Pulmonary Pathology Journal Club – AC Roden
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Anja C. Roden, MD
Consultant
Associate Professor
Director, Pulmonary Pathology Fellowship
Department of Laboratory Medicine & Pathology
Tel: 507-284-1192
Fax: 507-284-1875
E-mail: Roden.anja@mayo.edu

Articles for discussion

Otani K et al. Transbronchial lung biopsy for the diagnosis of IgG4-related lung disease. Histopathol 2018;73:49-58.

Background:
- Diagnosis of IgG4-RD requires multidisciplinary approach (clinical, imaging, serology-IgG4 >135 mg/dL, histology, IHC)

Purpose:
- To identify whether TBBx is useful in the diagnosis of IgG4-RD

Methods:
- Retrospective; 20 consecutive patients with IgG4-RD in other organs (8 had autoimmune pancreatitis 7 of which had serum IgG4 >135 mg/dL, 12 had biopsy-proven IgG4-RD in other organs and serum IgG4 >135 mg/dL) → TBBx for potential lung involvement; 1 case excluded because of granulomatous disease → 19 cases
- 43 control cases (various inflammatory conditions)
- Criteria for IgG4-RD in lung in non-SLB: >20 IgG4+ plasma cells/Hpf in hot spots; IgG4/IgG-positive plasma cells >40%

Results:
- Serum IgG4, median 606 mg/dL (194-1250)
- Imaging patterns: bronchovascular (n=10), alveolar interstitial (n=9), GGOs (n=0), solid nodular (n=1)
- 7/19 (37%) – normal lung tissue (sampling error)-excluded from further analysis
- Remaining 12 patients: median age 69 yrs (44-70), male:female=7:5
- 9/12 (75%) (or 9/19, 47%) – met criteria for IgG4-RD in lung
    Dense lymphoplasmacytic infiltrate (n=9) (peribronchiolar, n=4; alveolar interstitial, n=3; solid nodular and OP, n=2)
    Obliterative phlebitis (n=1)
    Storiform fibrosis (n=1)
    Obliterative arteritis (n=0)

3/12 (25%) had eosinophilic infiltrate (>10 cells/HPF)
- 1/43 control cases had >20 IgG4+ plasma cells/ hot spot; 1/43 had IgG4/IgG >40%; 1 fulfilled both criteria; all 3 showed eosinophilic pneumonia
  → Diagnostic sensitivity of TBBx for IgG4-RD in lung is 47%; 98% diagnostic specificity

Take home points:
- TBBx potentially useful and acceptable diagnostic approach for IgG4-RD in lung
- Don't forget about IgG4-RD in TBBx
- Diagnosis/suggestion of IgG4-RD seems highly dependent on IHC in TBBx

Su H et al. Characterization of TIM-3 expression and its prognostic value in patients with surgically resected lung adenocarcinoma. Lung Cancer 2018;121:18-24.

Background:
- T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is a promising immune checkpoint – might have synergistic effect with PD-1/PD-L1.
- Plays key role in inhibiting Th1 responses, T cell dysfunction and cytokine expression
- TIM-3 appears to be successful in some preclinical tumor models
- Compensatory upregulation of TIM-3 might be a targetable biomarker

Purpose:
- To characterize TIM-3 expression and its prognostic significance in patients with surgically resected lung adenocarcinoma.

Methods:
- Expression of TIM-3 is defined of expression on either tumor cells or TILs or both
- PD-1 – cutoff ≥8%
- CD8+ TILs – cutoff ≥25%
- Resected lung adenocarcinoma, no pretreatment.

Results:
- 223 patients, mean f/u 76 months (4-101)
- Tumor stage: I (66.8%), II (13.9%), III (19.3%); acinar subtype (39.5%), papillary (25.6%), lepidic (19.2%)
- Cutoff values of TIM-3 expression to best predict RFS in tumor cells and TILs based on ROC curves were 27% and 10%
- Cutoff values of TIM-3 expression to best predict OS in tumor cells and TILs: 24% and 11%
  → cutoff values chosen: ≥24% in tumor cells; ≥ 11% in TILs
- TIM-3 expression correlated with elevated preop CEA levels, higher grade of histologic pattern (micropapillary)
- TIM-3 expressed on tumor cells and TILs, PD-1 and CD8 only on TILs
- TIM-3 expression in 107/223 (48.0%), PD-1 (48.4%), CD8 (31.8%)
- TIM-3 expression correlated with PD-1 expression (p < 0.001) and high CD8+ TILs density (p=0.014) (same results if TIM-3 expression was separated between tumor cells and TILs).
- TIM-3 expression correlated with worse RFS (p=0.001) and OS (p=0.002).

