Pulmonary Pathology Journal Club
(Articles from November 2022)

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6. Ivanick NM, Oakley ER, Kunadharaju R, et al. First-In-Human Computer-Optimized Endobronchial Ultrasound-Guided Interstitial Photodynamic Therapy for Patients With Extrabronchial or Endobronchial Obstructing Malignancies. JTO Clin Res Rep. 2022 Jun 26;3(10):100372.

Non-Neoplastic

1. Korevaar DA, Colella S, Fally M, et al. European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases. Eur Respir J. 2022 Nov 10;60(5):2200425.

2. Riou M, Canuet M, Ghigna MR, et al. First histological description of pulmonary and vascular abnormalities of pulmonary hypertension associated with *KDR* pathogenic variant. Eur Respir J. 2022 Nov 3;60(5):2201197.

3. Magenheim J, Rokach A, Peretz A, et al. Universal lung epithelium DNA methylation markers for detection of lung damage in liquid biopsies. Eur Respir J. 2022 Nov 3;60(5):2103056.

4. Hoang ON, Ermund A, Jaramillo AM, et al. Mucins MUC5AC and MUC5B Are Variably Packaged in the Same and in Separate Secretory Granules. Am J Respir Crit Care Med. 2022 Nov 1;206(9):1081-1095.

5. Borie R, Cardwell J, Konigsberg IR, et al. Colocalization of Gene Expression and DNA Methylation with Genetic Risk Variants Supports Functional Roles of *MUC5B* and *DSP*in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2022 Nov 15;206(10):1259-1270.

Reviews & Editorials

1. Snyder ME, McDyer JF. Alveolar macrophage subsets: Accessories to lung alloimmune rejection. J Heart Lung Transplant. 2022 Nov;41(11):1570-1571.

2. Li Z, Xu H, Fan F. Approach to Mediastinal Fine Needle Aspiration Cytology. Adv Anat Pathol. 2022 Nov 1;29(6):337-348.

3. Myers JL, Costabel U. Transbronchial cryobiopsy: the right procedure for the right patient in the right place at the right time. Eur Respir J. 2022 Nov 10;60(5):2201648.

4. Williams JF, Vivero M. Diagnostic criteria and evolving molecular characterisation of pulmonary neuroendocrine carcinomas. Histopathology. 2022 Nov;81(5):556-568.

5. Torrealba JR, Waters J, Opsahl M, De Las Casas LE. Intraoperative cytopathology of thoracic surgery (ICTS). A captivating, worthwhile, and rewarding service line. Semin Diagn Pathol. 2022 Nov;39(6):383-388.

6. Beentjes D, Shears RK, French N, et al. Mechanistic Insights into the Impact of Air Pollution on Pneumococcal Pathogenesis and Transmission. Am J Respir Crit Care Med. 2022 Nov 1;206(9):1070-1080.

7. Kesimer M. Mucins MUC5AC and MUC5B in the Airways: MUCing around Together. Am J Respir Crit Care Med. 2022 Nov 1;206(9):1055-1057.

8. Schwartz DA, Blumhagen RZ, Fingerlin TE. Evolution of the Gain-of-Function *MUC5B*Promoter Variant. Am J Respir Crit Care Med. 2022 Nov 15;206(10):1189-1191.

9. Sung S, Heymann JJ, Politis MG, et al. Small Biopsy and Cytology of Pulmonary Neuroendocrine Neoplasms: Brief Overview of Classification, Immunohistochemistry, Molecular Profiles, and World Health Organization Updates. Adv Anat Pathol. 2022 Nov 1;29(6):329-336.

ARTICLES FOR DISCUSSION

1. **Shoemark A, Griffin H, Wheway G, et al. Genome sequencing reveals underdiagnosis of primary ciliary dyskinesia in bronchiectasis. Eur Respir J. 2022 Nov 17;60(5):2200176.**

Purpose:

To identify to what extent motile ciliopathies may account for otherwise idiopathic bronchiectasis, using molecular genetic testing in three different cohorts, including patients recruited to the UK 100,000 Genomes Project, patients within a large tertiary PCD and bronchiectasis center and PCD diagnostic data from the British Thoracic Society national audit.

