

Pulmonary Journal Club March 2022 (Articles from February 2022)

Presented by

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Articles for Discussion

Misleading Germ Cell Phenotype in Pulmonary NUT Carcinoma Harboring the ZNF532-NUTM1 Fusion. Agaimy et al. Am J Surg Pathol. 2022; 46 (2): 281-288. Discussed by Dr. Villalba Nunez.

Introduction: Historically considered a midline malignancy of children and young adults, NUT carcinoma can originate in almost any body site and in any age group. The only context-independent morphologic hint to diagnosis is the presence of abrupt squamous differentiation in a background of undifferentiated malignancy (33-40% of cases). Beside the classic BRD4-NUTM1 fusion (70% of cases), less common fusion partners include BRD3, NSD3, ZNF532, and ZNF592. Other fusions, including CIC, MGA, MXD4, MXD1, and BCORL1 are associated with sarcomas or cancers of unknown histogenesis. Involvement of the Z4 ZNF family members ZNF532 and ZNF592 is exceedingly rare with only 3 recently reported cases. Proteins of the Z4 ZNF complex colocalize and closely interact with the BRD4-NUT oncogenic complex.

Methods: The authors describe a case of a ZNF532-NUTM1–rearranged NUT carcinoma presenting as a 7.5 cm mass in the left lower lung lobe of a 65-year-old woman (40 pack/year). The case was misdiagnosed before the establishment of the diagnosis. A battery of IHC stains, RNA-seq and NUT FISH were performed. Additionally, the authors screened 7 NUT carcinomas from head and neck (n = 6) and lung (n= 1) with BRD4-NUTM1 (n = 5) and NSD3-NUTM1 (n =2) fusions for expression of germ cell markers.

Results: Case description: Histologically, the tumor was composed of undifferentiated monotonous small round cells with focal epithelioid and rhabdoid elements and few plasmacytoid-looking elements within a variably myxoid stroma, and with variable endobronchial / bronchocentric growth. Abrupt squamous differentiation and keratinization were absent. IHC showed paucity of keratins (only focal pankeratin), variable p63, and extensive CD30 and PLAP expression. This led to an initial diagnosis of combined small cell carcinoma (due to appearance and CD56+), CD30-positive unclassified hematolymphoid malignancy- and malignant germ cell neoplasm. After a fourth opinion, the tumor revealed diffuse expression of NUT (distinctive granular nuclear immunoreactivity). FISH confirmed the diagnosis. Targeted RNA sequencing revealed the ZNF532-NUTM1 fusion.

Control cases: Screening of 7 NUT carcinomas (5 with BRD4-NUTM1 and 2 with NSD3-NUTM1 fusions) for germ cell markers revealed focal SALL4 reactivity in 3 cases (combined with variable AFP expression in 2), but none expressed CD30, PLAP, beta-HCG, OCT3/4 or CD117.

Review of literature: The reported ZNF-rearranged NUT carcinomas affected 4 females aged 18-65 years, were characterized by nondescript undifferentiated epithelioid and round cell morphology with occasional minor rhabdoid component, were keratin poor and without squamous differentiation. Two lung cases (with ZNF532 fusion partner). Several reports have documented frequent elevation AFP in the serum of patients with NUT carcinomas. Review of 6 cases with an elevated serum AFP revealed no expression of the germ cell markers tested: PLAP (0/5), AFP (0/3), CD30 (0/3), beta-HCG (0/2), SALL4 (0/1), OCT3/4 (0/1), and CD117 (0/5). The abnormal association between the NUT and the BRDs/ZNFs chromatin regulatory complexes induced by the BRD4-NUT chimeric proteins leads to the formation of large domains of histone hyperacetylation via the interaction between NUT and p300.

Conclusion: An aberrant germ cell immunophenotype should be considered in NUT carcinoma to avoid misinterpretation as genuine germ cell malignancy as both diseases predominantly affect the young population, frequently involve the mediastinum and can be associated with elevated serum AFP.

Prospective nationwide multicentre cohort study of the clinical significance of autoimmune features in idiopathic interstitial pneumonias. Enomoto et al. Thorax 2022;77:143–153.

Discussed by Dr. Villalba Nunez.

Introduction: 20-30% patients with idiopathic interstitial pneumonia (IIP) show autoimmune features. Fischer et al proposed Interstitial pneumonia with autoimmune features (IPAF) as a research concept in these patients. However, retrospective studies reported conflicting results of its prognosis. This study was conducted to prospectively evaluate the clinical significance of autoimmune features in patients with IIP.

