

Pulmonary Journal Club January 2021 (Articles from December 2020)

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- 23 Laflamme P, Babak M, et. al; Phospho-histone-H3 immunostaining for pulmonary carcinoids: impact on clinical appraisal, interobserver correlation, and diagnostic processing efficiency. *Hum Path* 2020; 106, 74-81

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- 24 Graham J, Ventura I, et. al; Myositis-specific antibodies identify a distinct Interstitial pneumonia with autoimmune features phenotype. *Eur Respir J* 2020; 56 (6).
- 25 Hetzel J, Wells A, et. al; Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicenter trial. *Eur Respir J* 2020; 56 (6).
- 26 Sauter J, Baine M, et. al; Insights into pathogenesis of fatal COVID-19 pneumonia from histopathology with immunohistochemical and viral RNA studies; *Histopath* 2020; 77 (6), 915-925.
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- 27 Abengozar-Muela M, Esparza M, et. al; Diverse immune environments in human lung tuberculosis granulomas assessed by quantitative multiplexed immunofluorescence. *Mod Path* 2020; 33, 2507-2519.

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- 30 Smith M, Hariri L, et. al; Histopathologic Assessment of Suspected Idiopathic Pulmonary FibrosisL Where We Are and Where We Need to Go. *Arch Pathol Lab Med* 2020; 144 (12) 1477-1489.
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Articles for Discussion

Yatabe Y. Reassessing the SCLC Subtypes, Editorial. J Thorac Oncol. 2020 Dec;15(12):1819-1822.doi: 10.1016/j.jtho.2020.10.011.

Background

- NSCLC is recognized to consist of multiple disease entities, and its treatment now depends not only on histologic subtype but also on genetic subtype
- In contrast, SCLC remains a single disease entity, biologically and clinically and patients are treated with chemoradiation therapy
- Although the expression of NE markers is well known to be variable in SCLC, historically, the extent of NE marker expression has not been regarded as biologically relevant and was not known to be associated with any specific tumor characteristics.
- Genomically, SCLC is also a highly homogeneous disease, with most cases characterized by inactivating RB1 and TP53 alterations
- The biological heterogeneity of SCLC has started to emerge only recently but before discussing this will look at new knowledge about biology of airway epithelium from recent studies using animal models and human biopsies and incorporating scRNA-seq and CRISPR techniques
- The epithelial cell layer of the airways is a dynamic cellular structure encompassing a wide range of highly specialized cells that are able to respond to environmental change, interact with resident microbial communities and cooperate with multiple other specialized cellular systems such as the immune and neural systems
- Rare cells that comprise <1% of cells include **tuft, pulmonary neuroendocrine cells (PNEC) and CFTR-rich ionocytes**
- **Tuft cells/brush cells**, (fibrillovesicular cells, multivesicular cells and caveolated cells) Initially discovered in rat trachea > 60 y ago
- Found in mucosal tissues, thymus
- A rose is a rose, but what is a brush cell?' Thurlbeck (1990) in a comment on a paper in human fetuses.
- Chemosensory cells sentinels of their environment, to which they respond by secretion of diverse biological mediators such as IL25 or acetylcholine; in the intestine they mediate type 2 immunity against parasites
- Tuft cells are the likely progenitor of both PNEC and CFTR-rich ionocytes
- **PNECs** are cells (solitary or in neuroendocrine bodies) resident within the surface epithelium of the trachea, bronchi and bronchioles chemosensors of the airway and respond to changes in oxygen, stretch and chemical stimuli
- Rich source of neuropeptides and neurotransmitters that elicit immune and physiological effects.
- A defining characteristic marker of PNECs is the gene ASCL1, coding for a transcription factor
- Pan-epithelial effects of smoking reach the basal stem cells and include induction of chemokine signaling and xenobiotic metabolism at the expense of innate immune signaling.
 - Surface secretory cells shift their mucin programs toward a MUC5AC-dominated

- inflammatory state
Submucosal gland (SMG) secretory cells lose many of their distinctive defensive secretions
- Hybrid secretory/early ciliating cells preferentially lose ciliogenic function, hindering regeneration
 - **Tuft cells are pushed toward functionally impaired ionocyte- or PNEC-like states**
 - Smoker epithelium rendered more functionally monochromatic, collapsing on the secretory and proteosomal basal cell phenotypes at the expense of its normal defensive, interactive, and reparative roles essential to lung health and homeostasis.

Baine MK et al., SCLC Subtypes Defined by ASCL1, NEUROD1, POU2F3, and YAP1: A Comprehensive Immunohistochemical and Histopathologic Characterization. J Thorac Oncol 2020 Dec;15(12):1823-1835

Background:

- Rudin has proposed four molecular subtypes of SCLC defined by the expression status of key transcription factors in SCLC: ASCL1, NEUROD1, POU2F3, YAP1
- Problems with this – e.g. a subset of ASCL1/NEUROD1 double-negative, so-called non-NE SCLC (!!), was found to express and exhibit dependence on POU2F3 (marker of tuft cells)
- Very limited information on the expression of these genes in the native clinical samples of SCLC and the pathologic characteristics associated with these subtypes

Aims:

- To assess the distribution of gene expression at the protein level and associated pathologic characteristics in clinical SCLC samples
- Evaluate the expression of DLL3 as both an additional marker of NE differentiation and as a therapeutic target

Methods

- 122 samples SCLC Memorial Sloan Kettering Cancer Center
- 52 SCLC analyzed in tissue microarrays
- IHC
 - ASCL1, NEUROD1, POU2F3, and YAP1
 - synaptophysin, chromogranin A, CD56, and INSM1
 - TTF-1/NKX2-1 and Ki-67
 - TMA only -DLL3
- IHC Scoring Criteria:
 - percent of positive cells (1%–100%)
 - intensity of labeling (1 = weak, 2 = moderate, 3 = strong)
 - histoscore (H-score) percent positivity x intensity score = 0 to 300.

