October 2019 Journal Club (Articles from September 2019)

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Yell M et al. Pulmonary nodular hyperplasia. Arch Pathol Lab Med. 2019;143:1149-53. Review

Miller RT. Avoiding pitfalls in diagnostic immunohistochemistry–important technical aspects that every pathologist should know. Seminars in Diagnostic Pathology 36 (2019) 312–335. Review.

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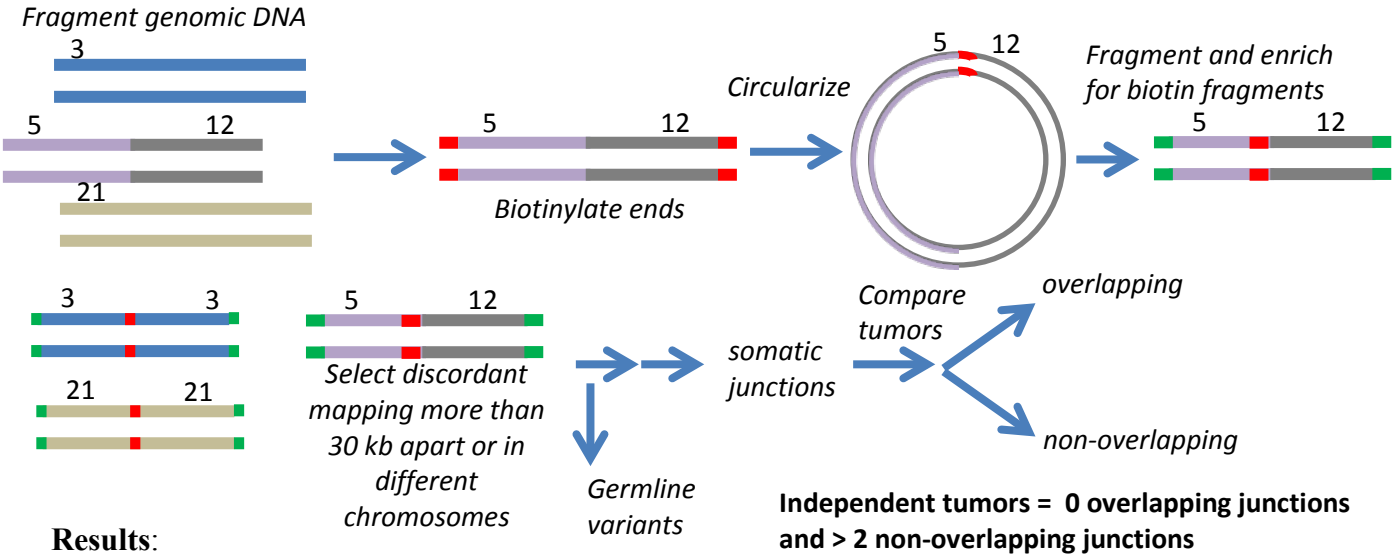
Articles for Discussion

Murphy SC et al. Using Genomics to Differentiate Multiple Primaries from Metastatic Lung Cancer. J Thorac Oncol 2019; 14(9):1567-1582. (Presented by Dr. Cecchini)

Background:

- In cases with more than one lesion histologic comparison of tumors is currently the main method for differentiating between multiple primaries and intrapulmonary metastasis. There is significant interobserver variability and imperfect concordance with genomic testing.
- Driver mutations (EGFR, KRas, BRaf), and structural rearrangements are not reliable due to field cancerization and recurrent structural changes.
- Somatic DNA junction breakpoints can be used as precise markers of tumor identity due to their unique specificity.

Methods: Frozen tissue from 76 tumors from 37 patients was utilized. All cases had independent blinded clinical and pathologic review. DNA extraction, whole genome amplification and Mate-Pair sequencing with analysis as outlined below;



Results:

- Histology called 59% independent primaries, 24% metastasis and 17% indeterminate.
- Genomics called 73% independent primaries, 27% metastasis and 0% indeterminate.
- There was concordance between genomics and histology in 78% of cases.
- Copy number variation was concordant in 66%, discordant in 7% and indeterminate in 27%.
- 17 cases were sequenced with NGS, the majority of cases had no driver mutations (53%) and two cases called independent by genomics had identical KRas mutations.
- The clinical inference disagreed with the histology call and/or genomics in 20% of cases.
- Full concordance between clinical review, histology, and genomics in 63% of cases.

Conclusion: Detection of chromosomal rearrangements is a useful and definitive technique in determining lineage in multifocal lung cancer.

Take home message: While accurate and definitive in determining lineage chromosomal rearrangement testing currently requires frozen tissue and is limited by cost and availability of testing.

Aly RG et al. Spread Through Air Spaces (STAS) Is Prognostic in Atypical Carcinoid, Large Cell Neuroendocrine Carcinoma, and Small Cell Carcinoma of the Lung. J Thorac Oncol; 14(9):1583-1593 (Presented by Dr. Cecchini)

Background:

- There is prognostic heterogeneity within the defined subtypes of neuroendocrine tumors.
- There are limited prognostic markers to further sub-classify the risk of recurrence and death.
- Spread through air spaces (STAS) has been shown to have prognostic significance in lung adenocarcinoma, squamous cell carcinoma, and pleomorphic carcinoma.

Methods:

- 487 consecutive patients (299 typical carcinoid (tc), 38 atypical carcinoids (ac), 93 large cell neuroendocrine carcinoma (LCNEC) and 57 small cell lung carcinoma (SCLC)) surgically treated from a single institution.
- Cases with positive margins or inadequate tissue for review were excluded.
- STAS was defined as, tumor cells within air spaces beyond the edge of the main tumor. STAS was in the form of solid nests (see figure 1) in all subtypes and STAS was distinguished from artifacts as outlined in figure 2.
- Study end points were recurrence and lung cancer specific-death.

Results:

- The incidence of STAS in the overall cohort was 26% and a higher incidence of STAS was seen in higher grade tumors (16% In TC, 37% in AC, 43% in LCNEC, and 46% in SCLC).
- The 5 year cumulative incidence of recurrence (CIR) and lung cancer-specific cumulative incidence of death (LC-CID) was higher in cases with STAS as outlined below;

	Overall		AC		LCNEC		SCLC	
	STAS +ve	STAS - ve	STAS +ve	STAS - ve	STAS +ve	STAS - ve	STAS +ve	STAS - ve
CIR	54%	24%	53%	27%	54%	29%	54%	14%
5-year LC-CID	43%	18%	15%	10% *	49%	24%	48%	14%

(p=0.097 Note all other differences are significant p < 0.05)*

- In the multivariate analysis STAS was independently associated with a higher risk of recurrence in cases of AC, SCLC and LCNEC (SHR = 2.85, 95% CI 1.73-4.68) and lung cancer specific death (SHR = 2.72, 95% CI 1.57-4.70).
- STAS was also independently associated with lung cancer specific death for SCLC (SHR = 4.06, 95% CI 1.33–12.35) and LCNEC (SHR = 2.42, 95% CI 1.21-4.84).

