Pulmonary Pathology Journal Club

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Articles for Discussion

Larsen BT et al. Clinical and histopathologic features of immune check point inhibitor-related pneumonitis. Am J Surg Pathol 2019;43:1331-40

Background:

- Immune checkpoint inhibitors (ICI) have become standard of care in the treatment of many cancer types. ICIs are monoclonal antibodies that target co-inhibitory molecules of the immunologic synapse including PD-1, PD-L1 and CTLA-4.
- ICIs are associated with a spectrum of immune-related adverse events (irAEs) that occur in 3-7% of patients and can sometimes be fatal.
- Recent reports suggest that ICI related pneumonitis may occur in up to 20% of NSCLC patients.

Methods:

- Institutional databases and consultation practices were reviewed for cases of patients receiving ICI therapy that underwent lung tissue sampling with biopsy or autopsy.
- Medical records and imaging was reviewed.
- All slides were reviewed by two thoracic pathologists with the original diagnosis confirmed.

Results:

- 13 patients with lung tissue sampling after receiving ICI therapy were identified. 5 were found to have active fungal infections and were excluded.
- 9 patients had clinically suspected ICI-related pneumonitis. They were treated for various malignancies including non-small cell lung carcinoma, Merkel cell carcinoma, metastatic melanoma, classic Hodgkin lymphoma and metastatic squamous cell carcinoma of the skin.
- Patients were treated with Pembrolizumab only (6), Nivolumab only (1), Ipilimumab followed by Pembrolizumab (1), and Pembrolizumab followed by nivolumab (1).
- Symptoms developed after a mean of 237 +/-178 days after ICI therapy initiation.
- Patients received concurrent chemotherapy in 3 cases and radiation in one case.
- Imaging showed bilateral and nodular ground glass opacities in all cases.
- 8 cases had biopsies (5 core biopsies, 3 transbronchial biopsies) and 1 case at autopsy.
- Organizing pneumonia was seen in 7 cases with 3 cases also having non-necrotizing poorly formed granulomata.
- 1 patient had acute fibrinous pneumonitis and 1 patient had diffuse alveolar damage.
- All cases showed a patchy accumulation of foamy macrophages and vacuolization of type II pneumocytes.
- The ICI agent was discontinued in all cases, 2 patients received supportive therapy and 7 patients received corticosteroids. The patients with acute fibrinous pneumonitis and DAD both died shortly after developing symptoms.

Conclusion: Pneumonitis is a complication of ICI therapy the pathology shows a spectrum of acute lung injury from organizing pneumonia to diffuse alveolar damage.

Take home message: There is no specific finding of pneumonitis related to ICI therapy. The diagnosis requires the exclusions of other causes of acute lung injury particularly infectious etiologies in these immunocompromised hosts.

Offin M et al. Current RB and TP53 alterations define a subset of EGFR-mutant lung cancers at risk for histologic transformation and inferior clinical outcomes. J Thorac Oncol 2019;14: 1784-93

Background:

- EGFR mutations are common driver mutations in lung adenocarcinoma that confer susceptibility to targeted inhibitors.
- One mechanism of resistance to target inhibitors is transformation into a small cell lung cancer (SCLC) that occurs in 3-14% of patients with sensitizing EGFR mutations after TKI therapy.
- SCLCs have bi-allelic loss of TP53 and RB1 genes.
- Transformed SCLC behaves in a similar manner to primary SCLC with rapid progression and transient response to chemotherapy.

Methods:

- Patients with sensitizing mutations in EGFR with concurrent RB1 and TP53 loss from a single institution from 2014 to Aug 2018 were identified.
- Time to treatment discontinuation was used as a surrogate for progression free survival.
- Patients with EGFR mutations without RB1/TP53 mutations over the same time period were utilized as controls.

Results:

- Of the 4112 patients 21% had EGFR mutations and 43 had concurrent loss of RB1/TP53 along with a sensitizing EGFR mutation.
- For the EGFR/TP53/RB1 triple mutant cases 9% were SCLC at initial diagnosis and 18% had SCLC transformation during the course of disease.
- There was an increased rate in small cell transformation in the EGFR-mutant RB1/TP53 loss group compared with the EGFR-mutant RR: 3.5; 95% CI 2.1-2.7 and EGFR mutant-TP53 loss groups RR: 2.9; 95% CI 1.8-3.8.
- There was a shorter time to progression in the EGFR/RB1/TP53 group (9.5 mo) compared with the EGFR/TP53 cohort (12.3 mo) and the EGFR cohort (36.6 mo).
- There was a trend towards reduced survival in the EGFR/TP53/RB1 group with a median overall survival of 29.1 months compared with 40.8 and 56.4 months for the EGFR/TP53 and EGFR only groups respectively.
- The EGFR/TP53/RB1 group had a higher incidence of whole genome doublings (80% versus 51%) that was seen in all cases diagnosed as SCLC or cases transformed to SCLC.
- The EGFR/RB1/TP53 mutant cancers had enrichment for the AID/APOBEC hypermutation signature.

