

Pulmonary Pathology Journal Club

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Articles for Discussion

Sasaki E et al. *AKT1* mutations in peripheral bronchiolar papilloma. Glandular papilloma and mixed squamous cell and glandular papilloma is distinct from bronchiolar adenoma. Am J Surg Pathol 2021;45:119-126

Background:

- Three types of pulmonary papilloma with intraluminal growth: squamous papilloma (SCP), glandular papilloma (GP), mixed squamous cell and glandular papilloma (MP)
- SCP with strong association with HPV as in laryngeal/tracheal SCP
- GP/MP: not HPV associated; central endobronchial and peripheral bronchiolar type
- Ciliated mucinodular papillary tumor (CMPT): grows peripherally in alveolar walls with no involvement of bronchial lumen; composed of ciliated, glandular and squamous cells with basal layer
- Bronchiolar adenoma (BA): benign peripheral non-endobronchial lung nodules in the proximal bronchioles or alveolar parenchyma; encompass wider range than CMPT by including those without ciliated or papillary element and may be composed of flat epithelial cells
- GP/MP and BA occur in different location but share some morphologic similarities and molecular change (BRAF mutation)
- The aim of this study was to examine whether GP/MP and BA represent the same tumor or not by detailed evaluation of histopathology and genetic analyses

Methods:

- 11 cases of peripheral tumors showing the histopathologic features of GP/MP or BA from database (2008-19) in one institution: original dx- CMPT (n=4), MP (n=2), solitary peripheral ciliated GP (n=2), solitary peripheral papilloma (n=2), BA (n=1)
- Re-classification by re-review by 3 pathologists as GP/MP (endobronchial /endobronchiolar tumor with mixture of glandular, ciliated, squamous and/or basal cells) and BA (situated in peripheral lung parenchyma with a peribronchiolar distribution)
- Measured the thickness from the epithelial surface to the basement membrane in 10 randomly selected points within each tumor using a Scan Scope ST, and calculated mean thickness of each tumor
- IHC: p40, BRAF V600E, ALK
- Genetic analysis: DNA panel sequencing, allele-specific real-time PCR, and fragment analysis, RT-PCR, digital PCR, HPV analysis

Results:

- Histopathology: 4 MPs and 7 BAs (2 papillary, 1 papillary/flat, 4 flat)
- Mean epithelial thickness: 112-242 μ m in MPs, 103-144 μ m in papillary BAs, 23-47 in flat predominant BAs
- Molecular findings summarized by EGFR-Ras-Raf and PI3K-Akt Pathways in Table 2

Conclusion: *AKT1* mutations are identified in GP/MP but not in flat BA and they show different histopathologic findings, suggesting that GP/MP is distinct from flat BA. Papillary BAs have *AKT* mutation and may be more in keeping with GP/MP

Take home message/Comments: Detection of *AKT1* mutation may be helpful for differentiating GP/MP from BA, though it is probably not necessary in the clinical practice. On the other hand, it is important to remember that not all abnormal glandular proliferation in the periphery of the lung is adenocarcinoma and consider these benign entities, in this era of CT screening that results in needle bx of small incidental lung nodules.

Richeldi L et al. Utility of a molecular classifier as a complement to high-resolution computed tomography to identify usual interstitial pneumonia. Am J Resp Crit Care Med 2021;203:211-220; Editorial by Cosgrove GP and Lasky JA. A new piece to help solve the interstitial lung disease. Diagnostic puzzle. Am J Resp Crit Care Med 2021;203:158-9

Background:

- BRAVE (Bronchial Sample Collection for a Novel Genomic Test) study cohort:
 - recruited from 30 BRAVE clinical sites in US and Europe between 2013-2019
 - underwent transbronchial bx for transcriptomic RNA seq and used to train a machine learning algorithm (Envisia Genomic Classifier)
 - had samples obtained by clinically indicated surgical bx, transbronchial bx, or cryobx for pathology; reviewed by 3 expert pulmonary pathologists
 - available HRCT scans reviewed by local radiologists underwent central review by expert thoracic radiologists
- Envisia Genomic Classifier:
 - developed with machine learning and whole-transcriptome RNA sequencing; previous studies have been published by this group for training and validation of classifier (Veracyte)
 - an expression signature including 190 genes was identified that could differentiate between UIP and other ILD in Tbbx samples
 - binary result of UIP or non-UIP; using tissue biopsy for dx as truth labels and the RNA sequencing derived from Tbbx samples as an input for the classifier
- Three BRAVE studies have been published for a proof of concept and validation of classifier. A recent study showed a clinical utility of classifier performed on TBBx to identify molecular signature of UIP, especially in those without a clear radiological dx, who would have needed a surgical lung bx for dx (Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL et al. Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung bx samples. A prospective validation study. *Lancet Respir Med* 2019;7:487-496)
- This is a follow up study using a new group of BRAVE patients allocated for independent clinical validation and evaluation of the combined accuracy of the Envisia Genomic Classifier and local radiologists' dx in the detection of UIP pattern (i.e. real life setting)

