

## Pulmonary Pathology Journal Club (Articles from March 2022)

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By

Julian Villalba Nunez, MD (pulmonary pathology fellow)  
(Joanne) Eunhee S. Yi, MD  
Mayo Clinic, Rochester, MN

### ***Articles for Discussion***

**Offin M, et al. Molecular characterization of peritoneal mesotheliomas. J Thorac Oncol 2022;17:455-60**

**Background:** Peritoneal mesothelioma (PeM) is an understudied malignancy with poor outcomes that is clinicopathologically distinct from pleural mesotheliomas (PM). There is a paucity of data on the genomic landscape of PeM using large scale multigene panels. Most clinical trials have excluded nonpleural disease.

#### **Methods:**

- Next-generation sequencing (NGS) was performed on PeM cases
- Genomic near-haploidization (GNH) was assessed [defined by > 80% genome-wide loss of heterozygosity]
- Positive specimens underwent further targeted analysis for alterations in SETDB1 as GNH is associated with inactivating alterations in SETDB1 (a gene involved in histone methylation and gene silencing)
- Immuno-histochemistry (IHC) for WT1, BAP1, mesothelin, VISTA, and programmed death-ligand 1 was evaluated when tissue was available
- Overall survival was stratified by selected genomic and IHC features.

#### **Results:**

- 50 patients with PeM (45 epithelioid, 5 nonepithelioid)
- Most common alterations were: BAP1 (60%), NF2 (24%) SETD2 (22%), and TP53 (16%); which is similar to the publicly available PM data set (Cancer Discov. 2018;8:1548-1565.), other than a reduction in CDKN2A/B alterations in this cohort ( $p < 0.0001$ )
- IHC positivity rates: WT1=96% (46/48), mesothelin=93% (37/40), VISTA=89% (34/38), PD-L1=50% (19/38)
- BAP1 IHC loss was seen in 76% (29/38) of specimens, including 96% (22/23) of specimens with BAP1 alterations on NGS, and 36 % (5/14) wild-type on NGS (four of those had equivocal BAP1 deletions below established thresholds for calling copy number changes—likely compounded by low tumor purity)
- BAP1 alterations (mutation or deletion on NGS or loss on IHC; n=37) portended a significantly shorter OS compared with BAP1 wild-type and retained (n=13; 43.8 versus 117.3 months,  $p=0.04$ )
- Patients with epithelioid PeM (n=45; median=58.0 mo), with wild-type CDKN2A/B (n=46), and with epithelioid PeM + with BAP1 wild-type and retained, had numerically longer OS, albeit not significant.

- 76% (38 of 50) of specimens were assessable for allele-specific copy number analysis; 8% (3 of 38) had genomic near-haploidization, and all harbored NF2 mutations with wild-type BAP1. Two of three cases also possessed TP53 and SETDB1 mutations. Three of 30 patients (10%) had a pathogenic germline variant: POT1 I78T, MUTYH R109Y, and BAP1 E402\*.

**Conclusion:**

- CDKN2A/B alterations were rare in PeM, whereas BAP1, NF2, TP53, SETD2, and LATS2 were common
- Genomic near-haploidization and germline events (similar rate to PM) are rare in PeM. BAP1 NGS/IHC discordance may be higher than PM.

**Take home message/Comments:** Small sample, difficult for evaluation of OS in patients with alterations other than BAP1 (e.g. CDKN2A/B). Conflicting results of OS with french cohort evaluating BAP1 loss, in which BAP1 wild-type had worse OS. French group used Cox proportional Hazard regression and MSKCC only Kaplan-Meier. Limited number of nonepithelioid cases.

**Leisman DE, et al. Alveolar, endothelial, and organ injury marker dynamics in severe COVID-19. Am J Respir Crit Care Med 2022;205:507-519**

**Background:** Alveolar and endothelial injury may be differentially associated with COVID-19 severity over time. In patients with a direct insult etiology (e.g., pneumonia, aspiration), ARDS is associated with higher plasma levels of pulmonary epithelial injury markers, whereas with indirect insults (e.g., sepsis, trauma, etc.), ARDS displays higher endothelial injury markers.