Methods:

- 142 people were recruited with non-CF bronchiectasis, with another 107 family members for a total cohort of 249.
- Inclusion criteria were severe disease (FEV1<30% predicated), or <50 years with multilobe involvement or *suspicion of inherited disease*.
- WGS carried out on Illumina platform, standard clinical pipelines
- Variants curated and classified according to ACMG guidelines.
- Bronchiectasis panel audits were done using a 52-gene PCD panel. PCD diagnostic evaluations in this cohort included nasal NO, high-speed video microscopy, IF, and TEM).

Results:

- 17 (12%) oof 142 individuals had pathogenic or likely pathogenic variatns in a motile ciliopathy gnee. Mean age was 45 years. M:F=6:11. 6 of these were in non-classical PCD situations with normal TEM and/or normal NO.
- 56 patients with idiopathic bronchiectasis were referred to the Brompton for diagnostic genetic testing. 4 (7%) received a definite PCD diagnosis with pathogenic/likely patghogenic variants identified in known PCD genes; 3 potential diagnoses (two with 1 P/LP variant + VUS; 1 with apparent homozygous exon duplication. Thus, a total of 12.5% of these patients had (or possibly had) underlying PCD.
- Of patients in the audit data, only 2% were tested for PCD, indicating a rather low rate of consideration of PCD.

Take home points:

- Functional testing and TEM do not capture all cases of PCD
- PCD explains a significant percentage of idiopathic bronchiectasis (likely >10%).
- PCD is insufficiently considered in cases of idiopathic bronchiectasis
- Molecular genetic testing is likely necessary in cases of unexplained bronchiectasis.

2. **Atari M, Imai K, Nanjo H, Wakamatsu Y, et al. Rapid intraoperative Ki-67 immunohistochemistry for lung cancer using non-contact alternating current electric field mixing. Lung Cancer. 2022 Nov;173:75-82.**

Purpose:

To determine the relationship between Ki-67 IHC and prognosis in patients diagnosed with R0 pStage IA NSCLC and to confirm the clinical reliability of rapid Ki-67 IIHC technique at frozen section for intraoperative evaluation of lung cancer for potential patient stratification.

Methods:

- To evaluate association between lung cancer prognosis and Ki-67, FFPE of 21 patients with NSCLC IA1-IA3 with recurrence were compared with 21 patients without recurrence
- In a second arm of study, 40 frozen section samples from consecutive resectable NSCLC had Ki-67 done on IHC and FFPE for comparison.
- NSCLC was treated with segmentectomy or lobectomy plus nodal dissection
- FS IHC involved applying an AC electric field to enhance Ag-Ab interaction (20 mins)
- ROC curves used to determine Ki-67 cutoffs

Results:

- Median follow-up was 5.66 years
- 11.3% tumor Ki-67 with FFPE or 7.5% with FS were the ROC cutoffs
- Ki-67high ≥ 11.3%; KI-67low < 11.3%
- Ki-67high, 5-year RFS 15.9% and OS 83.3%
- Ki-67low, 5-year RFS 100% and OS 100%
- FFPE and FS were not significantly different (at all disease stages)
- A cutoff of 7.5% distinguished pStage IA3 from less stages.
- Ki67>7.5% was independently predictive that segmentectomy was not feasible
-

Take home points:

- Post-operateive 5 year OS and RFS could be determined with Ki-67 cutoff of 11.3 and 7.5 (FFPE and FS, respectively)
- Rapid FS Ki-67 was significantly correlated with traditional FFPE Ki-67
- This methodology holds potential to further individualize surgery and may help with lung sparing techniques.

3. **Baxi V, Lee G, Duan C, et al. Association of artificial intelligence-powered and manual quantification of programmed death-ligand 1 (PD-L1) expression with outcomes in patients treated with nivolumab ± ipilimumab. Mod Pathol. 2022 Nov;35(11):1529-1539.**

Background: There is substantial inter-observer variability in manual PD-L1 scoring. AI-based scoring may have greater reproducibility and accuracy, but the correlation of AI-based scores with immunotherapy response is unclear, as clinical trials have relied on manual scoring.