Conclusion: Lung cancers with abnormalities in EGFR along with loss of TP53 and RB1 are at risk for SCLC transformation and have shorted time to progression. There is a current clinical trial

to investigate the combination of EGFR-TKI and small cell directed chemotherapy in patients with triple mutant (EGFR/TP53/RB1) lung cancers.
Take home message: Tumors with EGFR/TP53/RB1 abnormalities represent a genetically distinct group of tumors that may not respond as well to EGFR directed targeted therapies. There should be a high suspicion for SCLC transformation in these tumors after progression on EGFR directed therapies.

Troschel FM et al. Feasibility of perioperative-computed tomography of human lung cancer specimens. A pilot study. Arch Pathol Lab Med 2019;143:319-25

Background:

- Frozen section is an important aspect in the treatment of lung cancer to determine margin status and to confirm the diagnosis of malignancy.
- The localization of the lesion can be challenging intraoperatively and at frozen section.
- Micro-CT provides finer resolution than standard CT scans with a slice thickness below 100 microns and has been successfully utilized in breast lumpectomy specimens.

Methods:

- Prospective pilot study of 21 patients treated between March 2015 and April 2016 at a single institution.
- Fresh specimens were transported from the OR to the pathology department and imaged using two different micro-CT scanners. After imaging the specimens were returned to pathology for frozen section if required.
- Outcomes were rate of specimen adequacy for histology and molecular analysis and time required for micro-CT imaging. Secondary outcomes were assessment of micro-CT image quality and agreement of measurements with pathology.

Results:

- Specimens included wedge resections (50%), lobectomies (40.9%) and pneumonectomies (9.1%).
- Mean image acquisition time was 13 min +/- 6 min and the median estimated radiation dose was 0.43 Gy.
- Comparing the slides with 22 non-imaged controls there was no identifiable radiation changes identified.
- All tested specimens were adequate for molecular profiling.
- The target lesion was identified in only 12 of 22 scans. Artifacts included insufficient air-soft tissue contrast, motion generated by deflating of the specimen, suboptimal calibration.
- The median size of lesions was 14.7 mm with a mean difference of 2.8% with pathology
- Distance to the nearest margin (surgical clips) could be determined in 10/12 of scans and had a mean difference with pathology of 0.5 mm.
- Gold fiduciary markers could be visualized to direct sampling and incidental findings such as a granuloma with central calcification could be identified.

Conclusion: Micro-CT of fresh specimens has the potential to assist in the evaluation of specimens at the time of intraoperative consultation by identifying and characterizing the target lesions along with determining the distance to surgical margins.
Take home message: Micro-CT of specimens did not adversely impact the quality of histologic sections or molecular analysis. However, it is currently a relatively time consuming process that is limited by a number of artifacts in many cases. With further refinement of the techniques it may become a useful adjunct at the time of frozen section.

Zhang et al. Clinical significance of the cribriform pattern in invasive adenocarcinoma of the lung. J Clin Pathol 2019;72:682-8

Background: Cribriform pattern is defined as invasive back-to-back fused tumor glands with poorly formed glandular spaces lacking intervening stroma (see Figure 1 for illustration; panel A and B is more classical; panel C and D show glomeruloid and beaded pattern, as variant cribriform). It is not officially included as a subtype in 2015 WHO classification and technically included as a part of acinar type by some. However, it has been recognized that cribriform pattern is associated with worse outcome than in acinar type. The purpose of this study was to examine the correlations of cribriform pattern with the clinicopathology, molecular features and prognosis in patients with invasive adenocarcinoma.
Methods:

- A retrospective study including lung ADC consecutively resected between October 2012 and December 2018, at a single institution (n=279)
- Inclusion criteria: Complete resection with curative intent, pathologically confirmed lung adenocarcinoma with sufficient tissue for subtype analysis, solitary pure invasive of adenocarcinoma, and complete clinical pathology information.
- Exclusion criteria: History of other malignant tumors, preoperative chemoradiation.
- TNM stage based on the definition in the 8th edition of AJCC staging manual
- All available HE slides reviewed by 2 pathologists blinded to clinical information
- Comprehensive evaluation of histological subtyping in a semi quantitative manner by recording the percentage of each histological subtype in 5% increments: lepidic, papillary, acinar, solid, micropapillary, totaling 100% for each tumor
- *It did not say exactly in the methods, but it sounds like they also evaluated cribriform % including classic and variant cribriform (glomeruloid and beaded); then categorizes them as the acinar type in histological subtyping as acinar into pure acinar (i.e. non-cribriform) and cribriform predominant; pure acinar into <5% and ≥5% cribriform (Fig. 2)*
- Also evaluated nuclear atypia in the hot spot as mild, moderate and severe; mitotic counts (using at least 50 HPFs), tumor size, metastasis, lymphovascular invasion, STAS
- Statistical analysis: Pearson's chi-square test or Fisher's exact test; survival analysis by Kaplan-Meier method, log rank test, etc. OS and DFS were examined