**Methods:**

- To investigate the evolution of COVID-19, cell-type-specific markers pulmonary epithelial, endothelial, and organ injury blood proteomic markers (Olink proximity extension assay) were serially measured in an observational cohort of prospectively enrolled patients with COVID-19 presenting to the MGH ED with respiratory distress and requiring respiratory support (supplemental oxygen / invasive mechanical ventilation)
- Timeline, blood samples: Day 0, 3, 7. Clinical follow up: 28 days or until discharge
- Different models using different clinical groups (deceased, invasively ventilated, requiring supplemental oxygen, or without respiratory support)
- Sensitivity analysis and multiple covariates.

**Results:**

- Of 225 patients, 151 (67%) subjects received supplemental oxygen only, 74 (33%) received invasive ventilation at Day 0
- By Day 28, 37 (16%) patients had died, 37 (16%) continued receiving invasive ventilation, and 148 (68%) had been discharged
- Severe hypoxemia was most prevalent on Day 0, whereas severe abnormalities of renal, coagulation, and circulatory function became more prevalent over time
- Day 0 alveolar injury markers (Surfactant protein A1, A2, and RAGE) were generally higher in patients requiring invasive ventilation than those requiring only supplemental

oxygen; although remaining higher among invasively ventilated patients, these markers decreased over time in both groups

- Changes in alveolar markers did not correlate with changes in endothelial, cardiac, or renal injury markers; at Day 0, endothelial injury markers were comparable for all respiratory support levels, but then significantly increased over time only among intubated patients. Angiotensin-2 was similar to nonintubated patients at Day 0 but 1.80-fold higher (95% CI, 1.56–2.06) at Day 3
- There were few exceptions that were always higher in intubated patients (tPA, PAI-1, tissue factor, and protein C). ADAMTS13 had an inverse pattern. Among intubated patients, higher endothelial injury marker levels were not reliably associated with higher ventilatory ratios. Club cell proteins followed the pattern of endothelial rather than alveolar markers
- In multivariable regression, in invasively ventilated subjects, Day 0 alveolar injury markers were consistently higher in patients with COVID-19 than control subjects without COVID, while most endothelial injury markers were not
- Markers of RAS activation, cardiac injury, and kidney injury showed dynamics similar to the endothelial pattern, with similarities between intubated and nonintubated patients at Day 0; yet at Days 3 and 7, significant and progressively higher levels in intubated versus nonintubated patients
- Changes in cardiorenovascular injury markers were closely correlated with changes in endothelial, RAS activation, and club cell markers but not alveolar markers
- Changes in soluble tumor necrosis factor receptor 1 and D-dimer levels mirrored the endothelial pattern

**Conclusion:** Alveolar and endothelial injury contribute at different times to disease progression in severe COVID-19; alveolar injury markers peak early in severe COVID-19 and decrease among both spontaneously breathing and invasively ventilated patients, while endothelial injury markers increase with delayed kinetics and associated with systemic inflammation, renin angiotensin system activation, extrapulmonary organ injury, and 28-day outcome.

**Comments:**

- This is a secondary analysis of a cohort recruited for another study.
- IRB waived informed consent and there are limitations on the type of data that can be accessed from the subjects; for example, ventilatory mechanical force parameters were not available. Therefore, the effect of Ventilator-induced lung injury (VILI) cannot be assessed

**Ikegami N, et al. Clinical, radiological and pathological features of idiopathic secondary interstitial pneumonia with pleuroparenchymal fibroelastosis in patients undergoing lung transplantation. *Histopathology* 2022;80:665-76**

**Background:**

- Idiopathic pleuroparenchymal fibroelastosis (IPPFE) has been included as a rare type of IIP since 2013 ATS ERS statement of IIP classification

- Radiologic PPFE-like lesions are seen in >10% of fibrotic ILD patients, pathological confirmation is not feasible in most cases because not all of these patients undergo surgical lung bx (SLB) given the high risks associated with SLB
- The objective of this study was to evaluate the pathologic findings associated with radiological PPFE-like lesions and their clinical and morphological features according to idiopathic vs. secondary PPFE on histopathologic exam of consecutive lung tpx recipients