Conclusion: STAS is associated with increased recurrence and cancer specific death in patients with AC, LCNEC and SCLC. In LCNEC and SCLC, STAS is independently associated with increased lung cancer specific death.

Take home message: STAS is common in neuroendocrine tumors and patients with higher grade neuroendocrine tumors (AC, LCNEC and SCLC) may have worse outcomes if STAS is present.

Simbolo M et al. Gene Expression Profiling of Lung Atypical Carcinoids and Large Cell Neuroendocrine Carcinomas Identifies Three Transcriptomic Subtypes with Specific Genomic Alterations. J Thorac Oncol 2019; 14:1651-61.

Background

- Atypical carcinoids (ACs) and LCNECs share some molecular alterations, but have not been directly compared
- Some molecular alterations found in all 4 groups of pulmonary NETs (typical/atypical carcinoid, SCLC, LCNEC) (alterations in chromatin remodeling genes); MEN1 gene alterations predominantly in carcinoids; inactivation of TP53 and RB1 predominantly in Ca
- Variations in frequencies of same gene alterations in Ca and carcinoids (lower frequencies in carcinoids) may suggest progression of malignancy / development of secondary high-grade neuroendocrine carcinoma from preexisting carcinoid

Methods

- 35 AC, 32 LCNEC-surgically resected, no pre-op therapy
- Discovery set (14 ACs, 14 LCNECs): Ampliseq Transcriptome Human Gene Expression Kit, (20,815 human genes), Ampliseq Comprehensive Cancer Panel (409 genes).
- Validation set (21 ACs, 18 LCNECs): custom gene panels: (i) mRNA expression level of 60 genes, including 58 differentially expressed in discovery set and MEN1 and RB1; (ii) DNA alterations in 16 genes.
- IHC for menin (clone A300-105A) and Rb1 (4H1)

Results:

- 67 patients, mean age 66.2 yo; 49% stage I, 36% stage II, 9% stage III, 6% stage IV
- AC and LCNEC differed by age, sex, tumor size, Ki67 index; not for smoking or stage
- Discovery set – Hierarchical unsupervised clustering analysis $\rightarrow$ 4 clusters: (1) 11 LCNEC, 1 AC, (2) 5 AC, (3) 8 AC, 3 LCNEC, (4) non-neoplastic lung - 58-genes identified as differentially expressed between the 3 tumor clusters.

Table: Results of discovery and validation set (N=67)

Cluster	# LCNEC	# AC	Inactivation of RB (% cases)	Inactivation of TP53 (% cases)	MEN1 mutation (% cases)	Ki-67 LI mean (%)	Ca-specif surv (median, mos)
1	20	1	100	100	0	66	19
2	8	14	18.2	40.9	22.7	36	47
3	4	20	0	16.7	37.5	21	Not reached

- Cluster 2: subclusters: 2a: closer to cluster 1 (Ki-67 -mean 60%), including 8 LCNEC-all with TP53 mutations, 4 with heterozygous RB1 alterations; 2b: closer to cluster 3 – only AC, mean Ki-67 12%, enriched for MEN1 mutations

Take Home Points:

- ACs and LCNECs - 3 different, clinically relevant molecular diseases, (i) LCNEC-enriched group with RB1 inactivation, (ii) AC-enriched group, MEN1 mutation plays major role, (iii) mixed group
- At least a proportion of AC might progress to LCNEC

Swaminathan AT et al. Lung transplant outcomes in patients with pulmonary fibrosis with telomere-related gene variants. Chest 2019; 156:477-85

Background

- Telomeres protect chromosome ends from shortening during cell replication; Telomerase – enzyme that catalyzes the addition of telomeres; Short telomeres – associated with bone marrow failures, premature aging
- Variants in telomere-related genes (TERT, TERC, RTEL1, PARN) associate with familial PF
- Variants in TERT, RTEL1, PARN – associated with risk for sporadic or nonfamilial PF

Methods

- 262 PF lung transplant recipients – genotyped by whole exome sequencing
- Acute rejection (AR) burden quantified and compared over 1st posttransplant year. AR burden = sum of ISHLT grade A or B scores / total # TBBx with gradable rejection

Results:

- 262 patients; median age 65 (IQR, 58-69), 22% female, 13% family hx of PF, 81% IPF, 12% CTD-UIP, 7% fibrosing NSIP; 62% bilateral tx
- 31/262 (11.8%) – rare variants in TERT (N=13), RTEL1 (N=10), or PARN (N=8), none had systemic telomere syndrome before transplant (only a few with minor blood cell dyscrasia)
- Anemia more common post-tx in variant group (93 vs 77%, p=0.03)
- No difference in AR burden or rates of grade 3 primary graft dysfunction
- CLAD-BOS: overall: 56%; 50% amongst patients with variants, 57% w/o variants
- R-CLAD: overall: 44%; 50% amongst patients with variants, 43% w/o
- Onset of CLAD shorter in patients with variants (p=0.02); KM estimates for rate of CLAD at 1, 3, 5 years was 0%, 43%, 62% in variant group, 4%, 16%, 34% w/o variants
- Presence of TERT, RTEL1, PARN variants – independent predictor for CLAD after adjusting for age at transplant, type of transplant, sex, primary graft dysfunction, AR score
- Outcome: median f/u 2.8 yrs (IQR, 1.2-5.1)
- 44% died (58% amongst patients with variants, 42% w/o variants)
- Patients with PF with variants-higher risk of death (P =0.03), CLAD (P = 0.004) than patients without these variants.
- Presence of variants – higher risk of death after adjusting for age, sex, type of tx (p=0.03)
- Leading cause of death in patients with variants – CLAD (39%)

Take Home Points:

- Variants in telomere-related genes TERT, RTEL1, PARN - associated with poor posttransplant outcomes among PF lung transplant recipients independent of other known factors that are associated with worse outcome such as age, type of tx.
- Etiology of worse outcome not clear as no difference in AR score of PGD or CMV infection
- ?increased immunosuppression in variants; impaired cellular response to lung epithelial injury? abnormal interactions between recipient hematopoietic cells and donor alveolar epithelial cells provoke alveolar stem cell senescence, stimulating remodeling response resulting in fibrosis? PF and CLAD might share similar pathogenesis in these patients?

Brettfeld SM et al. SATB2 Versus CDX2. A Battle Royale for Diagnostic Supremacy in Mucinous Tumors. Arch Pathol Lab Med. 2019; 143:1119-25.

