June 2020 Pulmonary Pathology Journal Club
(Articles from May 2020)
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ARTICLE INDEX

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Thunnissen E, Kerr KM, Dafni U, et al. Programmed death-ligand 1 expression influenced by tissue sample size. Scoring based on tissue microarrays' and cross-validation with resections, in patients with, stage I-III, non-small cell lung carcinoma of the European Thoracic Oncology Platform Lungscape cohort. *Mod Pathol*. 2020;33(5):792-801.

Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol*. 2020;15(5):700-704.

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Welch CL, Chung WK. Genetics and Other Omics in Pediatric Pulmonary Arterial Hypertension. *Chest*. 2020;157(5):1287-1295.

ARTICLES FOR DISCUSSION

1. **Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thorac Oncol*. 2020;15(5):700-704.**

   Purpose:
   - To offer one of the first pathologic descriptions of the Coronavirus (COVID-19)-associated Pneumonia.
   - To clarify that the findings may be found serendipitously in specimens taken for other reasons.

   Methods:
   - This is a rather simple and straight-forward report of two cases out of Wuhan.
   - Originally published, with substantial fanfare, in February of 2020, shortly after the onset of the pandemic in the Wuhan Province.

   Results:
   - Case 1 was an 84 F, admitted for treatment and evaluation of a 1.5 cm lung mass found on chest CT. Some bilateral GGO were noted during her first week of admission (significance unknown). No fever or respiratory symptoms. Underwent lobectomy on day 12. On day 16, developed dyspnea and dry cough – s/o viral pneumonia. Despite aggressive therapy, she died on day 29.She was exposed to another patient in the same room during her stay with 2019-nCoV.
   - Case 2 was a 73 M who undersent lobectomy and on post-op day 2 had some GGOs. Fever on post-op day 9 with cough. Readmitted, recovered, discharged 20 days later.
   - Pathology of lobectomy specimens showed adenocarcinomas. Away from the tumors revealed alveolar edema and proteinaceous exudates with prominent spherical secretions. Intra-alveolar fibrin and giant cells were seen, with pneumocyte hyperplasia (?viral inclusions). No PMNs.

   Take home points:
   - This is the first formal report of the pathology of SARS-CoV-2 pneumonia.
   - Pathologic findings include proteinaceous exudates, vascular congestion, inflammatory clusters with intra-alveolar fibrin and multinucleated giant cells. ALI was seen (type 2 pneumocyte hyperplasia and OP). Hyaline membranes not prominent in these two examples (both believed to be of very early “asymptomatic” disease).

2. **Kneuertz PJ, Carbone DP, D'Souza DM, et al. Prognostic value and therapeutic implications of expanded molecular testing for resected early stage lung adenocarcinoma. *Lung Cancer*. 2020;143:60-66.**

Purpose:

- To evaluate the evolution of molecular testing, with regards to detection rates and the expanding prognostic and potential therapeutic implications.
- To assess the additive value of expanded molecular testing in identifying treatment targets and distinguishing independent primaries of resected lung ACA.
- To determine the association of detected mutations with disease recurrence and survival.

Methods:

- Retrospective analysis of patients undergoing lobectomy and mediastinal lymphadenectomy (curative intent) for stage I and II lung adenocarcinoma (2011-2017).
- Uniform treatment.
- Reflex molecular testing
    - Pre-2013 (1/3 of cohort): ALK FISH, Sanger KRAS exon 2, EGFR 19 indels and L858R, EGFR T790M
    - 2013-2015: FISH for MET amp, ROS1 rearrangement and hotspot for ALK, BRAF, KRAS, EGFR, ERBB2, MAK2K1, MET, NRAS, PIK3CA, STK11 and TP53 (full seq) [20-gene panel, essentially]
    - 2015-2017: expansion to 50 gene panel.
- Patients followed with surveillance visits every 3-6 mos for 3 years, then annually.
- DFS and OS were calculated.

Results:

- 324 patients (mean age 64.8 years), mostly white women.
- Most were current/former smokers.
- 2/3 of patients had stage I or stage II disease
- KRAS exon 2 (codon 12/13) most frequent, present in 38%. EGFR in 18% (mostly exon 19 indels or L858R mutations).
- Total mutations increased across the years:
    - Pre-2013: Total 49%; Theranostic: 18%
    - 2013-2015: Total 86%; Theranostic: 32%
    - 2015-2017: Total 91%; Theranostic 45%
- KRAS and BRAF mutations both showed worse DFS and OS
- Prognostic improvement could not be appropriately evaluated for in the cohort which had enhanced detection of driver mutation because it was done relatively late in the analysis.