### Methods:

- Cohort selection (Fig 1): among all lung transplant recipients 7/2009 – 3/2018 (n=178), fibrotic ILD or post-human stem cell transplantation (HSCT)/chemotherapy (CT) late-onset non-infectious pulmonary complications (LONIPCs) (n=107) were examined for radiological PPFE. 59 patients with radiologic PPFE like changes were found for this study and divided into with pathological PPFE (n=26; 14 idiopathic, 12 secondary) and without pathological PPFE (n=33).
- Radiological evaluation: HRCT taken the day before lung tpx and reviewed by two radiologists blinded to clinical information. Interobserver disagreement was resolved by consensus
- Pathological evaluation: 2 or more sections from each lobe of explanted lungs of patients with radiological PPFE pattern. Each slide was stained with HE, EVG, or elastic-masson, and scanned. All digital slides were reviewed by 3 observers and interobserver disagreement was resolved by consensus.
- Intraalveolar fibrosis (IAF) (prominent or not) and elastic fiber deposition (no, mild, moderate or severe elastosis) were evaluated semiquantitatively
- Intraalveolar fibroelastosis (IAFE): defined as both prominent IAF and moderate or severe elastosis
- Idiopathic PPFE is characterized by bilateral subpleural airspace consolidations in the upper lobe radiologically and IAFE pathologically
- Evaluation of other findings: lobar pathological pattern, presence and distribution of elastosis and pure collagenous fibrosis without elastosis, fibrotic changes, cellular infiltrates, vascular changes, OP, CBO, granuloma, emphysema.
- Clinical variables: demographics, BMI at the time of lung tpx, smoking hx, previous therapeutic hx, tpx procedure type, some laboratory and clinical fx such as PFT, 6 min walk, etc
- Statistical analysis: Wilcoxon test and Fisher's exact test for group comparisons. Kaplan-Meier curves and the log-rank test

### Results:

- Patient characteristics: Table 1
- Radiological PPFE-like lesions (n=59) with pathological PPFE: 14 of 35 IIP, 12 of 24 secondary lung dx patients
- Features of patients with pathological PPFE: Table 2; BMI lower (p=0.058), PaCO<sub>2</sub> higher (p=0.046), lower AP diameter of the thorax/transverse diameter % (p=0.007)
- Clinical, radiological and pathological comparison of patients with idiopathic and secondary disease with pathological PPFE:

- Idiopathic and secondary cases with pathological PPFE are similar except for more fibroblastic foci in idiopathic cases and more alveolar septal thickening (with elastosis or fibrosis) in secondary cases
- Post lung transplantation survival: similar in the two groups

#### **Conclusion/Comments:**

- Not all interstitial pneumonia patients with radiological PPFE-like lesions have pathological PPFE (i.e. radiology cannot be an alternative to the pathological dx of PPFE)
  - Radiological PPFE without pathological PPFE seems to be due to pure collagen fibrosis (without elastosis) (supplemental table 1)
  - Radiologic finding in the cases of radiologic PPFE with pathological PPFE showed previous pneumothorax, volume loss in the upper lobes and flat chest, more likely had no coexisting other ILD pattern, compared to those without pathological PPFE (Supplemental Table 2)
- Some clinical features can suggest the presence of pathological PPFE (lower BMI and flat chest in idiopathic patients)
- Idiopathic PPFE may show UIP like changes (fibroblast foci and honeycomb change) and secondary case shows alveolar septal thickening with elastosis or fibrosis, granulomas, and CBO

#### **Hondelink LM, et al. Development and validation of a supervised deep learning algorithm for automated whole-slide programmed death-ligand 1 tumour proportion score assessment in non-small cell lung cancer. Histopathology 2022;80:635-47**