Background:

- Metastatic mucinous tumors – primary site can be difficult to identify - IHC often non-specific using CK7, CK20, CDX2 (colorectal, ovarian, pulmonary)
- Special AT-rich sequence-binding protein 2 (SATB2) – marker of glandular epithelium of lower GI tract (including appendix) – used as marker of metastatic mucinous colorectal Ca most specifically when compared with ovarian mucinous neoplasms
- Sensitivity of SATB2 - lower in mucinous colorectal Ca vs non-mucinous (83 vs 98%)
- To compare expression of SATB2 and CDX2 between mucinous tumors of various origin

Methods:

- All primary mucinous epithelial tumors (>50% of mucinous component)
- Whole tissue sections of 44 mucinous colorectal Ca, 175 non-colorectal mucinous tumors (60 ovarian including 18 mucinous adenoCa, 41 mucinous borderline tumors, 1 mucinous cystadenoma; 31 breast; 26 lung; 28 uterus including 26 endometrial, 2 endocervical; 15 pancreas including 7 mucinous/colloid adenoCa, 6 mucinous cystic neoplasms, 2 IPMN; 15 stomach/esophagus)
- SATB2 (EP281, Cell Marque); CDX2 (EPR2764Y, Abcam); nuclear staining
- Scoring: intensity (0-3+); percent staining (0=<5%; 1=5-49%; 2=≥50%); H score (intensity + % staining score)

Results:

- SATB2: accuracy >90% for colorectal Ca at low - moderate expression levels (H-scores 1-4)
- CDX2: Overall accuracy 89% for identifying colorectal origin only at H-score of 5 – specificity lower at lower expression levels (<70% at H-scores 1-4)
- If H-score cutoff of ≥3 (moderate-high intensity staining in minority of tumor cells or weak staining in majority of tumor cells) – significant differences in sensitivity (p=0.01) and specificity (p<0.001) between SATB2 and CDX2 – but were near equivalent when each was interpreted as positive at its respective optimal H-score (SATB2 ≥ 3; CDX2 = 5)

SATB2 and CDX2 expression in primary mucinous tumors of colorectum and lung

	SATB2		CDX2	
Score N (%)	Colorectum (N=44)	Lung (N=26)	Colorectum	Lung
Intensity 1	8 (18.2)	0	0	9 (34.6)
2	18 (40.9)	0	8 (18.2)	5 (19.2)
3	13 (29.5)	0	36 (81.8)	0
All positive	39 (88.6)	0	44 (100)	14 (53.8)
Percentage 0	1 (2.3)	0	0	2 (7.7)
1	4 (9.1)	0	0	4 (15.4)
2	34 (77.3)	0	44 (100)	8 (30.8)

Take Home Message:

- SATB2 (not CDX2) might be useful in distinction of lung (pancreas) from colorectal origin of mucinous adenoCa in vast majority of cases; clinicopathologic correlation still required; not useful for mucinous carcinomas from other sites

Articles for Notation – Neoplastic

Porubsky S et al. EWSR1 translocation in primary hyalinising clear cell carcinoma of the thymus. Histopathology 2019. 75:431-6.

Background

- Thymic carcinomas often show focal clear cell change
- Some thymic carcinomas exhibit prominent, diffuse clear cell morphology with exuberant hyalinised extracellular matrix – likely different from thymic SQCC, possibly more analogous to hyalinising clear cell carcinomas of the salivary gland

Methods

- ITMIG database searched for thymic tumors with clear cell changes/features – contacted contributing institutions
- *EWSR1* break apart FISH
- NGS

Results

- N=11
- 9 thymic carcinomas with focal clear cell changes
    - No *EWSR* translocation
- 2 thymic carcinomas with pronounced hyalinised stroma; diffuse clear cell morphology.
    - Positive: p40, p63, CK5/6, CK19, focally GLUT-1
    - Negative: PAX8, CD5, CD117, CD34, FoxN1, NUT, GATA3, Pax8, TTF1, napsin, HepPar1, glypican 3, SALL4, chromogranin, synapto, S100, HMB45, MART1, inhibin, calretinin, CD99, WT1, SMA, desmin, EBV ish.
    - INI-1 retained
    - Ki-67 LI 10%
    - PD-L1 – TPS 70% and 0%
    - *EWSR1* translocation in both cases
    - Fusion between exon 13 and exon 6 of *EWSR1* and *ATF1* (NGS); assay failed in the other case, likely due to case >26 years old.
    - Outcome:
        - 1 patient: R1 resection - adj radiation (50.4 Gy) – 5 mets resected 12 months later; Pleural and pericardial mets 21 months after initial diagnosis (CT) – chemo; 40 months after diagnosis – alive, partial remission
        - no f/u on other patient

Take Home Message

- Hyalinising clear cell carcinoma of the thymus
- Immunophenotype unspecific → testing for *EWSR1* translocation might be helpful particular in cases with clear cell change.
- *EWSR1* translocation - not specific to hyalinizing clear cell carcinomas (also occurs in hyalinizing clear cell carcinomas of salivary gland of other organs, clear cell sarcomas [they all share recurrent t(12,22)(q13;q12) EWSR1–ATF1 translocation]) → clinico-radiologic and morphologic correlation necessary

Xie H et al: Expression of delta-like protein 3 is reproducibly present in a subset of small cell lung carcinomas and pulmonary carcinoid tumors. Lung Cancer 2019; 135:73-9.

Background

- Delta-like protein 3 (DLL3; inhibitory Notch ligand) - potential therapeutic target in SCLC (rovalpituzumab tesirine [Rova-T] - antibody-drug conjugate with high specificity for DLL3)
- In vivo studies: Rova-T induces durable tumor regression in patient-derived xenograft tumor models of SCLC with a strong correlation between level of DLL3 expression and therapeutic activity. Phase I clinical trial including patients with SCLC and LCNEC – objective response in 11/60 (18%) patients who received Rova-T [10] including 10/26 (35%) patients with available tissue and high DLL3
- To study the expression of DLL3, its reproducibility and prognostic role in pulmonary neuroendocrine tumors.

Methods

- Resected pulmonary neuroendocrine tumors (1995–2017).
- Expression of DLL3 (clone SP347) categorized as high (≥50% of tumor cells) or low (< 50%).
- Interobserver agreement among 5 thoracic pathologists, Krippendorff's α coefficient.
- Staging (N=148) by 8th AJCC.

Results

- 157 patients, median age of 62.2 years (range 23.2–88.1), 59 men (37.6%).
- 44 (28.0%) SCLC, 46 (29.3%) atypical and 67 (42.7%) typical carcinoid tumors
- Stages I (N=83, 56.1%), II (N=28, 18.9%), III/IV (N=37, 25.0%).
- Interobserver agreement for high vs low DLL3 expression (N=70) - 82.9% (α=0.79, substantial).
- High DLL3 expression in 35 (79.5%) SCLC, 17 (37.0%) atypical and 22 (32.8%) typical carcinoid tumors.
- High DLL3 associated with SCLC ($p < 0.0001$).
- Median F/U of 4.2 years (range, 2 days–20.3 years) - 70 patients died; 19 from disease.
- High DLL3 - associated with better OS in SCLC (p=0.049) but not after adjusting for age, tumor size and stage.

Take Home Points:

- DLL3 expression - reliably quantifiable
- DLL3 highly expressed in majority of SCLC and subset of carcinoid tumors
- could be an attractive target for anti-DLL3 treatment; however, based on clinical evidence, currently treatment appears to be too toxic (might need different conjugate)

Guo R et al. MET IHC Is a Poor Screen for MET Amplification or MET Exon 14 Mutations in Lung Adenocarcinomas: Data from a Tri-Institutional Cohort of the Lung Cancer Mutation Consortium. J Thorac Oncol. 2019; 14:1666-71.