Methods:

- Cases (n=96): from initial 447 BRAVE patient cohort, 220 pts were allocated for independent clinical validation, then many were excluded for various reasons, leaving 96 pts for final scoring (Fig. 1 for cohort description)

- Pathology: Centrally reviewed by a team of expert pathologists blinded for clinical or any other information. Path dx served as a reference truth label for this study if met the 2018 ATS criteria of UIP or probable UIP; “favor UIP” and “difficult UIP” included as probable UIP. If not UIP, alternative dx was recorded (Fig. 3)
- Radiology: HRCTs reviewed by both local radiologists and by central radiologists (2 experts)
 - Central radiology readings by Fleischner Society criteria for UIP (typical, probable, indeterminate) and specific non-IPF ILD dx
 - Local radiology readings were performed by local radiologists according to their own practice style
 - Original local HRCT scan reports were systematically reviewed by two qualified reviewers to convert to the Fleischner diagnostic category (typical, probably, indeterminate, and features most c/w non-IPF dx)
- Molecular testing: total RNA was extracted from 3-5 Tbbx per pt and pooled by subject, and single whole transcriptome library was generated and sequenced as previous described; results presented as binary result of UIP or non-UIP
- Standard statistical analyses

Results:

- Envisia Classifier achieved a specificity of 92.1% and a sensitivity of 60.3%, for histology proven UIP cases
- If Envisia Classifier is added, the sensitivity of local radiologist’s reading increases from 34.0% to 79.2% (Table 4 and 5)

Conclusion: Sustained accuracy and reproducibility of the molecular dx by the Envisia Genomic Classifier in a second independent validation cohort. It also showed the potential utility of increased identification of UIP by Envisia Genomic Classifier in the cases of inconclusive HRCT.

Take home message: Envisia Genomic Classifier may be useful as a surrogate histopathology in combination with HRCT image patterns and clinical factors for a MDD team to make the dx of UIP/IPF.

Comments: Since the Tbbx used for this molecular classifier did not undergo histopathology review, the tissue used for molecular study may or may not have significant fibrosis. The interval between the diagnostic bx and Tbbx for this study is not specified. So, it may imply that Envisia Genomic Classifier score based on potentially non-fibrotic lung tissue still predict the UIP, which opens door to an interesting concept....

GuillotinD et al. Transcriptome analysis of IPF fibroblastic foci identifies key pathways involved in fibrogenesis. Thorax 2021;76:73-82

Background:

- Fibroblast foci (FF) are one of the key features in IPF and comprised of activated fibroblasts and myofibroblasts
- Aim of the study was to identify a transcriptional signature associated with collagen gene expression in the FF by profiling unmanipulated myofibroblasts within FF in situ (as opposed to single cell RNAseq from dissolved tissue) by LCM

- They overcame challenges associated with deriving gene calls from low amounts of RNA and the absence of meaningful comparator cell type by advanced bioinformatics including novel data mining strategies and by using weighted gene-co-expression network analysis (WGCNA) and *eigengene*-based approach
- *Eigengene* (a term used in genetics and mathematics): One of a set of right singular vectors of a genes x samples matrix that tabulates, e.g., the mRNA or gene expression of the genes across the samples.