Methods: An AI-based algorithm for tumor cell PD-L1 (28-8) scoring in NSCLC, melanoma, squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma was developed. Training samples included 217 NSCLC biopsies. To validate the algorithm, image frames from a separate 'test set' (NSCLC n=45) were manually scored by 5 pathologists, and results compared to the AI scores. PD-L1 slides from clinical trials for nivolumab and ipilimumab treatment of these malignancies (inc. 448 NSCLC from checkmate 057 and 026) were then scored using the AI algorithm and compared with the manual scores from the trials. Correlation of the AI and manual scores with treatment response was assessed.

Results:
Validation results: the AI scores were well correlated with the median manual score (0.845) and AI scores fell within the range of scores of individual pathologists.
NSCLC clinical trial data: AI scoring resulted in significant more ≥1% and ≥5% scores than manual scoring (and significantly fewer scores above those thresholds for SCCHN). Across tumor types, the AUC for overall response rate was similar regardless of whether AI or manual scores were used (0.596 vs 0.602). A ≥1% and ≥5% score on either AI or manual scoring was significantly associated with longer OS in immunotherapy treated NSCLC, but not significantly associated with PFS. A ≥1% score using manual scoring (but not when using AI scoring), was associated with a greater overall response rate (manual: 28.3% vs 10.5%; AI 21.1% vs 5.3%).

Discussion: Although AI scores showed significant differences from manual ones, the AI and manual scores tended to predict immunotherapy response similarly well, with a few exceptions. AI and manual score therefore may be able to be used interchangeably for prediction of treatment response. However, a much larger proportion of patients may have favorable scores if using AI rather than manual scoring. Future directions include customization of algorithms for different tumor types and optimization of immune cell scoring.

Comments: Are AI or manual scores closer to 'truth'? Does that matter if we're just looking for a score that we can interpret regarding treatment response? Manual PD-L1 scores are only moderately predictive and AI scores don't appear

superior – more motivation to continue exploring other/additional markers of immunotherapy response?

4. **Zhu H, Zou J, Zeng B, et al. Expression of Programmed Cell Death 1 Ligand 2 in Patients With Thymoma and Thymomatous Myasthenia Gravis. Am J Clin Pathol. 2022 Oct 7:aqac108.**

Purpose:

To examine the expression of PD-L2 in thymoma and thymomatous myasthenia gravis (MG) and characterize associations between PD-L2 expression and clinicopathologic features of patients with MG.

Methods:

- Retrospective review of records on thymoma patients at one institution, 2017-2018
  - Gender, tumor size, WHO type, Masaoka stage, presence of MG, ectopic thymus
- IHC studies using anti-PD-L2 antibodies against FFPE tissue on each tumor
  - Consensus score between 2 pathologists
  - Positive = partial or complete membranous staining in 1% or more of tumor cells
  - Intensity scores: 0 (negative), 1 (very weak), 2 (moderate), 3 (strong).
  - PD-L2 expression score [avg. over 5 HPFs]: (% positive tumor area) x (intensity score)

Results:

- Table 1: Patient Characteristics (With vs without MG)
  - Mean age 49, M:F 1:0.67, 33/70 had MG
  - Patients with MG:
    - more likely to be age 50 or younger (70% vs 35%)
    - more type B thymomas (85% vs 65%)
    - smaller tumor size (4.1 cm vs 6.5 cm)
    - more likely to be positive for PD-L2 expression (79% vs 41%)
    - higher PD-L2 expression intensity, ratio, and score.
    - No differences in Masaoka stage
- Table 2: Patient Characteristics (Positive vs Negative PD-L2 Expression)
  - 41/70 were PD-L2 Positive
  - No differences in age, gender, or Masaoka stage.
  - Patients with PD-L2 expression in thymomas:
    - More likely B2 or B3 thymomas (71% vs 29%)
    - Smaller tumor size (4.7 cm vs 6.2 cm)
    - More likely to have ectopic thymus (27% vs 7%)
    - More likely to have MG (63% to 24%)
- Table 3: Factors associated with MG, by univariate and multivariate logistic regression
  - Less likely to have MG: over age 50 or tumor size >5 cm
  - More likely to have MG: positive PD-L2

- Figure 2: Multivariate logistic regression model based on age group, tumor size group, and PD-L2 expression to predict likelihood of MG. In ROC curve analysis of this model, the AUC was 0.859.