##### **Background:**

- PD-L1 IHC is currently used as the biomarker to select the patients for immunotherapy
- Different tx option depending on 3 TPS groups: <1%, 1-49%, 50-100%
- High interobserver and intraobserver discordance with 15.8% of cases around of 1% cutoff point (kappa coefficient:0.68) and 18.1% disagreement of cases around the 50% cut off (kappa 0.58) in the literature (Cooper et al. Clin Cancer Res 2017;23:4569-77)
- Computational analysis may help to improve interobserver variance
- Three computational PD-L1 TPS scoring methods have been proposed in the literature so far, all of which produced high rates of concordance with the reference scores and provided with relevant proof of concept that computer-aided PD-L1 scoring is possible (supplemental table 1)
- In this study, authors tried to recapitulate the daily routine process for PD-L1 TPS evaluation by routine diagnostic histology samples from stage IV NSCLC, rather than TMA or the slides in research/clinical trial setting.....

##### **Methods:**

- Fully supervised deep learning algorithm for whole slide PD-L1 assessment, consisting of 4 sequential convolutional neural networks (CNNs) – Fig 2
- 199 WSIs of routine diagnostic histology samples from stage IV NSCLC patients
- Trained the algorithm by using a training set of 60 representative cases

- Validated the algorithm by comparing the algorithm TPS with the reference score in a held-out 139 validation set
- Algorithm score compared with mean of three pulmonary pathologists' readings (ground truth)

**Results:**

- Algorithm had similar concordance with the reference score (79%) as the pathologists had with one another (75%)
- Intraclass coefficient was 0.96 and Cohen's kappa coefficient was 0.69 for the algorithm
- Around the 1% and 50% cutoff points, concordance was also similar between pathologists' and the algorithm

**Conclusion:** Successful validation on routine diagnostic WSIs and detailed visual feedback show that this algorithm meets the requirements for functioning as a "scoring assistant"

**Take home message/Comments:**

- Intended to develop a practically usable PD-L1 algorithm trained and validated on WSIs that originate from routine diagnostics
- Tried to address the issues in a wide variety of tissue context (e.g. benign bronchial epithelium, LN, adrenal bone and cartilage, artefacts) and deal with the positive immune cells, especially macrophages
- Two different areas of application:
  - PD-L1 scoring in a diagnostic setting: a potential scoring assistant or second-opinion tool, saving time for pathologists, especially in difficult cases
  - PD-L1 scoring of clinical trial material and/or large series in a research environment: in a situation in which scoring of large series or trial material is required, this algorithm may stand alone in the scoring of easy cases with <0.5% or >60% PD-L1 positivity. A second observer pathologist may be replaced by this algorithm
- Overall, this PD-L1 algorithm worked best as a scoring assistant or second observer, thereby saving time and human effort while remaining equally accurate
- Domain adaption process: when the algorithm is used in a new laboratory or when laboratory circumstances change, the algorithm needs to be adapted to the same task but in a new dataset
- Clear guidelines for domain adaptation process and "post-implementation monitoring" will need to be established
- Application in cytology is still a challenge; this algorithm is not applicable
- Double segmentation CNN and the human in the artificial intelligence loop (HAIL) annotations worked synergistically with the clinical perspective of highly experienced thoracic pathologists in this study

**Articles for Notation**

**Neoplastic**

Kao YC, et al. Pulmonary "inflammatory leiomyosarcomas" are indolent tumors with diploid genomes and no convincing rhabdomyoblastic differentiation. *Am J Surg Pathol* 2022;46:424-33

**Background:**

- First described in 1995 and recently recognized by the WHO classification of bone and soft tissue tumors
- Often occurs in deep soft tissue of lower limbs, trunk and retroperitoneum
- Low-grade appearance, mitotically inactive and composed of smooth muscle-like spindle cells (desmin+, variable SMA+, h-caldesmon-) arranged in fascicles, with strikingly prominent inflammatory cells including small lymphocytes, histiocytes (often xanthomatous/foamy cytoplasm)
- Specific genomic pattern: near-haploid genome with only a handful of chromosomes, most often chromosome 5 and 22, and sometimes 18, 20, and/or 21
- Overlapping features with histiocyte-rich rhabdomyoblastic tumor
- This study reports 4 pulmonary tumors histologically typical of inflammatory leiomyosarcomas (LMSs)

