Pulmonary Journal Club July 2023 (Articles from June 2023)

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Articles for Discussion

Bosse Y et al. A Simplified Version of the IASLC Grading System for Invasive Pulmonary Adenocarcinomas With Improved Prognosis Discrimination. Am J Surg Pathol 2023;47:686–693.

Purpose

- To validate prognostic value of IASLC 3-tiered grading system for invasive pulmonary adenoCa (grade 1-WD-lepidic predmoninant, <20% HG pattern [solid, micropapillary, complex glands-cribriform or fused]; grade 2-MD-acinar or papillary predominent, <20% HG pattern; grade 3-PD-≥20% HG pattern)
- To compare discriminatory performance of the IASLC grading system (I-GS) with conventional predominant pattern-based grading system (p-GS, grade 1-lepidic predom, grade 2-papillary/acinar predom; grade 3-micropapillary/solid predom) and simplified version of IASLC grading system w/o complex glandular patterns (s-GS)

Methods

- Single site, retrospective
- Resected invasive pulm adenoCa stages I-IVA; histologic re-review; 8th AJCC TNM
- Discovery (n=676; 2022-2012) and validation (n=717; 2013-2020) cohort
- Median f/u of combined dataset (n=1393) – 7.5 years
- Exclusion: Patients with neoadjuvant therapy, multifocal or synchronous tumors
- Patterns reported in 5% increments
- Interobserver reproducibility calculated for 4 pulmonary pathologists for 20 cases

Results

- Clinical characteristics - table 1
- Discovery cohort – all 3 classifications had similar predictive performance; best discriminatory performance (by multivariate log-rank p-values and AIC values): s-GS (fig.1); large number of patients upgraded by I-GS when compared to p-GS, s-GS (fig 2)

- Validation set and combined set only compared s-GS with p-GS.
- In combined set – both p-GS and s-GS strongly associated with survival in multivariate analysis; s-GS had lower p-values and AIC in multivariate analysis – best prognosticator (fig 3); also comparison of baseline model (age+sex+pathologic stage; already strongly associated with survival) to baseline model + s-GS – adding s-GS further improved association with survival → s-GS was associated with survival beyond baseline model (only trend if p-GS was used instead of s-GS)
- S-GS model performed well for both sexes and age groups but better in younger patients (<65 yo) and specifically in stage I
- Reproducibility: p-GS-κ=0.69; I-GS-κ=0.45; s-GS-κ=0.56

Take Home Points

- IASLC grading has prognostic value but simplier grading may be even better
- With IASLC grading more patients are in grade 3 – implications for adjuvant therapy, more aggressive postsurgical f/u
- Complex glands were removed from grade 3 in s-GS – where should they go?
- Still need prospective, ideally multicenter study

Fortin M et al. Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy: A Prospective Multi-Centre Agreement Clinical Trial (CAN-ICE). Am J Respir Crit Care Med. 2023. 207:1612–1619.

Purpose

- To assess within- and between-center histopathologic and MDD agreement between TBCB and SLB in diffuse ILD

Methods

- Multicenter, prospective study
- Matched TBCB and SLB in patients referred for SLB for unclassifiable or low-confidence diagnosis of diffuse chronic ILD after local MDD
- TBCB- ≥3 pieces from 2 lobes, 1-2 cm from pleural surface; 2.4 mm cryoprobe; presence of pneumothorax evaluated by endoscopist on fluoroscopy after TBCB
- During same anethesia - ≥ 2 SLB pieces by VATS from same lobes as TBCB specimens
- Sampled lobes identified by radiologists and respirologists during preproceedural MDD
- Blinded review by 3 pulmonary pathologists (aware of preprocedural local MDD diff diagn) – provided specific ILD histopathologic pattern for each TBCB based on 2013 guidelines (Travis 2013); listed most likely alternative diagnoses; degree of confidence
- 3 ILD teams reviewed cases per 1. Standardized clinical data, imaging → provisional diagnosis + degree of confidence; 2. Added TBCB path results → final TBCB-MDD diagnosis + degree of confidence → 3 TBCB MDD diagnoses/pertient
- ≥ 3 months after TBCB-MDD SLB reviewed by same 3 pathologists (aware of preprocedural MDD)-provided specific ILD histopathologic pattern, degree of confidence → 2nd MDD (same members/ 3 teams) → 3 SLB MDD diagnoses/pertient
- MDD (≥ 1 pulmonary pathologist, chest radiologist, respirologist specialized in ILD)
- Total 60 TBCB-MDD and 60 SLB-MDD diagnoses