Results:

- In all 279 cases, the cribriform pattern (≥5%) was strongly associated with lymphatic invasion, nuclear atypia and increased mitoses (all $p < .001$)

- Cribriform pattern was present in 111 (39.8%) cases with range of 5 – 100%; and predominant group in 33 (11.8%); frequency is highest in acinar predominant (70 of 117; 67.5%), followed by solid predominant (41 of 76; 53.9%), papillary predominant (19 of 45; 42.2%), micropapillary predominant (7 of 19; 36.8%) and lepidic predominant (1 of 22, 4.5 %)
- Cribriform pattern was associated with advanced clinical stage (p=.004), positive LN (p=0.018), distant metastasis (p=.004), and larger tumor sizes (p=0.02), nuclear atypia (p=.013)and increased mitosis (p<.001)
- Worse OS and DFS of patients with cribriform pattern (≥5%) compared with patients with <5% in the acinar predominant group as a whole or in the pure acinar predominant group (Figure 3A-B and 3E-F, respectively)
- Worse OS, but not DFS, when the cribriform-predominant as the pattern was considered as a separate pattern (Figure 3C-D)
- On multivariate analysis, cribriform pattern(≥5%) was an independent factor of OS (HR 2.768, p=.03) but not of DFS (HR 1.548, p=.221)
- Cribriform pattern was not associated with ALK expression or with *EGFR* and *KRAS* mutations
-

Conclusion: Cribriform pattern is associated with aggressive behaviors, including advanced stages of cancer, lymph node invasion, metastases and larger tumor sizes. In addition, it is an independent factor of prognosis in patients with resected acinar predominant adenocarcinoma.
Take home message: Separate cribriform pattern from acinar type

Chae KW et al. Clinical and immunological implications of frameshift mutations in lung cancer. J Thorac Oncol 2019;14:1807-17

Background: PD-L1 is the most commonly used biomarker to predict response to immune checkpoint inhibitors (ICI). There has been continuous search for more precise an reliable markers such as tumor mutational burden (TMB), though it is much less talked about than last year. Frameshift mutations by insertion or deletion (fsindels) are suggested to induce more immunogenic tumor specific neoantigens, conferring better response to ICIs, which has been reported in melanomas and RCC, but not in NSCLCs. A study from MSKCC
Methods:

- They used TCGA data set to analyze TMB, neoantigen burden and immune landscape in relation to fsindel status
- Also, clinical data from 122 patients treated with ICIs were evaluated for the influence of fsindels on disease resonse rates and survival outcomes

Results:

- A positive correlation between fsindel burden and TMB and activate CD4/CD8 T-cells infiltration was shown
- Presence of fsindels was also associated with significant prolongation of PFS in patients treated with ICIs (6.2 vs, 2.7 mos, p=.01)

- Significant differences in the overall response rates and disease control rates were observed in patients with fsindels

Conclusion: fsindels may be a predictive factor for ICI response in NSCLC

Comments: A recent report from CheckMate 227 clinical trial demonstrated that first-line tx with nivo plus ipi resulted in a longer duration of OS than did chemotherapy, independent of the PD-L1 expresion level! (Hellman MD et al. NEJM September 28, 2019). PD-L1 IHC may be replaced by something else in the near future…..

Articles for Notation

Neoplastic

Choe EA et al. Dynamic changes in PD-L1 expression and CD8+ T cell infiltration in non-small cell lung cancer following chemoradiation therapy. Lung Cancer 2019;136:30-6

Background: Data on the effects of neoadjuvant CCRT on the tumor microenvironment in NSCLC patients are lacking. The T cell phenotype of NSCLC (with high PD-L1 expression and CD8+ TILs) favors immune escape and has been known to be a predictive factor for responsiveness to anti PD-1 therapy. To improve treatment outcome in stage III NSCLC, more detailed data on PD-L1 expression and CD8+ TILS after CCRT and their relationship to treatment outcome are needed. This study investigated the dynamics of PD-L1 expression and CD8+ T cell infiltration following CCRT in patients with stage III NSCLC and how these are correlated with patient survival.