Take home points:

- Expanded panels have greatly improved our ability to detection a mutation (or multiple mutations).
- It’s clear that driver mutations are being picked up more, but the prognostic impact of this has yet to be fully quantified in a large cohort.

3. **Thunnissen E, Kerr KM, Dafni U, et al. Programmed death-ligand 1 expression influenced by tissue sample size. Scoring based on tissue microarrays' and cross-validation with resections, in patients with, stage I-III, non-small cell lung carcinoma of the European Thoracic Oncology Platform Lungscape cohort. *Mod Pathol*. 2020;33(5):792-801.**

Purpose:
To demonstrate the effect of harmonization of PD-L1 scoring on tissue microarrays by an external quality assessment program
To examine the heterogeneity by comparing extent of staining across different microarray cores as mimickers of biopsy

Methods:
- Retrospective analysis of stage I-III NSCLC
- 15 European Thoracic Oncology Platform centers provided data, 14 participated in the external QA program
- All 14 pathologists had a 2-day live training session for scoring with demonstrated ≥90% concordances between the DAKO trainer and the pathologist (cell lines and resection specimens used as testing set with varying PD-L1 expression levels.
- 3-months after initial training, study sets were read and scored.
- Scoring included % of tumor cell membrane staining and overall score (<1%, 1-5%, 5-10%, 10-25%, 25-50%, and ≥50%). Three different expression cutoffs used: 1, 50, and 25% (first 2 were primary interest)
- Cross-validation between cores and whole sections was performed in 10%.

Results:
- 2402 cases form 15 centers (2182 had PD-L1): 174 were “Not evaluable” and excluded: 2008 in final cohort-1. 237 whole sections available in 237 cases for cohort-2.
- First-round concordance on QA tool was 73%; Second-round (3 more months later) was 81%.
- Concordant cases at 1, 25, and 50% were: 85, 91, and 93%. Tissue microarray core results were identical for 70% of cases.
- Sensitivity of the tissue microarray method for 1, 25, and 50% was: 80, 78, and 79% (specificity: 90, 95, 98%).
- When comparing the microarray and whole sections, completely agreement was seen in 60%
- Higher sensitivity rates for 1% and 50% were detected when core # was higher

Take home points:

- Underestimation of PD-L1 expression is more common on small samples than overestimation
- Classification of PD-L1 on small biopsy samples does not represent the overall expression of PD-L1 in all non-small cell cancer carcinoma cases, although the majority of cases are ‘correctly’ classified
- Sampling more and larger biopsies, recording the biopsy size and tumor load may permit further refinement, increasing predictive accuracy.

4. **Thoré P, Girerd B, Jaïs X, et al. Phenotype and outcome of pulmonary arterial hypertension patients carrying a *TBX4* mutation. *Eur Respir J*. 2020;55(5):1902340. Published 2020 May 14.**

Purpose

To describe the clinical, functional, radiologic, histologic and hemodynamic characteristics, as well as long-term outcomes of PAH patients carrying a *TBX4* mutation.

Methods

- A retrospective population-based query of the French pulmonary hypertension (PH) network was performed to identify PAH patients carrying a *TBX4* mutation
- PAH predisposing genes were screened by NGS, including *BMPR2, TBX4, EIF2AK4, CAV1, KCNK3, SMAD9, ACVRL1, ENG, and BMP9.*
- Clinical, functional, hemodynamic and radiologic characteristics were reviewed.

Results

- 448 patients were included in the index and subsequently screened for PAH predisposing genes.
- 20 PAH patients in 17 unrelated families carrying heterozygous mutations in *TBX4* were identified, equating to 6% of childhood PAH and 3% of adult PAH.
- 11 known mutations, 2 CNVs and 1 promoter VUS.
- F:M = 3:1 (all the childhood cases were girls)
- All had pre-capillary PH with mean PAP of 60 mm Hg
- 60% had airway anomalies (bronchial thickening, diverticula, mucoid impaction, and cylindrical bronchiectasis. Peribronchial cysts were observed in 27%.
- Plexiform lesions in 66%, peripheral fibrosis, lymphoid nodules, and peribronchial inflammation (small airways disease).
- 80% had skeletal anomalies (peculiar and unique): foot abnormalities characterized by large gap between the first and second tones and low arch (flat feet)
- PDE and Ca blockade had some symptomatic improvement, but not hemodynamic.

Take home points:

- PAH due to TBX4 mutations is an AD condition (with incomplete penetrance) and may occur with or without skeletal abnormalities across a broad age range from birth to late adulthood.
- PAH is usually severe and associated with bronchial and parenchymal abnormalities.