Results

- N=20 patients (2014-2019) – 80% referred for UIP-IPF / FHP; 70% male, mean age 64.5
- Median of 3 (range, 3-5) TBCB specimens in 2 different lobes; moderate bleeding in 25%, no severe bleeding, pneumothorax 20%; median procedure time 11min
- Median of 3 (range, 2-4) SLB speimens
- 1 patient died on po day 17 due to ARDS that manifested on po day 4
- Overall agreement between TBCB-MDD and SLB-MDD in 37/60 (62%) paired observations – κ=0.46; 27% IPF, 52% FHP after SLB-MDD; 7% remained unclassifiable
- After TBCB-MDD-37% IPF; 13% unclassifiable; most discordant diagnoses were related to TBCB-MDD diagnosis of IPF being classified as FHP on SLB-MDD
- TBCB-MDD diagnostic agreement more likely (72%) in cases with high confidence/definite diagnosis than low-confidence diagnosis (61%)
- Within-center-κ-values for TBCB-MDD and SLB-MDD: 0.41-0.56 (3 centers)
- Proportion of TBCB-MDD cases with high confidence/definite diagnosis 20%-65%
- Between-center agreement TBCB-MDD; κ=0.29; SLB-MDD; κ=0.71
- Histopathologic agreement between TBCB and SLB in 57%; κ=0.38
- TBCB–MDD: sensitivity 81%, specificity 80%, positive 4.0 and negative 0.24 likelihood ratios for final SLB-MDD diagnosis of IPF (Table 3).
- TBCB–MDD sensitivity 52%, specificity 86%, positive 3.7 and negative 0.56 likelihood ratios for a final SLB–MDD diagnosis of FHP (Table 3).

Take Home Points

- If using SLB as the gold standard, TBCB with MDD appears sufficient in a subset but not all patients; potentially better in diagnosing UIP than FHP; also complications of TBCB need to be considered

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Haberecker M et al. A systematic comparison of pan-Trk immunohistochemistry assays among multiple cancer types. Histopathology 2023, 82, 1003–1012.

Purpose

- *NTRK* rearranged tumors rare; anti-TRK targeted therapies potentially useful
- Testing currently either by only NGS or IHC followed by NGS
- To compare performance of 4 pan-TRK IHC methods, using 3 different clones
- IHC staining pattern vary with *NTRK1* vs 2 vs 3 rearrangement (perinuclear, cytoplasmic, membranous)

Methods

- Clones: *EPR17341* (Abcam; *Ventana*), EP1058Y (Abcam), A7H6R (Cell Signaling)
- 81 neoplasms (22 *NTRK* rearranged tumors including 20 pathogenic and 2 non-pathogenic rearranegments; *NTRK* fusion-negative tumors including 8 *NTRK* mutated and 15 *NTRK* amplified tumors; 20 *NTRK* fusion-negative tumors with other gene fusions [ALK, ROS1, BCOR] and 16 salivary gland tumors
- Inter-rater agreement of 3 pathologists, H score
- Positive considered if ≥1% of tumor cell staining

Results

- All molecular pathogenic *NTRK1-3* rearranged tumors were +IHC (20/20) with clone EPR17341 (both companies); all clones were positive in all 11 *NTRK1*-rearranged tumors; Clone A7H6R missed 1/8 *NTRK3*-rearranged tumor, clone EP1058Y missed 1/1 *NTRK2*-rearranged case and 3/8 *NTRK3*-rearranged cases
- Among *NTRK*-fusion negative cases – A7H6R – overall highest true negative rate highest with 80%; EPR17341 – 74%, EP1058Y 33%
- Staining location (perinuclear, cytoplasmic, membranous) varied by fusion partner and by clone and protocol used; clone EP1058Y – frequent costaining of cytoplasm and nucleus
- In *NTRK* amplified subgroup – EPR17341 (Ventana) – highest true negative rate (80%); EPR17341 (Abcam) only clone/method that showed correlation between copy number and IHC staining
- Salivary gland tumors – highest false positive rates – 44% for EP1058Y to 69% for A7H6R; adenoid cystic carcinomas had highest false positive rate

Take Home Message

- IHC using pan-TRK for *NTRK* rearrangements in daily practice appears complicated and requires a high level of expertise

Sasaki E et al. Mucous Gland Adenoma of the Lung: A Neoplastic Counterpart of Mucinous Bronchial Glands. Mod Pathol. 36(6): 100182

Purpose

- Rare benign tumor; arises in proximal airway; consists of mucus-secreting cells resembling bronchial glands
- To describe morphologic, IHC, molecular profiles of 2 MGA and compare with other pulmonary tumors with mucinous cells

Methods

- 2 cases of MGA
- 19 pulmonary tumors of 5 other histologies with mucinous cells (9 IMA, 3 BA/CMPT, 3 mucoepidermoid Ca, 3 mixed squamous cell and glandular papilloma, 1 sialadenoma papilliferum)
- NKX3.1 (EP356)

Results

- 2 MGA, 1 in bronchus, 1 in trachea
- 1 male, 35 yo, sputum production since 2 yrs
- 1 female, 66 yo, cough and sputum production
- Never smokers
- Tumor size 0.4 – 1.1 cm
- Both underwent endoscopic snare tumorectomy
- No recurrence for 6 months – 3 years
- Histology: monotonous proliferation of small glands with abundant intracytoplasmic mucin and small basally oriented nuclei; a papillary structure is present in 1 case; no ciliated epithelium, no cytologic atypia or necrosis (Fig. 2).
- IHC: Mucus cells negative for p40, SOX10, TTF-1, HNF4a, pan-Trk, ALK.