Methods: A nationwide multicentre study prospectively enrolled consecutive patients with IIP (>15y) in 28 hospitals in Japan. Primary endpoint: Overall survival. All IPF and IIP Dx were made in accordance with the 2011 official ATS/ERS/JRS/ALAT statement on IPF, and the 2013 official ATS/ERS update of the classification of IIPs, on MDD by expert pulmonologists together with site radiologists and pathologists with more than 10 years of experience. In addition, radiological and pathological findings were evaluated by these site radiologists and pathologists. Patients diagnosed as defined systemic autoimmune diseases (following international criteria) within 3 months from the initial Dx of IIPs were excluded from the study. The relationship between autoimmune features and prognosis was prospectively analyzed.

At diagnosis, 63 features suggestive of connective tissue diseases using a checklist including symptoms / signs and autoantibodies were systematically evaluated. The checklist contained most items of the IPAF (except 3) criteria. Acute, subacute and chronic IPs were defined as duration of <1 month, 1–3 months and ≥ 3 months, respectively, from the onset of respiratory symptoms to the diagnosis of IIPs. Clinical phenotypes were included in a cluster analysis.

Results: 376 patients with IIP enrolled (median age: 71y). IPF (31%), NSIP (7%), COP (6%), unclassifiable IIP with surgical lung Bx (SLB, 5%), and without (50%). 72.3% with chronic onset (≥ 3 months). FVC relatively preserved (med. 81.8%), DLCO impaired (med. 66.2%). 22.3% patients underwent SLB. There were no significant differences in the frequencies of histologic findings (lymphoid aggregates with GCs, prominent plasmacytic infiltration, dense perivascular collagen and extensive pleuritis) between IPF and non-IPF. Patients with non-IPF had a relatively higher frequency of anti-aminoacyl tRNA synthetase antibody than patients with IPF (22.1% vs 4.8%, OR=5.95, $p=0.030$).

70 patients (18.6%) met the IPAF criteria. The percentage of patients meeting the IPAF criteria was significantly higher ($p<0.01$) in NSIP (50%) or COP (47.8%) than IPF (6%) or UCIIP (18.4%). IPAF vs. not IPAF significantly younger ($p=0.005$), predominantly women ($p=0.002$), more likely to be never smokers ($p=0.046$) and have NSIP ($p<0.001$) or COP ($p<0.001$) but not IPF ($p<0.001$). During a median observation period of 35 months, patients with IPAF more frequently developed systemic autoimmune diseases ($p<0.001$) and had less frequent acute exacerbation of IIPs ($p=0.019$) than patients with non-IPAF. IPAF diagnosis was significantly associated with better survival ($p<0.001$) and was an independent positive prognostic factor in total and patients with non-IPF, but not in IPF ($p=0.149$). Cox proportional hazard models: Even after adjustments, IPAF classification was still a significant favorable prognostic factor in all patients with IIPs (HR=0.149,

p=0.001). Multivariable analysis failed to show a prognostic factor for IPAF in IPF but showed it in non-IPF (p=0.013).

Cluster analysis: Clusters 2 and 3 had a significantly better prognosis than those in cluster 1 (p=0.006, p=0.024).

Cluster 1	Male patients with IPF with an UIP pattern on HRCT	➤ Chronic onset, smoking history, acute exacerbation, treatment with antifibrotics
Cluster 2	Male patients with chronic onset and preserved lung function	➤ Found by medical check-up without symptoms
Cluster 3	Female non-IPF patients with autoimmune features	➤ Subacute onset with symptoms and no smoking history than those in other clusters. ➤ Higher incidence of autoimmune symptoms, autoantibodies and IPAF diagnosis
Cluster 4	Patients with non-IPF with symptoms	➤ Acute/subacute onset and received more immunosuppressive agents than those in other clusters

Conclusion: Patients with IPAF less frequently experienced AE and developed defined systemic autoimmune diseases more often than patients with non-IPAF. In all patients, IPAF diagnosis was significantly associated with better survival. However, this prognostic impact of IPAF diagnosis was not significant in IPF alone.