Take home points:

- Thymoma PD-L2 expression is significantly associated with MG and type B2 and B3 thymomas, but not Masaoka stage.
- Further studies needed to assess association between PD-L2 expression and prognosis, as well as how PD-L2 may be involved in pathogenesis of MG.

ARTICLES FOR NOTATION

Neoplastic

1. **Lee GY, Chung JH, Cho S, et al. Impact of Preoperative Diagnostic Biopsy Procedure on Spread Through Airspaces and Related Outcomes in Resected Stage I Non-Small Cell Lung Cancer. Chest. 2022 Nov;162(5):1199-1212.**

   Purpose:

   To analyze the unexplored correlation between preoperative biopsy procedure and a higher risk of STAS and its impact on STAS-related outcomes in resected stage I non-small cell lung cancer (NSCLC).

   Take home points:

   - Pre-operative biopsy in stage I NSCLC was not associated with elevated STAS risk in a large cohort (2,169 patients)
   - Prognosis related to STAS was not influenced by pre-operative biopsy
   - Sub-lobar resection was a significant risk for recurrence in STAS patients

2. **Lim GHT, Balbi KJ, Poskitt B, et al. Prevalence and breakdown of non-small cell lung cancer BRAF driver mutations in a large UK cohort. Lung Cancer. 2022 Nov;173:71-74.**

   Purpose:

   To investigate the frequency of BRAF mutations, the breakdown of mutation classes and co-occurrence of other oncogenic driver mutations in a large archive of NSCLC samples.

   Take home points:

   - 3.4% of NSCLC in this cohort had BRAF mutations (40% class I, 33% class II, 28% class III)
   - KRAS and PIK3CA were most common co-occuring drivers.

3. **Nam JG, Park S, Park CM, et al. Histopathologic Basis for a Chest CT Deep Learning Survival Prediction Model in Patients with Lung Adenocarcinoma. Radiology. 2022 Nov;305(2):441-451.**

   Purpose:

   To provide histopathologic evidence underpinning the DL survival prediction model and to demonstrate the feasibility of the model in identifying patients with histopathologic risk factors through unsupervised clustering and a series of regression analyses.

Take home points:

- In a study of 1667 patients with lung adenocarcinoma, unsupervised clustering using pre-operative CT features on a deep learning prognostication model identified two clusters associated with aggressive morphology, venous invasion, pleural invasion.
- Clusters did not associated with EGFR drivers or lymph node met or lymphatic spread

4. **Heiden BT, Eaton DB Jr, Chang SH, Yan Y, Schoen MW, Patel MR, Kreisel D, Nava RG, Meyers BF, Kozower BD, Puri V. Assessment of Updated Commission on Cancer Guidelines for Intraoperative Lymph Node Sampling in Early Stage NSCLC. J Thorac Oncol. 2022 Aug 30:S1556-0864(22)01551-9.**

Purpose:

To evaluate the American College of Surgeons Commission on Cancers updates on nodal sampling recommendations for early stage NSCLC

Take home points:

- The results appear to support station-based sampling minimums (!three N2 and one N1 nodal stations) for early stage NSCLC; however, the marginal benefit compared with count-based guidelines is minimal.
- Further efforts to promote widespread adherence to intraoperative lymph node sampling minimums are critical for improving patient outcomes after curative-intent lung cancer resection.

5. **Higashiyama M, Kobayashi Y, Kashima J, et al. Invasive Mucinous Adenocarcinoma of the Lung With a Mural Nodule-like Lesion. Am J Surg Pathol. 2022 Nov 1;46(11):1524-1532.**

Purpose:

To investigate whether mural nodule lesions develop in IMA of the lung and to examine the prognostic impact of these lesions

Take home points:

- Molecular analysis of the components of differentiated IMAs and mural nodule–like lesions revealed a clonal relationship, suggesting a spectrum of tumors with different histology
- Clinicopathologically, an older age, male sex, and smokers were significantly associated with IMAs with mural nodule–like lesions
- Outcomes were unaffected by the presence or absence of these lesions
- Despite a histological impression of clinical aggressiveness, there was no clear trend in patient outcomes