Abluminal cells sparsely positive for p40 and SOX10 (Fig. 2)

- RNA sequencing (N=1) – no driver mutation (*BRAF, KRAS, AKT1*) or gene fusions
- Hotspot PCR (N=1) no *BRAFV600E* or *AKT1* mutation; RNA expression profile showed multiple genes enriched in salivary gland; gene expression of *NKX3.1* (one of 30 top differentially expressed genes in MGA; role in development of minor salivary glands) significantly higher expressed in MGA case than control lungs ($P < .001$).
- NKX3.1 IHC positive in MGA (2/2, 100%, Fig 3), negative in all other tumors (0%, 0/19), mucinous acinar cells of bronchial glands in normal lung tissue positive .

Take Home Points

- Findings suggest that MGA is neoplastic counterpart of mucinous bronchial glands
- NKX3.1 IHC sensitive and specific to distinguish MGA from histologic mimics but not benign bronchial seromucinous glands
- Distinction from low grade bronchial/tracheal adenoCa – latter lacks the p40/SOX-10 positive myoepithelial cell layer and can express pan-TRK and infiltrative growth
- Distinction from BA/CMPT – the basal cell layer is more dense than in MGA; also mutations including *BRAF* and *KRAS* in subset of BA/CMPT but not in MGA

Articles for Notation

Neoplastic Disease

Hou T et al. Morphologic Changes in the Thymus Following Chemotherapy for Anterior Mediastinal Germ Cell Tumors. Arch Pathol Lab Med. 2023;147:676–683.

Purpose

- Treatment-related changes in thymus may mimic residual teratoma or microcystic-pattern of YST
- Aim: To identify helpful clues to distinguish nonneoplastic thymic abnormalities secondary to chemotherapy from residual germ cell tumor.

Methods

- Retrospective; resections of primary anterior mediastinal GCT with recognizable thymic gland following cisplatin-based chemo for primary nonseminomatous mediastinal GCT

Results

- N=91; 90 male, median age, 29 yo (18-64); clinically diagnosed on imaging showing isolated anterior mediastinal mass and elevated serum AFP (N=79) and/or HCG (N=36)
- N=45 pretreatment biopsies: YST (n=23), seminoma (6), embryonal Ca (5), mixed GCT (4), chorioCa (2), teratoma (1); 4 bxs non-diagnostic; 6 with seminoma also had high AFP indicative of non-sampled YST elements

Postchemo specimens:

- No residual GCT (n=45), YST (19), teratoma (16), YST and teratoma (3), chorioCa (2), high grade sarcoma (somatic transformation) (2); teratoma with prominent vasculogenic features (2 with vasculogenic stroma, 2 with vasculogenic mesenchymal tumor).
- Tumor necrosis, mixed inflammation, fibrosis present in all cases

- Thymic epithelial alterations (see table): cystic changes (n=41; including macrocysts >0.5 cm [n=21] and microcysts <0.5 cm [n=20]); microcalcifications (n=52); increased tingible body macrophages in thymic medulla (15); diffuse cystic dilation of Hassall corpuscles (6); epithelial hyperplasia with reactive atypia (8); ciliated, mucinous, or columnar cell metaplasia (3); mature squamous metaplasia (2)
- Small tubular or pseudorosette structures (2)
- Changes similar to multilocular thymic cysts and often contiguous with and adjacent to normal thymic epithelium.
- In 1 case, confluent microcysts closely mimicked YST but lacked other distinctive features of that neoplasm and its characteristic immunoreactivity.

Take Home Points

- Recognize therapy-induced thymic changes to avoid misinterpretation as residual teratoma or YST.
- Isochrome 12p may be helpful to confirm residual teratoma in this setting; SALL4 can also be useful

Huang J et al, NCD Global Health Research Group, Association of Pacific Rim Universities (APRU). Global Incidence, Risk Factors, and Temporal Trends of Mesothelioma: A Population-Based Study. J Thorac Oncol. 2023; 18: 792–802.