- Subgroup analysis: TIM-3+/PD-1+/CD8 low group - worst RFS (5-year rate: 39.5%, p=0.002) and OS (5-year rate: 50.0%, p=0.035)
  TIM-3−/PD-1−/CD8 high group - best RFS (5-year rate: 93.8%, p=0.002) and OS (5-year rate: 100%, p=0.035).
- Advanced disease stage and TIM-3 expression – independent prognostic factors of worse RFS and OS; high CD8+ TILs density – independent favorable RFS

Take home point:
- TIM-3 might be a promising prognostic and theranostic marker – more to come

Agbor-Enoh S et al. Late manifestation of alloantibody-associated injury and clinical pulmonary antibody-mediated rejection: Evidence from cell-free DNA analysis. J Heart Lung Transpl 2018;37:925-32.

Background:
- AMR - diagnostic challenge in lung allografts due to lack of specific morphologic and clinical features, low sensitivity of C4d and C3d deposition.
- AMR often leads to CLAD
- Donor-derived cell-free DNA (ddcfDNA) appears promising and highly sensitive genomic tool to detect early graft injury; ddcfDNA – released from allograft into recipients circulation if cells die – sensitive, detects injury related to AMR, ACR, infection

Purpose:
- To examine the usefulness of ddcfDNA to detect lung AMR early and accurately

Methods:
- 157 lung transplant recipients examined for AMR and ACR per ISHLT guidelines; all had routine surveillance TBBx and DSA testing; additional testing when allograft dysfunction
- ddcfDNA – using SNPs between donors and recipients to identify and quantitate % of circulating ddcfDNA
- Clinical AMR – ISHLT guidelines: allograft dysfunction and: DSA+, histology+, C4d+, no alternative diagnosis → definite AMR (all 4 criteria present); probable (3/4), possible (2/4)

Results:
- 34 subjects – met ISHLT criteria of clinical AMR – total of 42 AMR events (38.1% probable, 61.9% possible)
- Median time transplant to AMR, 14.2 months (2.9 – 26); 104 ACR episodes
- Clinical risk factors of AMR: # ACR events, donor diabetes, race mismatch; recipient hyperlipidemia was protective
- Linear regression of decline of FEV1 on ddcfDNA → inverse, linear correlation
- All AMR subjects had +DSA; + relationship between DSA MFI and ddcfDNA
- Histopathology (available in 36 AMR events) abnormal in 69.4% including ACR (50.5%), capillaritis and DAD (28.4%), OB, BOOP, chronic vascular rejection (21.1%); +histopathology correlated with higher ddcfDNA; C4d+ only in 3 cases

- Potential alternate diagnoses in 45.2% of AMR episodes; mostly infection; after adjusting for DSA MFI levels – clinical infection and AMR was associated with higher ddcfDNA levels than AMR alone
- Patients with AMR event had greater allograft injury (greater decline in FEV1) and higher ddcfDNA than ACR
- ACR had higher ddcfDNA than controls w/o rejection
- AMR had higher ddcfDNA than subjects with asymptomatic DSA
- In AMR, initial transient rise in ddcfDNA several months before AMR diagnosis; second rise was sustained until clinical AMR diagnosis by median of 2.8 months
- Post-AMR f/u – 73.1% CLAD at 1 yr; 79.4% died 2 yrs after diagnosis, mainly graft failure

Take home point:
- ddcfDNA – promising tool; still not exactly sure how specific it is for AMR – probably has to be used in conjunction with other clinical and serologic data

Kuang M et al. Clinical significance of complex glandular patterns in lung adenocarcinoma: Clinicopathologic and molecular study in a large series of cases. AJCP 2018;150:65-73.

Background:
- Evidence from studies including white population suggests that complex glandular patterns (CGPs) (eg, cribriform, fused gland) are found mainly in high-grade lung adenoCa

Purpose:
- To explore whether CGPs might be important for clinical management of patients with lung adenoCa; specifically on an Eastern Asian population

Methods:
- Retrospective, 356 patients with stage I-III lung adenoCa who underwent surgical resection
- Cribriform pattern (nests of tumor cells with a sieve-like perforation); fused gland pattern (fused glands with irregular borders, back-to-back glands w/o intervening stroma, or ribbon-like formations)
- CGPs subdivided into single cribriform (SCP; SCP ≥10%, SFG ≤9%), single fused gland (SFG; SFG ≥10%, SCP ≤9%) coexistent cribriform and fused glands (CCFG; cribriform ≥10%, fused glands ≥10%)
- Genes evaluated: EGFR, KRAS, AKT1, HER2, BRAF, ALK, ROS1, P110