Limitations: The number of patients with IPF fulfilling the IPAF criteria was small for prognostic evaluation (6 cases). A central review of HRCT or SLB specimens was not performed. Treatment differences could not get evaluated as treatments for IIPs were not uniform because they depended on the decisions by attending physicians

Zhou F et al. Assessment of the feasibility of frozen sections for the detection of spread through air spaces (STAS) in pulmonary adenocarcinoma. Mod Pathol. 2022; 35:210-7.

Purpose:

- To evaluate reliability of STAS assessment on FS compared to permanent sections
- To assess associations among STAS, tumor grade, RFS after sublobar resection

Methods:

- Retrospective; stage I adenoCa who underwent FS (NYU Langone, MGH)
- VATS; LN dissection except N=18 (wedge; LN eval by imaging and EBUS-guided bxs)
- FS-1 section of tumor with adjacent benign lung; tissue remnant prepped as permanent “FS control”; after FS tissue inflated with formalin, fixed for ≥ 6 hours, entire tumor submitted
- STAS defined by 2015 WHO (spread of micropapillary clusters, solid nests, and/or single cancer cells into air spaces beyond edge of main tumor)
- Tumor grade per IASLC: grade 1 (well diff – lepidic predominant, $<20\%$ HG pattern), grade 2 (mod diff, acinar or papillary predominant, $<20\%$ HG pattern), grade 3 (poorly diff, any tumor with $\geq 20\%$ HG pattern); HG patterns: solid, micropapillary, complex glands

Results:

- N=163; 59 male, 33-97 yo (mean, 68 yo)
- 94 sublobar resections, 69 lobectomies, margins negative
- STAS prevalence: 28.3% FS, 19.4% FS control sections, 24% permanent
- STAS on FS (compared to permanent) – sensitivity 55%, PPV 48%, agreement $\kappa=0.34$, specificity 80%, NPV 85%, accuracy 74%; 24 false-positive STAS on FS (13 well/mod diff)
- Agreement of STAS between FS and FS control $\kappa=0.39$, accuracy 74.5 %
- If FS controls included \rightarrow sensitivity decreased to 52%, accuracy to 73% mostly due to \uparrow false STAS on FS controls due to FS artifacts \rightarrow FS controls excluded from further analysis
- Tumor grade at FS (vs permanent) – agreement $\kappa=0.54$
- If tumor grades 3 vs 1+2: at FS (vs permanent) – agreement $\kappa=0.72$, sensitivity 77%, PPV 90%, specificity 94%, accuracy 87%, NPV 85%
- Permanent sections: 48 well diff, 46 mod diff, 69 poorly diff adenoCa
- STAS associated with higher tumor grade; Highest percentage of STAS+ cases among grade 3 adenoCa on FS and permanent
- Sublobar resections and entire cohort:
 - STAS associated with RFS only on permanent, not FS
 - Grade associated with RFS on FS and perm
- No difference in recurrence between sublobar resection and lobectomy

Discussion:

- FS STAS – \downarrow sensitivity and PPV; false + results \rightarrow overtreatment; FS STAS – no prediction of RFS (vs permanent in sublobar resections of stage I adenoCa; many false + on FS \rightarrow Intraop STAS currently likely not a safe indicator for more extensive surgery)
- Tumor grade may be better predictor of tumor recurrence than STAS at time of surgery
- Not clear who evaluated cases – thoracic vs general pathologists – 1 or multiple pathologists – interobserver variability?
- STAS – covariate of high grade morphology

Kalchiem-Dekel O et al. Shape-Sensing Robotic-Assisted Bronchoscopy in the Diagnosis of Pulmonary Parenchymal Lesions. Chest 2022; 161:572-82.

Purpose:

- To identify feasibility, diagnostic yield, diagnostic sampling, safety of ssRAB
- Diagnostic yield of guided bronchoscopy 44-74%; percutaneous biopsy >90%
- RAB designed to allow endobronchial navigation into lung periphery while maintaining catheter stability and shape to maximize precision in sampling.
- FDA approved in 2019

Methods

- 131 consecutive ssRAB (10/2019-7/2020) – prospectively captured, retrospectively analyzed
- Positive bronchus sign = airway leading into lesion or coursing through (air bronchogram).
- ssRAB (Ion Robotic-Assisted Endoluminal Platform)
- Successful navigation = achieving catheter-target proximity that allowed lesion sampling
- ROSE of cytologic material always performed for adequacy