Purpose:

- To evaluate the global disease burden of mesothelioma; trends of mesothelioma by age, sex, and geographic locations; and its risk factors for the population.
- To explore the association between human development index (HDI), gross domestic product (GDP), and occupational exposure to asbestos and mesothelioma

Methods:

- Databases utilized: Global Cancer Observatory (185 countries, 2020), Cancer Incidence in Five Continents Plus (10-year cancer incidence in 108 countries, 2003-2012), Global Burden of Disease (156 countries and regions)

Results:

- 2020: estimated 30,870 new cases globally; age-standardized rate (ASR) 0.30/100,000 persons; highest incidence rates by region: Northern Europe (1.4) > Australia& New Zealand (1.3), Western Europe (0.79); 23-fold difference between locations; highest incidence rates by country: Luxembourg (4.1) > UK (1.9) > Australia/Netherlands (1.3 each)
- Incidence rate of male (global ASR 0.46) > females (0.17).
- Incidence rate of old (≥ 50 yo; 1.0) > young people (0.06)
- Countries with higher HDI (β=0.119, CI: 0.073–0.166, $p < 0.001$), gross domestic product/capita (β=0.133, CI: 0.106–0.161, $p < 0.001$), and asbestos exposure (β=0.087, CI: 0.073–0.102, $p < 0.001$) had higher incidence of mesothelioma; same associations for male, female, old people; in young people only higher GDP/capita associated with incidence of mesothelioma

- Overall trend of mesothelioma incidence decreasing in countries with higher HDI (≥0.9) including Australia, USA, Norway, Germany, Brazil; increase in Bulgaria (AAPC: 5.56, 95% CI: 2.94–8.24, p=0.001) and Korea (AAPC: 3.24, 95% CI: 0.08-6.49, p=0.045)
- Countries with lower HDI – decreasing trend in Philippines; increasing in Chile

Take Home Points

- Substantial declining incidence trend of mesothelioma in past decade particularly among younger people possibly related to restriction of asbestos use in some countries. However, that trend likely depends on when the bans of asbestos took place and therefore, in some countries the trend of incidence may still be increasing.
- Substantial geographic disparity in disease burden of mesothelioma; likely due to the high past asbestos use in early industrialized regions; probably also misdiagnosis due to lack of experience in developing countries
- Higher incidence associated with higher HDI, higher GDP/capita; likely due to more prevalent asbestos use in highly developed and industrialized regions
- Increasing trend of mesothelioma in female – authors speculate that this is possibly due to that not all asbestos was baned and for instance eritonite was still allowed to pave roads, build houses, and construct playgrounds in Turkey and USA
- Overall likely reporting bias including under-reporting and misclassification, especially from countries with low- to middle income

Kawai T et al. Liposarcoma of the pleural cavity. Human Pathology (2023) 136, 105e113

Purpose

- To identify whether the combination of clinicopathologic, IHC, and FISH allows for definite diagnosis

Methods

- Cases collected from several hospitals in Japan
- IHC: MDM2, CDK4 – only nuclear staining was counted – resulted as 0 (neg), 1+ (weak), 2+ (moderate), 3+ (strong); extent of staining: <1% (neg), 1-10% (focal), >10-100% (diffuse)

Results

- N=14 (6 WD liposarcomas, 5 dedifferentiated, 2 pleomorphic, 1 myxoid LS)
- Mean age, 57 yo (30-78), 9 male
- Incidental finding or chest pain, cough, SOB
- 10 left, 4 right pleura

Histology:

- WDLS: relatively mature adipocytic proliferation, accompanied by some lipoblasts
- DDLS: round-to-oval tumor cells with a high nucleus-to-cytoplasm ratio that proliferated in nests, accompanied by some giant cells but no fatty cells in 1 case
- PLS: varying proportion of pleomorphic lipoblasts.
- MLS: uniform round- to oval-shaped cells and small signet-ring lipoblasts in myxoid stroma.

IHC:

- Positive for S-100 in 79% of cases, p16 (79%), CDK4 (71%), MDM2 (43%), adipophilin (43%)
- WDLS: S-100 5/6; CDK4 3/6; p16 3/6; MDM2 2/6
- DDLS: p16 5/5; S-100 4/5; CDK4 4/5; MDM2 3/6; adipophilin 3/6
- PLS: positive for S-100, CDK4, p16; 50% positive for MDM2, adipophilin
- MLS: positive for CDK4, p16, adipophilin

FISH:

- *MDM2* amplification in 1 WDLS and 3 DDLS
- No *MDM2* amplification in both pleomorphic LPS

Outcome:

- WDLPS – most favorable outcome for survival
- Literature review + studied cases, N=45 (15 WDLS, 14 MLS, 9 DDLS, 3 PLS); multivariate analysis: females had worse outcome; WDLS had best outcome

Take Home Points

- Authors argue that IHC for CDK4, MDM2, adipophilin together with *MDM2* FISH are great diagnostic tools in that setting; however, they did not assess specificity of any of these markers
- No difference in histology to liposarcoma elsewhere

Woodard GA et al. Comparative genomics between matched solid and lepidic portions of semi-solid lung adenocarcinomas. Lung Cancer 180 (2023) 107211

Purpose

- To compare driver mutations and gene expression profiles between neighboring benign lung parenchyma, lepidic adenoCa, and solid adenoCa in resected semi-solid lung lesions
- To identify potential biomarkers in groundglass or semi-solid lung lesions that may predict their transition to solid, invasive carcinoma.