ARTICLES FOR NOTATION

Neoplastic

1. **Dagogo-Jack I, Schrock AB, Kem M, et al. Clinicopathologic Characteristics of BRG1-Deficient NSCLC. *J Thorac Oncol*. 2020;15(5):766-776.**

   Purpose:
   To assess the clinical features of patients with tumors harboring BRG1-inactivating mutations

   Take home points:
   - BRG1 deficiency is enriched in NSCLCs with truncating SMARCA4 mutations.
   - Clinical outcomes are poor in this molecular subgroup, highlighting the importance of developing novel strategies to target unique vulnerabilities associated with the BRG1-deficient state.

2. **Satoh Y, Matsuo Y, Kuba T, et al. EGFR mutation genotyping and ALK status determination in liquid-based cytology samples of non-small cell lung cancer. *Virchows Arch*. 2020;476(5):753-762.**

   Purpose:
   To assess the concordance between epidermal growth factor receptor (EGFR) gene mutation detection and echinoderm microtubule-associated protein-like (EML) 4-anaplastic lymphoma kinase protein (ALK) expression using liquid-based cytology (LBC) samples and matched histology samples of PLC patients

   Take home points:
   - The overall concordance rate of EGFR gene mutation status, including minor mutations and ALK status according to immunostains between histologic and paired LBC specimens, was 100% (105/105) and 100% (48/48), respectively.
   - Genotyping and protein expression studies can be reliably performed using LBC samples prepared with CytoRich Red.
   - Analysis of such samples may guide individual therapy in PLC patients.

3. **Paajanen J, Laaksonen S, Kettunen E, et al. Histopathological features of epithelioid malignant pleural mesotheliomas in patients with extended survival. *Hum Pathol*. 2020;98:110-119.**

Purpose:
To study prognostic histopathologic factors associated with extended survival in epithelioid DMM.

Take home points:

- The following three novel morphological features were identified to be associated with survival: exophytic polypoid growth pattern, tumor density, and single mesothelium layered tubular structures.
- After adjustments, low nuclear grade (P < 0.001) and presence of exophytic polypoid growth (P Z 0.024) were associated with prolonged survival.
- These results may aid in estimating DMM prognosis.

4. **Koh MJ, Shin DH, Lee SJ, et al. Gastric-type gene expression and phenotype in non-terminal respiratory unit type adenocarcinoma of the lung with invasive mucinous adenocarcinoma morphology. *Histopathology*. 2020;76(6):898-905.**

Purpose:
To determine if non-terminal respiratory unit (TRU) type adenocarcinoma of lung with invasive mucinous adenocarcinoma (IMA) morphology shows gastric differentiation.

Take home points:

- The level of genes expressed in stomach mucosa was increased in IMA compared to TRU type adenocarcinoma, supporting gastric differentiation of IMA.
- This finding may help the understanding of the pathogenesis of IMA and discovery of therapeutic targets.

5. **Jamme P, Fernandes M, Copin MC, et al. Alterations in the PI3K Pathway Drive Resistance to MET Inhibitors in NSCLC Harboring MET Exon 14 Skipping Mutations. *J Thorac Oncol*. 2020;15(5):741-751.**

Purpose:
To determine whether in METex14 NSCLC, PI3K pathway alterations might contribute to primary resistance to MET TKIs.

Take home points:

- Treatment combining a MET TKI with a PI3K inhibitor caused inhibition of both PI3K and MAPK signaling and restored sensitivity to MET TKIs.
- PI3K pathway alterations are common in METex14 NSCLC and may confer primary resistance to MET TKIs.

- In preclinical models, PI3K inhibition restores sensitivity to MET TKIs.

6. **Naso J, Bras J, Villamil C, et al. Cytologic features and diagnostic value of PeriView FLEX transbronchial needle aspiration targeting pulmonary nodules. *Cancer Cytopathol*. 2020;128(5):333-340.**

   Purpose:
   To evaluate and report the unique cytologic features, diagnostic value, and potential pitfalls of PeriView FLEX TBNA specimens.

   Take home points:
   - TBNA using the PeriView FLEX device to sample pulmonary nodules contributed to the diagnostic value of bronchoscopy and tended to provide sufficient tissue for ancillary studies.
   - Many of the possible pitfalls may be avoided through consideration of the unique cytologic features associated with this novel sampling method.