Background

- MET proto-oncogene, receptor tyrosine kinase – oncogenic driver in lung cancers
- MET pathway activation by MET amplification or splice site alteration in exon 14 → facilitates lung cancer growth, survival, metastasis
- MET amplification – a mechanism of acquired resistance to EGFR- and ALK receptor TKIs
- MET amplification (1-5% of lung cancers) and MET exon 14 (3-4% of lung adenoCa) affect sensitivity to MET proto-oncogene receptor TKIs.
- FISH, NGS, IHC – available for assessment of MET
- Trials with MET TKIs using IHC appear unsuccessful; trials using high MET copy numbers (>5) or *MET/CEP7* ratios appear more successful
- To determine the association of MET IHC with METex14 mutations and MET amplification.

Methods

- 3-institutional cohort from the Lung Cancer Mutation Consortium (University of Colorado, Dana Farber Cancer Institute, and Memorial Sloan Kettering Cancer Center)
- Prospective enrollment of all patients with stage IV or recurrent lung adenoCa
- All had to have metastatic lung adenoCa and no prior targeted therapies
- MET (clone SP44) IHC + = H-score ≥200
- MET amplification = copy# fold change ≥ 1.8 by NGS (assuming 50% tumor cell content) or *MET/CEP7* ratio > 2.2 by FISH
- METex14 testing

Results

- 181 patients, mean age, 65 yo (18-90), 57% women, 71% current/former smokers
- 71/181 (39%) – MET IHC+; of those: 1/71 (1%) MET-amplified; 2/71 (3%) METex14 mutation
- 110/181 (61%) – MET IHC-; of those: 2/110 (2%) MET-amplified
- 3/181 (2%) – MET-amplified (2 by FISH, 1 by NGS); of those: 1/3 MET IHC+; 2 of the IHC- cases had *KRAS G12C* mutation
- 2/181 (1%) – METex14 mutation; of those: 2/2 MET IHC+; 0/2 MET-amplified (age, 73 and 83; both female, both former smokers)
- No correlation between MET amplification and IHC
- Sensitivity and specificity for MET IHC to detect MET genomic alteration – 0.6

Take Home Points:

- MET IHC not specific or sensitive for MET amplification or METex14 mutation → IHC - not sufficient for screening for MET amplification of METex14 mutation
- For clinical trials – NGS or FISH should be used to detect MET genomic alterations

Wang S et al: Comparative study of EGFR mutations detected in malignant pleural effusion, plasma and tumor tissue in patients with adenocarcinoma of the lung. Lung Cancer 2019; 135:116-22.

Background

- To compare utility of malignant pleural effusion (MPE), plasma and tumor tissues for EFGR mutation analysis in lung adenoCa

Methods

- Retrospective study of Chinese patients
- MPE supernatant (20mL, not cell blocks) from lung adenoCa – all cytological positive.
- Matched tissue samples (N=92) and plasma (N=248)
- EGFR ex-19-del, ex 21-L858R mut - Denaturing high performance liquid chromatography for ctDNA-based EGFR mutation testing (sensitivity lower than current mutation detecting techniques for plasma, limited to certain mutations).

Results

- 295 patients, 52.9% male, 35.9% >65 yo; 38% current or former smokers
- 151/295 (51.2%) had EGFR mutation in either MPE, tissue or plasma
- MPE: 116/295 (39.3%) had EGFR mutation (25.8% E19, 13.9% E21, <1% E19 and E21)
- Tumor tissue: 35/92 (38%) had EGFR mutation;
- Plasma: 68/248 (27.4%) had EGFR mutation
- EGFR mutations more common in patients >65 yo; brain mets (vs liver or other sites)
- No association of EGFR mutation with age, gender
- MPE vs tissue (gold standard), concordance: 87.1% (κ=0.71)
    - 25 cases - EGFR mutation in both; 55 no mutation in both; 10 - EGFR mutation in tissue but none in MPE; 2 - EGFR mutation in MPE but negative tissue $\rightarrow$ 2 "false positive" (1 pat. received EGFR-TKI as 1st line – but ECOG 3 at diagnosis, died of pneumonia 2 wks later; 2nd pat. received EGFR-TKI - likely benefited from EGFR-TKI)
    - MPE: 71.4% sensitivity, 96.5% specificity, PPV 92.6%; NPV 84.6% for EGFR mutation
- 219 patients received EGFR-TKI and had complete follow up
    - 119 MPE collected before treatment; 79/119 – MPE with EGFR mutation
      48/79 received EGFR TKI as 1st line therapy, 31/79 as later line therapy
    - EGFR mutation in MPE – objective response rate (ORR) 56%, disease control rate 94%, PFS 9 months, OS 25.9 months vs wt MPE 19.3% (p<0.001), 63% (75/119) (p<0.001), 3.3 mos (p<0.001), 20.6 mos (p=0.032)
    - ORR - similar for EGFR mutation in tissues, MPE, plasma (57.6%, 56.0%, 47.4%).
    - PFS (8.9 mos vs 9.0 mos vs 7.7 mos) and OS (29.8 mos vs 25.9 mos vs 25.3 mos) similar amongst all 3 specimen types
    - No difference in TKI efficacy between E19 and E21 (trend - better outcomes with E19)

Take Home Message

- MPE could be used for EGFR mutation analysis for EGFR-TKIs treatment decision for advanced lung adenoCa patients if tissue and plasma are not available
- MPE might have higher concordance of EGFR mutations with tissue samples than plasma but more data needed
- Needs validation in non-Chinese patients

Shen Y et al. Lung cancers associated with cystic airspaces: CT features and pathologic Correlation. Lung Cancer 2019; 135:110-5.

Background

- Lung Ca associated with cystic airspaces (LCCA)- rare – in International Early Lung Cancer Action Program – 3.7% of lung cancers were associated with cystic airspaces
- NELSON lung cancer screening trial – LCCAs - 22.7% of missed/delayed cancer diagnoses

Methods:

- Preop CT scans of 10,835 patients with NSCLC
- Cystic airspace = round parenchymal lucency with well-defined interface with normal lung
- Exclusion: airspace in center of previously solid lesion suggesting cavitation, airspace cannot be differentiated from surrounding emphysema, bronchiectasis, cystic ILD
- Complete resection and systematic nodal sampling; SQCCs excluded
- Classification of LCCAs on CTs based on studies by Mascalchi & Fintelman:
  - Type I (thin-walled) = cystic airspace with mean wall thickness <2 mm
  - Type II (thick walled) = mean wall thickness ≥ 2 mm
  - Type III (CWN type) - cystic airspace with mural nodule (endophytic or exophytic)
  - Type IV (mixed type) – solid/nonsolid intermixed within clusters of cystic airspaces.
- AdenoCa classified as well-differentiated (AIS, MIA, lepidic predominant) vs moderately/poorly (M/P) differentiated (acinar, papillary, micropapillary, solid, mucinous)

Results:

- 123 LCCA, 82 men, mean age 60.2 +/- 9.5 yo, 117 with adenoCa
- Type I (18.7%); II (27.6%); III (35.0%); IV (18.7%); more likely peripheral (60.2%)
- 3.3% AIS, 4.1% MIA, 92.6% invasive (93 T1, 18 T2, 3 T4); 91.9% N0, 0.8% N1, 7.3% N2.
- Solid component in cyst wall predicts histological invasiveness in all 4 types of LCCA.
- Type III - highest proportion of M/P subtype (85.0% vs 50.0%, 50.0%, 69.6%) (p=0.005).
- M/P- adenoCa - more likely lobulated/spiculated margins and part-solid components in wall
- Type II LCCA (similar to type I) - more solid components in wall predicts M/P histology.
- Mean thickness and CT wall density - predictors for tumor histological behavior.
- Maximum tumor diameter and mean CT density correlated with pathological invasiveness
- M/P group was more likely to have irregular margins and more solid components in the wall. The mural nodule's size and density were significantly associated with histological subtype. Solid components in the nodule more common in M/P group
- Multivariate analysis: type III (vs type I), part solid and solid components (vs GG) and irregular inner surface of cyst- independent risk factors of M/P.
- F/U (N=13) 38 months (range, 7–76 months): 3/5 type I: nodule emerging from the cyst wall, became larger at later time; 2/5 - circumferential thickening of the cyst wall. 3/3 type II became completely solid. 5/5 type III - increasing attenuation and mural nodule sizes. 8 cancers - decrease in cystic airspace size with increasing solid elements; 1 cyst enlargement.
- 52.9% had EGFR mutations-no difference among patterns. KRAS mutations and ALK rare

Take Home Points:

- In LCCA, morphological patterns and wall components - important predictors for pathological invasiveness.

Mitchell KG et al. Tumor cellular proliferation is associated with enhanced immune checkpoint expression in stage I non–small cell lung cancer. J Thorac Cardiovasc Surg 2019;158:911-9.

Background

- Association of tumor proliferative activity and immune cell environment not well understood

Methods

- Resections of stage I - III NSCLC (1997-2012), all treatment-naïve, TMAs, retrospective
- Proliferative index = % malignant cells expressing Ki67 (clone MIB-1).
- Checkpoints expressed on malignant cells (PD-L1, B7H3, B7H4, indoleamine 2,3-dioxygenase 1-IDO1) and lymphocytes (T-cell immunoglobulin, mucin-domain containing 3, V-domain suppressor of T-cell activation, TNF receptor superfamily member 4, lymphocyte activation gene 3-LAG3, inducible T-cell co-stimulator-ICOS) - intratumoral and stromal
- Immune cell densities (cells/mm^2- quantified intratumoral and peritumoral in a subset.

Results

- N=190, median age 66 yo (IQR 60-74), 53.7% male, 90% former/current smokers
- 60% adenoCa, 37.9% SQCC, 2.1% NSCLC NOS
- Well/mod differentiated 57.9% (remainder poorly diff); Stage I 57.4%, II 25.3%, III 17.4%
- 95.8% R0 resection
- Higher Ki-67 in smokers (median 24.6% + malignant cells vs nonsmokers,median 11.4%), SQCC (median 31.4% vs 15.2% adenocarcinoma), advanced-stage (25.7% stages II/III vs 20.8% stage I), poorly diff. tumors (28.8% vs 15.4% well/moderately), larger tumors
- Ki67 correlated with intratumoral expression of PD-L1, B7-H3, IDO1, elevated stromal expression of LAG 3 and ICOS.
- Ki67 expression - inversely associated with intratumoral densities of CD57+ and CD4+ cells.
- Tumors with Ki67 > observed median had increased densities of cells expressing PD1 in intratumoral and peritumoral compartments
- Peritumoral compartment: increased infiltration by tumor associated immune cells expressing CD3, CD4, CD8, CD45RO, FOXP3, GZB was associated with Ki67 expression
- Median F/u 70 months
- Ki67 - checkpoint expression relationship - strongest in stage I tumors; increased Ki67 - associated with worse OS.
- Optimal cutoffs to define low-, intermediate-, and high-risk stage I tumors according to postoperative OS were Ki-67 <=7.17%, 7.17%-25.73%, > 25.73%
- PD-L1 expression - highest among Ki-67 high tumors
- Ki67 - independently associated with increased hazard of death and DFS events

Take Home Points

- Increased Ki67 expression - associated with biologically aggressive NSCLC, enhanced immune checkpoint expression, reduced intratumoral immune cell infiltration; findings strongest in early-stage disease
- Pretreatment expression of Ki67 might be predictive biomarker among patients with NSCLC receiving checkpoint inhibitors, cytotoxic agents, or novel combinations thereof but prognostic effect of Ki-67 was present only in stage I disease

Koezuko S et al Toward improving prognosis prediction in patients undergoing small lung adenocarcinoma resection: Radiological and pathological assessment of diversity and intratumor heterogeneity. Lung Cancer 135 (2019) 40–46.

Background

- Prediction of prognosis based on GGO ratio for small lung adenoCa not completely accurate.

Methods

- Retrospective; N=62 (64 lesions) - lobectomy for small (≤2 cm) lung adenoCa.
- Measured proportions of histological components
- STAS (tumor cells within air spaces at a distance of ≥ 1 alveolus away from main tumor)
- Intratumor heterogeneity of PD-L1 (clone 22 C3) expression analyzed in 40 lesions.
- CT image slices 1mm

Results

- 13/64 (20.3%) pure GGO, 9 (14.1%) part solid, 42 (65.6%) solid
- Predominant histologic subtype: lepidic 39% (including AIS, MIA???), papillary 32.8%, acinar 7.8%, solid 14.1%, colloid 6.3%, micropapillary 0
- STAS 28.1%
- LN mets in 4.8%
- Pathologic stage: 0 (17.1%), IA1 (45.3%), IA2 (20.3%), IA3 (3.1%), IB (9.4%), IIB (4.7%)
- Correlation coefficient between proportion of GGO and lepidic component 0.579 ($p<0.001$)
- 7/13 (53.8%) pure GGOs - contained invasive components (papillary, acinar, solid, colloid)
- Non-lepidic invasive components: - associated with a high CT value (high HU) ($p=0.002$)
- 1 pure GGO lesion → multiple lung metastases 3 years after lobectomy; re-review of the pure GGO lesion - heterogeneous density, high concentration of GGO components in center; CT value of the high concentration portion was -216 HU vs CT value of low concentration area (-414 HU). Histologically- lepidic-predominant adenoCa with papillary component at the center of the tumor, and a lepidic component
- STAS - identified in pure GGO lesions
- Pure GGO with invasive components ($p= 0.002$) and STAS ($p= 0.011$) had higher CT value.
- Papillary component, STAS+, or CT value ≥-140.6 HU – associated with worse DFS.
- No recurrence in patients with both measurements, CT value <-383.4 HU and GGO ≥50%

Take Home Points

- Invasive component and STAS can be present even in small GGO lesions
- Papillary components or STAS associated with worse prognosis
- STAS - associated with high CT value
- Combined use of GGO ratio and CT value may predict recurrences of small lung adenoCa more accurately than GGO alone.

Kadara H et al. Driver Mutations in Normal Airway Epithelium Elucidate Spatiotemporal Resolution of Lung Cancer. Am J Respir Crit Care Med Vol 200, Iss 6, pp 742–750, Sep 15, 2019.