Methods:

- Frozen IPF lung tissue from explants (n=10) or surgical lung bx (n=13)
- LCM and microarray analysis; FF were identified by SMA immunostain and captured by LCM; 3-6 captures per sample, and then RNA was extracted and processed for hybridization to microarrays
- RNAscope in situ hybridization was performed on independent IPF lung tissue
- WGCNA and collagen *eigengene* analysis
- Functional analysis using CRISPR-Cas9 gene-edited cells in vitro

Results:

- WGCNA identified clusters of genes associated with cell cycle, inflammation/ differentiation, translation and cytoskeleton/ cell adhesion
- Collagen *eigengene* analysis revealed TGFβ1, RhoA kinase and the TSC2/RHEB axis as major signaling clusters associated with collagen gene expression
- Functional studies demonstrated a key role for the TSC2/RHEB axis in regulating TGFβ1 (major fibrogenic cytokine)-induced target of rapamycin complex 1 activation and collagen I deposition in mesenchymal cells

Conclusion: Their human tissue-based approach with advanced bioinformatics was effective to identify “transcriptional node” associated with the fibroblast/ myofibroblast in FF and TSC2/RHEB axis as a potential target for interfering with excessive matrix deposition in IPF

Comments: Next question one can ask may be whether fibroblasts/ myofibroblasts in FF and in other contexts (e.g. OP and DAD) differ in their transcriptional signature or not

Makela K et al. Artificial intelligence identifies inflammation and confirms fibroblast foci as prognostic tissue biomarkers in idiopathic pulmonary fibrosis. Hum Pathol 2021;107:58-68

Background:

- FF and other histological parameters in IPF may be prognostic markers in IPF
- Aim of study: To evaluate the ability of AI in quantitating FF, interstitial mononuclear inflammation, and intraalveolar macrophages with a deep convolutional neural network (CNN) and their role as prognostic biomarker in IPF

Methods:

- Study population: from the FinnishIPF registry, a prospective multicenter study of IPF pts
- Respiratory medicine specialists or multidisciplinary teams re-evaluate the dx of IPF
- The most presentative HE slide with typical UIP features was selected in each pt (n=71); surgical lung bx (n=61; 87.3%), explant (n=6, 8.5%), autopsy (n=3; 4.2%)
- All slides scanned (at 40x) and digital imaged uploaded to image management and analysis platform (Aiforia Technologies, Helsinki, Finland) and then analyzed with an AI

model developed with a deep CNN and supervised learning, followed by complex training algorithm dealing with all kinds of issues...

- The AI model produced data of the surface areas and counts of every histological feature. The area of each feature was quantified as a % of whole tissue area, and the density of each feature was determined by dividing the counts by whole tissue area
- Explants and autopsy slides for testing lung tissue recognition; SLBs for the quantitative analysis of FF, interstitial mononuclear inflammation and intra-alveolar macrophages
- Of note, AI had a hard time to distinguishing FF vs. OP; OP was uncommon in their cases
- Validation of the AI model: a pulmonary pathologist annotated FF in the validation areas blinded to the results by AI (regarded as ground truth) and compared to the model's analysis; false positive, false negative, error, precision, sensitivity and F1 score values calculated for 30 validation regions

Results:

- A large area of FF predicted poor px in IPF (p=.01), low DLCO (p=.03)
- High numbers of interstitial mononuclear inflammatory cells and intra-alveolar macrophages were associated with prolonged survival (p=.01, in both) and high FVC

Conclusion: In the future, AI could be a novel tool for the pathologists in the histological dx and quantitating various parameters in IPF and other ILDs

Doward DA et al. Tissue-specific immunopathology in fatal COVID-19. Am J Resp Crit Care Med 2021;203:192-201

Background:

- It is not entirely clear whether organ damaging inflammation is due to a direct reaction to the presence of SARS-CoV-2 or an independent immunologic process
- They did the study to better understand the connection among viral presence, inflammation and organ injury

Methods:

- Postmortem examination of 11 patients with premortem PCR confirmation of COVID-19 and evidence of lower respiratory tract infection (median 19.3 hours after death)
- 37 tissue sites sampled according to standardized protocol for histologic and RNA analysis, including 23 sites from the respiratory tract; fixed in formalin, treated with TRIzol, snap frozen and stored at -80°C
- Tissue histology and IF: inflammation scored (0-3); multiplexed IF on FFPE (CD34, CD68, MRP8, CD4, CD8, CD20)
- Viral RNA and protein detection: total RNA extracted from homogenized TRIzol-treated tissue; PPFE examined for SARS-CoV-2 S (spike) protein on randomly selected PCR-confirmed SARS-CoV-2 positive tissue from 4 pts

Results:

- Mapping SARS-CoV-2 distribution to tissue inflammation: Multiple aberrant immune responses in fatal COVID-19 mainly involve the lung and the reticuloendothelial system (LN and spleen); and were NOT topologically associated with the virus.
- In some cases, inflammation was present in the sections of lung without detectable virus

- Conversely, even at the time of death, up to 42 days after illness onset, viral products (both RNA and protein) and evidence of viral RNA synthesis (subgenomic mRNA) could be detected in numerous tissues but were dissociated from host inflammatory responses

Conclusion: Significant component of the immune-mediated, virus independent immunopathologic process as a primary mechanism; i.e. the principal damage by SARS-CoV-2 may not be caused by the virus itself but by the subsequent immune response triggered by the virus.