**Methods:**

- Cases were identified from a search of surg path file in an institution (1996-2019)
- Medical records were reviewed
- IHC, SNP array using OncoScan, whole exome sequencing, transcriptomic sequencing, FISH

**Results:**

- All of their pulmonary inflammatory LMS seem clinically, pathologically and genomically alike with those is other sites

**Conclusion:** The term inflammatory rhabdomyoblastic tumor is inappropriate for this group of tumors

**Ricchiuti B, et al. Diminished efficacy of programmed death-(ligand) 1 inhibition in STK11- and KEAP1-mutant lung adenocarcinoma is affected by KRAS mutation status. J Thorac Oncol 2022;17:399-410 (with Editorial by Dziadziuzko R. 351-2)**

**Background:**

- *STK11/LKB1* gene encodes a protein involved in the maintenance of cell metabolism and energy homeostasis and its inactivation is common in lung adenoca; associated with reduced density of effector T cells, diminished response rate, inferior PRS of patients with co-occurring KRAS mutations, when treated with immune check point inhibitors
- *KEAP1* gene encodes KEAP1 protein and is a negative regulator of key transcriptional regulator (*NFE2L2* or *NRF2*) of endogenous antioxidant response. Its loss of function mutation activates KEAP1-NRF2 axis, leading to promotion of KRAS-driven lung adenocarcinomas
- Impact on immunotherapy efficacy in KRAS mutation status (wild type vs. mutant type) of lung adenoca by these two genes are unknown

**Methods:**

- Clinicopathologic and genomic data collected from advanced stage lung adenocarcinoma patients at three institutions (Dana-Farber, MSK, MD Anderson) from 9/2013 to 9/2020

- Clinical outcomes to PD-1 or PD-L1 inhibitors were analyzed in two independent cohorts
- TCGS data were interrogated to identify differences in tumor gene expression and tumor immune cells subsets, according to *KRAS/STK11* and *KRAS/KEAP1* comutation status

**Results:**

- Combination cohort (n=1261) showed KRAS mutation in 536 cases (42.5%), deleterious STK11 in 260 cases (20.6%) and KEAP1 mutations in 231 cases (19.2%)
- Both mutations were associated with significantly worse progression free survival and overall survival to immunotherapy uniquely among KRAS mutated but not KRAS wild type lung adenocarcinoma cases
- Gene expression ontology and immune cell enrichment analyses revealed that the presence of STK11 or KEAP1 mutations results in distinct immunophenotypes in KRAS mutants only, but not in KRAS wild type lung cancers

**Conclusion:** STK11 and KEAP1 mutations portend worse outcomes to immunotherapy among patients with KRAS mutation only, but not in those with wild type KRAS

**Kosari F, et al. Tumor junction burden and antigen presentation as predictors of survival in mesothelioma treated with immune checkpoint inhibitors. J Thorac Oncol 2022;17:446-54**

**Background:**

- Mesotheliomas have low tumor mutation burden but have been shown to respond to immunotherapy with favorable outcome
- Chromosomal rearrangements with neoantigenic potential are common in mesotheliomas
- They sought to determine whether they are associated with survival in patients treated with immunotherapy

**Methods:**

- Pleural bx of mesothelioma after at least one line of therapy from patients (n=44) before nivolumab alone or in combination with ipilimumab
- RNA and whole-genome sequencing were performed to identify the junctions resulting from chromosomal rearrangements and antigen processing and presentation gene set expression
- Overall survival (OS) were estimated using Cox models
- OS cutoff of 1.5 years was used to distinguish patient with and without durable benefit for use in ROC curves

**Results:**

- Significant interaction between the junction burdens and multiple antigen processing and presentation gene sets, though junction burdens were not predictive of OS
- Regulation of antigen processing and presentation of peptide antigen gene set revealed an interaction with tumor junction burden and was predictive of OS
- This interaction also predicted 1.5 year or greater survival with an area under the ROC curve of 0.83



- This interaction was not predictive of survival in a separate cohort of patients with mesothelioma who did not receive immune checkpoint inhibitors

**Conclusion:** Analysis structural variants and antigen presentation gene set expression may be useful to select the patients for immunotherapy