Results:
- 48.3% acinar, 11.2% solid, 17.1% micropapillary, 13.2% papillary, 10.1% lepidic predominant
- 43.8% had CGPs [SCP (14.0%), SFG (25.0%), CCFG (4.8%)]; 15.2% were CGP predominant
- CGP associated with acinar subtypes, lymphovascular invasion, higher TNM, ALK rearrangements, HER2 mutation, worse OS and RFS compared with acinar-predominant
- SFG associated with acinar subtype, higher TNM, larger tumors, EGFR mutation

- SCP associated with solid subtype, lymphovascular invasion, tumor size, higher TNM, ALK rearrangement, EGFR mutation, AKT1 mutation
- CCFG had worst OS and RFS
- Multivariate analysis: pT, pN, CCFG pattern – independent prognostic factors
                               In stage I patients with lobectomy/segmentectomy CCFG pattern independent prognostic factor of OS

Take home points:
- Confirms that complex glandular pattern might be considered a distinct subtype of adenoCa and might be added to the pathology report as they appear to be more aggressive subtypes
- Do CGP really need to be further subtyped into SFG, SCP and CCFG? That seems maybe a bit cumbersome and I wonder how the interobserver variability might be
- Still needs to investigated whether CGP needs to be a predominant subtype or whether <5% or <1% components might also harbor a worse outcome

Articles of Neoplastic Lung/Mediastinal Disease for Notation

Miyamoto A et al. Expanded acceptance of acute exacerbation of nonspecific interstitial pneumonia, including 7 additional cases with detailed clinical pathologic correlation. Pathol Internat 2018;68:401-8.

Background:
- Acute exacerbation (AE)-usually diagnosed in IPF/UIP (histologic features: DAD, extensive fibroblastic foci, OP lesions)
- Characterized by progressive respiratory failure of unidentifiable alternative cause over appr. 1 month; only uncommonly diagnosed in NSIP

Purpose:
- To determine whether any histopathologic features distinguish NSIP patients with AE vs stable disease

Methods:
- Retrospective
- 14 consecutive cases of histopathologically proven NSIP by SLB (13 patients, 2004-2012)
       Idiopathic NSIP (n=8); CVD-associated NSIP (n=5)
- All had HRCT
- Diagnosis of AE was clinically confirmed based on criteria in IPF/UIP: (1) previous or concurrent diagnosis of an underlying ILD, (2) unexplained worsening of dyspnea within last month, (3) new GGOs and/or consolidation superimposed on chronic interstitial changes c/w underlying ILD on CT; (4) no evidence of infection; (5) exclusion of alternative causes-PE, heart failure, identifiable cause of ALI → "definite AE" (all 5 criteria met), "suspected AE" (first 3 criteria met), "stable" (no criteria met) – defined at time of biopsy

- Analysis of 4 histologic patterns: (1) OP lesions, (2) alveolar hemorrhage (red blood cells associated with fibrin deposition and/or hemosiderin-laden macrophages), (3) many fibroblastic foci ($\geq$ 5 foci/slide), (4) focal hyaline membranes

Results:
- 8 cases diagnosed as AE (definite-n=4; suspected-n=3) with OP lesions (n=7), alveolar hemorrhage (n=7), many fibroblastic foci (n=6), focal hyaline membranes (n=3)
- 6 cases diagnosed as stable had OP lesions (n=2), many fibroblastic foci (n=3) (1 case had both, many fibroblastic foci and OP lesions)
- AE was associated with having > 2 components (p=0.003)
- Focal hyaline membranes and acute alveolar hemorrhage – specificity for AE in NSIP 100% (sensitivity, 37.5% and 87.5%, respectively)
- Median survival, 246 days (6-1,675) in AE (3 died of respiratory failure, 4 alive, 1 lost) and 1,416 days (71-2,133) in stable disease (4 alive, 2 lost)

Take home points:
- 4 histologic features may be useful to report on to possibly predict AE in NSIP
- Would have been a great opportunity to look into AE-characteristic HRCT findings

Zhao J et al. A genomic and clinicopathological study of non-small-cell lung cancers with discordant ROS1 gene status by fluorescence in-situ hybridisation and immunohistochemical analysis. Histopathology 2018;73:19-28.

Background:
- ROS1 IHC can be false positive in lung adenoCa (only 1 reported case of false negative IHC)
- According to the latest molecular testing guidelines of CAP/IASLC/AMP, the set of EGFR, ALK and ROS1 should be the absolute minimum for testing in lung cancer patients – ROS1 IHC may be used as screening but positive result must be followed by molecular or cytogenetic tests
- Crizotinib appears promising in preclinical and phase I trials in treatment of ROS-1-rearranged NSCLC

Purpose:
- To compare clinic-pathologic and molecular features of ROS1 IHC-molecular discordant with concordant lung adenoCa cases.

