Pulmonary Journal Club November 2024 (Articles from October 2024)

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Case Reports

ARTICLES FOR DISCUSSION

Gorbokon, N, et al. Prevalence of S-methyl-5′-thioadenosine Phosphorylase (MTAP) Deficiency in Human Cancer: A Tissue Microarray Study on 13,067 Tumors from 149 Different Tumor Types. Am J Surg Pathol, 2024; 48(10), 1245–1258.

Background

- Loss of expression of MTAP - approved by FDA for clinical trials of targeted therapies
- MTAP deficiency interrupts adenine salvage, potentially enhancing cell death when pathways like folate synthesis are targeted.
- Gene encoding *MTAP* is adjacent to *CDKN2A* on chromosome 9p21.3
- To profile loss of MTAP expression across various tumors to evaluate its diagnostic utility and potential for targeted therapy.

Methods

- TMAs (1 core per case, 0.6 mm)
- IHC for MTAP (clone MSVA-741R; validated on benign tissue using clone 2G4 with manual protocol) – positive internal control required
- IHC for PD-L1 (clone not provided), CD8
- FISH for *MTAP* (probe for 9p21 including *MTAP* and *CDKN2A* genes) performed in cases with loss of MTAP expression.

Results

- 13,067 tumor samples interpretable (149 tumor types, 76 non-neoplastic)
- MTAP loss (Table 1, "0" = loss of MTAP expression) - 7.1% of tumors; 55.1% of all tumor categories; common in Hodgkin lymphoma (50%), NETs (up to 80%), mesothelioma (32-36.8%).
- Homozygous deletions in 90-100% of cases with loss of MTAP expression for several cancers (Fig. 4; red indicates correlation) but not in Hodgkin lymphoma, other lymphomas, and certain NETs
- Association of MTAP loss: HCC: LN metastases (p=0.03), high grade (p=0.02); NET: advanced pT stage (p=0.02); SQCC: high grade, advanced pT stage, absence of HPV (p=0.003, 0.03, <0.01, respectively)
- Loss of MTAP expression associated with PD-L1 expression (p=0.01), fewer CD8+ lymphocytes (p=0.004) (likely poor immune response).

Take Home Message

- Loss of MTAP expression in multiple cancer types → potential for targeted therapies.
- Loss of MTAP expression not useful in distinction between mesothelioma and metastasis
- Besides homozygous deletion, other mechanisms such as promoter hypermethylation may result in loss of MTAP expression
- TMA, only 1 tissue spot per tumor (0.6 mm) – did not evaluate potential heterogeneity of expression

Renaud-Picard, B, et al. Spectrum of Chronic Lung Allograft Dysfunction Pathology in Human Lung Transplantation. J Heart Lung Transplant. 2024; 43(10), 1701–1715.

Background

- CLAD – main limitation to long-term survival in LTx
- CLAD – subtypes according to 2019 ISHLT guidelines: BOS (bronchiolitis obliterans), RAS (PPFE, IAFE, DAD, OP, BO), mixed, undefined
- To study the morphologic spectrum of CLAD and to evaluate a semiquantitative morphologic grading system that was developed in mice.

Methods

- Explants (for retransplantation): 20 end-stage CLAD, 13 non-transplant controls.
- CLAD phenotype adjudicated by 2 reviewers for each patient (pulmonary functional obstruction and/or restriction; fibrosis-like opacities on imaging)
- Lung biopsies - 4 locations including 1 peripheral, 1 central (1 RUL, 2 LUL, 1 LLL).
- Histopathologic grading system: Scores (Table 1) for peri-airway fibrosis (PAF), BO, epithelial hyperplasia (EH), epithelial flattening (EF), peri-airway inflammation, parenchymal fibrosis (PF), pleural fibrosis (PLF), lymphoid aggregates (LA), endothelialitis, vascular fibrosis
- ISHLT grades A and B
- IF staining

Results

- 12 BOS, 7 RAS, 1 mixed by clinical assessment
- Patients in control group older; no difference in patient characteristics BOS - RAS
- Inter-rater agreements: PAF (ICC 0.60-0.74, good), all others (ICCs 0.75-1.0, excellent).
- Histologic features that were higher scored in both BOS and RAS when compared to controls but no difference between BOS and RAS: PAF, BO, PLF, EH, EF, peri-airway inflammation, A- and B-grades, number of LA/cm2
- Histologic features that were higher scored in RAS than BOS and control: PF (heterogeneous within RAS, often IAFE and diffuse septal fibrosis), endothelialitis, vascular fibrosis
- Fibrosis parameters correlated with each other. Positive correlation between PAF, BO, and EH, negative correlation between PAF and EF. PAF and BO correlated with EH.
- Epithelial Cell Composition: Reduced frequency of club cells in CLAD, especially in BOS. Club cell apoptosis higher in BOS, which correlated with inflammation and BO presence.