6. **Ivanick NM, Oakley ER, Kunadharaju R, et al. First-In-Human Computer-Optimized Endobronchial Ultrasound-Guided Interstitial Photodynamic Therapy for Patients With Extrabronchial or Endobronchial Obstructing Malignancies. JTO Clin Res Rep. 2022 Jun 26;3(10):100372.**

   Purpose:
   To reveal that a computer-optimized interstitial photodynamic therapy (I-PDT) is safe and potentially effective in the treatment of patients with inoperable extra or endobronchial malignancies inducing central airway obstructions.

   Take home points:
   - Image-guided light dosimetry for I-PDT with linear endobronchial ultrasound transbronchial needle is safe and potentially beneficial in increasing overall survival of patients
   - I-PDT has a positive effect on the immune response including an increase in the proportion of programmed death-ligand 1–expressing monocytic myeloid- derived suppressor cells

Non-neoplastic

1. **Korevaar DA, Colella S, Fally M, et al. European Respiratory Society guidelines on transbronchial lung cryobiopsy in the diagnosis of interstitial lung diseases. Eur Respir J. 2022 Nov 10;60(5):2200425.**

   Purpose:
   To provide evidence-based clinical practice recommendations for the role of transbronchial lung cryobiopsy (TBLC) in obtaining tissue-based diagnosis in patients with undiagnosed ILD.

   Take home points:
   - TBLC provides important clues to ILD
   - Diagnostic yield is lower than with wedge biopsy, but adverse events and length of hospitalization are reduced
   - TBLC is recommended when patient is ineligible for surgical biopsy
   - Certainty of evidence is “very low.”

2. **Riou M, Canuet M, Ghigna MR, et al. First histological description of pulmonary and vascular abnormalities of pulmonary hypertension associated with *KDR* pathogenic variant. Eur Respir J. 2022 Nov 3;60(5):2201197.**

Purpose:
To provide the first histological description of pulmonary and vascular abnormalities of pulmonary hypertension associated with *KDR* pathogenic variant.

Take home points:
- Significant extravascular parenchymal changes were identified with this genetic form (including emphysema and parenchymal scarring)
- The findings were more aking to hypertension associated with ILD rather than primary pulmonary hypertension

3. **Magenheim J, Rokach A, Peretz A, et al. Universal lung epithelium DNA methylation markers for detection of lung damage in liquid biopsies. Eur Respir J. 2022 Nov 3;60(5):2103056.**

Purpose:
To report an analysis of lung epithelial cell methylomes, and characterization of a universal lung marker panel.

Take home points:
- Universal cfDNA methylation markers of normal lung epithelium allow for mutation-independent, sensitive and specific detection of lung-derived cfDNA, reporting on ongoing lung injury.
- Such markers can find broad utility in the study of normal and pathologic human lung dynamics.

4. **Hoang ON, Ermund A, Jaramillo AM, et al. Mucins MUC5AC and MUC5B Are Variably Packaged in the Same and in Separate Secretory Granules. Am J Respir Crit Care Med. 2022 Nov 1;206(9):1081-1095.**

Purpose:
To determine the packaging of MUC5AC and MUC5B within individual secretory granules in mouse and human airways under varying conditions of inflammation and along the proximal–distal axis.

Take home points:
- MUC5AC and MUC5B are variably stored both in the same and in separate secretory granules of both mice and humans
- The high fraction of granules containing both mucins under a variety of conditions makes it unlikely that their secretion can be differentially controlled as a therapeutic strategy.

5. **Borie R, Cardwell J, Konigsberg IR, et al. Colocalization of Gene Expression and DNA Methylation with Genetic Risk Variants Supports Functional Roles of *MUC5B* and *DSP*in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2022 Nov 15;206(10):1259-1270.**

   Purpose:
   To determine functional relevance of the 10 IPF- associated common genetic variants we previously identified.

   Take home points:
   - There is a relationship of the common IPF genetic risk variants rs35705950 and rs2076295 with respective changes in MUC5B and DSP expression and methylation.
   - These results provide additional evidence that both MUC5B and DSP are involved in the etiology of IPF.