Background

- "Field cancerization" in NSCLC
- Uninvolved normal-appearing airway epithelium exhibits specific mutations characteristic of nearby NSCLCs including
- Somatic mutational landscape in patients with early-stage NSCLC - unknown.

Methods

- N=48 stages IA–IIIA; 37 adenoCa, 11 SQCC; 42 ever-smokers, no neoadjuvant therapy
- Deep-targeted DNA sequencing (409 cancer-associated genes), genome-wide genotype array profiling of multiple regions of normal airways (tumor-adjacent small airways, tumor-distant large airways, nasal epithelium, uninvolved normal lung = collectively airway field), matched NSCLCs, blood cells (n = 498 including 450 somatic, 48 germline/control subjects)
- Phylogenetic analysis to assess spatiotemporal relation between airway field and NSCLCs.

Results

- 3,286 somatic mutations in 285 samples, mostly in NSCLCs (3,017 mutations in 209 samples from 48 patients)
- Mean somatic mutational burden (MB) higher in NSCLCs (13.9 mutations/sample) than in airway field (1.2)
- 269 somatic mutations in 76 airway field samples from 36 patients, most in airways adjacent to tumor (226/269 field mutations); airway field MB the more distant from tumors
- MB higher in smokers NSCLCs than nonsmokers but only marginal in airway field; smoker NSCLCs had more tobacco-associated C>A base substitutions than nonsmoker tumors; similar enrichment in smoker airway field samples but lesser extent.
- Variant allele frequencies (VAF) of mutations in airway samples decreased as distances from matched NSCLCs increased
- NSCLCs - relative high abundance of somatic SNVs and AI. Matched airway field samples also positive relationship between AI and SNV but lesser extent
- Genomic airway field carcinogenesis seen in 25 cases (52%).
- 28 mutated drivers displaying protein-damaging mutations in airway field samples; TP53, KRAS, KEAP1, KMT2D, KMT2C, STK11, ATRX, IDH1, JAK1 mutated in normal appearing airway samples from >1 case, 19/28 of these genes - same mutation in matched NSCLCs, some of which were shared within multiple field samples for the patient
- The airway field epithelium - 269 somatic mutations in 36 patients including key drivers that were shared with the NSCLCs.
- Uninvolved normal lung tissue (n = 4) and nasal epithelium (n = 4) – mutations in RB1, RET, TSHR, and ATK1, none were shared with matched NSCLCs

Take Home Points

- Tumor-adjacent and tumor-distant normal appearing airway epithelia exhibit somatic driver alterations that undergo selection-driven clonal expansion in NSCLC.
- Potential targets for early treatment.

Buza N et al. Precision genotyping diagnosis of lung tumors with trophoblastic morphology in young women. Modern Pathology (2019) 32:1271–1280.

Background

- Lung Ca with trophoblastic morphology in women during reproductive age – diagnostic challenge (morphology & IHC overlap with met chorioCa) – different treatment, prognosis.
- Trophoblastic differentiation arise as (1) gestational trophoblastic tumors (gestational chorioCa, epithelioid trophoblastic tumor, placental site trophoblastic tumor) - develop from prior gestational event → unique paternal genetic material; (2) gonadal/extragonadal germ cell tumors – lack paternal genetic material; (3) focal trophoblastic differentiation – thought to arise from somatic component
- Gestational chorioCa – during reproductive years (mean age, 30 yo), following normal pregnancy, complete hydatidiform mole or abortion in 50%, 22.5%, and 20% of cases usually within a few months (rarely > 20 years). Serum βhCG usually >10,000 mIU/mL
- Germ cell tumors - rare, usually in children/young adults, ovary
- Features favoring somatic origin: older, postmenopausal, βhCG <10,000 mIU/mL

Methods

- Short tandem repeat (STR) genotyping to confirm/rule out gestational origin of tumor

Results

- Case 1: 37 yo, para 4, gravida 3103; bilateral lung nodules, hemorrhagic mass in right pelvic sidewall; 2 mos prior stillborn with postpartum hemorrhage; βHCG 520,000 mIU/mL; core bx-tumor pos for panCK, βHCG; neg for hPL, p40, SALL4, TTF-1; STR – unique alleles in tumor tissue at 9/15 loci – not present in patient's normal tissue – c/w paternal alleles from prior biparental gestation – c/w gestational chorioCa; placenta with identical genetic profile; no tumor in placenta or hysterectomy – chemo – alive well for 17 months, βHCG <1mIU/mL
- Case 2: 41 yo, para 5; gravida:2032; bleeding for 4 mos; + pregnancy test. Last pregnancy 6 yrs ago; now MTX for possible extrauterine pregnancy. βhCG - 10,727 mIU/mL – did not normalize. 9.7 cm RUL mass, hilar lymphadenopathy, LLL nodule; core bx - tumor + CK AE1/AE3, βhCG, GATA3, focal + EMA, p40; neg TTF-1, CK5-6. PD-L1 – TPS 30%; STR – LOH within tumor at 3 loci, no distinct paternal alleles within tumor. C/w primary lung Ca with trophoblastic differentiation. Targeted NGS - mutations in SMARCA4, ARID1A, NF2, ATR, CDK12, POLE; chemo; f/u enlarging pulmonary mass, now 11.8 cm and multiple lung, liver, brain, bone mets; pembrolizumab; died of disease 15 months after presentation
- Case 3: 48 yo, gravida 3, para 2; right hemothorax, 1.5 cm right lung nodule; last pregnancy 6 yrs prior – retained placenta; wedge resection – 7 cm centrally cystic, hemorrhagic mass; >90% necrotic; IHC: + CK7, GATA3; weak PAX8, neg: p40, TTF-1, Napsin A, CK5-6, OCT4, ER, CDX2; STR - unique alleles in tumor at 11/15 loci → c/w paternal alleles from prior biparental gestation = metastatic gestational chorioCa. NGS – no mutations. Completion lobectomy & LN - no residual carcinoma. Postsurgical βHCG - 315mIU/mL. Chemo - βhCG normalized; no evidence of disease at 4 months.
- Clinical history, imaging – inconclusive for distinction between primary and met disease

Take Home Message

- Beware of diagnostic pitfall of lung Ca with trophoblastic differentiation in young women
- Genotyping analysis - can help in that diagnostic distinction; IHC not helpful

Dermawan, JK et al. The Prognostic Significance of the 8th Edition TNM Staging of Pulmonary Carcinoid Tumors A Single Institution Study With Long-term Follow-up. (Am J Surg Pathol 2019;43:1291–1296).