Take Home Message

- BOS and RAS represent phenotypic extremes rather than entirely separate entities.
- RAS is more associated with parenchymal and vascular fibrosis
- BOS predominantly involves bronchiolar fibrosis.
- Histopathologic scoring system cumbersome – proposed as consistent framework to evaluate CLAD progression and could guide personalized clinical approaches – maybe OK for research purposes.

Suster DI, et al. Inflammatory Giant Cell Carcinoma of the Lung: Clinicopathologic, Immunohistochemical, and Next-generation Sequencing Study of 14 Cases. Am J Surg Pathol. 2024;48(10):1215–1223.

Background

- To describe a distinct variant of sarcomatoid carcinoma

Methods

- 14 cases from pathology archives (1980–2020).
- IHC and NGS (Oncomine Precision Assay, 50 cancer-related genes, covering mutations, copy number variations, and fusions)

Results

- Clinical Features:
  - M:F=1:1, Age: mean: 57 yo (42-73); 7 smokers; 7 smoking hx unknown
  - Most presented with cough, hemoptysis
  - All tumors peripheral; mostly subpleural, 86% in upper lobes
  - Tumor size, mean 4.6 cm (1.3-9 cm); tan-white lobulated, necrotic cut surface
  - All underwent resection +/- chemotherapy and/or radiation
- Histopathology:
  - Sheets of discohesive tumors cells in abundant inflammatory cell background (polymorphonuclear leukocytes, lymphocytes, plasma cells, histiocytes), focally microabscesses; Fig 1
  - Tumor cells resembling histiocytes, giant multilobated and multinucleated tumor cells, Reed-Sternberg-like cells; cells resembling ALCL (Fig 2), "rhabdoid" cells
  - Emperipolesis in tumor giant cells (Fig 4)
  - Extensive necrosis, high mitotic activity (8-18 mites/2mm^2)
  - N=6: Focal transition to minor components (10-20%) of adenoCa or SQCC
  - pT1 (N=4), pT2 (N=4), pT3 (N=3), pT4 (N=2); pN0 (N=12), pN2 (N=1), pN3 (N=1), pM1a (N=1), pM1b (N=1)
- IHC:
  - Tumor cells + keratin AE1/AE3, CK8/18
  - Tumor cells - TTF1, napsin, p40, CK5/6 (foci of adenoCa and SQCC pos for TTF1, napsin, p40, respectively), S100; expression of BRG1 preserved
  - Ki-67 high (50-80% of tumor cells)
- Molecular:
  - *TP53* mutations (60%), pathogenic variants in *KRAS* (29%, including G12D, G12V, 2xG12C), *MAP2K1/2* (29%), *EGFR* mutation (7%), mutations in *FGFR1*, *GNA11*, *HRAS*, *PIK3CA* (7% each), *MET*ex14skip (7%), *RET* rearrangement (7%)
  - Low level *AKT1* amplification (60%)
- F/U: N=13; 8 DOD (6 mo-8 yrs, mean 2.7 yrs); 3 alive w/o disease 4-6 yrs

Take Home Message

- Diff diagnosis: Melanoma, sarcoma, large cell lymphoma, Hodgkin lymphoma, ALCL, SMARCA4-DUT
- Aggressive; in smokers; potential for targeted therapy in a subset
- We only know about surgically treated patients as only resection specimens
- Didn't do EBV; no comparison of NGS data or PD-L1 to "usual" sarcomatoid Ca, how about "carcinoma" markers (claudin 4, pCEA)?

Weissferdt A, et al. Primary Extraskeletal Osteosarcomas of the Pleura: A Clinicopathological, Immunohistochemical, and Molecular Analysis of 4 Cases. Hum Pathol. 2024;152:105635.