Methods:
- ROS1 IHC – clone D4D6; intensity 3+ = strong, granular cytoplasmic stain diffusely and homogeneous; 2+ = moderate, smooth cytoplasmic staining in most tumor cells, occasional strong, 1+=faint; 0= negative.
- H-score
- Mutation analysis for EGFR, KRAS, ERBB2, BRAF, PIK3CA
- Fusion analysis for ALK, RET
- Amplification analysis for MET, ERBB2, ROS1

Results:
- 1638 – ROS1 IHC tested → 80 had ROS-1 expression → all 80 FISH and RT-PCR → 31 rearranged by both FISH and RT-PCR → concordant cases; 49 not rearranged → 26 had strong ROS1 expression → discordant cases
- ROS-1 concordant cases were younger (mean age, 53 vs 64 yo), had higher disease stage, more commonly acinar or cribriform predominant with more commonly identified extracellular mucus and psammoma bodies and less commonly lepidic predominant than ROS1 wild-type and IHC+ discordant cases
- ROS-1 concordant cases had no concurrent mutations; 73% of discordant cases had concurrent mutations (53.8% EGFR, 11.5% ERBB2, 3.8% KRAS; 1 case EGFR+ERBB2)
- ERBB-2 abnormalities appeared higher in discordant cases than in general lung adenoCa (based on literature) (ERBB2 mutations 11.5% vs 2-4%; ERBB2 amplification 7.7% vs 2%)
- H-score >150 in 23/26 discordant cases; in concordant cases – "heterogeneous staining was very rare"
- Identified optimized scoring criteria for ROS1 IHC as 'H score >150 and no concurrent mutations' → specificity or 81.6%

Take home points:
- ROS1-discordant patients are clinically, morphologically and molecularly distinct from concordant patients
- Unclear whether ROS-1 discordant patients are similar to all other lung adenoCa as they show differences in percent ERBB2 alterations – was not studied

Nakajima N et al. GATA6-positive lung adenocarcinomas are associated with invasive mucinous adenocarcinoma morphology, hepatocyte nuclear factor 4a expression, and KRAS mutations. Histopathology 2018;73:38-48.

Background:
- GATA6 = zinc finger transcription factor – expressed during development of several organs including lung – in mature lung activates transcription of surfactant A and C and regulates progenitor cell number during airway regeneration.

Purpose:
- To analyze GATA6 expression in lung adenoCa and to evaluate for clinicopathologic and molecular associations

Methods:
- Retrospectively, consecutive patients who underwent resection for lung adenoCa → TMAs
- Also TMAs including ovarian epithelial tumors, endometrial, uterine cervical, pancreatic, colorectal, bile duct adenoCa
- GATA6 – rabbit polyclonal – nuclear staining; H-score of 50-300 counted as positive
- Normal lung tissue – absent of extremely low GATA6 expression
- Correlation with expression of: CDX2, HNF4α, MUC2, MUC5AC, MUC5B, TTF-1
- Correlation with gene alterations: EGFR, KRAS, HER2, BRAF, ALK, ROS1

Results:
- 348 lung adenoCa – 13.5% GATA6+
- GATA6-expression associated with younger age (≤65 yo), absence of LN mets, well- and moderately differentiated tumors, absence of vascular and lymphatic invasion, presence of

lepidic component, invasive mucinous adenoCa, mucin production, and absence of micropapillary and solid components
- GATA6-expression associated with absence of TTF-1 expression and with expression of MUC5AC, MUC2, CDX2, HNF4α
- GATA6-expression associated with KRAS mutations
- GATA6-expression – not associated with outcome; GATA6-/ HNF4α+ cases had worst outcome
- GATA6 is also expressed in 21.7% ovarian epithelial tumors (4/5 mucinous type), 6.3% endometrial adenoCa (mucinous subtype), 82.4% pancreatic, 52.8% colorectal, 27.6% bile duct adenoCa

Take home points:
- GATA6 expression associated with mucinous-type adenoCa – therefore, might play a role in the development of mucinous-type lung adenoCa or mucinous-type Ca in general
- Not useful to distinguish primary lung adenoCa from met
- Mainly of research interest currently

Calio A et al. Cathepsin K expression in clear cell "sugar" tumor (PEComa) of the lung. Virchows Arch 2018;473:55-9.