Methods

- Retrospective identification of surgically resected semi-solid lesions (SSL, based on imaging)
- Thoracic pathologist confirmed diagnosis; 7th AJCC TNM staging, restaged to 8th TNM
- Stage I SSL (n=65) and stage IA >75% solid adenoCa (n=120) resected during same time period
- Patients with neoadjuvant therapy excluded
- Microdissection of normal lung, in situ adenoCa, and invasive solid tumor from within same SSL specimens for NGS (25 common lung cancer driver mutations) and affimetrix microarray for gene expression in 22 cases; 19 had sufficient DNA for NGS
- For driver mutation comparison to a large population of stage I lung adenoCa TCGA data were used (n=274 stage IA and B)

Results

- Patients with SSL – older, more commonly never smoker, Asian, more commonly underwent sublobar resections, lower tumor stage
- No difference in 5-yr DFS, OS between SSL and solid adenoCa

- Cancer-related mortality 0% for SSL, 3% for solid adenoCa stage I; 5-yr OS 93% for SSL, 94% for solid adenoCa
- Driver mutations in both lepidic and solid invasive portion in 68% of cases including *EGFR* (43% including L858R in 26%, exon 19 16%), *KRAS* codon 12 (21%), DNMT3A (5%)
- Comparison of driver mutations between SSL in this study and stage I all comer adenoCa in TCGA: *EGFR* more common in SSL (SSL: 43%; TCGA 12%); *KRAS* similar (SSL 21%, TCGA 25%), *DNMT3A* same (5% both populations)
- Gene expression – 105 and 128 upregulated and 282 and 319 downregulated in lepidic and solid areas, respectively when compared to normal lung; 21 upregaulated and 11 downregulated in solid areas when compared to lepidic
- *CEACAM5* – most upregulated gene in solid invasive and 2nd most upregulated in lepidic portion of SSL when compared to normal
- *SPP1* gene expression– unique biomarker for invasive component in comparison to lepidic of SSL

Take Home Points

- Common lung Ca driver mutations appear to develop early
- *CEACAM5* and *SPP1* – promising biomarkers of invasive potential in semi-solid lesions

Finall A et al. Integration of rapid PCR testing as an adjunct to NGS in diagnostic pathology services within the UK: evidence from a case series of non-squamous, non-small cell lung cancer (NSCLC) patients with follow-up. J Clin Pathol 2023;76:391–399.

Purpose

- To determine whether TAT for reporting *EGFR* by NGS alone is sufficient to meet the needs of lung cancer patients

Methods

- Retrospective series of consecutive lung cancer samples of non-squamous NSCLC that were sent for *EGFR* mutation testing by DNA panel NGS as per routine reflex; 100 cells – minimum requirement to proceed with companion diagnostics
- All sample types including cytology specimens
- Outcomes of *EGFR* testing by NGS was compared with rapid, fully automated PCR-based platform (Idylla) in local histopathology labs
- Idylla –can detect 51 activating mutations in FFPE tissue in exons 18-21 including G719/A/CS, L861Q, S768I, L858R, exon 20 insertion, multiple deletions on exon 19, T790M; results possible within 3 hours; uses 5µm FFPE biopsy tissue (NGS 60µm), generates valid results with tumor neoplastic cell content as low as 10%
- NGS panel: EGFR, KRAS, NRAS, PIK3CA, CDKN2A, PTEN, RET, BRAF, ERBB2

Results

- 96 lung adenoCa patients, 49% male
- EGFR: 102 tests in 96 patients, mean age 72 (41-92)
- Clinical stable group, n=79; group who deteriorated rapidly, n=17
- EGFR mutation in 15% of patients 79% of which were exon 19 deletion or L858R mut

- 32% of patients were deceased by conclusion of study (10 months); 18% deteriorated rapidly (=reduction in ≥2 ECOG PS scores within 8 weeks of histologic diagnosis) – 3 (of 17) patients had actionable *EGFR* mutation (TAT of NGS report 15-28 calendar days) – 1 patient died of brain met 1 week before report came; 2 patients deteriorated to PS4 before NGS report came → ineligble for treatment with TKI inhibitors
- 6% were dead before NGS report was available
- TAT for reporting NGS – 17 calendar days from day slides were sent to lab; mean TAT overall for DNA NGS incorporation into histology report and authorization – 23.3 days from request to report being emailed to pathologist and oncologist (not including time for cutting sections, track on LIS, package and post material to external lab).
- TAT for reporting Idylla *EGFR* mutation 3.8 days from request to authorization of report; that time includes cutting sections, pathologist checking and authorization
- ¾ of patients with stage IV disease had performance status 0-2; 18% experienced rapid clinical deterioration
- Test performance: agreement between NGS and Idylla – 96%; NGS failed in 10% while Idylla still could produce results; 2 of the NGS failures revealed actionable mutation with Idylla; one case – NGS showed mutation, Idylla failed as no tissue was left