Background

- To explore the clinicopathologic, immunohistochemical, and molecular features of primary pleural extraskeletal osteosarcomas (no connection to skeletal system) in the differential diagnosis of mesothelioma with heterologous elements

Methods

- N=4; spindle cell neoplasms with malignant osseous elements arising from pleura from pathology files at MD Anderson CC
- Thoracoscopic biopsies
- IHC, FISH for *CDKN2A*

Results

- Clinical:
    - All male, age, mean, 70.5 yrs (63–78 yo)
    - Presentation: Chest pain, cough, and/or shortness of breath.
    - Imaging: pleural-based masses (N=3) with 1 associated pleural thickening, N=1 – diffuse pleural thickening w/o dominant mass; N=4 calcifications
    - No known exposure to asbestos, 1 with hx of prostate cancer
- Histopathology:
    - Gross: Firm, fibrotic portions of membranous tissue, gritty calcified cut surface
    - Malignant spindle cell proliferations; in one case more pleomorphic (Fig 2)
    - Abundant osteoid matrix in all; in one case additional chondroblastic differentiation (Fig 3)
    - 3 osteoblastic and 1 chondroblastic osteosarcoma
- **IHC**:
    - SATB2 diffusely + in 1 tumor tested (Fig 4)
    - All tumors neg for keratin AE1/AE3, CK 5/6, D2-40, calretinin, WT-1, HEG1, EMA, Ber-EP4, STAT6; BAP1 expression retained, FISH for *CDKN2A* – no homozygous deletion
- **F/U:** N=2, 1 DOD 8 mos after diagnosis, 1 alive 2 mos after diagnosis (disease status unknown)

Take Home Message

- Authors argue that osteosarcoma diagnosis should be rendered for tumors with malignant osseous/cartilaginous differentiation with comprehensive IHC and FISH analysis that failed to support meso – other studies argue that in the absence of keratin expression – anatomic distribution will sort out meso vs osteosarcoma
- Other studies show that patients with osteosarcoma can have hx of asbestos exposure
- Authors argue that distinction is important, even though outcome appears equally as poor, maybe different treatments/managements
- Authors do not provide any cases of mesothelioma with heterologous elements for comparison
- F/u sparse to non-existent
- SATB2 should have been stained in all cases (supposedly neg. in mesos)
- Homozygous deletion of *CDKN2A* has been reported in extraskeletal osteosarcomas

ARTICLES FOR NOTATION

NEOPLASTIC

Abia-Trujillo D, et al. Cryobiopsy Versus Fine-Needle Aspiration for Shape-Sensing Robotic-Assisted Sampling of Small Lung Nodules. Lung Cancer. 2024;196:107967.

Summary

- To compare the diagnostic yield and sensitivity for malignancy of cryobiopsy using 1.1 mm probe and fine-needle aspiration (FNA) in shape-sensing robotic-assisted bronchoscopy (ssRAB) for peripheral pulmonary nodules (PPNs) smaller than 20 mm.
- Using IonTM Endoluminal System (Intuitive surgical, Sunnyvale, Ca) with shape-sensing technology, under general anesthesia; pre-procedural ultrathin HRCT scan was uploaded to the IonTM System software for a mapping course and navigation planning towards the virtual target, and to calculate the size, location, and distance from the pleura of the PPN.
- Used radial EBUS and 3D fluoroscopy with mobile cone-beam three-dimensional CT 3D Spin Mobile C-arm for tool-in lesion verification.
- Cryobiopsy → ROSE → EBUS with TBNA
- Retrospective study
- N=256 patients who underwent ssRAB with both sampling methods; with a combined 284 procedures, 324 nodules sampled by cryobiopsy, 7% did not undergo FNA.
- Malignancy found in 62 % (n = 202) of PPN including 37 % (n = 120) diagnosed as adenocarcinoma
- N=5 false negative (4 diagnosed on subsequent surgical bx, 1 by subsequent ssRAB)
- Cryobiopsy - significantly higher diagnostic yield (92% vs 70.4%) and sensitivity for malignancy (96% vs 79.3%) compared to FNA
- No difference in sensitivity between cryobiopsy and FNA in mixed-type (solid+subsolid) lesions.
- Cryobiopsy performance was consistent across all nodule types and sizes; FNA showed a reduced yield, especially in nodules smaller than 15 mm.
- Complications, primarily pneumothorax, rarely significant bleeding, occurred in 6% of cases.