- NE score: average of H-scores for chromogranin A, synaptophysin, CD56, and INSM1
 - NE low: 0-150
 - NE-high > 150
- ASCL1, NEUROD1, POU2F3, YAP1, DLL3: H-scores 0-50 ‘low’, >50 ‘high’
- H-scores ASCL1 > NEUROD1 “ASCL1-dominant” and vice versa
- The Ki-67 index - percentage of positive cell
- TTF-1 was scored as either positive (any extent and intensity of labeling) or negative.
- JMP version 14.0 software (SAS Institute); two-tailed t test analysis of continuous variables (H-scores, Ki-67 proliferative index, etc); likelihood-ratio chi-square test was used for the analysis of categorical data.

Results

- Histologically:
 - 82% pure SCLC
 - 18% combined: AdCa (7%), SCC (3%), and LCNEC (9%)
- Tumors with dual-high ASCL1 and NEUROD1 expression revealed that all but one case had both markers coexpressed in the same tumor cell populations
- POU2F3 expressed in 7% of SCLC - mutually exclusive of ASCL1 and NEUROD1 and significantly enriched in the combined SCLC.
- YAP1 expressed at low levels, primarily in combined SCLC (expression often higher in the NSCLC component), and was not exclusive of other subtypes
- **Final grouping:**
 - ASCL1-dominant (AD)
 - NEUROD1-dominant (ND)
 - ASCL1/NEUROD1 double-negative with POU2F3 expression (POU2F3) (PO)
 - ASCL1/NEUROD1 double-negative not otherwise specified (NOS)
- AD and ND subtypes: with NE marker high/TTF-1high/DLL3high profile
- PO and NOS: NE marker low/TTF-1low/DLL3low
- Ki-67 revealed equivalent distribution in all groups
- TTF-1 strongly linked with ASCL1
 - Most SCLC with ASCL1 were TTF-1-positive
 - NEUROD1-only expression were entirely TTF-1-negative
 - Nearly all PO and most of NOS tumors were TTF-1-negative.
- DLL3:
 - High in AD and ND tumors
 - negative in PO & NOS tumors
- Comparison of patient and tumor characteristics, including age, sex, pack-year smoking history, tumor site (primary versus metastatic), site of metastasis (lymph node versus other organs), and specimen type yielded no significant difference in SCLC subtypes (Supplementary Table 4).

Conclusions

- Confirmed that ASCL1/NEUROD1 double-negative tumors represent a distinct NE-low subtype of SCLC, which is either uniquely associated with POU2F3 or lacks a known dominant regulator
- TTF-1 was consistently negative in NEUROD1-only tumors but positive in nearly all tumors with ASCL1 expression at any level
- YAP1 had a distinctly low expression and did not define a distinct subtype of SCLC.
- The distinctive nature of POU2F3-positive SCLC, characterized by NE markerlow/TTF-1low/DLL3low phenotype requires more study.
- Therapies targeting DLL3 should be considered to patients with the SCLC-A and SCLC-N subtypes, who express high levels of DLL3
- For now, it would be reasonable to classify SCLC into three subtypes (SCLC-A, SCLC-N, and double negative [DN]) or four subtypes (SCLC-A, SCLC-N, DNPOU2F3, DN-NOS)
- Further studies are warranted to determine whether expression-based subtypes of SCLC are associated with distinct patient outcomes and/or predict distinct therapeutic vulnerabilities.

Pearsall SM, Humphrey S, Reville M, Morgan D, Frese KK, Galvin M, Kerr A, Carter M, Priest L, Blackhall F, Simpson KL, Dive C. The Rare YAP1 Subtype of SCLC Revisited in a Biobank of 39 Circulating Tumor Cell Patient Derived Explant Models: A Brief Report. J Thorac Oncol. 2020 Dec;15(12):1836-1843.

Background:

- The tumor-suppressive Hippo pathway controls cell proliferation, apoptosis, and organ size
- Active Hippo signaling - YAP1 is inactivated and sequestered in the cytoplasm for degradation.
- Inactive Hippo signaling - YAP1 binds nuclear TFs to direct prosurvival gene expression, proliferation, and tissue growth
- YAP1 nuclear activity correlates with chemoresistance, cancer stem cell renewal, and metastasis.

Aim: To evaluate YAP1 RNA and protein expression in circulating tumor cell–derived explant (CDX) models, to provide a characterization of YAP1 at single-cell resolution.

Methods:

- CDX models were generated from patients' CTCs enriched from blood samples pre-chemotherapy baseline or at posttreatment disease progression time points (designated P or PP)
- YAP1 transcript and protein expression were assessed by RNA sequencing and IHC or multiplexed IF of NE and non-NE CDX subpopulations.
- IHC included SYP and REST, a repressor of NE differentiation in SCLC
- Western blots for protein for YAP1, SYP, and AXL.

Results:

- Where YAP1 expression was confined to cell clusters, it colocalized with REST, a repressor of NE differentiation in SCLC, concordant with reduced expression of the SCLC diagnostic NE marker SYP, indicating non-NE cell expression of YAP1
- YAP1 expression is predominantly in non-NE cells but can also be present at lower levels in NE-low cells.

Conclusions:

- YAP1 was predominantly expressed in non-NE cell clusters
- Similar to the results by Baine *et al.* YAP1 expression alone did not define a single group
- In some models, NEUROD1 expression declined with disease progression and in others YAP1 lineage emerged - suggests that SCLC molecular subtypes may have some plasticity
- In future, SCLC subtyping may need to account for both temporal and spatial expressions of SCLC transcriptional drivers to fully appreciate intratumoral heterogeneity,

Take home message

- Overall, the emerging data on molecular heterogeneity of SCLC holds promise for biomarker-driven personalized therapeutic approaches for this aggressive disease
- Further studies are needed to determine if IHC for the transcription factors discussed here will be useful in diagnosis/prognosis of SCLC or can be used to guide new therapies

Marshall K, Jackson S, et. al; Homozygous deletion of CDKN2A in malignant mesothelioma: Diagnostic utility, patient characteristics and survival in a UK mesothelioma centre. Lung Can 2020; 150, 195-200.