Take home message: This may be the main reason why antiviral therapies have no effect on the second phase of COVID-19 despite the presence of detectable virus, while anti-inflammatory therapy (e.g. corticosteroid) seems to be effective.

Articles for Notation

Neoplastic

Elfving H et al. Evaluation of NTRK immunohistochemistry as a screening method for NTRK gene fusion detection in non-small cell lung cancer. Lung Cancer 2021;151:53-59

Background:

- NTRK inhibitors larotrectinib and entrectinib have been approved as cancer agnostic drugs in pts with tumors harboring a NTRK rearrangement that is rare in NSCLC
- They evaluated NTRK IHC as a screening test on a NSCLC cohort

Methods:

- Tissue microarray of 688 NSCLC cases that have been annotated (clinical and molecular)
- IHC with a pan TRK ab (clone EPR17341) and TruSight tumor RNA assay (illumine) for all IHC positive cases; NanoString NTRK fusion assay on selected cases; some cases with available previous RNA expression data (n=199)

Results:

- 617 cases with interpretable staining patterns. 4 (0.6%) had a strong diffuse cytoplasmic and membranous staining; whole sections staining with marked heterogeneity in these 4 cases; and seven cases with a moderate staining
- None of the IHC positive cases had NTRK fusion on molecular analysis

Conclusion and Comment: All of their NTRK positive IHC cases were false positive with no demonstrable fusion; they did not address the false negative (i.e. IHC negative cases not thoroughly examined for NTRK fusion. So, I am not entirely sure if it can be used as a screening test

De Michele S et al. SATB2 in neoplasms of lung, pancreatobiliary, and gastrointestinal origins. Am J Clin Pathol 2021;155:124-132

Background:

- SATB2IHC has been reported to be highly sensitive and specific marker of colorectal ca
- Data on other sites such as lung, gastric, small bowel and pancreaticobiliary ADCs are limited and so they checked SATB2 expression in these organs

Methods:

- SATB IHC on 335 tumors (40 lung ADC; 165 pancreaticobiliary including 34 IPMNs, 19 pancreatic, 112 cholangiocarcinoma; 35 gastric, 13 small bowel, 36 ampullary, 46 colorectal)
- Positive ($\geq 5\%$ nuclear) and H score based on % of SATB+ cells and staining intensity

Results:

- 3% of lung, 2% of cholangiocarcinoma, 17% of gastric, 38% of small bowel, and 6% of ampullary
- None of pancreatic adenocarcinoma and IPMN; 87% colorectal carcinoma were positive

Conclusion and take home message: SATB2 is not entirely specific for colorectal carcinoma, but still can be useful to differentiate between colorectal vs. lung origin (given its low prevalence)

Dutta R et al. Cytomorphology of primary pulmonary NUT carcinoma in different cytology preparation. Cancer Cytopathol 2021;129-53-61

Background

- Cytology is often the mode of primary diagnostic modality for dx of NUT carcinoma
- Different cytology samples and preparations were evaluated for cytomorphologic features of NUT carcinoma

Methods:

- 15 cytology specimens from 10 pts with primary pulmonary NUT carcinoma that have been diagnosed by histology
- Aspirates from primary and metastatic sites (n=5, each), sputum (n=1), effusions (n=4)
- Direct smears, centrifuged smears and cell blocks

Results:

- Cohesive clusters of primitive appearing tumor cells with scant cytoplasm, ovoid nuclei with coarse granular chromatin and consistently conspicuous single nucleoli in a neutrophil-rich necrotic background with dispersed bare tumor nuclei
- 3 dimensional tight tumor clusters or single dispersed tumor cells with focal squamous differentiation in rare cases
- NUT stain on CB showing speckled nuclear staining

Conclusion and take home message: Consider NUT carcinoma for any poorly differentiated lung carcinoma with prominent nucleoli and focal to absent squamous differentiation

