may explain the different population susceptibility to COVID infection.

Case Report

1. A 43-Year-Old Man With Rapidly Respiratory Failure and Spontaneous Massive Hemothorax. Nakwan et al. Chest 2021; 159:e243
Case report of intrathoracic extramedullary hematopoiesis in a patient with Beta-thalassemia, which resulted in a hemothorax. Intrathoracic EMH can result in mediastinal masses, often posterior and is associated with patient with hemoglobinopathies.

2. A 51-Year-Old Woman With Rapidly Progressive Dyspnea. Stern et al. Chest 2021l 159:e251
Case report of a patient with rapid onset of SOB found to have a large uterine and pulmonary hypertension. Cause: Pulmonary tumor thrombotic microangiopathy. Typically diagnosed at autopsy as this is a difficult diagnose to make clinically, especially when a history of malignancy is not known.

3. Eosinophilic Pleural Effusion in a Young Woman With Pleural Nodularity and Lytic Skeletal Lesions. Tendolkar et al. Chest 2021; 159:e203-8
A case of disseminated TB causing eosinophilic pleural effusion. A nice review of the differential diagnosis for EPE.

4. Women Presenting With Asthma and Persistent Wheezing- A Case Series. Benzaquen et al. Chest 2021; 159:e267-75
A small series of 3 patients with endobronchial granular cell tumor causing wheezing clinically. Nice short review of the clinical, radiologic and pathology features of common benign and malignant endobronchial tumors in a table format.

Review articles

1. Controversies and challenges in the pathologic examination of lung resection specimens after neoadjuvant treatment. Weissferdt et al. Lung Cancer 2021; 154:76-83

Excellent review of studies assessing pathologic treatment response in neoadjuvant therapy and highlighting the various issues associated with the methods – including around 1- how a specimen is grossly examined and processed 2- what constitute histologically tumor response and how to measure and score the amount of residual tumor and the appropriate thresholds 3- possible variation of tumor response depending on type of treatment, more specifically chemotherapy versus immune therapy. So there needs to be more studies that are evidence-based, with uniform approach on the processing and scoring of these type of cases.

2. The evolving landscape of biomarker testing for non-small cell lung cancer in Europe. Kerr et al. Lung Cancer 2021; 154:161-75

Interesting review highlighting differences between the USA and Europe, and then within the various regions and/or countries in Europe, the limitations and constraints due to financial resources and reimbursements. This review also provides suggestion for best practices around tissue utilization and liquid biopsy, and testing.

3. Malignant Mesothelioma: Advances in Immune Checkpoint Inhibitor and Mesothelin-Targeted Therapies. Hu et al. Cancer 2021; 127:1010-20

Excellent review of all clinical trials (national and international) in which ICI or mesothelin-targeted therapies are/were used, with details of the results. One of the many studies had enough significant results to lead to FDA approval of Nivolumab and Ipilimumab for first-line treatment in advanced MM.