Background

- Homozygous deletion of cyclin-dependent kinase inhibitor 2A (CDKN2A) one of commonest mutations in MM. Tumor suppressor gene that codes for p16 (activates retinoblastoma protein) and p14 (activates p53).
- CDKN2A FISH (referred to herein as p16 FISH) is used to detect homozygous deletion of the gene.
- The Manchester University NHS Foundation Trust is a regional mesothelioma centre for the North West of England where p16 FISH testing has been available as an ancillary diagnostic test for cases of suspected mesothelioma since 2012.

Aims:

- To investigate the diagnostic performance of this test from 2012-2019
- To investigate the clinical characteristics and outcomes of patients with p16 FISH positive mesothelioma compared to p16 FISH negative mesothelioma.

Methods

- All patients that had undergone p16 FISH testing for suspected mesothelioma over a 7-year period
- p16 FISH testing only utilized when atypical mesothelial cells are present but a definitive diagnosis not possible. Atypical cells must first be confirmed as mesothelial in origin by IHC. This isn't always possible, sometimes just keratins are positive.
- Patients that had a final diagnosis of mesothelioma were categorized as p16 FISH positive / negative to allow comparison of patient characteristics and survival

Results

- 206 pathological samples from 205 patients with a suspicion of mesothelioma but no definitive diagnosis and which had successful p16 FISH performed were included. (The largest sample size studied to date)
- 48 (23 %) samples were cytology samples (pleural fluid n = 46, ascitic fluid n = 2)
- 158 (77 %) samples were histological (pleural biopsy n = 153, peritoneal biopsy n = 3, lymph node biopsy n = 1 and orchidectomy n = 1)
- Final diagnosis
 - mesothelioma in 163 cases, epithelioid in 43%
 - lung cancer in 3 cases
 - benign pleuritis in 39 cases
- p16 FISH positive: 99 (48 %) – all mesothelioma; 99/164 = 60% sensitivity
- No false positive p16 FISH results (specificity 100 %, positive predictive value 100 %).
- p16 FISH negative: 107 (52 %) - all 39 benign pleuritis, 3 lung cancer, 65 mesothelioma (negative predictive value 39 %).
- The highest proportion of cells with homozygous deletion of CDKN2A in cases of benign pleuritis was 13 % in two cases.

- Cut-off for a positive p16 FISH test of ≥ 20 % of cells displaying the homozygous deletion of CDKN2A appropriate (no false positives)
- No difference in the sensitivity of the test in different morphologic types of MM
- Sensitivity of p16 FISH higher in cytology than histology (75 % vs 58 %, $p = 0.03$)
- Prevalence of p16 FISH positive mesothelioma was lower in women compared to men (33 % vs 66 %, $p = 0.003$).
- p16 FISH positive mesothelioma was associated with significantly worse survival (median overall survival 285 vs 339 days, $p = 0.0018$) even after adjusting for confounding variables (age, performance status, mesothelioma sub-type and treatment)

Take home message

- Corroborates previous studies which indicate 100% specificity for differentiating mesothelioma from reactive
- No increased sensitivity in sarcomatoid meso: for pleural sarcomatoid mesotheliomas sensitivity of p16 FISH has been reported in 80-100%; might be because constituted only 35 in total of the 163 cases of mesothelioma in this paper therefore not enough power to show a difference.
- Suitable for cytology samples and its sensitivity appears to be higher in this type of sample- evidence for incorporation of diagnostic pleural fluid aspiration into mesothelioma guidelines
- Worse survival in p16 FISH cases needs further study ?related to increased positivity in sarcomatoid meso as shown by other studies

Chevrier M, Monaco S, et. al; Testing for BAP1 loss and CDKN2A/p16 homozygous deletion improves the accurate diagnosis of mesothelial proliferations in effusion cytology. Can Cyto 2020; 128 (12), 939-947.

Background

- 2018 American Society of Clinical Oncology -the cytological evaluation of pleural fluid an initial screening test for mesothelioma, - not a sufficiently sensitive diagnostic test.

Aim: to determine whether testing for BAP1 and CDKN2A/p16 status in effusion specimens preceding the definitive tissue diagnosis of malignant pleural and peritoneal mesothelioma would significantly change the diagnostic interpretation and lead to an earlier diagnosis of malignancy.

Methods

- Retrospective study
- Diagnosis of epithelioid/biphasic MM pleura/peritoneum on histology randomly selected from the archives of the University of Pittsburgh Medical Center - 5 years.
- Corresponding pleural and peritoneal effusion specimens

- None of the effusion specimens were tested for BAP1 loss or CDKN2A/p16 homozygous deletion at the time of the initial diagnostic workup
- P16 FISH -positive if homozygous deletion was identified in at least 20% of tumor cells.
- samples were considered a true positive if they were labeled as malignant, showed BAP1 loss, and/or showed CDKN2A/p16 homozygous deletion.

Results

- A total of 99 matched sufficient cytology fluid specimens were identified in **74 patients** with surgical biopsy or resection specimen diagnosis of malignant mesothelioma – [this gives rise to confusion in the numbers stated in the body of the report vs the tables; authors refer to ‘cases’ or ‘specimens’ of MM.](#)
- 67 epithelioid, 7 biphasic; 55 pleural and 19 peritoneal mesotheliomas
- Cytology morphologically interpreted as
 - negative for malignancy (18)
 - atypical (36)
 - suspicious for malignancy (15)
 - malignant (30).
- BAP1 lost in 69% **cases** of mesothelioma
 - 73% pleural
 - 58% peritoneal
- p16 FISH positive 41% **cases** of mesothelioma
 - 50% pleural
 - 16% peritoneal
- BAP1 loss plus p16 FISH positive 31% **cases** (20 pleural and 3 peritoneal).
- Overall, loss of BAP1 and/or *CDKN2A/p16* homozygous deletion would change the diagnostic interpretation in 37 of 60 (62%) ($P = .07$) effusion **specimens**, particularly in **pleural** effusions (32 of 48 samples) ($P = .002$)
- BAP1 loss – in ~ half of the cases interpreted as negative or indeterminate (atypical or suspicious); ~ two thirds of the cases interpreted as malignant
- P16 FISH positive in approximately 25% ‘negative’ and 45% atypical cases
- BAP1 and/or p16 testing would have changed the diagnosis from benign to malignant in 7 cases and from atypical to malignant in 10 cases therefore overall change in diagnosis (based on cytology specimen) estimated at 23%
- The sensitivity of morphologic interpretation alone was 30.3%; adding testing for BAP1 and *p16* resulted in an increase in sensitivity to **68.7%**. ($P < .0001$).
- The group that was diagnosed as malignant had the largest proportion of cases with BAP1 and CDKN2A/p16 loss
- In one patient, the diagnosis could have been made up to 9 months prior to a definitive diagnosis of malignant mesothelioma on a biopsy specimen

Take home message

- Looked at 99 paired specimens in 74 patients – confusing presentation of results, no mention/discussion of how the multiple specimens from the same patient behaved.