7. **Trejo Bittar HE, Jerome JA, Hartman D, Pantanowitz L, Mehrad M, Dacic S. Prognostic significance of microscopic size in peripherally located scar-associated clinical stage I lung carcinomas. *Lung Cancer*. 2020;143:12-18.**

   Purpose:
   To investigate if subtraction of the size of the central scar from the total gross size of surgically resected peripheral clinical stage I non-small cell lung carcinoma improves patient stratification into more accurate prognostic groups.

   Take home point:
   Our study suggests that microscopic size of the invasive component in acinar and papillary predominant adenocarcinoma with scar might be a better predictor of survival than the total gross size.

8. **Vaghjiani RG, Takahashi Y, Eguchi T, et al. Tumor Spread Through Air Spaces Is a Predictor of Occult Lymph Node Metastasis in Clinical Stage IA Lung Adenocarcinoma. *J Thorac Oncol*. 2020;15(5):792-802.**

   Purpose:
   To investigate the association between occult LN metastasis (ONM) and STAS and to assess their prognostic value in patients with clinical stage IA lung ADC.

Take home point:
Presence of STAS predicts ONM in patients with clinical stage IA lung ADC and can help stratify risk of recurrence by extent and type of resection.

Non-neoplastic

1. **Hanley B, Lucas SB, Youd E, Swift B, Osborn M. Autopsy in suspected COVID-19 cases. *J Clin Pathol*. 2020;73(5):239-242.**

   Purpose:
   To summarize and interpret the guidelines of the Royal College of Physicians missive on performing autopsies in individuals with COVID-19.

   Take home points:
   - Autopsy of COVID-19 patients is safe, provided proper precautions and measures are taken.
   - If COVID-19 is deemed the primary cause of death, it should be dnoted such on the last line of part 1 in the death certificaiton.
   - Universal Precautions should be used with approaching COVID-19 cases.

2. **Morrow JD, Make B, Regan E, et al. DNA Methylation Is Predictive of Mortality in Current and Former Smokers. *Am J Respir Crit Care Med*. 2020;201(9):1099-1109.**

   Purpose:
   To identify DNA methylation marks in blood that are predictive of mortality in a subset of the COPDGene (Genetic Epidemiology of COPD) study, representing 101 deaths among 667 current and former smokers.

   Take home point:
   This study is the first to identify variable DNA methylation associated with all-cause mortality in smokers with and without COPD. Evaluating predictive epigenomic marks of smokers in peripheral blood may allow for targeted risk stratification and aid in delivery of future tailored therapeutic interventions.

3. **Sattler EC, Syunyaeva Z, Mansmann U, Steinlein OK. Genetic Risk Factors for Spontaneous Pneumothorax in Birt-Hogg-Dubé Syndrome. *Chest*. 2020;157(5):1199-1206.**

   Purpose:
   To study nonenvironmental risk factors for pneumothorax in a large sample of patients with BHDS.

Take home point:
There are differences for the spontaneous pneumothorax risk regarding both age and sex in patients with BHDS. Two *FLCN* mutations were identified that are associated with significantly increased pneumothorax risk. This improves risk stratification for patients with BHDS.

4. **Iwen PC, Smith PW, Hewlett AL, et al. Safety considerations in the laboratory testing of specimens suspected or known to contain Ebola virus. *Am J Clin Pathol*. 2015;143(1):4-5.**

   Purpose:
   To compare and contrast the COVID-19 pandemic with those pandemics we have encountered in the past.

   Take home point:
   The balance of safety and providing a quality result is a delicate process and requires administration support and leadership. The important message is that not all laboratories are alike, and through a risk assessment, managers can put into place a process necessary to be able to provide a safe environment for the staff.
   .
5. **Hume PS, Gibbings SL, Jakubzick CV, et al. Localization of Macrophages in the Human Lung via Design-based Stereology. *Am J Respir Crit Care Med*. 2020;201(10):1209-1217.**

   Purpose:
   To determine the precise number and anatomic location of human pulmonary macrophages in non-diseased lungs and to quantify how this is altered in chronic cigarette smokers.

   Take home point:
   The precise locations occupied by pulmonary macrophages were defined in non-diseased human lungs from smokers and nonsmokers. IM density was greatest in the alveolar septa. Lungs from chronic smokers had increased IM numbers and overall density, supporting a role for IMs in smoking-related disease.

Reviews

1. Welch CL, Chung WK. Genetics and Other Omics in Pediatric Pulmonary Arterial Hypertension. *Chest*. 2020;157(5):1287-1295.

2. Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. *J Thorac Oncol*. 2020;15(5):709-740.

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Case Reports / Letters to the Editor / Editorials

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