Malpica A et al. Malignant mesothelioma of the peritoneum in women. Am J Surg Pathol 2021;45:45-58

Background:

- They presented clinicopathologic features of peritoneal MM that is very rare

Methods:

- 164 cases found over 42 years (1974-2016) at MD Anderson
- Clinical info, path findings, IHC results and f/u data recorded

Results:

- Typically seen in white women with median age of 49 yrs and a strong family hx of other malignancies, some of which could be syndromic (e.g. BAP-1 germ line mutation, type 2 NF, Lynch syndrome, McCune-Albright syndrome)

- Delay in dx is common due to atypical presentations (e.g. paraneoplastic syndromes, cervical lymphadenopathy, absence of discrete masses/lesion, well diff papillary meso-like or adhesion-like areas and the lack of invasion)
- Easily confused with other neoplasms and a panel of IHC is necessary to exclude other tumors (of note, up to 23% showed PAX8 positivity)
- Px is not dismal with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (3- and 5-yr OS were 88.9% and 77.8%, respectively)
- Worse px is associated with predominance of decidual cells, high nuclear grade, absence of surgical tx on multivariate analysis

Gassa A et al. Detection of circulating tumor DNA by digital droplet PCR in resectable lung cancer as a predictive tool for recurrence. Lung Cancer 2021;151:91-96

Background:

- Given the high recurrence rates (30-70%) after resection of lung cancer despite follow up CT scans, other minimally invasive modalities are needed to detect predictive markers for metastases and postsurgical recurrences
- This is a prospective study to test the value of ctDNA in presurgical plasma samples with lung cancers by digital droplet PCR (ddPCR)

Methods:

- Resected tumor tissue and simultaneous blood samples collected from 24 pts with lung ca in stage I-IIIa
- Genomic DNA from the tumor tissue samples analyzed for hotspot mutations (17 gene panel NGS)
- ctDNA from corresponding plasma samples were analyzed with ddPCR and correlated with patient's outcome

Results:

- 23 of 24 pts had at least one somatic mutation in the primary tumor and tumor-specific mutation was detectable in 39% from the blood of early stage lung cancer pts (amenable for resection) by ddPCR
- A preoperative detection of ctDNA did not predict postsurgical recurrences, however!

Lee E. Reduced sensitivity for EGFR T790M mutations using the Idylla EGFR mutation test. J Clin Pathol 2021;74:43-47

Background:

- Osimertinib is a third generation EGFR inhibitor that is effective in NSCLC with EGFR T790M mutation
- Idylla EGFR mutation test is a recently introduced rapid cartridge-based method for detecting T790M and other EGFR mutations but false negative T790M results have been reported with this technique

Methods:

- 80 NSCLC tested by both Idylla and NGS assay
- ddPCR was used to confirm NGS findings in the samples with the T790M mutation

Results:

- 5 of 19 samples with T790M mutation were missed by Idylla
- 2 of 19 samples with EGFR exon 19 indel were also missed by Idylla

Take home message: Idylla EGFR mutation test may not be feasible for T790M mutation detection given its limited sensitivity

Gaudreau PO et al. Neoadjuvant chemotherapy increases cytotoxic T cell, tissue resident memory T cell, and B cell infiltration in resectable NSCLC. Am J thorac Oncol 2021;16:127-39

Background:

- Mechanisms of synergistic effect of checkpoint inhibitors and chemotherapy are incompletely understood
- This study explored the relationships between neoadjuvant chemotherapy and immune microenvironment (IME) of resectable NSCLC to identify novel mechanisms by which chemotherapy enhance the effect of immune checkpoint blockade

Methods:

- Genomic, transcriptomic and immune profiling data of 511 pts treated with neoadjuvant chemotx followed by surgery vs upfront surgery were compared with determined differential characteristics of IMEs derived from whole exome sequencing, RNA microarray, flow cytometry, multiplex IF, T cell receptor sequencing and circulating cytokines

Results:

- Tumor with neoadjuvant tx showed increased infiltration of cytotoxic CD8+ T cells and CD20+ B cells; also increased CD8+CD103+ and CD4+CD103+Pd1+TIM3- tissue resident memory T cells; but did not affect T cell receptor clonality, richness or tumor mutational burden;
- Gene expression profiling supported memory function of CD8+ and CD4+ T cells
- Associated with decreased plasma TrkB at baseline and week 4 after surgery