- However, good evidence for routine use of validated assays for BAP1 IHC and/or p16 FISH for earlier, more definitive, and accurate cytologic diagnoses of mesothelioma in effusion specimens.
- Step wise testing, BAP1 first and if intact, recommend p16 FISH
- Identification of either BAP1 loss or CDKN2A/p16 homozygous deletion in effusion specimens in a patient without a mass lesion should prompt a more aggressive pleural or peritoneal tissue sampling.

Articles for Notation – Neoplastic

Prabhakaran S, Hocking A, et. al; The potential utility of GATA binding protein 3 for diagnosis of malignant pleural mesotheliomas. Hum Path 2020; 105, 1-8.

Background:

- Usefulness of IHC for diagnosis of sarcomatoid mesothelioma, especially the desmoplastic type, is limited
- GATA binding protein 3 (GATA3) has been suggested as a diagnostic marker for sarcomatoid mesothelioma.

Aim: To determine the potential usefulness of GATA3 for prognostication and its clinical and pathological correlations in different subtypes of mesothelioma

Methods:

- 149 MM – 3 major types
- IHC: GATA3, BRCA1-associated protein 1 (BAP1), and Ki67 labeling
- 10 cases of fibrous pleuritis IHC- GATA3

Results:

- Fibrous pleuritis GATA negative
- GATA3 positive in 75 of 149 (50%) mesotheliomas
 - sarcomatoid subtype (73%)
 - biphasic (50%)
 - epithelioid (40%)
- A total of eight desmoplastic mesotheliomas -100% GATA3 positive
- GATA3 labeling did not have a statistically significant association with survival
- No association of GATA3 labeling and BAP1 status or Ki67 index

Take home message: GATA3 is a useful marker for sarcomatoid mesothelioma, including the desmoplastic subtype.

Matsumura E, Kajino K, et. al; Expression status of PD-L1 and B7-H3 in mesothelioma. Pathology International 2020; 70, 999-1008.

Background: Mesothelioma is a rare, aggressive malignancy with poor outcome, and has limited treatment options

Aim: Comprehensive analysis of programmed death ligand 1 (PD-L1) and B7 homolog 3 (B7-H3) expression in mesothelioma and their potential correlation with histological subtype, which might help to develop new therapies targeting these immune checkpoint molecules

Results:

- 31 patients - 22 epithelioid, 6 sarcomatoid, and 3 biphasic types
- 13 (41.9%) positive for PD-L1 and 28 (90.3%) B7-H3 positive. 12 positive for both.
- PD-L1 and B7-H3 were widely co-expressed in non-epithelioid type
- No PD-L1 and B7-H3 expression in normal mesothelial cells,

Take home message: More work needs to be done to determine the value of IC therapy

Bubendorf L, Conde E, et. al; A noninterventional, multinational study to assess PD-L1 expression in cytological and histological lung cancer specimens. Can Cyto 2020; 128 (12), 928-938.

Background:

- The diagnosis of advanced lung cancer is made with minimally invasive procedures often with only cytological material available
- Companion diagnostic testing only technically and clinically validated on histological material

Aim: to assess programmed death ligand 1 (PD-L1) protein expression on cytology samples as surrogates for histology samples in patients with lung cancer.

Methods

- Histological samples and cytological cell blocks from 190 patients
- PD-L1 expression was quantified on both tumor cells (TC) and tumor-infiltrating immune cells (IC)

Results:

- NSCLC histology and cytology samples
 - PD-L1 (SP142) antibody ICC were 0.40 and 0.06 on TC and IC, respectively
 - With SP142 and SP263, accuracies of 74.1% for TC and 51.9% for IC and accuracies of 75.2% for TC and 61.2% for IC, respectively, were reported.

Take home message:

- PD-L1 analysis on TC is feasible in cytological material, but quantification is challenging
- Tumor tissue still preferred over cell block cytology for PD-L1 unless laboratories have validated their cytology preanalytical approaches and demonstrated the comparability of histology and cytology for TC PD-L1 results.

Krause A, Roma L, et. al; Deciphering the clonal relationship between glandular and squamous components in adenosquamous carcinoma of the lung using whole exome sequencing. Lung Can 2020; 150, 132-138.

Background:

- Adenosquamous carcinoma of the lung (ASC) is a rare subtype of non-small cell lung cancer, consisting of lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) components
- ASC shows morphological characteristics of classic LUAD and LUSC but behaves more aggressively
- Genomic background poorly understood

Aim

- Macrodissected LUAD and LUSC components of three ASC using whole exome sequencing (WES)

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Results:

- Identified truncal mutations - *TP53*, *EGFR*, *BRAF*, and *MET*, which are characteristic for LUAD but uncommon in LUSC.
- No truncal mutation of classical LUSC driver mutations were found.
- Both components showed unique driver mutations that did not overlap between the 3 ASC.
- Detected loss of *STK11* and *SOX2* amplification in ASC, which has previously been shown to drive transdifferentiation from LUAD to LUSC in preclinical mouse models.

Take home message: Suggest that the LUAD and LUSC components of ASC share a common origin and that the LUAD component appears to transform to LUSC.

Kriegsmann K, Zgotzelski C, et. al; Immunohistological expression of oestrogen receptor, progesterone receptor, mammaglobin, human epidermal growth factor receptor 2 and GATA-binding protein 3 in non-small-cell lung cancer. Histopath 2020; 77 (6), 900-914.