Take Home Message

- Cryobiopsy, when used with ssRAB for small PPNs, outperforms FNA in diagnostic yield and sensitivity for malignancy, particularly in nodules smaller than 15 mm.

Gonnelli, F, et al. Pulmonary fibrosis and lung cancer: an analysis of the Clinical Practice Research Datalink linked to the National Cancer Registration Dataset. Thorax, 2024; 79:982-985.

Summary

- To study the relationship between pulmonary fibrosis (PF), including IPF, and lung cancer
- Data from the UK Clinical Practice Research Datalink and the National Cancer Registration Dataset (2000-2015).
- 25,136 lung cancer patients and 250,583 matched controls

- PF more prevalent in patients with lung cancer than in the control group (1.5% vs 0.8%; OR 1.97; 95% CI 1.77 to 2.21; increased after adjusting for smoking habit, BMI and CCI [Charlson Comorbidity Index], [3.10, 95% CI 2.76 to 3.49])
- Patients with lung cancer and PF were older, more commonly male, ex smoker, overweight/obese than patients w/o PF
- SQCC more common among cancer patients with IPF after adjusting for age, sex, smoking habit, BMI and CCI; adenocarcinoma less common.
- Patients with both PF and lung cancer had lower likelihood of presenting with stage IV disease after adjusting for age, sex, smoking habit, BMI and CCI
- Patients with both PF and lung cancer had poorer survival outcomes compared to lung cancer patients without PF.

Take Home Message

- Not a new finding; both groups have some common risk factors (for instance smoking)
- Important to monitor lung cancer patients for PF to potentially improve management strategies (and vice versa – monitor PF patients for lung cancer).

Sun, Y, et al. Rapid examination of lung tissues by nonlinear microscopy. Am J Clin Pathol, 2024; 162:369-378.

Summary

- To study the use of nonlinear microscopy as a rapid imaging modality for lung tissues, assessing its ability to replicate traditional H&E-stained sections for both tumor and non-tumor lung structures.
- Nonlinear microscopy: High-resolution imaging using ultrashort pulse laser to induce nonlinear optical interactions in the sample at the beam focus. When the laser beam focus position is raster scanned and the resulting optical signals digitized, a virtual representation of the sample at the image plane is obtained ("optical section.") The signals may be endogenous (eg, harmonic generation) or from exogenous contrast agents. To facilitate pathologic evaluation, the detected optical signals can be processed and color mapped to mimic standard histology stains, such as H&E.
- Nonlinear microscopy
    - Can image tissue without freezing, fixing, embedding, or microtome sectioning → rapid examination of large tissue specimens without damaging or destroying the tissue sample.
    - Can image at a depth of up to approximately 100 μm below the tissue surface, avoiding surface contamination from surgical debris or electrocautery and providing 3-dimensional visualization analogous to serial H&E sectioning.
    - Does not to interfere with subsequent H&E histology or IHC
- 73 specimens from 13 patients (lobectomy, segmentectomy, wedge resection for pulmonary nodules)
- Lung tissue is serially sliced, areas of interest are selected, cut to a slice thickness of 2 to 4 mm, with sizes ranging from 10 × 20 mm to 70 × 100 mm, stained simultaneously with acridine orange and sulforhodamine 101 (Acridine orange binds to DNA and primarily serves as a nuclear stain, also aids in cytosol imaging by staining RNA, similar to hematoxylin; Sulforhodamine 101 stains the cytosol and stroma comparable to eosin and also binds RNA). Staining takes 2.5 min.

- 2 pathologists reviewed the digital nonlinear microscopy images and compared them to corresponding histopathologic H&E slides – no interobserver variability study; unclear whether both pathologists evaluated all cases or only a subset
- Nonlinear microscopy provides high-resolution images comparable to conventional histology without tissue processing.
- Nonlinear microscopy captures essential histological features of various lung cancers and highlights structural elements like elastic fibers, aiding in the identification of lymphovascular and pleural invasion.