Background:
- Cathepsin K is target of MITF family which includes TFEB and TFE3 transcription factors.
- Small subgroup of PEComas arising outside of the lung harbor TFE3 gene rearrangement

Purpose:
- To investigate the IHC expression of PEComas and whether they harbor TFEB and/or TFE3 rearrangements

Methods:
- 5 PEComas of lung; IHC and FISH

Results:
- 4 male, 1 female
- Median age 46 yo (20-62)
- All incidental findings; no patient had tuberous sclerosis; no necrosis or mites
- Expression of   Cathepsin K   (5/5; 60-100% of tumor cells +)
                     HMB45   (5/5; 15-30% of tumor cells +)
                     MITF   (0/5)
                     CD68, clone PGM1   (5/5; 80-100%)
                     CD68, clone KP1   (5/5, 100%)
                     TTF1, clone 8G7G3/1   (0/5)
                     PAX8, clone BC12   (0/5)
- No rearrangements of TFE3 or TFEB

Take home points:
- Cathepsin K might be useful for diagnosis of PEComa

- Panels useful for distinction of pulmonary PEComa from metastatic RCC include Cathepsin K, HMB45, PAX8; distinction of pulmonary PEComa from NSCLC include Cathepsin K, HMB45, TTF-1
- Diffuse expression of CD68 might represent a pitfall

Li Y et al. Recurrently mutated genes differ between leptomeningeal and solid lung cancer brain metastases. JTO 2018;13:1022-7.

Background:
- Leptomeningeal disease (LMD) as metastatic disease of NSCLC has a unique diffuse growth pattern and is rapidly fatal in contrast to solid brain mets from NSCLC

Purpose:
- To identify whether LMD harbors a distinct mutation profile compared with that of solid brain mets
- To compare whole exome profiles of a cohort of NSCLC LMD with previously sequened, publicly available solid brain mets of NSCLC to discover differences in their mutational landscape

Methods:
- Whole genome sequencing (WES) of 8 LMD
- Compare with 26 solid brain mets from NSCLC (from publicly available database)
- Compare with 44 previous LMD (chart review only)

Results:
- Recurrent mutations among LMD samples of taste 2 receptor member 31 gene (TAS2R31) and phosphodiesterase 4D interacting protein gene (PDE4DIP) were recurrently mutated among
- LMD   – only 4 (of 52, 7.7%) LMD harbored KRAS mutations
        - 33 (of 52, 63.5%) harbored EGFR mutations
- Median interval for development of LMD from NSCLC - shorter in patients with mutant EGFR (16.3 months) than wild-type EGFR (23.9 months)
- TP53 mutations in 4 (of 8, 50%) of LMD
- Additional mutations in LMD: PIK3CA (n=1 of 8), FGFR1 (n=1), MET (n=1), PDE4DIP (n=1)
- Comparison of LMD with solid brain mets
     Same % of TP53 mutations
     More EGFR mutations in LMD vs solid brain mets (63.5% vs 3.8%)
     No KRAS mutation in LMD vs 50% of solid brain mets
     Low mutation rate (4 of 52); lower than in solid brain mets
- EGFR mutation in LMD – median survival, 16.3 months (vs 23.9 months for wt EGFR)
- Cox proportional hazard model: EGFR mutation increased hazard, targeted therapy decreased hazard

Take home points:
- Apparently there are intrinsic differences in tumor biology between LMD and solid brain mets of NSCLC
- LMD develop faster in patients with EGFR mutation

Bagir EK et al. PD-1 and PD-L1 expression in thymic epithelial tumours and non-neoplastic thymus. J Clin Pathol 2018;71:637-41.

Background:
- PD-1 expression still underinvestigated in thymic epithelial tumors (TET) and thymic hyperplasia
- PD-L1 expression has been shown in neoplastic cells of thymoma and thymic carcinoma, however, high variability between studies, possibly in part due to use of different antibodies, thresholds and percent of thymoma
- Association between expression of PD-L1 or PD-1 and clinicopathologic parameters in TET still controversial

Purpose:
- To evaluate PD-1 and PD-L1 expression in epithelial and "microenvironmental" components in TET and thymic hyperplasia and correlation with clinicopathologic parameters

Methods:
- PD-1 (clone MRQ-22); PD-L1 (AM26531AF-N)
- Scoring: intensityof cytoplasmic and/or membranous staining: 0-3+; epithelial and microenvironmental staining considered positive if > 5% staining
- Thymic carcinoma and B3 thymoma were grouped together for statistical analysis

Results:
- 44 TET (38 thymoma, 6 carcinoma); 8 thymic hyperplasia; 53.8% had MG
- Median f/u 47 months

Number of patients	Epithelial	Microenvironmental	Both
PD-1 thymic hyperplasia (n=8)	0	0	0
PD-1 thymoma (n=38)	17	4	0
PD-1 carcinoma (n=6)	3	1	1
PD-L1 thymic hyperplasia	5	0	2
PD-L1 thymoma	17	0	14
PD-L1 carcinoma	3	0	3

- 18 patients had MG (27 thymoma, 1 Ca); PD-1 or PD-L1 did not correlate with MG
- MG correlated with lower age and smaller tumors
- PD-1 microenvironmental expression correlated with lower estimated 2-year survival
- No association between PD-L1 and outcome observed
- Pictures are impossible to interpret

Take home points:
- Association between PD-L1 expression and outcome still controversial
- Need for unified studies using same clones, same cutoffs for PD-L1 expression

Liu J et al. High expression of synthesis of cytochrome c oxidase 2 and TP53-induced glycolysis and apoptosis regulator can predict poor prognosis in human lung adenocarcinoma. Hum Pathol 2018;77:54-62.