Background

- IARC and WHO consensus conference for neuroendocrine neoplasms proposed uniform classification that would designate carcinoid tumors as differentiated neuroendocrine tumors, in keeping with other organ systems
- To compare the ability of the 7th and 8th TNM classification of lung cancer to predict recurrence in typical and atypical lung carcinoid tumors

Methods

- Resection specimens of primary lung carcinoids (1995-2016)
- Recurrence – only measurement for outcome
- Mitotic counts: at least 50 HPF counted; mean # mitoses per 10 HPF; typical (<2 mitoses/HPF) or atypical (2 to 10 mitoses/HPF) carcinoids [that should have been /10Hpf and also actually should have been per mm2]; it sounds like that not all tumors re-reviewed
- Exclusion: concurrent/preexisting malignancies, + margins; mitotic count not in report and no archived material, lost to F/U (CT scan ≥ 3months after resection); no LN

Results

- 205 carcinoids: 188 (92%) typical, 17 (8%) atypical; median age 55 (14-81), 36% male; 9% current smoker; 36% past smokers, 47% never smokers
- Lobectomy 81%, wedge 8%, segmentectomy 5%, sleeve 3.4%, pneumonectomy 2.9%
- Recurrence rate 8% (N=16; 5 local [interlobar or mediastinal], 11 distant [brain, liver, bone], median time 37 mos, range, 5-113 mos); Death from metastasis 2% (N=4)
- Atypical carcinoids – more likely to recur (median time to recurrence 3 yrs); >50% of typical carcinoids were recurrence-free throughout the entire time period
- Multivariate analysis (sex, age, histology (typical vs. atypical), LVI, tumor size, nodal stage): histology, tumor size, nodal stage = significant predictors of recurrence; histology - highest odds ratio (HR 16.2 p<0.001) (atypical – shorter RFS) > nodal stage > tumor size.
- Between 7th and 8th TNM – 18% upstaged (Ib→IIA [N=11], IIA→IIB [4], IIB→IIIA [1]) – due to T and N stage including T2a→T2b [11]; T2b→T3 [5], T3→T4 all due to size criteria
- 14 (7%) downstaged, all T3→T2, involving main bronchus
- 8th TNM – more atypical carcinoids with increasing stage. Only trend in 7th TNM
- In both TNM – stage correlates with recurrence but KM curves separate better in 8th TNM; overlapping curves of IA3 and IIA for 8th TNM
- More atypical carcinoids in stage III of 8th TNM – significant, not significant in 7th

Take Home Points

- 18% of patients upstaged in 8th TNM due to increased emphasis in tumor size, N1 disease in tumors <4cm and de-emphasizing main bronchus involvement
- 8th TNM – better predictor of recurrence
- No definite incremental stratification between stage II and III in 8th – tumor size and nodal status might not be sufficient for therapy decision in these stages
- Authors conclude - histology & stage are interdependent and not independent predictors of recurrence amongst carcinoids → do we need to distinguish between typical and atypical?

Altinay S et al. Spread through air spaces (STAS) is a predictor of poor outcome in atypical carcinoids of the lung. Virchows Archiv (2019) 475:325–334. (Summarized by Dr. Cecchini)

Background: Spread through airspaces (STAS) is the presence of floating tumor cells arranged in clusters in the peri-tumoral alveolar spaces. This process has been likened to tumor budding in colorectal carcinoma. STAS has been shown to be an independent predictor of recurrence and survival in adenocarcinoma and squamous cell carcinoma. STAS has been previously reported in high frequency of resected small cell lung carcinomas. The association of STAS with outcome has not been investigated in atypical carcinoid.

Methods: Retrospective study of 91 surgically resected atypical carcinoids from a single institution during 1989 to 2015. Inclusion criteria included availability of H&E slides/paraffin blocks and availability of follow-up. 161 typical carcinoids and 30 high-grade large and small cell neuroendocrine carcinomas were also included. STAS was independently assessed by 3 reviewers who were blinded to the outcome. In cases of diagnostic discrepancy a consensus was reached at the multiheaded microscope. STAS was evaluated as "floating tumor nests or single cells in the air spaces beyond the outer border of the neoplastic mass". STAS was present as either tumor nests or single cell pattern.

Results:

- STAS was identified in 48% of atypical carcinoids, 20.5% of typical carcinoids and 76.7% of high-grade carcinomas (small and large cell neuroendocrine carcinoma).
- STAS was associated with features of aggressive disease including high T stage, positive nodes, necrosis and high proliferation index.
- The presence of STAS was a predictor of an adverse prognosis for all carcinoids (HR = 6.49, 95% CI 2.15–19.62, p = 0.0009) and atypical carcinoid only (HR = 2.45. 95% CI 0.91–6.61, p= 0.049) on univariate analysis but not multivariate analysis.

Conclusion: STAS is associated with features of aggressive disease in carcinoid tumors and is associated with an adverse prognosis.

Take home message: STAS is common in carcinoid tumors and more commonly observed in higher grade tumors. STAS may help identify patients with a poor prognosis.

Reviews, Case Reports, Editorials, Perspectives, Research Statements

Denisov EV et al. Premalignant lesions of squamous cell carcinoma of the lung: The molecular make-up and factors affecting their progression. Lung Cancer 2019; 135:21-28 - Review

- Review of genetic, epigenetic, transcriptomic and proteomic profiles of premalignant lesions of lung SQCC
- Environmental causes, inflammation, and gene polymorphism that may govern the progression or regression of premalignant lesions of SQCC are discussed.
- Review of strategies for lung cancer prevention and proposed new models and research directions for studying premalignant lesions and developing new tools to predict the risk of their malignant transformation.
- Lung SQCC evolution in bronchial epithelium: basal cell hyperplasia, squamous metaplasia, grade I–III dysplasia, carcinoma in situ, invasive SQCC
- Each of the lesions preceding lung SQCC can progress, remain unchanged, and partially or completely regress. Progression takes a period of several months to several decades, but the rate of progression increases as the premalignant process becomes more severe. In cases with severe dysplasia/CIS, progression is more likely.
- Checkpoint blockade immunotherapy can be used at the precancerous stage when immune-inflammatory reactions are not diverse as in cancer. PD-L1 expression is induced in bronchial epithelial cells by cigarette smoking and the carcinogen benzo(a)pyrene and elevated in premalignant airway cells. Anti-PD-L1 antibodies significantly suppress carcinogen-induced lung Ca $\rightarrow$ checkpoint blockade may be a successful approach to prevent progression of lung premalignant lesions.

Yell M et al. Pulmonary nodular hyperplasia. Arch Pathol Lab Med. 2019;143:1149-53. Review

- Reviews clinical features and histopathologic findings of the entity, specifically focusing on the differential diagnoses of MALT lymphoma and IgG4-related disease
- Nice table with distinguishing features of pulmonary nodular hyperplasia from MALT lymphoma and IgG4-related disease

Miller RT. Avoiding pitfalls in diagnostic immunohistochemistry–important technical aspects that every pathologist should know. Seminars in Diagnostic Pathology 36 (2019) 312–335. Review.

Purpose

- Review technical aspects of diagnostic IHC, with an emphasis on aspects of methodology and interpretation
- Review of pitfalls in IHC
- Importance of good controls and use of multi-tissue controls
- Optimal use of IHC in cytologic specimens and specimens where no paraffin block is available.
- Discussion of artifacts in IHC
- Useful techniques such as multi-tissue control material, tissue and cell transfer techniques, and tissue protection techniques.

Snell G et al. Consequences of donor-derived passengers (pathogens, cells, biological molecules and proteins) on clinical outcomes. J Heart Lung Transplant. 2019; 38:902-6. Review.