Take Home Message

- Nonlinear microscopy readily replicates traditional H&E staining for both lung tumors and nonneoplastic pulmonary structures.
- Provides real-time 3-D visualization of the tissue, similar to serial H&E sections
- The approach is promising for intraoperative margin assessments, specifically in stapled resection margins, where traditional histological methods are limited.
- Visualizations of elastic fibers helps with assessment of pleural and vascular invasion
- Images generated digitally
- By eliminating the need for tissue processing, it accelerates diagnosis and provides high-resolution, H&E-like imaging suitable for tumor assessment and surgical margin evaluation.

Spicer, JD, et al. Neoadjuvant and Adjuvant Treatments for Early Stage Resectable NSCLC: Consensus Recommendations from the International Association for the Study of Lung Cancer. JTO, 2024; 19(10): 1373-1414.

- IASLC- multidisciplinary expert panel → to create expert consensus recommendations for the management of early-stage resectable NSCLC.
- Informed by multiple recent phase 3 trials data
- Emphasizes a structured, team-based approach to patient evaluation and treatment, particularly for those with resectable stage II and III disease.
- 19 recommendations; 18 achieved >85% consensus among panel members
- Public voting process

Key recommendations:

1. Multidisciplinary Care: Patients should be evaluated by a team comprising surgeons, oncologists, radiologists, and pathologists.
2. Biomarker Testing: Testing for *EGFR* and *ALK* mutations is required, PD-L1 status should be considered, for patients considering neoadjuvant or adjuvant therapies.
3. Neoadjuvant chemoimmunotherapy is preferred for stage III resectable NSCLC, irrespective of PD-L1 status, potentially improving event-free survival over traditional approaches.
4. <85% agreement on: optimal management of patients with stage II disease between upfront surgery followed by adjuvant therapy and neoadjuvant or perioperative strategies
5. For patients with resectable NSCLC and sensitizing *EGFR* and *ALK* alterations, neoadjuvant chemoimmunotherapy or adjuvant immunotherapy is not recommended
6. Use of intraoperative frozen sectioning is recommended to assure complete resection and limit excessive parenchymal resection

Definition of complete resection (R0) status requires the fulfillment of all the following conditions:
   - All free resection margins have been proven microscopically (bronchial, venous, arterial stumps, peribronchial soft tissue, any peripheral margin near the tumor or of additional resected tissue;
   - Systematic nodal dissection in its wider form or lobe-specific systematic nodal dissection must have been performed and proven negative;
   - No extracapsular extension of tumor in lymph nodes removed separately or in those at the margin of the main lung specimen;
   - The highest mediastinal node that has been removed must be negative.
7. Surgical pathology reporting for neoadjuvant therapy-treated patients, at minimum, a determination of pathologic complete response, percent residual viable tumor and ypTNM status, is recommended
8. Adjuvant Therapy: Immunotherapy or targeted therapies, such as osimertinib for *EGFR*-mutated tumors, are recommended post-surgery for specific genomic profiles.
9. Biomarker testing for oncogenic drivers other than *EGFR* and *ALK* alterations and PD-L1 status is highly encouraged in patients with early-stage disease
10. Future Trials and Research: Due to the lack of long-term data directly comparing neoadjuvant to adjuvant-only strategies, the panel suggests ongoing research and refinement of these recommendations.

- Workflow for neoadjuvant or adjuvant therapy for clinical stage II and III NSCLC – figures 1 and 2, respectively

ARTICLES FOR NOTATION

NON-NEOPLASTIC

Ang, HL, et al. Pulmonary Hypertension in Interstitial Lung Disease: A Systematic Review and Meta-Analysis. *Chest*, 2024; 166(4):778-792.

- To assesses the prevalence, risk factors, prognosis, and outcomes of pulmonary hypertension (PHT) in patients with interstitial lung disease (ILD).
- 302 studies; patients ≥ 18 yrs old, 56% used right heart catheterization, 50% transthoracic echo
- Definitions of PHT varied among studies (publications 2004-2022 included)
- ILD subtype: mixed (93 studies), IPF (77), SSc-ILD (61), other (71)
- PHT present in approximately 36% of general ILD populations when measured by right heart catheterization, 34% by echocardiography.
- If using mPAP ≥20-24 mmHg (current PHT definition mPAP >20 mmHg): prevalence of PHT 40% in unselected ILD cohort (48% in lung transplantation cohort)
- Lower diffusion capacity for carbon monoxide, reduced exercise capacity, worsened oxygenation, elevated serum BNP levels were associated with presence of PHT in ≥60% of studies.
- PHT – associated with increased symptom burden, worse prognosis.
- Clinical trials on PH treatments in ILD have primarily focused on hemodynamic improvements and increased six-minute walk distance as outcome measures.