Conclusion and take home message:

- In resectable tumor setting, neoadjuvant chemotx promoted antitumor immunity through T and B cell recruitment in the IME and through a phenotypic change toward cytotoxic and memory CD8+ and Cd+ memory helper T cells
- These results suggest that potential combinations including T-cell activating agents may represent promising approaches to further augment antitumor immune responses for the tx of NSCLC

Buikhuisen WA et al. Risk of second primary malignancies among patients with carcinoid of the lung. Lung Cancer 2021;151:5-7

Background:

- Associations with other types of cancer may identify shared risk factors for pulmonary carcinoid (PC) that are not known
- To explore the association between PC and other primary malignancies for identifying risk factors

Methods:

- Cases searched from the nationwide Netherlands Cancer Registry for PC diagnosed during 1989-2018 period
- Occurrence of second primary malignancies was evaluated for year 1 and years 2-30
- Expected numbers of second primary were calculated using incidence reference tables, controlling for age, gender and period
- Confidence intervals (95% CI) for the ratio between observed and expected numbers (SIR; standardized incidence ratio) were calculated

Results:

- In 2,933 pts of PC, 425 consecutive primary malignancies were observed in 376 pts
- Concomitant dx in the year 1 mainly comprised lung (n=59) and kidney (n=14) cancers
- Metachronous malignancies in year 2-30 were most common for breast (n=50), colorectal (n=41), prostate (n=32), and lung cancer (n=29)
- The overall risk of second primary cancer in PC pts was similar to the risks within the general population (n=256, SIR=1.12, 95% CI 0.99-1.27), except for soft tissue sarcoma (n=5, SIR 3.52, 95% CI 1.14-8.22) and gastro-entero-pancreatic neuroendocrine tumor (GEPNET) (n=4, SIR 4.30, 95% CI 1.17-11.01)

Conclusion and take home message: Other than a high SIR for GEPNET, no relevant associations with other types of cancer were found, leaving the etiology of PC a mystery

Non-Neoplastic

Roden AC et al. The spectrum of histopathologic findings in lungs of patients with fatal coronavirus disease 2019 (COVID-19) infection. Arch Pathol Lab Med 2021;145:11-21

Background:

- To report comprehensive postmortem lung findings in patients with COVID-19 infections

Methods:

- Patients who had confirmed COVID-19 infection and underwent autopsy (March-May, 2020) were included and slides were independently reviewed by 4 thoracic pathologists and imaging studies were reviewed by a thoracic radiologist.

Results:

- 8 pts (7 men, median age 79 yrs, 69-96 yrs) were included (died 6-100 days after dx; median 17 days)
- On histologic exam, all had acute bronchopneumonia, 6 also had DAD, 2 had aspiration pneumonia, 5 had thromboemboli in small vessels or pulmonary arteries
- Postmortem bacterial culture was positive in 4 pts
- Imaging studies were available in 4 pts, with typical (n=2), indeterminate (n=1) and negative (n=1) findings for COVID-19

Conclusion and take home message: COVID-19 is known to show DAD but also commonly showed other findings including acute bronchopneumonia and aspiration pneumonia, which would have therapeutic implications

Brody SL et al. Chemokine receptor 2-targeted molecular imaging in pulmonary fibrosis. A clinical trial. Am J Respir Crit Med 2021;203:78-89

Background:

- Monocyte and interstitial macrophages that express the C-C motif CCR2 (chemokine receptor 2) are active in IPF and central to fibrosis
- To phenotype IPF patients for potential targeted therapy and monitor responses to therapy, they developed a radiotracer (^{64}Cu -DOTA-ECL1i) to noninvasively track CCR2⁺ monocytes and macrophages using PET

Methods:

- CCR2⁺ cells were investigated in mice with bleomycin- or radiation-induced fibrosis and in human subjects with IPF
- With immunolocalization, single-cell mass cytometry and Ccr2 RNA ISH, the CCR2⁺ cell populations were localized relative to fibrotic regions in the lung tissue and correlated with parallel quantitation of lung uptake by ^{64}Cu -DOTA-ECL1i PET

Results:

- Mouse models established that increased ^{64}Cu -DOTA-ECL1i uptake in the lung correlates with CCR2⁺ cell infiltration associated with fibrosis (n=72)
- As therapeutic models, the inhibition of fibrosis by IL-1 β blockade (n=19) or pirfenidone (n=18) reduced CCR2⁺ macrophages accumulation and uptake of the radiotracer in mouse lungs
- In human lungs of IPF patients, CCR2⁺ cells concentrated in perifibrotic regions and correlated with radiotracer localization (n=21)
- Human imaging revealed little lung uptake in healthy volunteers (n=7) while IPF patients (n=4) showed intensive signals in fibrotic zones

Conclusion and take home message: Imaging identifies profibrotic interstitial macrophages in mouse models and perifibrotic uptake in the lungs of IPF patients, suggesting as a non-invasive tool for clinical assessment

Hariri LP et al. Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory syndrome and H1N1 influenza. A systematic review. Chest 2021;159:73-84

Background:

- How does the lung histopathology described in COVID 19 compare with the lung histopathology described in SARS and H1N1 influenza was their question for this study

Methods:

- Systematic literature review to characterize the lung histopathology of COVID-19 and compare with those of H1N1 influenza and SARS; key words pathology, biopsy and sutopsy
- 26 articles on 171 COVID-19 pts; 20 articles on 287 H1N1 pts; 8 articles on 64 SARS pts

Results:

- DAD in 88% of COVID-19, similar to H1N1 (90%) and SARS (98%) pts
- Microthrombi in 57% of COVID-19, 58% of SARS, and 24% of H1N1 influenza pts

Conclusion and take home message: DAD is the main finding in all three conditions, while microthrombi are less prevalent in H1N1 pts than in COVID and SARS

Massoth LR et al. Comparison of RNA in situ hybridization and immunohistochemistry techniques for the detection and localization of SARS-CoV-2 in human tissues. Am J Surg Pathol 2021;45:14-24

Background:

- To explore easier detection method for SARS-CoV-2 than EM using FFPE

Methods:

- They compared the two methods: IHC for viral nucleocapsid protein and ISH for viral RNA on FFPE
- Gold standard: qRT-PCR; negative control: lungs from autopsies before pandemic
- 4 observers reviewed the slides to record a consensus result; 4 independent observers reviewed the selected IHC and ISH slides
- 19 pulmonary and 39 extrapulmonary samples (heart, liver, kidney, small intestine, skin, adipose tissue and bone marrow)
-

Results:

- Both IHC and ISH detected the virus
- Viral cytopathic effect on HE also appreciated in some cases (smudgy chromatin or peripherally margined nuclear chromatin)
- Replication assay by detecting negative-sense viral via total RNA-seq showed active viral replication in 4 of 5
- In the lung, intracellular (pneumocytes, immune cells) or extracellular (hyaline membranes of DAD) viral RNA and protein identified; viral RNA in 68% and viral protein in 88% (including equivocal cases) of lung tissue tested
- By qRT-PCR, 86.7% sensitivity and 100% specificity for ISH, 85.7% and 53.3%, respectively for IHC
- Interobserver variability: ISH - moderate to perfect; IHC - slight to moderate
- All extrapulmonary samples from COVID-19 positive cases were negative by ISH, IHC and qRT-PCR

Conclusion and take home message:

- ISH performed better than IHC; more specific, easier to analyze and better interobserver agreement
- ISH, IHC and qRT-PCR failed to detect the virus in extrapulmonary sites

Lee TS et al. Interstitial lung abnormalities and the clinical course in patients with COPD. Chest 2021;159:128-137

Background:

- To elucidate the clinical course according to interstitial lung abnormalities (ILAs) in COPD

Methods:

- A retrospective study on COPD pts who had chest CT and longitudinal PFTs during 1/2013-12/2018 period
- Evaluation of radiologic findings, hx of acute exacerbation of COPD, and PFT changes

Results:

- Of 363 COPD pts, 44 and 103 pts had equivocal and definite ILAs, respectively

- Pts with ILAs were older and had lower FEV1 and FVC than those without ILAs
- During the mean f/u of 5.2 yrs, ILAs were associated with the annual incidence of moderate to severe acute exacerbation of COPD and with the risk of frequent exacerbation
- Pts with progressive ILAs showed a significantly higher rate of annual decline in FEV1 and FVC than though with no change or improved ILAs

Conclusion and take home message: ILAs in COPD adversely affect the px

Case Reports

Mayer N et al. Sclerosing pneumocytoma. A host for a typical carcinoid with pleural metastasis- a wolf in sheep's clothing. Chest 2021;159:e1-e5