- Summarizes evolving lung transplant literature, focusing on donor "passenger" organisms, cells, hormones, and proteins transferred to the recipient.
- Many extrinsic and intrinsic donor features or properties have important consequences for subsequent allograft function/outcome in the recipient.
- Infectious pathogens – Mycoplasma hominis, Ureaplasma (some are associated with hyperammonemia syndrome)
- Microbiome – specifically of the GI tract and lung – pathogenetic bacteria and virus in one tract can affect the flora of the other and vice versa through innate and adaptive immune system – these effects increase allograft rejection rates. Levels of anellovirus suggested as biomarker of efficacy of immunosuppression – low levels = immunocompetence; some suggestions that low levels of anellovirus are a marker of primary graft dysfunction; potential for adjuvant sputum and fecal transplants to restore a normal microbiome
- B-lymphocytes/plasma cells – passenger lymphocyte syndrome (recipient hemolysis because of donor B-cell production of anti-red blood cell antibodies); antibodies may mask true recipient-generated DSA; donor antibody production may confuses antibody testing results post-tx (e.g., EBV serology, allergy testing, etc) or contributes to recipient symptomatology
- Tissue resident lymphocytes – persistent donor-tissue resident memory T cells might be associated with improved outcome; donor immune cells may remain in the allograft, potentially contributing to tissue repair, or tissue inflammation and rejection
- Exosomes (very small extracellular vesicles released from donor cells); donor dendritic cell exosomes contain donor MHC molecules that circulate to the recipient's lymphoid tissues, are taken up by recipient cells, then the donor MHC is presented on their surface (so-called MHC cross-dressing), in turn activating recipient T cells.
- Donor-derived cell-free DNA (dd-cfDNA = DNA fragments resulting from apoptosis or necrosis) - levels of dd-cfDNA - potential biomarker for LTx injury; increased in PGD, rejection, and BOS; infection, particularly CMV, may confound clinical results
- Allograft circadian clock proteins - donor lung reperfusion in recipients between 4:00 and 8:00 AM was associated with PGD - donor lung cooling might shift donor circadian clock, causing desynchrony with the recipient, noting that the clock protein REV-ERBa directly regulates PGD biomarkers, and in animals, synthetic REV-ERB ligands ameliorate PGD.
- Gender factors – female-male donor-recipient pairings affect outcomes – possibly due to increased estrogen signaling in females (promotes proinflammatory cytokine production and toll-like receptor expression on female APCs – stimulate recipient T-cell activation; effects of increased expression of X-chromosome innate and adaptive immunity genes leading to higher acute rejection rates; in males – testosterone inhibits proinflammatory cytokine production, toll-like receptor expression and female T-cell activation.)
- Age: Older donor organs - higher immunogenicity, heightened recipient T-cell responses

Take Home Points:

- Donor's age, gender, pregnancy history, infection and partner contact history, sleep patterns, and bowel and airway microbiological health are important as complex innate and adaptive alloimmmune interactions follow.

Sears CS et al. Knowledge Gaps and Research Priorities in Immune Checkpoint Inhibitor–related Pneumonitis. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med Vol 200, Iss 6, pp e31–e43, Sep 15, 2019.

Background:

- ICI pneumonitis increasingly diagnosed
- Increase in immune-related adverse side effects (irAEs), including potentially fatal ICI-related pneumonitis (ICI-pneumonitis).
- Development - sporadic, unpredictable, relatively uncommon
- To summarize evidence, identify knowledge and research gaps, prioritize topics and propose methods for future research on ICI-pneumonitis.

Key Topics

- Need for consistent and accurate terminology for describing features of ICI-pneumonitis
- Understanding of biological mechanisms (possibly increased T cell activity against autoantigens, increased levels of inflammatory cytokines, enhanced complement mediated inflammation)
- Identifying risk factors and populations at risk for ICI-pneumonitis (RA, treatment with other anti-cancer agents?)
- Optimizing diagnostic evaluation, significance of superimposed infections is unclear
- Optimal management of ICI-pneumonitis

Thoughts

- irAEs - 70-91% of patients with ICI treatment – incidence might vary by type of immune treatment, underlying malignancy; in clinical trials more common in NSCLC (4.1%; 7-19% outside of trials) than melanomas (2.7%); most frequent in patients with combination therapy
- ICI-pneumonitis = most common fatal irAE from anti–PD-1/PD-L1 monotherapy (35% of anti–PD-1/PDL1–related deaths)

Methods:

- Multidisciplinary international panel organized by ATS

Results

- Agreed upon "immune checkpoint inhibitor–related pneumonitis (ICI pneumonitis)"
- Biological mechanisms of ICI pneumonitis – likely heterogeneous – including immunological mechanisms, role of microbiome, underlying lung disease, other exposures in development of ICI pneumonitis
- What are risk factors and which populations are at risk? KEYNOTE-001 trial suggests history of asthma or COPD and prior thoracic radiation may be associated with increased incidence of ICI-pneumonitis.
- Research of diagnostic evaluation
- Research of management and follow up

Zheng Q et al. Primary Gastrointestinal-Type Clear Cell Sarcoma–like Tumor of the Bronchus: A Hitherto Unreported Bronchial Tumor. J Thorac Oncol 2019; 14:e202. Case Report.

Background:

- Clear cell sarcoma–like tumor/malignant gastrointestinal neuroectodermal tumor (CCSLT/MGNET) - uncommon aggressive neoplasm of GI tract (predilection for small intestine, stomach) - overlapping morphologic and molecular features with clear cell sarcoma of soft tissue.
- Predominantly affects young to middle-aged adults
- Highly aggressive, poor prognosis.
- Thought to be derived from autonomic nervous system–related primitive cells within GI tract
- To present a case occurring outside GI as a primary bronchial tumor.

Methods:

- IHC
- FISH for EWSR1 break apart
- NGS

Case:

- 40-yo male - progressive dyspnea, cough, hemoptysis for several weeks. CT and bronchoscopy: polypoid 1.5 x 1 cm lesion in proximal left main bronchus, almost occluding bronchial orifice. Bronchoscopic resection, subsequent radiotherapy/chemotherapy → remission
- Local recurrences after 1 and 1.5 yrs, treated with bronchoscopic resection. No other lesions by PET-CT. Alive 2 yrs after initial presentation
- Tumor centered in bronchial submucosa – sheets, nests, fascicles of epithelioid and spindly tumor cells with eosinophilic and focally clear cytoplasm in fibrous stroma; prominent nucleoli, focal pseudopapillary growth, focal necrosis, frequent mitoses, scattered osteoclast-type giant cells; diffuse S100+ and SOX10+; HMB45-, Melan A-, tyrosinase A-, PNL2-
- *EWSR1-ATF1* fusion and novel *SOX1-OT* fusion

Take Home Points:

- CCSLT/MGNET - relatively indolent case in main stem bronchus in contrast to usually aggressive nature in GI tract
- Probably shouldn't be unexpected in bronchus because the upper digestive tract and the respiratory bud share the same embryonic origin from the foregut.