REVIEWS

1. **Snyder ME, McDyer JF. Alveolar macrophage subsets: Accessories to lung alloimmune rejection. J Heart Lung Transplant. 2022 Nov;41(11):1570-1571.**

   Summary:
   This is a pretty nice review outlines the cumulated evidence that T-cells aren't the only player when it comes to allograft rejection and that myeloid cells (macrophages, in particular) likely also play a role.

2. **Li Z, Xu H, Fan F. Approach to Mediastinal Fine Needle Aspiration Cytology. Adv Anat Pathol. 2022 Nov 1;29(6):337-348.**

   Summary:
   This review proposes a practical approach to interpret mediastinal fine needle aspirations and emphasizes potential diagnostic pitfalls for mediastinal lesions including benign cysts, thymic neoplasms, lymphoproliferative disorders, germ cell tumors, mesenchymal tumors, and metastatic tumors.

3. **Myers JL, Costabel U. Transbronchial cryobiopsy: the right procedure for the right patient in the right place at the right time. Eur Respir J. 2022 Nov 10;60(5):2201648.**

Summary:
Nice commentary on the use of TBLC recommendations that are provided by Korevaar and colleagues by one of our own, Dr. Myers!

4. **Williams JF, Vivero M. Diagnostic criteria and evolving molecular characterisation of pulmonary neuroendocrine carcinomas. Histopathology. 2022 Nov;81(5):556-568.**

   Summary:
   This review summarizes the current diagnostic criteria, prognostic and predictive correlates of classification, and evidence of previously unrecognized subtypes of small cell and large cell neuroendocrine carcinoma.

5. **Torrealba JR, Waters J, Opsahl M, De Las Casas LE. Intraoperative cytopathology of thoracic surgery (ICTS). A captivating, worthwhile, and rewarding service line. Semin Diagn Pathol. 2022 Nov;39(6):383-388.**

   Summary:
   Citing the increasing use and advantages (TAT, cost, on-site visualization etc.) of cytopathology, this review set out to present their experience with the technique and provided perspective about using cytopathology for surgeons.

6. **Beentjes D, Shears RK, French N, et al. Mechanistic Insights into the Impact of Air Pollution on Pneumococcal Pathogenesis and Transmission. Am J Respir Crit Care Med. 2022 Nov 1;206(9):1070-1080.**

   Summary:
   This review provides an in-depth understanding of the interaction between air pollution and the pneumococcus, which has the potential to aid the development of novel treatments or alternative strategies to prevent disease, especially in areas with high concentrations of air pollution.

7. **Kesimer M. Mucins MUC5AC and MUC5B in the Airways: MUCing around Together. Am J Respir Crit Care Med. 2022 Nov 1;206(9):1055-1057.**

   Summary:
   Editorial summary on the roles of MUC5AC and MUC5B, secretory airway mucins, in the progression of COPD. Basically, they note that while initially promising, targeting these two MUCs therapeutically as a mechanistic means to slow progression has not been as successful as hoped and that the pathobiology is far more complicated than initially thought.

8. **Schwartz DA, Blumhagen RZ, Fingerlin TE. Evolution of the Gain-of-Function *MUC5B* Promoter Variant. Am J Respir Crit Care Med. 2022 Nov 15;206(10):1189-1191.**

   Summary:
   The role of the MUC5B promoter variant is summarized in this review – both in terms of its beneficial and detrimental effects. It's role inSARS-CoV-2 and lung fibrosis is discussed.

9. **Sung S, Heymann JJ, Politis MG, et al. Small Biopsy and Cytology of Pulmonary Neuroendocrine Neoplasms: Brief Overview of Classification, Immunohistochemistry, Molecular Profiles, and World Health Organization Updates. Adv Anat Pathol. 2022 Nov 1;29(6):329-336.**

   Summary:
   This review provides a brief overview of the cytomorphologic features and the 2021 World Health Organization classification of these tumor types on small biopsy and cytology specimens. Also discussed are the role of immunohistochemistry in the diagnosis and molecular signatures of pulmonary neuroendocrine tumors.