Take Home Message

- PHT is a prevalent and impactful complication in ILD, associated with poorer outcomes.
- Various PHT definitions were used, at least in part due to including studies as old as 2004 → need to standardize PHT definitions for studies
- Evaluated ILD at various stages, many studies focus on lung transplantation cohorts
- Not evaluated for individual ILDs

Beber, SA, et al. The CD8+ T cell content of transbronchial biopsies from patients with a first episode of clinically stable grade A1 cellular rejection is associated with future chronic lung allograft dysfunction. J Heart Lung Transplant, 2024; 43(10): 1654-1664.

- To study whether the CD8+ T cell content in TBBx from lung transplant recipients with stable grade A1 rejection (clinically stable patients who have A1 rejection within 13 months post-transplantation, A1 was not treated in these patients) is predictive of future chronic lung allograft dysfunction (CLAD).
- Method: Imaging mass cytometry (IMC, 35 antibodies), IF, epigenetic analyses
- Profiling immune cell populations in TBBx of N=62 with first episode of A1 rejection – 13 developed CLAD within 2 years; 49 CLAD-free for ≥5 years
- No difference in Tregs (CD4+FOXP3+) between early and no early CLAD
- Higher proportions of CD8+ T cells (of total cells) in stable A1 biopsies were associated with a greater likelihood of developing CLAD within two years
- CD4+ regulatory T cell content did not correlate with CLAD outcomes.
- Early CLAD group – younger age at transplantation (median 50 vs 58), fewer days to stable A1 (median 51 vs 113 days)

Take Home Message

- CD8+ T cell levels - potential biomarker/prognostic marker for CLAD risk in lung transplant recipients.
- Needs validation in multicenter studies
- Unclear where the CD8+ T cells were located – figure 6 does not seem typical of a focus of A1 – appear to be too many cells, however, no corresponding HE provided

Cortes-Santiago N, et al. The Pathology of Pulmonary Disease After Pediatric Hematopoietic Stem Cell Transplantation. Am J Surg Pathol. 2024;48(10):1201–1214.

- To examine pulmonary complications following pediatric hematopoietic stem cell transplantation (HSCT), with emphasis on histopathology
- 56 specimens including 53 bxs; 53 patients.
- Major findings include:
    - Infections:
        - Most common diagnosis (n=20)
        - Often detected via microbiology rather than histopathology.
    - Noninfectious Complications:
        - Chronic GVHD (n=13); associated with lymphocytic inflammation and airway fibrosis

    - Vasculopathy (n=26; in n=5 vasculopathy was the sole finding); mostly fibromyxoid intimal expansion, poor prognosis.
- Indeterminate (n=10), frequently showing DAD, which correlated with high mortality.
- Overall clinicopathologic concordance – 40%, most common agreement in infectious category
- Surgical biopsies provided more diagnostic clarity and impacted management decisions in 69% of cases versus 23% for limited biopsies (core needle biopsies).

Merlo CA, et al. Long-term impact of ivacaftor on mortality rate and health outcomes in people with cystic fibrosis. Thorax. 2024;79:925-933.

- To evaluate the long-term effects of ivacaftor, a CFTR modulator, on people with cystic fibrosis (CF) with gating mutations.
- Data from the US Cystic Fibrosis Foundation Patient Registry (2010-2019)
- Ivacaftor-treated population: patients with *CFTR* gating mutation (excluding *R117H*) (n=736)
- Controls: age-matched patients with a *F508del* and a minimal function *CTFR* mutation n=733)
- Maximum f/u 7.9 years without prior CFTR modulator treatment
- Findings show that ivacaftor significantly reduced:
    - Mortality: by 78% compared to untreated group (HR 0.22).
    - Lung Transplantation: risk was reduced by 89% (HR 0.11).
    - Pulmonary Exacerbations: halved in frequency (rate ratio 0.49).
    - Hospitalizations and Clinic Visits: both markedly decreased (rate ratio 0.5).
- The ivacaftor group exhibited sustained improvements in lung function (ppFEV1, mean difference 8.46) and BMI (mean difference 1.2 kg/m2), especially among adolescents

Take Home Message

- Study reinforces ivacaftor's role as a transformative therapy for CF, suggesting similar potential benefits for newer modulator combinations, such as elexacaftor/tezacaftor/ivacaftor, which may further expand the treatment's impact on the CF population.