Background: NSCLC and breast cancer are common entities. Staining for oestrogen receptor (ER), progesterone receptor (PgR), mammaglobin (MAMG) and GATA-binding protein 3 (GATA3) is frequently performed to confirm a mammary origin in the appropriate diagnostic setting.

Aims: to analyse a large cohort of NSCLCs and correlate the staining results with clinicopathological variables.

Methods and results

- A tissue microarray was stained for ER, PgR, MAMG, human epidermal growth factor receptor 2 (HER2), and GATA3, and included 636 adenocarcinomas (ADCs), 536 squamous cell carcinomas (SqCCs), 65 large-cell-carcinomas, 34 pleomorphic carcinomas, and 20 large-cell neuroendocrine carcinomas.

- Among ADCs, 62 (10%), 17 (3%), one (<1%), seven (1%), and 49 (8%) cases were positive for ER, PgR, MAMG, HER2, and GATA3, respectively.
- Among SqCCs, 10 (2%), 14 (3%), two (<1%) and 109 (20%) cases were positive for ER, PgR, HER2, and GATA3, but none of the samples showed positivity for MAMG.
- ER positivity was associated with ADC, female sex, smaller tumour size, and lower clinical stage.

Take home message: Unlikely to change anyone's practice.

Laflamme P, Babak M, et. al; Phospho-histone-H3 immunostaining for pulmonary carcinoids: impact on clinical appraisal, interobserver correlation, and diagnostic processing efficiency. Hum Path 2020; 106, 74-81.

Background:

- Lung carcinoid tumors are classified as either typical or atypical based on the presence of necrosis and the maximum mitotic count per 2 mm² area.
- Determining the mitotic count is time-consuming and subject to high interobserver variability

Aim: to test the sensitivity and specificity of a surrogate mitosis marker, phospho-histone-H3 (PHH3) immunostaining, in the processing of pulmonary carcinoids as compared with the standard HE evaluation.

Methods

- Carcinoid tissue blocks that were available from lung resection specimens were analyzed using HE and PHH3 stains.
- Two thoracic pathologists and two residents determined the mitotic count on HE and PHH3 stains in accordance with the 2015 WHO guidelines and recorded the time required to complete this task.

Results:

- for both pathologists and residents, the time required to determine the mitotic count using the PHH3 method was reduced compared with the traditional HE method.
- residents detected more mitoses/2 mm² using the PHH3 stain compared with the HE method.
- PHH3 method yielded better interobserver agreement than the HE method in terms of mitoses/mm² detection.

Take home message: PHH3 staining provides practical benefits in terms of scoring times, mitosis detection, and reproducibility of mitotic counts.

Articles for Notation – Non-Neoplastic

Legendre M, Butt A; et. al; Functional assessment and phenotypic heterogeneity of SFTPA1 and SFTPA2 mutations in interstitial lung diseases and lung cancer. Eur Respir J 2020; 56 (6).

Background:

- Interstitial lung diseases (ILDs) can be caused by mutations in the *SFTPA1* and *SFTPA2* genes, which encode the surfactant protein (SP) complex SP-A.
- Only 11 *SFTPA1* or *SFTPA2* mutations have so far been reported worldwide, of which five have been functionally assessed. In the framework of ILD molecular diagnosis, we identified 14 independent patients with pathogenic *SFTPA1* or *SFTPA2* mutations.

Aim: to functionally assess the 11 different mutations identified in 14 patients with pathogenic *SFTPA1* or *SFTPA2* mutations and to accurately describe the disease phenotype of the patients and their affected relatives.

Results

- For the 11 identified mutations, protein production was preserved but secretion was abolished.
- The expression pattern of lung SP-A available in six patients was altered and the family history reported ILD and/or lung adenocarcinoma in 13 out of 14 families (93%).
- Among the 28 *SFTPA1* or *SFTPA2* mutation carriers, the mean age at ILD onset was 45 years (range 0.6–65 years) and 48% underwent lung transplantation (mean age 51 years).
- Seven carriers were asymptomatic.

Take home message: pathogenic *SFTPA1* or *SFTPA2* mutations share similar consequences for SP-A secretion in cell models and in lung tissue immunostaining, whereas they are associated with a highly variable phenotypic expression of disease, ranging from severe forms requiring lung transplantation to incomplete penetrance.

Graham J, Ventura I, et. al; Myositis-specific antibodies identify a distinct interstitial pneumonia with autoimmune features phenotype. Eur Respir J 2020; 56 (6).

Background:

- Interstitial pneumonia with autoimmune features (IPAF) characterises individuals with interstitial lung disease (ILD) and features of connective tissue disease (CTD) who fail to satisfy CTD criteria.
- Inclusion of myositis-specific antibodies (MSAs) in the IPAF criteria has generated controversy, as these patients also meet proposed criteria for an antisynthetase syndrome.

Aim: To assess clinical features and outcomes in patients meeting IPAF criteria stratified by the presence of MSAs and MAAs.

Methods:

- A multicentre, retrospective study to assess clinical features and outcomes in patients meeting IPAF criteria stratified by the presence of MSAs and MAAs.
- IPAF subgroups were compared to cohorts of patients with idiopathic inflammatory myopathy-ILD (IIM-ILD), idiopathic pulmonary fibrosis and non-IIM CTD-ILDs.
- The primary end-point assessed was 3-year transplant-free survival.

Results:

- 269 patients met IPAF criteria, including 35 (13%) with MSAs and 65 (24.2%) with MAAs.
- Survival was highest among patients with IPAF-MSA and closely approximated those with IIM-ILD.
- Survival did not differ between IPAF-MAA and IPAF without MSA/MAA cohorts. Usual interstitial pneumonia (UIP) morphology was associated with differential outcome risk, with IPAF patients with non-UIP morphology approximating survival observed in non-IIM CTD-ILDs.
- MSAs, but not MAAs identified a unique IPAF phenotype characterised by clinical features and outcomes similar to IIM-ILD. UIP morphology was a strong predictor of outcome in others meeting IPAF criteria.

Take home message: Because IPAF is a research classification without clear treatment approach, these findings suggest that MSAs should be removed from the IPAF criteria and such patients should be managed as an IIM-ILD.