Results

- 159 pulmonary lesions targeted during 131 ssRAB procedures
- Lesion size, median, 1.8 cm (1.3-2.7); 56% ≤ 2cm; 59% in UL, 66.7% beyond 6th generation airway
- Central location (inner 2/3) 61%
- Navigational success rate 98.7%
- Overall diagnostic yield 81.7% (66.6% for lesions ≤ 1cm, 70.4% for 1.01-2cm)
- 29 lesions non-diagnostic
- 8/10 previous non-diagnostic TBBx → diagnostic; 6/10 previous non-diagnostic needle core bx → diagnostic
- Lesion size ≥1.8cm and central location associated with diagnostic procedure
- Multivariate analysis: lesion size ≥1.8 cm more likely to be diagnostic than lesions <1.8 cm after adjusting for lung centrality
- Sensitivity of ssRAB for primary thoracic malignancies 79.8%; NPV 72.4%
- Overall complication rate 3%; pneumothorax rate 1.5%

Discussion

- Possibly useful in challenging lung lesions (no direct comparison to forceps or cryobiopsy)
- Good safety
- Lesion size appears major predictor of success of the biopsy
- Diagnostic yield for traditionally challenging lesions seems improved compared with prior studies. Diagnostic yield for lesions in the outer 1/3 of the lung was 70.9%, (vs 51.3% reported previously)
- ssRAB allowed sampling of more than one target in 19% of cases, in significant proportion of those, bilateral lesions were targeted.
- Smaller and peripheral lesions remain challenging

Articles for Notation

Neoplastic Disease

Zhang Y et al. Surgery for pre- and minimally invasive lung adenocarcinoma. J Thorac Cardiovasc Surg. 2022;163:456-64.

Purpose: Investigate safety & outcome of various types of surgical resection in AIS or MIA.

Methods:

- Retrospective (unrandomized); surgical resection of AIS or MIA (2012-2017)
- Exclusion: Concurrent/prior invasive lung cancer
- Inclusion: Multifocal lesions – only largest or the one with MIA recorded
- FS – benign, AAH, AIS, MIA → wedge resection/segmentectomy; if (mis)interpreted as invasive adenoCa → lobectomy

Results:

- N=1644; no add. therapy; 74% women, 84% never smoker, median age 53 yo
- 88.3% incidental on CT (some companies in China offer screening also to non-high-risk)
- 76.3% pure GGO, 22.6% part-solid GGO
- 7 with preop bx – all adenoCa
- Surgery within 1 month after detection of nodule: 37.5% (2012), 22.5% (2017)
- FS: 2.5% overestimated as invasive adenoCa; 0.6%/4.5% underestimated as benign/AAH
- Sensitivity of FS for AIS/MIA: 92.4%; specificity not provided

N=1644	AIS (N=422)	MIA (N=1222)	p-Value
CT size (cm)	0.8 (0.63-0.9)	0.9 (0.7-1.2)	<0.001
CT (%) Pure GGO	86.3	72.8	<0.001
Part-solid	13.3	25.9	
Solid	0.5	1.3	
Surgery (%) Wedge	75.4	58.9	<0.001
Segmentectomy	14.5	22.6	
Lobectomy	10.2	18.5	
FS Diagnosis (%) Benign	1.4	0.3	<0.001
AAH	11.8	2.0	
AIS	73.5	25.1	
MIA	12.6	69.5	
Invasive adenoCa	0.7	3.1	
Pathologic tumor size (cm)	0.6 (0.5-0.8)	0.8 (0.6-1)	<0.001

- Preop hookwire localization 100% wedge, 94.1% segmentectomies, 75.4% lobectomies
- LN dissection/sampling 734 – all negative
- Wedge: ↓surgery, ↓chest tube and output, ↓hospital stay than segmentectomy, lobectomy; segmentectomy all variables advantageous over lobectomy
- Surgical compl. rate ↓wedge resection (1%); segmentectomy (3.3%)=lobectomy (5.6%)
- 10 ≥ grade 3 complications (massive hemorrhage): wedge (0.1%) vs segmentectomy (1.5%), lobectomy (1.5%)
- No death within 30 days of surgery

- 5-yr RFS 100%; all procedure types; 5-yr OS 98.8%; no diff. by surgery; no DOD
- 1 patient developed 2nd GGO during f/u
- Flow chart – figure 3

Discussion:

- Confirms prior studies
- Surgical procedure biased by FS diagnosis
- Postop f/u intervals may be extended if no risk factors (less radiation exposure from CT)
- Authors conclude that LN dissection may not be necessary – however, some patients with wedge did not undergo LN dissection
- Are we ready to distinguish AIS and MIA from invasive adenoCa at FS?