REVIEW

Pelosi, G, & Travis, WD. Head-to-Head: Should Ki67 Proliferation Index Be Included in the Formal Classification of Pulmonary Neuroendocrine Neoplasms? Histopathology, 2024, 85:535–548.

Background

- Pulmonary NENs - classified by the 2021 WHO (mitotic count, necrosis)
- Ki-67 proliferation index increasingly recognized as useful, especially in other organ systems (e.g., gastrointestinal and pancreatic NENs).
- To evaluate whether Ki-67 should be an essential criterion in classifying lung NENs, given its potential to aid in diagnosis, prognosis, and therapeutic planning.

Arguments For Ki-67 Inclusion

- Ki-67 is reliable for distinguishing between carcinoids and high-grade NECs (SCLC, LCNEC), especially in small or crushed biopsies
- Ki-67's expression within tumors can reveal biologically distinct regions, which may correlate with aggressive behavior, offering additional prognostic insights.
- Studies suggest Ki-67 is a robust prognosticator for survival and recurrence-free intervals in lung NENs, especially carcinoids, and may complement mitotic count and necrosis.
- A stratification approach using Ki-67 has been proposed to refine clinical decisions, particularly for metastatic carcinoid tumors where therapeutic responses can vary significantly.

Arguments Against Ki-67 Inclusion

- In lung NENs, high-grade NECs (SCLC and LCNEC) are vastly more common than low- or intermediate-grade carcinoids. The clinical utility of Ki-67 is less clear for these higher-grade tumors.
- The WHO's existing classification criteria (mitotic count, necrosis) are often adequate for diagnosing most lung NENs without needing Ki-67.
- Quantifying Ki-67 can suffer from interobserver variability, especially in the absence of standard guidelines for counting. For instance, Ki-67 hot-spot counting methods can vary across labs.

Conclusion

The review suggests that Ki-67, while valuable in specific contexts (e.g., in differentiating tumor grades in small biopsy samples), may not yet have sufficient evidence to warrant universal inclusion in lung NEN classification.
Consensus on standardized counting and validation in larger studies is needed to justify expanding Ki-67's role.

Le, L, et al. Diseases Involving the Lung Peribronchovascular Region: A CT Imaging Pathologic Classification. Chest, 2024; 166(4), 802-820.

Background

- To review the radiologic findings of diseases involving the lung peribronchovascular region and to correlate them with pathologic findings

Anatomy and Pathology of the Peribronchovascular Region:

- Arteries, airways, lymphatics, lymph nodes, and interstitial connective tissues.
- Interstitium = network of hyaluronic acid-filled spaces that facilitate fluid and immune cell movement, impacting the radiographic appearance in disease states.

Imaging Characteristics:

- Diffuse Peribronchovascular Thickening:
    - Edema, hemorrhage, lymphangitic carcinomatosis, sarcoidosis, silicosis
    - Smooth or nodular thickening on CT is associated with specific conditions such as neoplasms and sarcoidosis.
- Fibrosis:
    - Peribronchovascular fibrosis may be indicative of NSIP, IPF, HP.
    - Key CT features: GGO, tractionbronchiectasis, reticulation.
- Masses and Masslike Consolidations:
    - Neoplasms (e.g., lymphomas, Kaposi sarcoma), sarcoidosis, OP.
    - Masses often appear as large, rounded, or nodular opacities +/- air bronchograms.

- GGO and Airspace Consolidation:
    - Infection, OP, eosinophilic pneumonia, vasculitis (GPA, IgG4, EVALI)
    - Mucinous neoplasms
- Peribronchovascular Cysts:
    - LIP and amyloidosis/light chain deposition disease, presenting as cysts near vessels or bronchi on imaging.