Take Home Message

- Integration of rapid PCR testing alongside NGS appears important
- Stage IV patients should get reflex Idylla and NGS, stages I-III may only need NGS

Bironzo P et al. Real-world retrospective study of KRAS mutations in advanced non–small cell lung cancer in the era of immunotherapy. *Cancer.* 2023;129:1662–1671.

Purpose

- To generate real-world data of clinical characteristics of patients with NSCLC by *KRAS* mutation subtype in the era of immunotherapy
- Currently standard 1st line treatment in patients with advanced, *KRAS* mutation-positive NSCLC is ICI +/- platinum-based chemo
- Some concurrent genomic alterations or isoforms of *KRAS* mutations may be associated with different outcomes

Methods

- Retrospective, single institution
- Molecular studies: DNA and RNA-based NGS and PD-L1 expression (22C3)

Results

- 199 consecutive patients with *KRAS*-mutated, advanced or metastatic NSCLC; median age 69 yo (38-90), 68% male; 99% stage IV disease; ECOG PS 0 (54%), 92% concurrent or former smokers; 85% adenoCa; PD-L1 "high" in 22%, "intermediate" (not defined in methods) in 29%, negative in 44%
- 1st line treatment for advanced disease in 67% including platinum-based chemotherapy (*n* = 42), single-agent anti–PD-(L)1 immunotherapy (*n*= 35), chemoimmunotherapy (*n* = 27), single-agent chemotherapy (*n* = 22), clinical trials (*n* = 8; 6%); 19% supportive care
- *KRAS* mutations: p.G12C (39%), p.G12V (17%), p.G12D (15%), 2 patients with double *KRAS* mutations; co-mutations with other than *KRAS* mutations in 22%, mainly *TP53*

- *pG12C* mutation was only associated with smoking
- Median OS 10.7 months, no difference by mutation subtype
- 134 patients received systemic 1st line treatment – median OS 12.2 months, median PFS 5.6 months
- Multivariate analysis – ECOG PS 2-associated with shorter PFS and OS
- No association between PD-L1 expression level and survival

Take Home Message

- *KRAS*-mutated, advanced NSCLC – poor prognosis despite introduction of immunotherapy – although the authors did not compare ICI and chemo
- Survival not associated with *KRAS* mutation subtype
- Unclear survival if treated with *KRAS* G12C-targeted therapy

Non-neoplastic Disease

Li Y et al. ABCA3-related interstitial lung disease beyond infancy. Thorax 2023;78:587–595.

Purpose

- Most patients with childhood ILD (chILD) caused by pathogenic variants in ATP binding cassette subfamily A member 3 (ABCA3) develop severe respiratory insufficiency
- ABCA3 – plays critical role in surfactant metabolism
- ABCA3 variants grouped according to their effect on ABCA3 function into "null" variants (do not produce functional protein due to frameshift or nonsense variants or deletion of entire exon) or "hypomorphic" mutations (some residual function of ABCA3 transporter protein, missense variants, in-frame insertions or deletions).
- Appr. 2/3 of patients present during neonatal period, severe clinical course, die <1yr of age
- To study patients with ABCA3 lung disease who survive >1yr

Methods

- Kids Lung Register database searched for patients diagnosed as chILD due to ABCA3 deficiency; (2001-2021); patients survived >1yr of life
- Molecular – whole blood genomic DNA, Sanger sequencing, some whole exome analysis
- Chest HRCT scored blindly by pediatric radiologists (by agreement) based on Fleischner Society criteria
- Histopathology scored blindly as re-review by a pediatric ILD pathologist – score of extent of histologic changes by severeity (0-none; 1-discrete, 2-moderate, 3-strong)

Results

- 398 of 1707 patients with chILD in database were tested for ABCA3 sequence variations
- 142 with ≥1 ABCA3 variant, 79 had 2 variants
- Exclusion of patients who received lung transplant, died or lost to F/U in 1st yr of life $\rightarrow$ 44;
- Median age 6.3 yrs (IQR: 2.8-11.7) at end of observation period
- 36/44 (82%) alive w/o transplant