Methods:

- Patients (n=43): retrospective analysis on patients diagnosed with stage III NSCLC and underwent neoadjuvant CCRT followed by curative surgery at a single institution (6/2008-10/2010); staged with 7th edition of TNM classification
- Treatment: weekly standard chemotherapy with 5-6 cycles of CCRT including docetaxel plus cisplatin or paclitaxel plus carboplatin; radiation 40-50 Gy;
- Bx review: pre CCRT specimen at the time of initial dx; post CCRT specimen at the time of surgery; OS and RFS with f/u until 1/2017
- IHC for PD-L1 expression (22C3 n=33 or SP263 n=10; same clone for paired assay) in tumor cells (TCs) and immune cells (ICs), evaluated for the same, decrease, or increase in % positivity
- CD8+ TILs by CD8 staining. total number of nucleated cells in the stroma was assessed using the following cutoff values: low $\leq$ 25%; intermediate >25% to 50%; high >50%
- Statistical analysis

Results:

- after CCRT, 7 of 43 (16%) patients had a pathologic complete response (pCR); baseline PD-L1 and pCR was not associated; no correlation between the amount and morphology of immune infiltrate after CCRT; no correlation between residual tumor cellularity and CD8+ TIL infiltration;

- unable evaluate post CCRT PD-L1 expression on tumor cells in 7 patients with pCR and additional 3 patients due to a lack of specimens (so a total of 10 cases excluded in the analysis of PD-L1 expression)
- of the 33 pts analyzed, no change in 16 (48%)[13 of 16 was 0% of PD-L1 expression in pre and post], increase in 7 (21%), and decrease in 10 (30%) of pts.
- of 21 pts that allowed analysis of pre- and post CD8+ TIL infiltrates, increase in 13 (62%), no change in 4 (19%), and decrease in 4 (19%); most patients showed increased CD8+ TIL density (71%, 75%, and 50% among decreased, increased and no change in PD-L1 expression after CCRT, respectively)
- the statistical difference among groups with PD-L1 expression though increased PD-L1 expression group after CCRT showed the steepest survival curve in the OS (p=.220)
- increase of CD8+ TILs after CCRT was significantly associated with longer OS (p=.017)

Conclusion:

- rationale for immunotherapy after neoadjuvant CCRT and surgery, especially in those with increased PD-L1 expression who would otherwise undergo poor OS

Jin J et al. Diminishing microbiome richness and distinction in the lower respiratory tract of lung cancer patients: A multiple comparative study design with independent validation. Lung Cancer 2019;136:129-35

Background: The role of the airway microbiome in lung cancer remains unknown, though increasing evidences indicate that microorganisms are associated with neoplastic disease. Most studies have been on the gut microbiome of GI tract. Authors tried the taxonomic profiles of the lower respiratory tract (LRT) microbiome

Methods: BALF were assessed by metagenomics analysis; random forest regression analysis for selection of a diagnostic panel

- Discovery set: n=150 including 91 with lung cancer, 29 with nonmalignant pulmonary ds, and 30 healthy subjects
- Independent validation set: n=85

Results:

- reduced richness in lung cancer patients compared with that in healthy subjects
- microbiome of nonneoplastic lung ds resembled that of lung cancer patients
- *Bradyrhizobium japonicum* only in lung cancer patients; *Acidovorax* was in patients with cancer and nonmalignant lung ds
- the area under the curve (AUC) established for discriminating the pts with cancer in training set and in the independent validation set

Conclusion:

- lower respiratory tract microbiome richness is diminished in lung cancer patients compared with that in healthy subjects; might be a useful biomarker for dx in certain patients with difficulty in bx

Davis R et al. Pulmonary granular cell tumors. A study of 4 cases including a malignant phenotype. Am J Surg Pathol 2019;43:1397-1402

Background: Pulmonary granular cell tumors (pGCTs) are exceedingly rare and only a handful of cases worldwide have been reported as malignant
Methods: They reported 4 pGCTs, including 1 malignant case with a novel pathologic *ATM* mutation
Results: 75% women, a mean age of 57 y (range 49-66) and variable smoking hx. associated lung ca was found in 2 pts (adenoca and small cell ca)
Conclusion: Due to the rarity of malignant pGCT, the px is still unclear. Look for *ATM* mutation in case suspicious for malignant granular cell tumor

Song Z et al. Cytological-negative pleural effusion can be an alternative liquid biopsy media for dete ction of EGFR mutation in NSCLC patients. Lung Cancer 2019;136:23-29