**Batra U, et al. Next generation sequencing for detection of EGFR alterations in NSCLC: is more better? J Clin Pathol 2022;75:164-7**

**Background:**

- This study aimed at highlighting the benefit of NGS approach for EGFR mutation testing in NSCL

**Methods:**

- 1350 NSCLC cases were screened and 490 EGFR mutated cases were taken and checked the medical records to determine those that were missed on single gene testing

**Results:**

- Among 490 cases with EGFR mutation detected by NGS, there were 11 cases (2.2%) tested negative by single gene testing by PCR (Therascreen); on retest, there were 13 different EGFR mutations with response to EGFR inhibitor in 5 of 11 cases who received TKI

**Conclusion:** The advantages of NGS over single gene testing is evident

**Qiu JH, et al. Optimized architecture-based grading system as an independent prognostic factor in resected lung adenocarcinoma. J Clin Pathol 2022;75:176-84**

**Background:** they aim to establish an “optimized architecture-based grading system” (OAGS) for lung adenocarcinomas

**Methods:**

- Multicenter study with three independent cohorts of lung adenoca
- Recurrence-free probability (RFP) and OS were assessed for predictive ability of their OAGS
- Training cohort (n=228) and validated in two sets (n=135 and n=226)

**Results:**

- Grade 1: lepidic, papillary or acinar predominant with no or less than 5% of high-grade patterns (cribriform, solid and/or micropapillary)
- Grade 2: lepidic, papillary or acinar predominant with 5% or more of high-grade patterns
- Grade 3: cribriform, solid or micropapillary predominant tumor
- In all stages, the OAGS outperformed the pattern-dominant grading system and IASLC grading system for predicting RFP and OS; maintained the efficacy in T1-2aNOMO subgroup
- Independent predictor of both RFP and OS on multivariate analysis

**Conclusion:** Their grading showed robust prediction of prognosis of resected lung adenocarcinomas

**Calvani J, et al. A comprehensive clinicopathologic and molecular study of 19 primary effusion lymphomas in HIV-infected patients. Am J Surg Pathol 2022;46:353-62**

**Background:**

- HHV-8 causes Kaposi's sarcoma and several lymphoproliferative disorders including primary effusion lymphoma (PEL), HHV-8-positive multicentric Castleman disease, HHV-8-positive DLBCL, NOS, etc.
- PEL is also frequently associated with EBV

**Methods:**

- This study reports 19 HIV-associated PEL from a single institution comprised of 14 EBV+ and 5 EBV- PELs to describe clinicopathologic features
- PD1 and PD-L1 expression, targeted deep sequencing analysis for genetic alteration to find differences between EBV+ and EBV- cases

**Results:**

- All male, median age at dx was 47 years
- Low expression levels of B-cell markers including CD19 (0/19), CD20 (1/19), CD79a (0/19), PAX5 (1/19), BAB1 (3/19), OCT2 (4/19), reflecting the terminal B-cell differentiation
- CD38 (10/19), CD138 (7/19), IRF4/MUM1 (18/19)
- Aberant expression of T-cell markers CD3 (10/19), CD2 (2/19), CD4 (3/19), CD5 (1/19), CD8 (0/19)
- 2 cases were PD-L1 + on tumor cells and none was PD-1 +
- Immune cells: PD-L1+ (n=3), PD-1 + (n=5)
- 36 gene lymphopanel showed 7 distinct variants in 5/10 PELs, with a single or 2 mutations per sample
- No major clinical pathologic or immunohistochemical differences between EBV+ and EBV- PELs with similar outcome (2 year survival at 61.9% and 60.0%, respectively)

**Non-neoplastic**

**McElroy AN, et al. Candidate role for toll-like receptor 3 L412F polymorphism and infection in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2022;205:550-562 (with Editorial by Vancheri C et al. 489-91)**