Disease-Specific Imaging Patterns and Clinical Correlations:

- Sarcoidosis and Silicosis:
    - Nodular thickening along lymphatic pathways, peribronchovascular masses, upper-lobe-predominant fibrosis.
- Neoplasms:
    - Lymphoma and Kaposi sarcoma typically appear as peribronchovascular masses. Other cancers may present with masslike consolidations or nodules.
- Autoimmune Diseases and Vasculitis:
    - Including GPA and IgG4-related disease
    - Often present with nodules or GGOs along peribronchovascular paths

Multidisciplinary approach to correlate CT imaging patterns with clinical features, pathology, and laboratory findings important.

CASE REPORTS

Jamjoom M, et al. A 78-Year-Old Man With Shortness of Breath After Radioembolization of the Liver. Chest. 2024;166(4)

- A 78-year-old man with a history of metastatic gastrointestinal stromal tumor (GIST) treated with liver radioembolization using yttrium-90 (Y-90) microspheres
- Progressive shortness of breath, dry cough, and fever one week post-procedure
- CT: new bilateral airspace consolidation and ground-glass opacities in the left lung.

Diagnosis

- Radiation pneumonitis (RP) caused by the escape of Y-90 microspheres into the pulmonary vasculature, likely due to a hepatopulmonary shunt.
- Lung biopsy confirmed the presence of these microspheres alongside fibrinous exudate and inflammatory cells – watch out for well circumscribed dark lesions in small vessels

Treatment:

- Corticosteroids led to improvement of symptoms

Nakamura, H, et al. Thoracic Small Round Cell Sarcoma with FGFR2::DCTN2 Fusion. Histopathology, 2024; 85(4), 690–698.

- A 57-year-old male presented with severe chest pain
- A 25 cm heterogeneous thoracic tumor compressing heart and mediastinum, pleural dissemination, LN metastases.
- Bx: “Ewing-like sarcoma”
- Several chemotherapeutic agents were ineffective
- Patient died from tumor growth, carcinomatous peritonitis, bilateral renal dysfunction, 4 months after presentation

- Microscopy: Small, round, monomorphic cells with low pleomorphism, high mitotic index (7/mm²), geographic necrosis.
- IHC: weak CD99 positivity, focal S100 staining, retained BRG1 and BRM expression, negative for keratin AE1/AE3, EMA, desmin, myogenin, MyoD1, ASMA, SOX2, ERG, ETV4, WT1, BCoR.
- RNA sequencing: in frame *FGFR2::DCTN2* fusion
- IHC: strong membrane positivity for FGFR2, diffuse dot-like cytoplasmic positivity for p50 dynamitin, focal strong nuclear expression of ERK1/2.
- *FGFR2* break-apart FISH – split signals and a signal suggesting the presence of a triploid *FGFR2* gene

Joueidi, F, et al. An Unusual Cause of Lung Abscess in a Previously Healthy Girl. Chest, 2024, 166(4), e117-e120.

- A 15-year-old girl presented with fatigue, weight loss, and recent fever, cough, and chest pain.
- Examinations revealed lung abscess in the left lower lobe lung and a left renal mass.
- Imaging confirmed an 8 cm cavitary lung lesion, pleural effusion, and a 13.5 cm renal mass invasion through the diaphragm into thoracic cavity.
- Histopathology from lung and renal biopsies demonstrated foamy macrophages and chronic inflammation →
- Diagnosis: Xanthogranulomatous pyelonephritis (XGP) with a rare nephrobronchial fistula causing the lung abscess.
- Left radical nephrectomy, diaphragm repair, and abscess drainage.
- Postoperative asymptomatic, weight gain at an 11-month follow-up.

Merrell, E. A 63-Year-Old Presents With Acute Fatigue, Dyspnea, and Hypoxia. Chest, 166(4), 2024, e113-e116.

- A 63-year-old woman presented with fatigue, shortness of breath, and hypoxia
- Chest CT: Diffuse ground-glass opacities with interlobular septal thickening (classic “crazy paving” pattern)
- Antibiotics for presumed infection
- Symptoms worsened
- History of environmental exposure in India
- BAL: Turbid white effluent; PAS-positive debris on cytology (Figure 4)
- Serology: High levels of GM-CSF antibodies

→ Diagnosis: Autoimmune PAP

- Whole lung lavage on both lungs
- Nebulized sargramostim (recombinant GM-CSF) for maintenance.