Background: Cell-free circulating tumor DNA (ctDNA) released from primary tumors or metastases represents genomic aberrations in cancer cells and has potential as liquid biopsy to monitor tumors in real-time. Numerous studies have shown ctDNA derived from plasma can be used as a surrogate for reflecting the genomic alterations present in tumor as well as for diagnosis, monitor tumor progression and response to treatments. Moreover, ctDNA in CSF better represents the genomic landscape of brain tumors than plasma. Recently, the gf are mutations using CT T an 80 right from MPE Superman a tent samples and demonstrated that PE super Nate and had significantly higher tumor specific mutation detection rate and sensitivity compared to PE sediment containing tumor cells. Thus, DNA from the supernatant of PE is a promising source for genetic testing to guide treatment decision making in lung cancer patients.
Methods: This study interrogated the genomic profiles and *EGFR* mutation status in 121 malignant pleural effusion (MPE) and 40 cytological-negative pleural effusion (CNPE) specimens from 161 advanced lung adenocarcinoma patients. Patients underwent TKI tx with gefitinib, icotinib, or erlotinib if EGFR sensitizing mutations were detected from their tissue bx or PE sediments. Mutation detection rate was comparable in MPE and CNPE.
Results: A mutation detection rate was 99.2% and 100% for MPE and CNPE, respectively. CNPE supernatant is comparable to MPE in reflecting the mutational profile of lung adenocarcinoma. CNPE sample was actually superior to the matched tumor bx tissues in identifying *EGFR* mutation.
Conclusion: This study demonstrated that CNPE supernatant provided a comprehensive profile of NSCLC and can serve as a reliable liquid biopsy media for detecting *EGFR* mutations.

Sumimoto R et al. PD-L1 expression on tumor-infiltrating immune cells is highly associated with M2TM and aggressive malignant potential in patients with resected non-small cell lung cancer. Lung Cancer 2019;136:136-44

Background: The mechanistic and clinical significance of the fact of PD-L1 on tumor cells versus immune cells remains unclear. On the other hand, tumor-associated macrophages (TAMs), M2 macrophages in particular, can promote tumor progression.

Methods: They evaluated PD-L1 expression on tumor cells and immune cells using SP 263 assay and the stromal M2 TAM distribution using CD163 staining in 160 consecutive patients with resected non-small cell carcinoma.

Results:

- Stromal M2 TAM density was associated with PD-L1 expression both on tumor cells and immune cells.
- The PD-L1 expression on tumor cells was associated with tumor histology, tumor differentiation, lymph node metastases and disease free survival among patients with receptive id non-small cell carcinomas.
- The PD-L1 expression on immune cells was associated with more aggressive malignant potentials in non-small cell carcinomas. The PD-L1 expression on immune cells was associated with tumor histology, tumor differentiation, tumor status, lymph node metastases and pathologic stage; high expression of PD-L1 on immune cells was a poor progressive factor both in disease-free survival and in overall survival among patients with resectable non-small cell carcinoma

Conclusion: During tumor progression in non-small cell carcinoma, the tumor-promoting M 2 TAM might affect PD-L1 expression both on tumor cells and immune cells. PD-L1 expression on tumor cells was associated with aggressive malignant behaviors. Furthermore, PD-L1 expression on immune cells was associated with more aggressive malignant potentials in non small cell carcinomas.

Take home message: M2 TAM might be the main player that orchestrates the PD-L1 expression in both tumor and immune cells in NSCLC

Wang G et al. PD-L1 testing on the EBUS-FNA cytology specimens of non-small cell lung cancer. Lung Cancer 2019;136:1-5

Background: It is not clear if cytology specimen could be used for PD-L1 testing to guide immunotherapy. In this study, they assessed the suitability of the WBUS-FNA cytology specimens for testing PD-L1.

Methods:

- 265 EBUS-FNA specimens from 262 patients with non-small cell carcinoma who underwent trans-bronchoscopic FNA for PD-L1 testing (1/1/2017-3/31/2018)
- Cellblock specimens were used for PD L1 testing using Dako 22C3 antibody pharmdx testing according to Dako protocol

Results: 230 of 265 (86.8%) EBUS FNA specimens were adequate for PD-L1 testing and 34 patients with the results of PD-L1 testing on different types of specimens had concordant results in 91.3%.

Take home message: The EBUS-FNA cytology specimen is suitable for PD-L1 testing in patients with advanced non-small cell lung carcinoma.

He Y et al. Galectin -9 in non-small cell lung cancer. Lung Cancer 2019;136:80-85

Background:

- The role of galectin-9 in cancer is complicated. Galectin-9 is a ligand of TIM-3; combining of TIM-3 and galectin-9 triggers termination of the cell mediated immunity. Galectin-9 also impairs innate immunity by down regulating natural killer cell function. However, former studies reported that in certain scenarios, galectin -9 could promote the function of some immune cells.
- In this study, they tested galectin-9 level in NSCLC tumor tissues with IHC to describe galectin-9 status and to correlate with immune checkpoints and patient survival.