Hetzel J, Wells A, et. al; Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicenter trial. Eur Respir J 2020; 56 (6).

Background

- The accurate diagnosis of individual interstitial lung diseases (ILD) is often challenging, but is a critical determinant of appropriate management.
- If a diagnosis cannot be made after multidisciplinary team discussion (MDTD), surgical lung biopsy is the current recommended tissue sampling technique according to the most recent guidelines.

Aim: to determine feasibility of transbronchial lung cryobiopsy (TBLC) as an alternative to surgical lung biopsy.

Methods

- This prospective, multicentre, international study analysed the impact of TBLC on the diagnostic assessment of 128 patients with suspected idiopathic interstitial pneumonia by a central MDTD board (two clinicians, two radiologists, two pathologists).
- The level of confidence for the first-choice diagnoses were evaluated in four steps
 - 1) clinicoradiological data alone
 - 2) addition of bronchoalveolar lavage (BAL) findings
 - 3) addition of TBLC interpretation
 - 4) surgical lung biopsy findings (if available).
- The contribution of TBLC to the formulation of a confident first-choice MDTD diagnosis was evaluated.

Results

- TBLC led to a significant increase in the percentage of cases with confident diagnoses or provisional diagnoses with high confidence (likelihood $\geq 70\%$) from 60.2% to 81.2%.
- In 32 out of 52 patients nondiagnostic after BAL, TBLC provided a diagnosis with a likelihood $\geq 70\%$.

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- The percentage of confident diagnoses (likelihood $\geq 90\%$) increased from 22.7% after BAL to 53.9% after TBLC.
- Pneumothoraces occurred in 16.4% of patients, and moderate or severe bleeding in 15.7% of patients.
- No deaths were observed within 30 days.

Take home message: TBLC increases diagnostic confidence in the majority of ILD patients with an uncertain noninvasive diagnosis, with manageable side-effects.

Sauter J, Baine M, et. al; Insights into pathogenesis of fatal COVID-19 pneumonia from histopathology with immunohistochemical and viral RNA studies; *Histopath* 2020; 77 (6), 915-925.

Background: We describe post-mortem pulmonary histopathologic findings of COVID-19 pneumonia in patients with a spectrum of disease course, from rapid demise to prolonged hospitalisation.

Methods and results

- Histopathologic findings in PM lung tissue from eight patients who died from COVID-19 pneumonia
- Immunohistochemistry (IHC) and next-generation sequencing (NGS) were performed to detect virus.
- Diffuse alveolar damage (DAD) was seen in all cases with a spectrum of acute phase and/or organising phase.
- IHC with monoclonal antibodies against SARS-CoV-2 viral nucleoprotein and spike protein detected virus in areas of acute but not organising DAD, with intracellular viral antigen and RNA expression seen predominantly in patients with duration of illness less than 10 days.
- Major vascular findings included thrombi in medium- and large-calibre vessels, platelet microthrombi detected by CD61 IHC and fibrin microthrombi.

Conclusions: Presence of SARS-CoV-2 viral RNA by NGS early in the disease course and expression of viral antigen by IHC exclusively in the acute, but not in the organising phase of DAD, suggests that the virus may play a major role in initiating the acute lung injury of DAD

Take home message: Doesn't add much new

Youd E, Moore L; COVID-19 autopsy in people who died in community settings: the first series. *J Clin Pathol* 2020; 73, 840-844.

This series is the first in the world to describe autopsy findings in 9 individuals dying suddenly in the community, not previously known to have COVID-19 infection, and the first autopsy series in the UK.

Take home message: Findings not different to other series.

De Michele S, Sun Y, et. al; Two Distinct Pathologic Phenotypes and Correlation with Clinical and Radiologic Findings. Am J Clin Pathol 2020; 154: 748-760.

Background; Although diffuse alveolar damage is the most common microscopic pattern in coronavirus disease 2019 (COVID-19), other pathologic patterns have been described.

Aim: to review autopsies from COVID-19 decedents to evaluate the spectrum of pathology and correlate the results with clinical, laboratory, and radiologic findings.

Methods

- A comprehensive and quantitative review from 40 postmortem examinations was performed.
- The microscopic patterns were categorized as follows: “major” when present in more than 50% of cases and “novel” if rarely or not previously described and unexpected clinically.

Results

- Three major pulmonary patterns were identified:
 - ALI in 29 (73%) of 40
 - intravascular fibrin or platelet-rich aggregates (IFPAs) in 36 (90%) of 40
 - vascular congestion and hemangiomatosis-like change (VCHL) in 20 (50%) of 40
- The absence of ALI (non-ALI) was novel and seen in 11 (27%) of 40.
- Compared with ALI decedents, those with non-ALI had a shorter hospitalization course ($P = .02$), chest radiographs with no or minimal consolidation ($P = .01$), and no pathologically confirmed cause of death (9/11).
- All non-ALI had VCHL and IFPAs, and clinically most had cardiac arrest.

Take home message: an interest approach to the findings dividing into ALI and non-ALI with non-ALI being a rarely described phenotype. The images of VCHL are striking.

Lieberman-Cribbin W, Rapp J, Alpert N, et. al; The Impact of Asthma on Mortality in Patients with COVID-19. Chest 2020 December; 158 (6), 2290-2291.

Suggests there is no increased risk of dying from Covid if asthmatic.

Davis G, Williamson A. Risk of Coronavirus Disease 2019 Transmission During Autopsy. Arch Pathol Lab Med 2020; 144 (12), 1445a-1445.

PPE works!

Abengoza-Muela M, Esparza M, et. al; Diverse immune environments in human lung tuberculosis granulomas assessed by quantitative multiplexed immunofluorescence. Mod Path 2020; 33, 2507-2519.

- IHC descriptive study which is interesting and surprisingly not done before.

- Definition of a granuloma here differs from that in most pathology text books – epithelioid histiocytes and is described as - is a compact, organized immune aggregate of macrophages surrounded by myeloid, B and T cells.
- significantly more CD68+ macrophages and CD8+ T cells were found in Mycobacterium tuberculosis-infected granulomas, as detected by Ziehl–Neelsen staining.
- Only a small fraction of the CD4+ and CD8+ T cells expressed PD-1.
- multinucleated giant cells showed strong PD-L1 but not CTLA-4 membrane staining.