Wu J et al. Heterogeneity of programmed death-ligand 1 expression and infiltrating lymphocytes in paired resected primary and metastatic non-small cell lung cancer. Mod Pathol 2022; 35:218-27.

Purpose: Assess heterogeneity of PD-L1 expression in tumor cells and TILs in paired primary and metastatic NSCLC

Methods:

- Paired resected primary and mets from NSCLC, tumor size ≥ 0.5 cm, no neoadjuvant therapy
- All reviewed by 2 expert pathologists (thoracic? consensus?)
- Multiplex IF (PD-L1 [73-10], CK AE1/AE3 [to define tumor cells for TPS], CD8, CD68)
- DIA for immune contexture of PD-L1 expression, TILs, immune-to-tumor cell distance

Results:

- N=64 paired NSCLC from 28 patients including 14 intrapulmonary and 22 extrapulmonary mets; primary tumors: 23 adenoCa, 4 SQCC, 1 large cell Ca
- 8th AJCC stage: 22 IB-IIIB, 6 IIIA-IV
- 50% of primary tumors – EGFR mutation, no ALK or ROS1 rearrangements
- Synchronous mets N=14, metachronous mets N=22
- All specimens: Mets had higher PD-L1 expression levels in PD-L1+ cell population and higher TPS, lower density of CD8+ T cells
- Paired primary-mets: significant change in density of PD-L1+ cells and heterogeneity in TPS; in most paired samples – mets showed increase in TPS
- Mets – significantly different density of CD8+ T cells; most mets had decreased density of CD8+ T cells; longer spatial distance between CD8+ T cells and tumor cells in mets
- Heterogeneity of immune markers more obvious in extrapulmonary, metachronous, treated mets; fewer differences in intrapulmonary, synchronous, untreated mets
- Mets of NSCLC with EGFR mutations - higher PD-L1 expression, less lymphocyte infiltrate
- Primary tumors: no immune marker associated with OS
- Increased density of CD8+ T cells in mets associated with better OS
- Multivariate analysis: increase in CD8+ T cells in mets (vs primary tumor) – independent factor with low risk of cancer-related death in metastatic NSCLC

Discussion:

- → significant discrepancies in PD-L1 expression and lymphocyte infiltration in met. NSCLC – most likely associated with temporal heterogeneity with a history of treatment and correlated with EGFR mutations
- Possibly need to rebiopsy metastasis for immunotherapy prediction in met. NSCLC
- Rebiopsy of metachronous mets after adjuvant treatment for detection of biomarkers; in intrapulmonary and synchronous mets – both primary and metastatic tumor are suitable for detection of immune markers
- If met and primary tumor available – detection and comparison of changes in status of immune infiltrates may be clinically useful for predicting OS

Chen S et al. Prognostic implication of tumor spread through air spaces in patients with pathologic N0 lung adenocarcinoma. Lung Cancer 2022; 164:33-8.

Purpose: To evaluate STAS in pN0 lung adenoCa after resection

Methods:

- Retrospective; 1/2017-12/2018; single institution
- Patients with multiple nodules excluded
- Completely resected pN0 lung adenoCa
- Grading: low (lepidic pred), intermediate (acinar/papillary pred, invasive mucinous), high (micropapillary/solid pred)
- STAS – tumor cells within alveolar spaces beyond the edge of the main tumor
- Lepidic pred. and pure GG nodules on CT excluded from outcome analysis

Results

- 796 patients, 44% male, median age 60 y (17-83); median f/u 28 months
- 68.1% lobectomy, 31.9% sublobar resection
- Preop CT: 7.7% pure GG nodules, 64% part-solid nodules, 28.3% solid nodules
- STAS 25.3%; no STAS in pure GG nodules and lepidic pred adenoCa
- STAS more common in tumors with solid nodules on preop CT
- STAS more common in micropapillary/solid predominant and invasive mucinous adenoCa than lepidic/acinar/papillary predom
- STAS associated with larger tumor size, VPI, LVI; higher pT stage
- Median f/u 28 months; 3% recurrence, 2.1% DOD – worse RFS associated with larger tumor size, micropapillary/solid pred, VPI, STAS – worse OS associated with smoking, larger tumor size, micropapillary/solid pred, STAS
- Multivariate analysis: STAS, larger tumor size - independent prognostic factors for RFS; independent prognostic factor for RFS and OS in acinar predominant/papillary predominant/invasive mucinous adenoCa and patients who underwent lobectomy; STAS – not independent prognostic factor for OS
- Stratified analysis: among patients with part solid or solid nodules – STAS – no difference in RFS, OS; among patients with acinar/papillary pred and invasive mucinous adenoCa – worse RFS for patients with larger tumor size, STAS; worse OS for smokers and STAS –