Methods: Expression of galectin-9 on the tumor cells and TILs in 136 NSCLC cases

Take home message:

- galectin-9 expression is present in both tumor cells and TILs in NSLCL and found in all pathologic types
- galectin-9 level on TILs correlates with TIM-3, PD-1 and PD-L1 level
- on tumors, galectin-9 level has correlation with TIM-3 level
- poor px with low galectin-9 level on tumor cells or high galectin-9 level on TILs

Garmendia I et al. YES1 drives lung cancer growth and progression and predicts sensitivity to dasatinib. Am J Respir Crit Care Med 2019;200:888-899

Background: To identify a subset of patients with specific druggable mutations is critical to develop personalized treatments in NSCLC patients. In this context, they identified YES1 (v-YES-1 Yamaguchi sarcoma viral oncogene homolog 1) genomic alteration as a potential stratification biomarker that critics benefit from SFK (SRC [protooncogene tyrosine-protein kinase Src] family kinases) inhibitors such as dasatinib.

Methods:

- Functional significance was evaluated by *in vivo* models of NSCLC and metastases and patient-derived xenografts as well as abrogating *YES1* by CRISPR technique
- *In vitro* functional assays for signaling, survival and invasion
- Association between *YES1* alterations and prognosis evaluated in clinical samples

Results:

- YES1 is essential for NSCLC carcinogenesis and YES1 overexpression induced metastatic spread in preclinical *in vivo* models
- YES1 genetic depletion by CRISPR technology reduced tumor growth and metastasis.
- YES1 status as a stratification biomarker for the dasatinib response
- High YES1 is an independent predictor for poor prognosis in patients with lung cancer

Take home message: *YES1* as a new potential therapeutic target and predictive biomarker

Pei J et al. Detecting MYB and MYB1 fusion genes in tracheobronchial adnoid cystic carcinoma by targeted RNA-sequencing. Mod Pathol 2019;32:1416-20

Background: Primary tracheobronchial adenoid cystic carcinoma (ACC) is rare (< 1%) with a known specific chromosome translocation t(6;9)/*MYB-NFIB* in some. More recently, a t(8;9)/*MYBL1-NFIB* in salivary gland ACCs as an alternative translocation, but not in tracheobronchial ACCs

Methods: Targeted RNA sequencing for fusion genes in tracheaobronchial ACCs (n=7)
Results: t(6;9)/*MYB-NFIB* in 3 cases, t(8;9)/*MYBL1-NFIB* in 3 cases, and a rare *MYBL1-RAD51B* fusion cells in the remaining 1 case
Take home message: Additional ammunition with newer fusion types in the dx of ACCs

Lindholm KE et al. Cystic and encapsulated atypical thymoma (World Health Organization type B3). A clinicopathologic and immunohistochemical study of eight cases. Am J Clin Pathol 2019;152:512-6

Background: The predominant cystic architecture is uncommon in B3 thymomas (they called it as atypical thymoma) and they reported 8 cases of encapsulated and cystic B3 thymomas
Methods: They found the cases after review of more than 500 resected thymoma specimens.
Results:

- 7 men and 1 woman; 4-6 cm in greatest dimension and showed prominent cystic changes with epithelial proliferation arranged in sheet ad cords; no increased mitotic activity or nuclear pleomorphism; all encapsulated; + for CK5/6, and p63; 5 with f/u data are alive without recurrence

Take home message: May be a diagnostic challenge and misdiagnosed as thymic carcinoma or multilocular thymic cysts

Non-Neoplastic

Williams BJ et al. Maintaining quality diagnosis with digital pathology: a practical guide to ISO 15189 accreditation. J Clin Pahol 2019;72:663-8

Background: Digital pathology is an evolving technology and it is important that departments uphold of or improve on current standards
Methods: The authors' hospital (Lees Teaching Hospitals NHS Trust in UK) now scans 100% of histology slides since September 2018. They developed validation and validation protocols to train 38 histopathology consultants in primary distal diagnosis
Results:

- They shared their approach to ISO (an laboratory accreditation agency in UK, I guess) inspection of the digital pathology service, which resulted in successful ISO accreditation for primary digital diagnosis.
- There offered practical advice on what types of procedure and documentation are necessary, both from the point of view of the laboratory and the reporting pathologists.
- They also explore topics including risk assessment, standard operating procedures, validation and training, calibration and quality assurance and provide a checklist of the key digital pathology components

Take home message: a useful practical paper to refer to as they claimed!

Liu GY et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Northe American patients with idiopathic pulmonary fibrosis. Chest 2019;156:715-23

Background: Antinuclear cytoplasmic antibodies (ANCAs) may occur in 7-10% of IPF patients but there clinical relevance remains unclear. This study estimated the prevalence of ANCAs in North American population of IPF patients and evaluate their clinical significance.
Methods: A retrospective study of 2 independent cohorts of patients diagnosed with IPF at UCSF (discovery cohort) and the University of Chicago (replication court). MP0 and PR-3 ANCAs were measured in all patients. Prevalence and location of ANCAs with clinical characteristics and transplant-free survival were evaluated.
Results:

- A total of 14 of 353 and 20 of 392 patients with IPF were positive for and cuss at the time of diagnosis in the discovery and replication court, respectively.
- Among those with MP0 antibodies, 2 of 6 (33%) in the discovery cohort and 3 of 12 (25%) in the replication cohort developed vasculaitis.
- None of PR-3-positive IPF cases developed vasculalitis
- ANCA-positive patients tend to be women and were more likely to have some ground glass opacities on CT scan; in the combined cohort of 745 patients, media and transplant-free survival was not significantly different

Conclusion: ANCA positivity is uncommon in IPF patients in North America and not associated with baseline disease severity or transplant-free survival. Of note, MPO-positive IPF patients tend to develop clinical vasculitis

Moore C et al. Resequencing study confirms that host defense and cell senescence gene variants contribute to the risk of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2019;200:199-208

Background: Several common and rare genetic variants located in multiple loci have been associated with risk for IPF.
Methods: deep targeted resequencing (3.69Mb of DNA) in cases (n= 3,624) and control subjects (n=4,442) across genes and regions previously associated with disease. Testing of associations between disease and 1) individual common variants by logistic regression and 2) groups of rare variants via sequence kernel association test
Results:

- The strongest risk with the *MUC5B* promoter variant (rs35705950, with an odds ratio of 5.45 for 1 copy of the risk allele and 18.68 for 2 copies of the risk allele
- Also with rare variation in *FAM13A* and rare variation in the *TERT* and *RTEL1* gene

Take home message: A limited number of common and rare variants contributes substantially to the population risk of IPF and these genetic variants focus on biologic mechanisms of host defense and cell senescence.

Tarres MT et al. The FMS-like tyrosine kinase-3 ligand/lung dendritic cell axis contributes to regulation of pulmonary fibrosis. Thorax 2019;74:947-57

Background: Dendritic cells (DCs) accumulated in the lungs all patients with IPF but their pathogenetic relevance is poorly understood. They interrogated the role of the FMS-like tyrosine kinase-3 Ligand (Flt3L)/DC axis in pulmonary fibrogenesis that is still unclear.
Methods:

- A mouse model of adenoviral gene transfer of active TGF-β1, flt3L knockout and DC depletion
- measurement of Flt3L level in serum and lung tissue; counting DC in lung tissue in human IPF as well as in animal models

Results and Conclusion: Flt3L/DC protein is increased in human IPF lungs and mice with established lung fibrosis, and contributes to regulation of pulmonary fibrosis in mice through mobilization of CD 11b-positive dendritic cells.
Take home message: Possible role of Flt3L/DC-based immunotherapy as a novel intervention against pulmonary fibrosis in humans

Griese M et al. Quantitative lipidomics in pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2019;200:881-7

Objectives: Quantitative lipidomic analysis of lipids and surfactant proteins A, B and C in lavage fluid from patients with PAP of different causes in comparison with healthy control subjects, in order to explore therapeutic strategies to treat PAP
Methods: BAL specimens collected over the last two decades from PAP patients due to autoantibodies against GM-CSF, genetic mutation in CSF2RA, MARS, FARSB, NPC2 and secondary to myeloid leukemia. Their lipid composition was quantified.
Results: Various lipids were increased up to over 100 fold and the changes did not differ among the various diseases that caused PAP. Large quantitative changes in lipids related to surfactant, including free cholesterol and cholesterol esters, but only moderate change in lipid is derived from cellular debris. Therapies targetting such changes may be assessed by monitoring the alveolar lipidome.
Take home message: Got lipidome?

Li HY et al. The alveolar lipoidoe in pulmonary alveolar proteinosis. A new target for therapeutic development? Am J Respir Crit Care Med 2019;200:800-2
An editorial for the paper by Griese M et al.

Hayes D et al. The international thoracic organ transplant registry of international society for heart and lung transplantation: twenty-second pediatric lung and heart=lung transplantation report-2019; Focus theme: Donor and recipient sie match. J Heart Lung Tranpl 2019;38:1015-27

Background: The 22nd International Society of Heart and Lung Transplantation (ISHLT) transplant registry report summary data from pediatric lung and combined heart and lung transplant recipients and their donors for transplants that occurred through June 30, 2018.