A unique case of a metastasized typical carcinoid (TC) enclosed by a sclerosing pneumocytoma (SP) with the TC macroscopically breaking through the visceral pleura

Mart MF et al. Pneumomediastinum in acute respiratory distress syndrome from COVID-19. Am J Respir Crit care Med 2021;203:237-238

Barotrauma from COVID-19 has been increasingly described. This study reported 5 pts with pneumomediastinum found in 92 critically ill, mechanically ventilated adults with ARDS from COVID-19 at one institution

Odackal J et al. A 28-year-old man with chest pain, shortness of breath, and hemoptysis after recovery from coronavirus disease 2019 pneumonia. Chest 2021;159:e35-e38

A man presented with SOB, chest pain and scant hemoptysis 3 weeks after recovering from COVID-19 and eventually was diagnosed as rupture of COVID-19 induced pneumatocele caused by a pneumothorax and loculated hydropneumothorax. This is another case illustrating that pneumatocele developed during the course of COVID-19 pneumonia.

Kidane B et al. Identification and resolution of asymptomatic COVID-19 pneumonitis and colitis: serial assessment of fluorodeoxyglucose positron emission tomography-computed tomography for evaluation of lung cancer. J Thorac Oncol 2021;16:e1-e3

A 67-year-old man with no smoking hx had a chest radiograph for dyspnea, which revealed a right lung nodule. He subsequently had a CT chest which confirmed a spiculated lung nodule suggestive of lung cancer and nothing else. PET/CT was taken 4 weeks later and he traveled to Egypt and Jordan after the first CT and 3 weeks prior to PET/CT. He reported mild GI sx while traveling, attributed to traveler's diarrhea. The diarrhea resolved rapidly, 3 weeks prior to PET/CT. He underwent a needle bx of the lung mass and had GGOs at the time of bx. Coronavirus testing was taken and returned as positive. He did not receive any COVID therapy since he was asymptomatic. The needle bx showed lung adenoca. The repeat PET/CT was taken for follow up. During this course of work up, they observed resolution of COVID-19-related abnormalities in both lung and bowel.

Park SY et al. Case of a 21-year-old man with hemoptysis, recurrent pneumothorax and cavitary lung lesions. Chest 2021;159:e13-e17

A case of vascular Ehlers-Danlos syndrome presenting with a manifestation that mimics vasculitis

Rodriguez-Lopez J et al. When imaging in chronic thromboembolic pulmonary hypertension is not enough. Am J Respir Crit Care Med 2021;203:e3-e4

Pulmonary artery sarcoma mimicking pulmonary embolism that was difficult to distinguish from chronic thromboembolic PHT

Zirek F. A 2-year-old boy with hypoxemia, pulmonary hypertension, and digital clubbing. Chest 2021;159:e45-e48

A case of congenital extrahepatic portosystemic shunt (Abernethy malformation) type II

Reviews

Jutant EM et al. The thousand faces of leptin in the lung. Chest 2021;159:239-248

Leptin is a pleiotropic hormone known to regulate a wide range of systemic function, from satiety to inflammation. Leptin signalling pathway is also involved in immune modulation and cell proliferation, and its dysregulation can lead to the onset of lung disease. Aside from obesity, independently from body weight, leptin plays many lung functions. Leptin may also play a role in idiopathic lung fibrosis and may be associated with acute exacerbation of IPF

Thillai M et al. BTS clinical statement on pulmonary sarcoidosis. Thorax;76:4-20

Bradley KL et al. Role of unfolded proteins in lung disease. Thorax 2021;76:92-99

Editorial and Letters

Cosgrove GP et al. A new piece to help solve the interstitial lung disease diagnostic puzzle. Am J Resp Crit Care Med 2021;203:158-160

Welte T. SARS-CoV-2-triggered immune reaction: for covid-19, nothing is as old as yesterday's knowledge. Am J Resp Crit Care Med 2021;203:156 (for 5th discussion paper)

Montesi SB. Molecular imaging of pulmonary fibrosis: another step forward. Am J Resp Crit Care Med 2021;203:6-7 (for a non-neoplastic paper of notation)

Arakwa S et al. RB1 loss induced small lung cancer transformation as acquired resistance to pembrolizumab in an advanced NSCLC patient. Lung Cancer 2021;151:101-103

Lynch DA. Interstitial lung abnormality incidentally detected on CT. An important prognostic indicator. Chest 2021;159:5-6