multivariate analysis: STAS – independent prognostic factor for RFS and OS; STAS – worse RFS and OS when lobectomy – multivariate – STAS – independent predictor for RFS and OS in patients who underwent lobectomy; no prognostic value of STAS in sublobar resections.

Discussion

- STAS is an independent prognostic factor for RFS in pN0 lung adenoCa
- STAS is an independent prognostic factor for RFS and OS in patients with acinar and papillary pred adenoCa and invasive mucinous adenoCa and those who underwent lobectomy but not sublobar resection
- F/u time relatively short

Yang Y et al. Clinicopathological characteristic of ciliated muconodular papillary tumour of the lung. *J Clin Pathol* 2022;75:128-32.

Purpose: To elucidate clinicopathologic characteristics and treatment methods of CMPT

Methods

- Retrospective
- All cases reviewed by 2 pathologists
- All cases stained with: p40, CK7, CK20, CK5/6, Napsin A, MUC5AC, p63, panCK, TTF1 (SPT24), ALK (D5F3), Ki-67, HNF4A
- NGS for EGFR, KRAS, BRAF, ALK, MET, ROS1, HER1, RET

Results

- N= 26, 50% male; mean age 64.4 y (52-80); 19.2% smokers
- 24 incidentally identified; 2 patients presented with cough
- 46.1% in RLL, 30.8% LLL
- Tumor size 0.3-1.4 cm
- CT: subsolid nodules (42.3%), GGN (38.5%), cavitory nodules (19.2%)
- All resected (8 lobectomies, 4 segmentectomy, 14 wedge resections), no additional therapy
- 6 patients had synchronous MIA which was resected in same procedure
- None diagnosed on frozen section. Frozen section diagnosis: 8 “benign”, 7 “AAH”, 3 “AIS”, 2 “MIA”, 1 “invasive malignancy”; no conversion to lobectomy after frozen diagnosis
- All diagnosed using IHC: CK7, panCK + ciliated cells, goblet cells, - basal cells; p40, CK5/6 + basal cell layer, more specific than p63; TTF-1+ entire tumor cells; Napsin, CK20 -; ALK + in 1 case (c/w NGS ALK-EML4 gene fusion)
- NGS: 59% of cases with genetic alterations in lung cancer-related driver genes: EGFR, KRAS, BRAF mutations, ALK rearrangements
- EGFR mutations in exon 19, exon 20, exon 25 in 32% of patients; 1 patient with synchronous EGFR exon 20 mutation and KRAS exon 2 missense variant (very rare in lung Ca); BRAFV600E mutations (23%); ALK-EML4 (5%)
- F/u 5-65 months, no recurrence

Discussion

- Confirmation of earlier data
- Good prognosis
- Sublobectomy may suffice
- Relatively high rate of driver gene mutations; mutation sites differ from lung adenoCa
- MUC5AC expression unclear (results: ciliated cells; discussion: goblet cells not ciliated cells)

Boch T et al. Pathologic responses in oligometastatic NSCLC patients treated with neoadjuvant immune checkpoint blockade with and without chemotherapy followed by surgery. Lung Cancer 2022; 164:46-51.