Background:
- Synthesis of cytochrome c oxidase 2 (SCO2) and TP53-induced glycolysis and apoptosis regulator (TIGAR) = p53-mediated proteins; play regulatory role in cancer energy metabolism.

Purpose:
- To examine the association of SCO2 and TIGAR with the prognosis of patients with lung adenocarcinoma.

Methods:
- 75 lung adenoCa who underwent surgery before chemo, radiation or both
- TMAs included 75 cancers and 75 non-cancerous tissue
- Quantum dots–based immunofluorescence histochemistry staining
- Scoring of SCO2, TIGAR: areas of positive cells – score 0 (0-<5%), 1 (5-25%), 2 (26-50%), 3 (51-75%), 4 (>75%); staining intensity (0-3); final score: intensity distribution=area of positive cells * staining intensity
- P53 staining – high expression = strong and unequivocal red nuclear staining in ≥ 10% of tumor cells

Results:
- Stage I (33.3%), stage II (61.3%), stage III (5.4%)
- F/U, mean 45 months (1-115); 45.3% alive, 54.7% died of lung adenoCa
- ROC analysis to identify the cutoff for SCO2 and TIGAR expression levels (intensity distribution) = 6.5 for SCO2 (≥ 6.5 considered high expression); 1.75 for TIGAR
- P53 almost absent in normal lung but detected in lung adenoCa cells
- Expression of SCO2 (51/75, 68%) and TIGAR (59/75, 78.6%) was higher in lung adenoCa than in non-cancer (9.3% and 6.6%, respectively)
- High p53 expression in 18/75 (24%) lung adenoCa – no correlation with clinicopathologics
- High TIGAR expression - associated with a history of smoking, male gender
- High SCO2 expression – associated with age
- high TIGAR expression positively correlated with high SCO2 expression
- High expression of SCO2 and TIGAR – associated with worse survival, higher mortality rate, lung adenoCa progression
- No independent prognostic parameter

Take home points:
- SCO2 might promote tumor growth theough the acceleration of oxidative phosphorylation

- TIGAR might protect the tumor cell from oxidative stress and ROS-induced death
- SCO2 and TIGAR may have synergistic effect on tumor progression by promoting mitochondrial respiration
- High expression of SCO2 and TIGAR might be markers of worse prognosis in lung adenoCa

Articles of Non-Neoplastic Lung Disease for Notation

De Vries M et al. Lung tissue gene-expression signature for the aging lung in COPD. Thorax 2018;73:609-17.

Background:
- There are parallels between ageing and COPD

Purpose:
- To investigate genes underlying lung ageing in general and abnormal lung ageing in COPD

Methods:
- Whole genome mRNA profiling, 1197 lung samples (resection, volume reduction, explant)
- Subsequent pathway analysis performed using GeneNetwork; the gene-expression signature was compared with lung ageing in the Genotype-Tissue Expression (GTEx) project.
- In a subset of patients with COPD (n=311 well defined current or ex-smoking [>5-pack-years] patients with COPD [FEV1/FVC <70%) and non-COPD controls (n=270 [FEV1/FVC >70%]), interaction analysis between age and COPD, followed by gene set enrichment pathway analysis.

Results:
- Strong gene-expression signature for lung ageing: 1980 genes – higher expressed, 1529 lower expressed with increasing age
- EDA2R (DNA damage response) > MAP4K1 > FRZB – most significantly upregulated with age.
- MGST1 (detoxification, defense response to oxidative stress) > ZNF518B > ATP8A1 – most significantly downregulated with age
- Genes upregulated with age – enriched for processes related to calcium signaling, immune responses; genes downregulated – enriched for processes related to lung development, cell-cell contacts
- The age*COPD interaction analysis revealed 69 genes significantly differentially expressed with age between COPD and controls including:
    - DNASE1L3 (complement activation cascade) and RBP5 (cellular binding of retinol) – most significantly increased with age in COPD (vs non-COPD)
    - KIAA1462 (angiogenesis, blood vessel development), GPR173 (tissue homoeostasis) – most significantly decreased with age in COPD (vs non-COPD_
    - Genes enriched in extracellular matrix-receptor interaction pathway were more decreased in COPD with age

Take home points:
- Processes related to lung development, cell-cell contacts, calcium signalling and immune responses are involved in lung ageing in general.