Take home message: Interesting but not really that informative. Would have been nice to have culture confirmation

Case Reports

Komatsu M, Sakai Y; et. al; EWSR1-CREM fusion in pulmonary mesenchymal neoplasm showing distinctive clear cell morphology. Pathology International 2020; 70, 1020-1026.

Case R, Ramaniuk A, Martin P, et. al; Systemic Capillary Leak Syndrome Secondary to Coronavirus Disease 2019. Chest 2020 December; 158 (6), e267-e268.

Delcros Q, Rohmer J, Tcherakian C, Groh M, et. al. Extensive DVT and Pulmonary Embolism Leading to the Diagnosis of Coronavirus Disease 2019 in the Absence of Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. Chest 2020 December; 158 (6), e269-e271.

Geier M, Picart G, Khatchatourian L, et. al; A 60-Year-Old Woman With Recurrent Hemoptysis. Chest 2020 December; 158 (6), e273-e277.

Hensley M, Deng J; A 35-Year-Old Smoker With Dyspnea and Chest Pain. Chest 2020 December; 158 (6), e279-e282.

Hoan L, Hang L, et. al; A 69-Year-Old Man with Chronic Cough and Recurrent Pneumonia. Chest 2020 December; 158 (6), e283-e287.

Bateman M, Kaphle U, et. al; 54-Year-Old Man with Cough, Chest Pain, and Dyspnea on Exertion. Chest 2020 December; 158 (6), e299-e303.

Mainardi A, Siddon A, et. al; Progressive Dyspnea and Hypoxemia With Diffuse Pulmonary Infiltrates in a Previously Healthy Woman. Chest 2020 December; 158 (6), e327-e334.

Hidaka K, Takeda T, et. al; Development of mesothelioma in situ and its progression to invasive disease observed in a patient with uncontrolled pleural effusions for 15 years. Pathology International 2020; 70, 1009-1014.

Laforga J, Garcia AG; Biphasic malignant mesothelioma with epithelioid and sarcomatoid components (dedifferentiated mesothelioma) and intrapulmonary growth: a rare entity mimicking desquamative interstitial pneumonia. J Clin Pathol 2020; 73.

Parama J, Hashimoto N, et. al; Pulmonary tumor thrombotic microangiopathy caused by urothelial carcinoma: An autopsy-proven case of rare etiology. Pathology International 2020; 70, 1037-1039.

Reviews, Statements, Letters

Mehrad M, Colby T, et. al; Transbronchial Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Disease. Arch Pathol Lab Med 2020; 144 (12), 1501-1508.

Background

- In approximately 30% of ILD patients, the specific diagnosis cannot be made from the clinical (including serologic) findings and HRCT features, resulting in diagnostic and management uncertainty and warranting tissue biopsy for histology.
- SLB is highly specific and sensitive ($\cong 95\%$) in diagnosing ILD but is associated with significant side effects and varying mortality
- Transbronchial cryobiopsy is less invasive and has a lower rate of complications compared with SLB.
- The main complications of transbronchial cryobiopsy are pneumothorax and bleeding.

Aim To provide an overview of the status of the medical literature regarding transbronchial cryobiopsy.

Methods

- A literature search - PubMed search engine. The terms “cryobiopsy” or “cryoprobe” and “interstitial lung disease” or “diffuse parenchymal lung disease” or “pulmonary fibrosis” were used, with the search concluding at the end of November 2019.

Conclusions

- Transbronchial cryobiopsies are generally larger than conventional transbronchial biopsies - 9 - 64.2 mm².
- A good cryobiopsy should comprise primarily alveolar tissue and be at least 5 mm in longest axis and reflective of pathologic regions seen radiologically
- Better preserved than forceps biopsy, without crush artifact
- Those that are 5 mm or greater in diameter often provide sufficient tissue to identify a pattern, such as UIP or nonspecific interstitial pneumonia
- Suggest giving a level of confidence (high versus low) for the pathologic interpretation
- Both pathologic impression and level of confidence should be correlated with clinical and radiologic findings at the time of multidisciplinary discussion, as part of the patient management.

- A standardized report proposed: site from which the sample was taken, size of tissue specimen assessed at the microscope, “central sampling” (mainly bronchial with cartilage plates identified or bronchiolar structures in greater than 40% of the surface of the sample), “peripheral sampling” (with or without visceral pleura, with alveoli present in at least 60% of the surface of the sample), and histologic pattern (eg, respiratory bronchiolitis, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, UIP, capillaritis, etc).
- If no pattern can be suggested a description of the changes present is appropriate (eg, normal lung tissue only, lung tissue with minimal focal inflammation/fibrosis, etc).
- Interobserver agreement between pathologists in cryobiopsies is similar to that of SLB. E.g. UIP versus non-UIP: 0.72.
- The diagnostic yield of transbronchial cryobiopsy in ILD varies from 51% to more than 90%, with an average of 80% to 85%*, and is greater than conventional transbronchial biopsy but lower than SLB (\cong 10%–30% for fibrotic diffuse lung disease and \cong 95%, respectively)
- The diagnostic yield is significantly increased when at least 2 samples are obtained from 2 different sites (either in the same lobe or in different lobes).
- Few studies comparing the diagnostic yield of transbronchial cryobiopsy and SLB in the same patient but larger studies show relatively good agreement and diagnostic yield of cryobiopsy was 82.8% compared with SLB, which was diagnostic in 98.7%.
- The main reasons for an inadequate/nondiagnostic cryobiopsy are (1) the presence of only bronchial wall with minimal or no peribronchial alveolar tissue-inexperienced operators and (2) the presence of only normal lung tissue or lung tissue with focal/mild nonspecific changes
- Similar to SLB, cryobiopsy should target areas with abnormal CT
- In the near future, integration of new endoscopic guidance tools for the cryoprobe may be helpful to target the best biopsy areas with greater precision

Take home message: Cryobiopsy appears to be safer than SLB and its clinical utility following multidisciplinary discussion is essentially similar to that of SLB when local expertise (clinicians, radiologists, and pathologists) is available and therefore it may be considered as an alternative to SLB in the appropriate clinicopathologic setting, limiting SLB to those patients in whom cryobiopsy is nondiagnostic

Smith M, Hariri L, et. al; Histopathologic Assessment of Suspected Idiopathic Pulmonary FibrosisL Where We Are and Where We Need to Go. Arch Pathol Lab Med 2020; 144 (12) 1477-1489.