Purpose

- Feasibility and efficacy of neoadjuvant ICI in oligometastatic disease in NSCLC

Methods

- Multicenter, retrospective study, N=13 patients with NSCLC and OMD (≤ 3 distant mets)
- Treated with neoadjuvant ICI alone (n=4), + neoadj chemo (n=9); 1 with N2 disease - adjuvant radiation to mediastinum; no neoadjuvant mediastinal radiotherapy.
- pCR and MPR
- Radiologic response by RECIST criteria

Results

- N=13 (12 adenoCa, 1 SQCC), median PD-L1 TPS 70% (0-100)
- pCR 45%, MPR 69%
- 85% of patients progression-free, median f/u 9 months (3-28)
- Single cell RNAseq of tumor from 1 patient treated with chemo-ICI – strong predominance of adaptive immune cell populations over small minority of epithelial (tumor) cells
- 11/13 patients (84.6%) - radiographic partial response (PR) after neoadjuvant therapy, 2/13 (15.4%) stable disease (SD).
- Postoperative nodal downstaging (ypN0-1) in all 7 patients with initial nodal disease including 1 patient with a multilevel N2 stage who had full metabolic and pathologic clearance of LNs after 2 cycles of neoadjuvant ICI + chemo.
- 54% of patients achieved pCR; 69% MPR.
- No correlation between % viable tumor cells in primary tumor and PD-L1 TPS.
- N=2 disease progression after 5 and 6 months (brain); N=10 remission; N=1 died of unknown reasons.
- scRNA Seq analysis of the primary tumor (N=1) with 60% viable tumor cells after 2 cycles of neoadjuvant chemo-ICI. Cell type annotation indicated a 79% share of adaptive immune cells (predominantly B and T cells) in surgical specimen vs only 2% of epithelial cells containing tumor cells. The dominance of IC was confirmed by the expression of canonical markers and subsets thereof expressed genes associated with T cell cytotoxicity or antibody production.

Discussion

- Neoadjuvant ICI with or w/o chemo – feasible and promising therapeutic concept in patients with OMD of NSCLC

Letters

Pelosi G The Natural History in Lung Neuroendocrine Neoplasms: The Stone Guest Who Matters. J Thorac Oncol 2022; 17:e5-e7.

- Response to Derks et al. on the article “Clinical-pathologic challenges in the classification of pulmonary neuroendocrine neoplasms and targets on the horizon for future clinical practice,”
- Concerns in lung neuroendocrine neoplasms (NEN):
 - Disappointing interobserver variability in tumor diagnosis
 - Carcinoids with elevated proliferations rates straddling LCNEC
 - Mutational, transcriptomic, and regulatory profiles common to carcinoids and neuroendocrine carcinomas
 - Difficulties in foreseeing clinical outcome and therapy susceptibility in similarly looking tumors
 - Lack of adequate terminology envisaging cytology and biopsy samples
 - Irrelevance of histopathologic assessment in identifying diversely behaving neuroendocrine carcinomas
- Author suggests to add the recently published suggestion of NEN progressing or transitioning from carcinoids to neuroendocrine Ca, possibly through the accumulation of genetic anomalies in the lung, thymus, gastroenteropancreatic tract
- Primary vs secondary high grade neuroendocrine tumors vs indolent neuroendocrine tumors
- Primary high grade neuroendocrine tumors – derive from de novo mechanisms of carcinogenesis
- Secondary high grade neuroendocrine tumors – derive from pre-existing carcinoids or possibly NSCLC
- Indolent neuroendocrine tumors represent persistently indolent carcinoids

Case Report

Rudin J et al ARDS With Pneumothorax in a Young Adult. Chest 2022; 161:e111-6

- Trimethoprim-sulfamethoxazole-associated fulminant respiratory failure (DAD)

Reviews

Marx A et al. The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors? J Thorac Oncol 2022; 17:200-213.

- Review of changes to the 2021 WHO in thymic epithelial tumors, germ cell tumors, thoracic mesenchymal tumors
- Review of recent advances in IHC characterization of thymic adenocarcinomas; recognition of molecular alterations in metaplastic thymoma, a subset of B2 and B3 thymomas and hyalinizing clear cell carcinoma
- Update in thymic neuroendocrine neoplasms

Thunnissen E et al. Elastin in pulmonary pathology: relevance in tumours with a lepidic or papillary appearance. A comprehensive understanding from a morphological viewpoint. Histopathol 2022; 80:457-67.

- This review summarizes the use of elastin in pulmonary pathology including visceral pleural invasion, vascular invasion, pre-existing disease, distinction of AIS (presence of elastin in alveolar walls) from papillary (absence of elastin in papillae) or acinar adenoCa
- Discussion of iatrogenic collapse and suggestions that perfusion fixation may mitigate that kind of collapse

Rosen Y. Pathology of Granulomatous Pulmonary Diseases. Arch Pathol Lab Med. 2022; 146:233-51.

- Everything you ever wanted to know about granulomatous lung disease