- Genotype is a prognostic parameter: 67.6% and 62.5% patients classified as hypo/hypo or hypo/null survived beyond 1 yr vs only 15.4% null/null patients; in appr. ½ of patients diseases started in neonatal period
- Patients w/o O_2 therapy had longer survival vs patients with O_2 (9.7 vs 3 years, p=0.01)
- ILD was progressive over time based on lung function (FVC % predicted absolute loss 1.1%/year; 1.7% for FEV1); most had restrictive pattern; some had additional obstruction
- Most common CT patterns in <2 yo: GGOs, linear or reticular opacities, focal consolidations; >2yo: GGO, linear or reticular opacities, cystic parenchymal lesions; cystic lesions more common in >2yo (p=0.03) – may serve as marker of progression
- Histology: variable patterns including chronic pneumonitis of infancy, NSIP, DIP
- Tissue rare because of genetic testing (n=7): 4 chronic pneumonitis of infancy (CPI), 1 chronic bronchiolitis, 1 mixed NSIP, 1 DIP, 1 combined CPI and DIP; predominantly diffuse and heterogeneous distribution of features affecting mainly alveoli; most common and severe abnormalities: type II pneumocyte hyperplasia, alveolar enlargement, alveolar septal thickening
- 37/44 ABCA3 sequence variants were missense variants, small insertions or deletions with in-silico tools predicting some residual ABCA3 transporter function

Take Home Points

- ABCA3-related ILD progresses during childhood and adolescence

Reviews

Herrera-Juarez M et al. Targeted therapy for lung cancer: Beyond EGFR and ALK. *Cancer.* 2023;129:1803–1820.

- Driver alterations in NSCLC
- BRAFV600E – 2% of NSCLC, most common in adenoCa with aggressive histologic features – testing is minimum requirement in NSCLC; dabrafenib + trametinib combination is current standard targeted therapy option for *BRAF* V600Emutated NSCLC; resistance mechanisms (additional acquired mutations in the MAPK pathway and chromosome instability) may arise. Non-V600E mutations are less sensitive to this combination.
- *HER2* exon 20 mutations – 1.5% of NSCLC (*HER2* amplifications in 2-5% of NSCLC, HER2 overexpression in 2.5-35% of NSCLC); may occur as acquired resistance following *EGFR T790M* in *EGFR*-mutant NSCLC; *HER2* mutations more common in woman, non-smoker, adenoCa; *HER2* amplifications and overexpression more common in men, smoker; trastuzumab-deruxtecan-FDA approved for HER2 exon 20 insertions
- *KRAS* mutations – 25-30% of NSCLC, most commonly *KRAS* p.G12C, most common in non-squamous NSCLC of current/former smokers; major limitation to KRAS inhibition is occurrence of acquired resistance, such as *KRAS a*mplifications or new *KRAS* mutations or loss of mutation. Currently only KRAS G12C selective inhibitors available; addition of ICI encouraging but associated with high hepatotoxicity
- *MET* alterations; *METex14* skipping mutations (3-4% adenoCa, 1-2% squam, 10-30% of sarcomatoid Ca; more common in older patients, smokers), most relevant in NSCLC; MET alterations may be primary or secondary resistance to EGFR TKI; Crizotinib for

MET mutations; Compounds that selectively inhibit the ATP binding site of the MET receptor (Capmatinib, tepotinib) specifically for *METex14* skipping mutations
- *NTRK* fusions – 0.1-1% of NSCLC; entrectinib, larotrectinib; repotrectinib and selitrectinib – development of resistance is problematic; no word on whether IHC or NGS should be used for detection
- *RET* fusions – 0.5-2% of NSCLC; more common in females, nonsmoker, adenoCa; RNA sequ preferred, IHC and FISH possible; selective *RET* inhibitors (pralsetinib, selpercatinib) approved by EMA and FDA. Regarding NSCLC that progresses after platinum-based chemotherapy, selpercatinib and selpercatinib; possibly also in first-line therapy.
- *ROS1* fusions – 1-2% of NSCLC – most commonly adenoCa, women, non-smoker, young; also higher incidence of thromboembolic disease and brain met; DNA or RNA sequ recommended, IHC as screening followed by FISH if positive is also OK; crizotinib and entrectinib (both approved by FDA; crizotinib approved also by EMA) for first line therapy
- Other potential druggable targets: *FGFR* alterations controversial; *NRG1* fusions in clinical trials (0.5% of solid tumors)

Parsons MG et al. What is new in fungal infections? Mod Pathol 36 (2023) 100187

- Emerging pathogens: Candida auris – multidrug resistant – mass spec and molecular assays for detection; mostly skin and extremities but can be identified in organs as well
- New endemic mycoses (Emergomyces spp, Blastomyces helicus)
- Increasing range for existing endemic mycoses (e.g., histoplasmosis in Montana and Nebraska)
- Increasing at-risk populations; per self reporting – 3% of US adults are immunocompromised; estimated 3-5%; also severe respiratory viral infection can increase risk
- Increasing antifungal resistance
- Histopathology play an important role in the diagnosis of fungal infections because lab tests are often insensitive and is available to a majority of providers although negative histopathology does not rule out the possibility of infection
- Advances in antifungal therapy

Case Reports

Jimenez-Heffernan JA et al. Cytologic features of a pleural effusion after silicone breast implant rupture. Virchows Archiv (2023) 482:1065–1068.