**Background:**

- Toll-like receptor 3 Leu412Phe (TLR3 L412F) polymorphism attenuates cellular antiviral responses
- This group previously demonstrated that 412F-variant patients with IPF have a significantly accelerated decline in FVC and greater risk of mortality in two independent cohorts of IPF patients
- The role of TLR3 L412F in bacterial infection in IPF or in acute exacerbations (AE) has not been reported
- The aims of this study were
  - to characterize the association between TLR3 L412 and AE-related death in IPF
  - to determine the effect of TFR3 L412F on the lung microbiome and on antibacterial TLR responses of primary lung fibroblasts from patients with IPF

**Methods:**

- TLR-mediated antibacterial and antiviral responses were quantified in L412F wild-type and 412-heterozygous primary lung fibroblasts from IPF patients using ELISA, Western blot analysis, and quantitative PCR
- Hierarchical heatmap analysis was used to establish bacterial and viral clustering in nasopharyngeal lavage samples for IPF patients in AE
- 16S ribosomal RNA quantitative PCR and pyrosequencing were used to determine the effect of TLR3 L412F on the IPF lung microbiome

**Results:**

- Significant increase in AE-related death in patients with 412F-variant IPF
- 412Fheterozygous IPF lung fibroblasts reduced antibacterial TLR responses to LPS (TLR4), TLR1/2, TLR5, TLR6/1 and have reduced responses to live *Pseudomonas aeruginosa* infection
- On 16S ribosomal RNA sequencing, 412F-heterozygous patients with IPF have a dysregulated lung microbiome with increased frequencies of *Streptococcus* and *Staphylococcus* species

**Conclusion:**

- TLR3 L412F, a functional SNP, is a significant risk factor for mortality and accelerated decline in lung function in 412F-variant patients with IPF
- They identified for the first time an SNP of TLR3 that could represent a significant risk factor for mortality secondary to AE in IPF patients, likely via disruption of IPF microbiome and reduces the responses of IPF lung fibroblasts to bacterial TLR-agonists in live bacterial infection.

**Take home message:** Microbiome of the lung may matter as in guts and other sites!

**Wu J, et al. Artificial intelligence-associated system for precision diagnosis of PD-L1 expression in non-small cell lung cancer. *Mod Pathol* 2022;35:403-11****Background:**

- PD-L1 assessment in NSLC is challenging with interobserver variability and use of different antibodies
- They sought to develop a fully automated method that enables tumor area detection and quantitative scoring of TPS n digital PD-L1 IHC slides of NSCLC

**Methods:** Illustrated in Figure 1

- 5 parts of datasets: training set (173 WSIs of 22C3); 1) DL model test set (78 WSIs of 22C3, 114 selected regions); 2) TPS comparison set (110 slides by pathologists and 61 WSIs, 3) 111 regions to test the tumor detection performance; 4) AI system-assisted test set (40 WSIs) to test the performance of the AI-assisted procedure of the TPS analysis for pathologists in 22C3 assay; 5) Ventana PD-L1 (SP263) assay test set (61 WSIs, 114 region)
- TPS interpretation by trained and untrained pathologists as negative (<1%), low expression (1-49%), high expression (50% or higher)
- AI system development:
  - annotation by 5 pathologists using QuPath

- DL model development
- cell segmentation and TPS calculation
- AI visualization to enable pathologists to visualize reliability of TPS by AI system
- TPS comparison test in 22C3 assay by 3 highly trained pathologists and 3 untrained pathologists
- AI system assisted dx test in 22C3 assay
  - 3 trained pathologists evaluated TPS by WSI only
  - 3 untrained pathologists evaluated TPS with WSIs that contained the pre-read results and visualized figures by the proposed AI system to mimica computer-aided dx workflow
  - Time cost was recorded for each participant with and without the aid of the AI system
- Ventana PD-L1 (SP263) assays test:
  - DL model trained on 22C3 assay was directly tested on SP263 assay
  - Two trained pathologists independently evaluated SP263 stained slides under a microscope; inconsistent cases were resolved by the third consultant pathologists for consensus
  - TPS by AI and by consensus results of pathologists were compared
- Precision, recall, specificity, F1-score, IoU and accuracy were used ot evaluate the performance of the DL model for tumor detection
- Appropriate statistics for different variables