Methods: Focus theme methods was donor and recipient size match; the full registry slide set available online the provides more detail, additional analysis and other information not included in the printed report.
Results: Lots of well-illustrated tables and figures
Conclusion: The 2019 ISHLT registry report on pediatric lung and heart-lung transplantation demonstrate continued improvement in survival of children after lung and heart-lung transplantation. Their analyses provide additional insights into the role of donor-recipient height or weight differences in children after lung and heart-lung transplantation.
Take home message: Heavy data set useful for anybody who is involved in Tx biopsies

Reviews, Letters, and Case Reports

Tsao MS et al. Pathologic considerations and standardization in mesothelioma clinical trials. J Thorac Oncol 2019;14:1704-17
It is a special article that seems to be one of the series published in this theme; radiologic consideration is also published in the same issue.
Here is the summary of their recommendation:

Diagnostic biopsies	Sampling of multiple areas is preferable to facilitate diagnosis.
	Full thickness samples help identify invasion of subpleural fat.
	Specimens that are not frozen should be fixed in formalin for 6 to 72 hours.
	Sections perpendicular to the surface improve assessment of spindle cell proliferations and invasion.
Pleurectomies	Because a complete resection is not possible other than in localized subtypes, assessment of surgical margins in pleurectomy is not necessary.
	Specimens should be sampled in areas of nodularity which are more likely to contain tumor cells.
Biobanking	Informed consent in concordance with the International Conference on Harmonisation Guideline for Good Clinical Practice should be obtained from all patients who provide specimens.
	Standard procedures facilitate successful specimen acquisition and appropriate handling.
	Standardized datasets should be used for clinical and pathologic annotations.
Pathologic classification and diagnosis	MPM must be distinguished from reactive proliferations and metastases.
	Histologic subtypes must be determined. IHC and FISH (p16) may help in differential diagnosis from metastatic tumors or reactive mesothelial proliferation.
	Nuclear grading may provide an opportunity to validate its utility in prognostication and patient stratification in clinical trials.
Biomarkers and techniques	IHC often plays an indispensable role in confirming the diagnosis of mesothelioma; BAP1 and p16 FISH may distinguish malignant from reactive mesothelial cell

proliferation.

Reporting recommendations for tumor marker prognostic studies (REMARK) should be followed.

Correlative studies for translational research should be designed to answer hypotheses and should be feasible to complete with the materials that can be obtained.

Maddock SD et al. Pulmonary lipid-laden macrophages and vaping. New Engl J Med 2019;381:1488-9

A letter to the editor that made a sort of storm in a teacup; Due to their last sentence "…the presence of lipid-laden macrophages in BAL fluid may suggest beeping-related lung injury as a provisional diagnosis", I got quite a few emails and phone calls to ask about this, and I was busy saying that the mere presence of lipid-laden macrophage is not going to be really helpful.

Henry TS. Imaging of vaping-associated lung disease. New Engl J Med 2019;381:1486-7

Another letter to the editor in the same issue.

They collected 19 cases and reviewed the literature regarding another 15 cases and described the radiologic findings in those that met the definition of vaping-associated lung injury. Imaging patterns that correlated with pathological findings attributable to vaping included acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, lipoid pneumonia, variegated imaging patterns. Most of the patterns have basilar-predominant consolidation and ground glass opacity, often with areas of lobular or subpleural sparing.

Remon J et al. Is there room for immune checkpoint inhibitors in patients who have NSCLC with autoimmune diseases? J Thorac Oncol 2019;14:1701-3

A commentary on this very pressing issue

On their analyses, current data suggests that ICIs are a reasonable strategy in patients with some quiescent autoimmune disease (AID) and life-threatening malignancy without effective alternative treatment. There is a risk of AID exacerbations in up to half of cases, which usually are manageable without increased risk of hospitalizations. However, a discussion about the risk-benefit ratio with the patient as well as a close monitoring of these patients by multi disciplinary team are necessary to identify AID flares and implement early therapeutic intervention.

Park H et al. Imaging of precision therapy for lung cancer: Current state of the art. Radiology 2019;293:15-29

A review of current state of the art in this issue

The focus of the article included an update on the recent advances in precision therapy for NSCLC and their implication on imaging, molecular and genomic biomarkers and pitfalls of image interpretation for lung cancer precision therapy, and review of the current approaches and future direction of precision imaging for lung cancer, emphasizing emerging observation in lung that the radiologists to know tumor kinetics radio mix and molecular and functional imaging, etc. I thought this summary looks useful for pathologists in these regards.

Suzuki Y et al. A case of primary lung squamous cell carcinoma mimicking malignant mesothelioma producing granulocyte colony stimulating factor with chemotherapy (cisplatin and gemcitabine)-associated thrombotic thrombocytopenic purpura; An autopsy case report. Lung Cancer 2019;136:105-8
the title say it all…

Kawai H et al. A case of invasive mucinous adenocarcinoma of the lung showing stepwise progression at the primary site. Lung Cancer 2019;136:94-7
Case of invasive mucinous adenocarcinoma mixed with non-mucinous component, suggesting stepwise progression within the tumor. The two different components were separately examined by IHC and amplicon sequencing. The tumor cells in the main part showed abundant intracytoplasmic mucin, whereas those in the solid part showed scant intracytoplasmic mucin and high-grade nuclear atypia. Both parts harbored the same *kras* mutation, while *TP53* p.P278L mutation only in the solid part, suggesting that p53 mutation promoted a stepwise progression.