- Pathways related to extracellular matrix, mammalian target of rapamycin signalling, splicing of introns and exons and the ribosome complex are proposed to be involved in abnormal lung ageing in COPD.

Kawabata Y et al. Grade 4 asbestosis does not extend directly from the respiratory bronchiole to the peripheral lung. Histopathol 2018;73:29-37.

Background:
- Asbestosis – believed to start in respiratory bronchiole (RB) (grade 1) – extending outwards until separate foci of fibrosis link (grade 3) eventually resulting in diffuse fibrosis (grade 4)

Purpose:
- To confirm whether grade 4 asbestosis progresses from RB to peripheral lung

Methods:
- Retrospective examination of autopsy or lobectomy specimens
- 31 cases (29 males, mean age 64) with pathologic grade 4 asbestosis (Helsinki criteria)
- Quantification of asbestos bodies (AB) by dissolved lung and on glass slides
- Grading of respiratory bronchiolar lesions: 0, 1, ≥2
- Grade 4 asbestosis subdivided into atelectatic induration (AI) and UIP-pattern
- AI pattern: subpleural fibrosis +/- scanty HC (grossly), fibroelastosis with collapse w/o structural remodeling (micro)
- UIP pattern: subpleural fibrosis with many HC (grossly), subpleural dense fibrosis with structural remodeling and frequent HC (micro)
- Fibrosis starting in the periphery: peripheral intraluminal fibrosis showing more collapse and more fibroelastosis than centriacinar intraluminal fibrosis or subpleural lobular fibrosis showing more collapse and more elastosis than inner lobular fibrosis

Results:
- Mean# slides 13 (5-30)
- LL predominance in 18/26 autopsies; UL predom in 3, diffuse in 5

Grade of RB lesions	# cases	Mean # ABs in dissolved lung/g dry lung	Mean # ABs in tissue preps on glass slide/1cm^2
0	5	117,000	7
1	10	468,000	34
≥2	16	968,000	195
p-value		<0.05	<0.01

Grade 4 patterns	# cases	Mean # ABs in dissolved lung/g dry lung	Mean # ABs in tissue preps on glass slide/1cm^2
AI	15	1,006,000	186
UIP	16	354,000	56
p-value		<0.05	<0.01

- No NSIP pattern
- AI patterns originated in subpleural lobules or subpleural zonal areas (figure 3)
- UIP pattern originated in subpleural, peripheral lobules

Take home points:
- Grade 4 asbestosis does not start in respiratory bronchiole
- Grade 1 lesion is not required for diagnosis of grade 4 asbestosis
- NSIP pattern might not be a dominant pattern in asbestosis

Letters / Correspondence

Richardson TE et al. Meningothelial-like nodules of the lung show SSTR2a immunohistochemical staining. Pathol Internat 2018;68:401-8.

Background:
- Pathogenesis of meningothelial-like nodules (MLN) still unclear
- SSTR2a is expressed in meningiomas

Purpose:
- To determine whether SSTR2a is expressed in MLN

Methods:
- 5 cases from lung explants for various non-neoplastic primary lung diseases with at least one incidentally discovered MLN

Results:
- Strong SSTR2a expression in all 5 MLN; they were also positive for EMA

Take home point:
- One more common protein expression between MLN and menignioma

Cattino A et al. Breast metastasis from malignant pleural mesothelioma: A rare challenging entity. JTO 2018;13:e117-118.

Background:
- Metastases account for <1% of all breast cancers

Purpose:
- Report of a case of known MPM metastatic to breast

Case:
- 61-yo female with advanced epithelioid MPM underwent first-line therapy with cisplatin and pemetrexet
- Relapse of mesothelioma – at same time onset of 5-cm breast lump and axillary lymphadenopathy
- Diagnosis of metastatic MPM made on core biopsy of mass and LN
- Panel of calretinin, WT-1 (usually absent in breast cancer), podoplanin

Take home point:
- I wonder whether MPM was ever diagnosed in a breast mass first – usually the history is likely to be known – nevertheless, metastases can occur in the breast once in a while

Reviews / Perspectives

Roden AC et al. Iatrogenic pulmonary lesions. Sem Diagn Pathol 2018;35:260-71.