Background: Accurate diagnosis of idiopathic pulmonary fibrosis (IPF) requires multidisciplinary diagnosis that includes clinical, radiologic, and often pathologic assessment. In 2018, the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/ERS/JRS/ALAT) and the Fleischner Society each published guidelines for the diagnosis of IPF, which include criteria for 4 categories of confidence of a histologic usual interstitial pneumonia (UIP) pattern.

Aim: To (1) identify the role of the guidelines in pathologic assessment of UIP; (2) analyze the 4 guideline categories, including potential areas of difficulty; and (3) determine steps the Pulmonary Pathology Society and the greater pulmonary pathology community can take to improve current guideline criteria and histopathologic diagnosis of interstitial lung disease.

Methods: Data were derived from the guidelines, published literature, and clinical experience.

Conclusions: Both guidelines provide pathologists with a tool to relay to the clinician the likelihood that a biopsy represents UIP, and serve as an adjunct, not a replacement, for traditional histologic diagnosis. There are multiple challenges with implementing the guidelines, including (1) lack of clarity on the quantity and quality of histologic findings required, (2) lack of recognition that histologic features cannot be assessed independently, and (3) lack of guidance on how pathologists should incorporate clinical and radiographic information. Current criteria for "probable UIP" and "indeterminate for UIP" hinder accurate reflection of the likelihood of IPF. **These challenges highlight the need for further morphologic-based investigations in the field of pulmonary pathology.**

Churg. Centrilobular Fibrosis in Fibrotic (Chronic) Hypersensitivity Pneumonitis, Usual Interstitial Pneumonia, and Connective Tissue Disease- Associated Interstitial Lung Disease. Arch Pathol Lab Med 2020; 144 (12), 1509-1516.

Background: Various pulmonary diseases can produce centrilobular (peribronchiolar) fibrosis, which may be isolated or associated with other patterns of more diffuse fibrosis. The major forms of interstitial lung disease in which centrilobular fibrosis is found are fibrotic (chronic) hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, and (a disputed issue) usual interstitial pneumonia/idiopathic interstitial fibrosis.

Aim: To review recent literature that addresses separation of these entities.

Data sources: Data comprised recent publications.

Conclusions:

- In a specially constructed multidisciplinary discussion exercise, it was found that peribronchiolar metaplasia affecting more than half the bronchioles or more than 2 foci of peribronchiolar metaplasia per square centimeter of biopsy area was strongly associated with a confident diagnosis of fibrotic hypersensitivity pneumonitis.
- Giant cells or granulomas were only found in cases with a greater than 50% diagnostic confidence in hypersensitivity pneumonitis.
- Conversely, greater numbers of fibroblast foci per square centimeter and increasing measured amounts of subpleural fibrosis favored a diagnosis of usual interstitial pneumonia.
- Connective tissue disease is a major confounder because many patterns are very similar to fibrotic hypersensitivity pneumonitis or usual interstitial pneumonia.
- Genetic abnormalities, such as the MUC5B minor allele overlap, in these conditions and at this point cannot be used for discrimination.

- Thus, the separation of fibrotic hypersensitivity pneumonitis and usual interstitial pneumonia remains a difficult problem.

Accurate biopsy diagnosis of all of these diseases requires correlation with imaging and clinical findings, and is crucial for treatment.

Cecchini M, Mukhopadhyay S, et. al; E-Cigarette or Vaping Product Use – Associated Lung Injury: A Review for Pathologists. Arch Pathol Lab Med 2020; 144 (12), 1490-1500.

Background: A recent outbreak of severe respiratory illness primarily in the United States has put a spotlight on vaping and its potential risks.

Objective: To familiarize pathologists with vaping, the cytologic and histopathologic features of vaping-associated acute lung injury, and the role of pathology in this diagnosis.

Data sources: A targeted literature review was performed.

Conclusions:

- Most cases of vaping-associated lung injury have been linked to vaping products containing tetrahydrocannabinol or other cannabinoids.
- Lung biopsies show a spectrum of nonspecific acute lung injury patterns (organizing pneumonia, diffuse alveolar damage, acute fibrinous, and organizing pneumonia, or combinations of the above), accompanied by prominent, foamy macrophage accumulation.
- Injury is usually accentuated around small airways.
- Lipid-laden macrophages can be identified in bronchioloalveolar lavage fluid in most patients
- To date, no specific pathologic features for vaping-related injury have been identified, and it remains a diagnosis of exclusion that requires clinicopathologic correlation.

Parekh M, Donuru A, et. al; Review of the Chest CT Differential Diagnosis of Ground-Glass Opacities in the COVID era. Radiology 2020; 297, E289-E302.

The authors discuss differential pathology with close imaging resemblance to typical CT imaging features of COVID-19 and highlight CT features that may help differentiate COVID-19 from other conditions. A good summary for pathologists

Vasquez-Bonilla W, Orozco R, et. al; A review of the main histopathological findings in coronavirus disease 2019. Hum Path 2020; 105, 74-83.

An understanding of the spectrum and frequency of histologic findings in COVID-19 is essential for gaining a better understanding of disease pathophysiology and its ongoing impact on public health.

Farne H, Singanayagam A. Why asthma might surprisingly protect against poor outcomes of COVID-19. Eur Respir J 2020; 56: 2002045.

Thought provoking letter

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Gilbert C, Wahidi M, Yarmus L, et. al; Key Highlights for the College of American Pathology Statement on Collection and Handling of Thoracic Small Biopsy and Cytology Specimens for Ancillary Studies. Chest 2020 December; 158 (6), 2282-2284.