Background

- Pleural effusion-rare complication of ruptured breast silicone implant
- To describe a silicone foreign body reaction in pleural effusion

Case

- 37-yo female
- Bilateral breast implants

- Admitted for chest pain and pleural effusion
- CT: left effusion with secondary atelectasis, bilateral breast rupture with LN "silicomas"
- Pleural fluid: dense, slightly turbid, straw colored
- Cytology of effusion: well-defined droplets or globules of transparent material (10-150μm) in microvacuolized background – abundant silicone droplets induced a staining artifact of smears; numerous macrophages containing large vacuoles displacing nuclei to the periphery; some with signet cell ring appearance, others multinucleated
- Polarization negative
- Phase contrast and dark field microscopy: part of the extracellular material revealed a bright contrast signal.
- Flocytometry: 51% monocytes/macrophages, 31% granulocytic, 11% lymphoid cells.

Take Home Message

- Silicone possibly disseminated via lymphatics into pleura?
- Distinction from foreign body material – usually intracytoplasmic (phagocytosis), associated with multinucleated giant cells, possibly polarizes
- Distinction from artifacts and contamination during smear prep – no phagocytosis; potentially repeat smearing
- Exclude breast implant associated anaplastic large cell lymphoma
- Know the history

Li Y et al. A 75-Year-Old Man With Irregular Solid Components Within an Emphysematous Bulla. CHEST 2023; 163(6):e265-e273.

Case

- 75-yo man
- Cough and sputum ≥ 1 year; 2 previous hospital admissions
- Smoker
- CT: Centrilobular & paraseptal emphysema and bullae, diffusely bilateral
- Within a bulla cavity of LLL, irregular solid components presenting as tube-like or tortuous shape, grew adhering to the wall of the bulla; solid component slightly contrast enhancing; several small pulmonary vascular branches entered lesion through wall of bulla – no signifcant change 3 months later
- Wedge resection of LLL – pulmonary cavernous hemangioma within a bulla
- Tumor arose in lung parenchyma; pulmonary bronchioles near tumor
- Relatively circumscribed vascular proliferation composed of dilated thin-walled congested vessels. The outer walls of the vessels covered with remnant alveolar epithelial cells; vessels have well-defined pericytes covered by a single layer of endothelial cells; flattened endothelial cells without cytologic atypia. Mitoses infrequent.
- Endothelial cells positive for CD31, negative for D2-40; outer vessel walls covered with remnant alveolar epithelial cells-creatin kinase+, NapsinA+, TTF+; vessel wall pericytes SMA+

Take Home Message

- Pulmonary cavernous hemangioma – considered slow-flow pulmonary venous malformation; any age; single or multiple; may be infiltrating; can coexist with cavernous hemangiomas in other organs
- Male predominant
- Diff diagnosis: Sclerosing pneumocytoma

Schroeder B et al. A 40-Year-Old Man With Multiple Pulmonary Nodules and Mediastinal Lymphadenopathy With Positive Anti-Neutrophil Cytoplasmic Antibody Reveals an Unexpected Diagnosis. CHEST 2023; 163(6):e259-e263.

Case:

- 40-yo man presented to ED with 2-days of right-sided chest pain, shortness of breath, night sweats, chills, dry, nonproductive cough without hemoptysis.
- Occupation: Air traffic controller, side business of buying, renovating, selling houses.
- Lives in Missouri with recent travel to Utah.
- Non-smoker
- Mild hemoglobinuria- serology workup revealed mildly elevated MPO and PR3.
- CT: multiple nodules 0.2-1 cm; subcarinal and hilar lymphadenopathy
- EBUS-guided FNA of station 7 LN and transbronchial bx of RML nodule – non-necrotizing granulomas; GMS+ for histoplasma

Take Home Points:

- There is some suggestion in the literature of an uncommon link between ANCA+ and histoplasma infection

Sherman SV, M.D., Editor. Idiopathic Pulmonary Hemosiderosis. N Engl J Med 388;23.

Case:

- 3-year-old girl referred to pediatric rheumatic disease clinic for recurrent fevers
- 3 months earlier: anemia
- CT: diffuse GGOs and consolidations
- Blood transfusions, antibiotics, steroids; when steroids were tapered fevers recurred.
- BAL fluid reddish-pink, cytology revealed hemosiderin-laden macrophages
- Broad evaluation for causes of diffuse alveolar hemorrhage, including infections, rheumatologic conditions, and congenital heart disease, negative.
- At a 10-month follow-up visit, symptoms had abated.