Background:
- Treatment-associated lung injuries occur and although usually mild, they can occasionally be severe and life-threatening

Purpose:
- To review histopathologic features of iatrogenic pulmonary changes and important medications, radiation and devices that can elicit characteristic pulmonary findings

Discussion:
- Common morphologic patterns in drug-associated ILD that are discussed include: cellular interstitial pneumonia, NSIP, OP, eosinophilic pneumonia, pulmonary edema, DAD, hypersensitivity pneumonitis pattern, chronic bronchiolitis, pulmonary hemorrhage, pulmonary vascular disease, constrictive bronchiolitis, granulomatous disease
- Common drugs that are associated with ILD and are discussed: Nitrofurantoin, bleomycin, methotrexate, amiodarone, rituximab, immune checkpoint inhibitors
- Radiation-induced pulmonary toxicity
- Hydrophilic polymer catheter coating embolizing to lung
- Less common iatrogenic lesions including application of silicone, activated charcoal, polyacrylamide hydrogel, cement, barium sulfate, dinitrophenol, catheter ablation for atrial fibrillation

Beattie J et al. The immune landscape of non-small-cell lung cancer. Am J Respir Crit Care Med 2018;198:24-38.

Review of:
- Immunobiology that underlies the importance of evaluation of tumor specimens for predicting positive clinical outcomes from immunotherapy
- Clinical evidence for biomarkers from landmark ICI trials
- Limitations of the currently used biomarker PD-L1 (programmed death ligand 1) and prospective future biomarkers
- Challenges of acquiring and using minimally invasive samples to represent immunologic biomarkers
- Technical considerations of acquiring and using minimally invasive samples to represent immunologic biomarkers

- The chasm between specimen selection in major clinical trials and real-world sampling.

  Interesting read that goes into details of individual immune checkpoint inhibitors, their original clinical trials including which biomarkers and thresholds were used; pitfalls of PD-L1 as biomarker; limitations of immune checkpoint inhibitors; specimens to evaluate the immune landscape in NSCLC; the usefulness and indications of liquid biopsies.

Aguilera N et al. Reexamining post-transplant lymphoproliferative disorders: Newly recognized and enigmatic types. Sem Diagn Pathol 2018;35:236-46.

Background:
- PTLD = known risk factor for both solid organ transplant (SOT) and stem cell transplant (SCT) recipients (6x risk for developing any kind of non-Hodgkin lymphoma; PTLDs occur in up to 10% of SOT recipients)
- 60-80% of PTLDs are associated with EBV but EBV-negative PTLDs are increasing
- Several new entities in 2018 update of WHO classification of tumours of hematopoietic and lymphoid neoplasms including
  - Florid follicular hyperplasia
  - Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT-lymphoma) (excluding common locations such as stomach and salivary gland)
  - EBV-associated mucocutaneousulcer – now diagnosis on its own – not polymorphous PTLD

Review of:
- Non-destructive PTLD-florid follicular hyperplasia
- Monomorphic PTLD-extranodal marginal zone lymphoma or mucosa associate lymphoid tissue (MALT lymphoma)
- Monomorphic T/NK-cell PTLD
- EBV-positive mucocutaneous ulcer
- Lymphomatoid granulomatosis
- Hepatosplenic T-cell lymphoma
- EBV-negative PTLD

Case Reports

Salzer HJF et al. An unexpected endobronchial mass appearing during bronchoscopy. Chest 2018;154:e13-21.

Case:
- 60-yo male admitted with cough and yellow sputum, severe fatigue, 4 kg weight loss over past month, slowly progressing SOB on exertion over 6 months; antibiotics without improvement
- Pulmonary TB 34 years ago
- Smoker
- PFTs: severe obstructive airway disease, additional restrictive defect
- Chest X-ra: diffuse bronchial wall thickening, localized opacities in left middle and upper field, moderate to severe emphysema
- Sputum negative for TB (including RT-PCR)
- Bronchoscopy: ubiquitous atrophic endobronchial mucous membrane; obstruction of endobronchial lumen of LUL by an irregular brown-yellow mass
- BAL: dominated by neutrophils

Diagnosis:
- Chronic cavitary pulmonary aspergillosis with an endobronchial aspergilloma

Discussion:
- Chronic pulmonary aspergillosis (CPA) usually in immunocompetent patients with underlying structural respiratory disorders
- Table 1 – nice resource for different manifestations of CPA
- Symptoms non-specific
- Prevalence of CPA as sequel to TB – 8-22%
- Increased Aspergillus IgG antibody titer – most promising parameter to prove mycologic evidence - sensitivity up to 96%, specificity up to 98%
- Reference standard: histopathologic examination of lung tissue
- Galactomannan antibody test – good for invasive pulmonary aspergillosis, inferior in CPA
- 5-yr survival 40-60%
- Only chance of relapse-free survival: in toto resection
- Otherwise at least 6 months antifungal agents – sometimes lifelong
- TBBx or percutaneous bxs – often not diagnostic – just show chronic inflammation and fibrosis; hyphae not always present
- Molecular methods to identify Aspergillus sp. Are very limited

Take home point:
- Keep fungus ball in mind – still a serious complication of old TB