#### **Results:**

- DL model for automated tumor detection with an accuracy and specificity of 0.9326 and 0.9641, respectively, and concrete value of TPS after tumor cell segmentation
- Strong consistency between TPS by AI and by trained pathologists (R=0.9429-9458)
- Repeatability and efficiency of untrained pathologists can be improved using AI system
- SP263 assay also showed high-consistency in TPS calculations between the AI system and pathologists (R=0.9787)

**Conclusion:** AI assisted system could be an effective and valuable tool to overcome the challenges of PD-L1 assessment in the field of immunotherapy

**Comment:** This study also reveals excellent performance as in the Dutch study included in Discussion

#### **Reviews**

##### **Mclean AEB, et al. The emerging role of the lung microbiome and its importance in non-small cel lung cancer diagnosis and treatment**

- An excellent review in the emerging field of lung microbiome worth reading
- Lower airways are home to a dynamic bacterial population sustained by the migration and elimination of microbes from the GI and upper airway tracts
- As in the gut, the lung microbiome plays an important role in regulating mucosal immunity and maintaining the balance between immune tolerance and inflammation and function of lung microbiome in health and disease

- Concept of lung microbiome as a novel biomarker and predictor of treatment response in non-small cell lung cancer

**King TE and Lee JS. Cryptogenic organizing pneumonia. *New Engl J Med* 2022;386:1058-69**

- A comprehensive review from A to Z on COP

**Ghosh S and Farber CF. Birt-Hogg-Dube Syndrome. *Radiology* 2022;302:514**

- Nice illustration and brief summary on a one-page report

**Nicholson AG, et al. The 2021 WHO Classification of lung tumors: Impact of advances since 2015. *J Thorac Oncol* 2022;17:362-87**

- A concise review (only 25 pages!) on the recent changes reflected in 2021 WHO classification of lung tumors since 2015

**Hechtman J. NTRK insights: best practices for pathologists. *Mod Pathol* 2022;35:298-305**

- It is not entirely for lung cancers but it is a nice overview for NTRK testing in general

**Prays J and Ortiz-Villalon C. Molecular landscape of thymic epithelial tumors. *Sem Diag Pathol* 2022;39:131-6**

- This paper and three additional papers listed below are from the March issue of *Seminars in Diagnostic Pathology* dedicated to thymic/mediastinal pathology (guest editor: Dr. Cesar Moran)

**Oramas DM and Moran CA. Multilocular thymic cyst (MTC) and other tumors with MTC features: Pitfalls in diagnosis. *Sem Diag Pathol* 2022;39:105-12**

**Oramas DM and Moran CA. Thymoma: Histologically a heterogenous group of tumors. *Sem Diag Pathol* 2022;39:93-104**

**Lin J and Jimenez CA. Acute mediastinitis, mediastinal granuloma, and chronic fibrosing mediastinitis: A review. *Sem Diag Pathol* 2022;39:113-9**

**Conde E, et al. Molecular diagnosis in non-small-cell lung cancer: expert opinion on ALK and ROS1 testing. *J Clin Pathol* 2022;75:145-53**

**Rosen Y. Pulmonary neuroendocrine carcinomas in situ: do they exist? *Histopathology* 2022;80:627-34**

- Precursors of SCLC and LCNEC have been never clearly identified as opposed to other types (e.g. ADC, Sqcc, carcinoid tumors)
- 5 previous studies looking at the bronchial epithelium in cases of SCLC in the literature (nicely summarized in table 1)
- Intellectually stimulating discussion and critical review of literature

**Editorials, letters to the editor, case reports**

**Schaheen, L et al. Lung transplantation for coronavirus disease 2019 (COVID-19): The who, what, where, when, and why. J Thorac Cardiovascular Surg 2022;163:865-8**

**Culebras M, et al. Histological findings in transbronchial cryobiopsies obtained for patients after COVID-19. Chest 2022;161:647-50**

**Martinez-Morilla S, et al. Standardization of PD-L1 immunohistochemistry. Mod Pathol 2022;35:294-5**

**Tsao MS, et al. Reprint of “introduction to 2021 WHO classification of thoracic tumors”. J Thorac Oncol 2022;17:337-40**

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