PULMONARY JOURNAL CLUB
OCTOBER 7, 2024 (JULY 2024 ARTICLES)
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ARTICLES FOR DISCUSSION

Tsushima Y, Okoshi EN, Ishijima S, …, Fukuoka J. Presence of focal usual interstitial pneumonia is a key prognostic factor in progressive pulmonary fibrosis. Histopathology. 2024 Jul;85(1):104-115.

Background:

- Progressive pulmonary fibrosis (PPF)
  - Defined as at least two of the following criteria
    - Worsening symptoms
    - Radiological progression
    - Physiological progression
  - These should occur within a year with no alternative explanation in a patient with an ILD other than IPF

Aims:

- To investigate the histopathological characteristics of progressive pulmonary fibrosis (PPF) and
- To examine the correlation between UIP-like fibrosis and prognosis in this new disease type

Methods:

- Patients
  - 355 ILD patients with progressive phenotype
  - (-) 154 patients with IPF were excluded
  - (=) 201 patients with progressive pulmonary fibrosis (PPF)
- Digital histological analysis
  - Whole slide images were evaluated by three pathologists
  - Areas of UIP-like fibrosis were measured and the percentage of the total lesion area they occupied were calculated
- Definitions
  - UIP-like fibrosis
    - Defined as destructive fibrosis or marked distortion
    - It did not necessarily include fibroblastic foci or temporal heterogeneity
  - Pathological UIP-positive
    - Cases that fell under the diagnoses of definite, probable, or possible UIP were labelled as “pathological UIP-positive”
  - Focal UIP-positive
    - Cases were labelled “focal UIP-positive” if the area of UIP-like fibrosis was greater than 10%

Results:

- 135 cases met the criteria for “focal UIP-positive” (by consensus)
- Survival analysis showed that the presence of focal UIP-like fibrosis correlated with worsened survival

Conclusions:

- UIP-like fibrosis is a core pathological feature of PPF
- Its presence is associated with poorer prognosis

Cool CD, Murray J, Vorajee NI, …, Cohen RA. Pathologic Findings in Severe Coal Workers' Pneumoconiosis in Contemporary US Coal Miners. Arch Pathol Lab Med. 2024 Jul 1;148(7):805-817.

Background:

- Changes in mining practices and technologies may have contributed to higher airborne concentrations of silica and silicates

Aim:

- To update the description of pathologic features of coal workers' pneumoconiosis (CWP) in contemporary miners compared to historical miners

Methods:

- Study population
    - Lung tissue from 85 underground coal miners with progressive massive fibrosis (PMF) met the inclusion criteria for the study
    - This population was divided into 2 groups:
        - Historical miners (n=62)
            - Born between 1910 and 1930
            - Worked mainly with conventional mining technology that relied on drilling and blasting
        - Contemporary miners (n=23)
            - Born in or after 1930
            - Spent a substantial portion of their mining tenure working with powerful mechanized equipment
    - Definitions
        - Progressive massive fibrosis (PMF)
            - Mineral dust–laden fibrotic lesion with dense deposition of collagen fibers, measuring more than 10 mm in diameter
            - Subclassification of PMF
                - Coal-type
                    - Composed of up to 25% silicotic nodules
                - Mixed type
                    - Composed of more than 25% and up to 75% silicotic nodules
                - Silica-type
                    - Composed of more than 75% silicotic nodules
        - Rapidly progressive pneumoconiosis (RPP)
            - Development of progressive massive fibrosis (PMF) over 5 years
            - Histologic features often seen in RPP include
                - Mature silicotic nodules
                - Immature (early stage) silicotic nodules
                - Mineral dust-associated alveolar proteinosis (MDAP)

Results:

- Silica dust-associated histologic features, including silica-type progressive massive fibrosis (PMF), immature (early stage) silicotic nodules, and mineral dust alveolar proteinosis (MDAP), were increased in contemporary miners

Conclusions:

- The findings underscore the urgent need to revise current exposure limits and monitoring of respirable crystalline silica in US coal mines

Villalba JA, Cheek-Norgan EH, Johnson TF, Yi ES, Boland JM, Aubry MC, Pennington KM, Scott JP, Roden AC. Fatal Infections Differentially Involve Allograft and Native Lungs in Single Lung Transplant Recipients. Arch Pathol Lab Med. 2024 Jul 1;148(7):784-796.

Background:

- Respiratory infections complicate lung transplantation and increase the risk of allograft dysfunction

Aim:

- To study whether infections affect allograft and native lungs differently in single lung transplant recipients (SLTRs) but similarly in double LTRs (DLTRs)

Methods:

- An institutional database of LTRs was searched for patients who died of an infectious complication involving the lungs and who underwent an autopsy at Mayo Clinic Rochester
- Histopathologic features were recorded per lung lobe and graded semiquantitatively
- A multilobar-histopathology score (MLHS) (including histopathologic data from each lung) and a bilateral ratio (MLHS ratio) (comparing histopathologies between both lungs) were calculated in SLTRs and compared to DLTRs

Results:

- SLTRs (n=6)
    - All allografts showed multifocal histopathologic evidence of infection
    - At least 1 lobe of the native lung was uninvolved
    - MLHSAllograft was higher than MLHSNative ($P = .02$)
- DLTRs (n=5)
    - In 4 of 5 DLTRs, histopathologic evidence of infection was seen in all lung lobes
- The MLHS ratio of SLTR and DLTR were significantly different ($P < .001$)

Conclusions:

- Allograft and native lungs appear to harbor different susceptibilities to infections

Travis WD, Eisele M, Nishimura KK, et al. The International Association for the Study of Lung Cancer (IASLC) Staging Project for Lung Cancer: Recommendation to Introduce Spread Through Air Spaces as a Histologic Descriptor in the Ninth Edition of the TNM Classification of Lung Cancer. Analysis of 4061 Pathologic Stage I NSCLC. J Thorac Oncol. 2024 Jul;19(7):1028-1051.

Background:

- Spread through air spaces (STAS) is a lesion where tumor cells are identified microscopically beyond the edge of the main tumor in the adjacent alveolar parenchyma
- It has been reported in 20% to 40% of surgically resected lung cancers and is associated with poor prognosis in all major histologic types
- Multiple investigators have suggested that STAS be incorporated in the TNM stage classification of lung cancer in a variety of ways such as
    - Tumor size
    - Residual tumor (R) status or
    - A histologic descriptor that could upstage T1 lung cancer to T2a like visceral pleural invasion (VPI)

Aim:

- To investigate whether STAS could be a useful additional histologic descriptor to supplement
    - Visceral pleural invasions (VPI)
    - Lymphatic/vascular invasion (LVI)
    - Perineural invasion (Pn)
- It was not a goal of this paper to propose that STAS be used to modify overall stage groupings

Methods:

- The authors evaluated 4061 completely resected (R0) pathologic stage I NSCLC collected from around the world in the IASLC database

Results:

- STAS was found in 930 of the 4061 pathologic stage I NSCLC (22.9%)
- Patients with tumors exhibiting STAS had a significantly worse recurrence-free and overall survival in both univariate and multivariable analyses involving cohorts consisting of all NSCLC, specific histologic types (adenocarcinoma and other NSCLC), and extent of resection (lobar and sublobar)
- Interestingly, STAS was independent of visceral pleural invasion (VPI) in all these analyses

Conclusion:

- These data support the recommendation to include STAS as a histologic descriptor for the Ninth Edition of the TNM Classification of Lung Cancer

ARTICLES FOR NOTATION: NEOPLASTIC

Sholl LM, Awad M, Basu Roy U, Beasley MB, …, Furtado LV. Programmed Death Ligand-1 and Tumor Mutation Burden Testing of Patients With Lung Cancer for Selection of Immune Checkpoint Inhibitor Therapies: Guideline From the College of American Pathologists, Association for Molecular Pathology, International Association for the Study of Lung Cancer, Pulmonary Pathology Society, and LUNGevity Foundation. Arch Pathol Lab Med. 2024 Jul 1;148(7):757-774.

Background:

- Rapid advancements in the understanding and manipulation of tumor-immune interactions have led to the approval of immune therapies for patients with non-small cell lung cancer
- Certain immune checkpoint inhibitor therapies require the use of companion diagnostics, but methodologic variability has led to uncertainty around test selection and implementation in practice

Aims:

- To develop evidence-based guideline recommendations for the testing of immunotherapy/immunomodulatory biomarkers, including programmed death ligand-1 (PD-L1) and tumor mutation burden (TMB), in patients with lung cancer

Methods:

- The College of American Pathologists convened a panel of experts in non-small cell lung cancer and biomarker testing to develop evidence-based recommendations in accordance with the standards for trustworthy clinical practice guidelines established by the National Academy of Medicine
- A systematic literature review was conducted to address 8 key questions
- Using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, recommendations were created from the available evidence, certainty of that evidence, and key judgments as defined in the GRADE Evidence to Decision framework

Results:

- Six recommendation statements were developed

Conclusions:

- This guideline summarizes the current understanding, and hurdles associated with the use of PD-L1 expression and TMB testing for immune checkpoint inhibitor therapy selection in patients with advanced non-small cell lung cancer and presents evidence-based recommendations for PD-L1 and TMB testing in the clinical setting

EDITORIAL

Cecchini MJ. Pathways to Precision: Guideline for Programmed Death Ligand-1 and Tumor Mutation Burden Testing to Support the Selection of Immune Checkpoint Therapies in Lung Cancer. Arch Pathol Lab Med. 2024 Jul 1;148(7):754-756.

Suster DI, Ronen N, Suster S. Pseudosquamous Adenocarcinoma of the Lung: Clinicopathologic and Immunohistochemical Study of 10 Cases. Am J Surg Pathol. 2024 Jul 1;48(7):901-908.

Background:

- Pseudosquamous adenocarcinoma of the lung is an unusual morphologic variant of poorly differentiated non-small cell lung carcinoma that superficially resembles a squamous cell carcinoma

Methods:

- The authors examined 10 cases of these tumors in 4 women and 6 men, aged 47 to 93 years

Results:

- The tumors were all peripheral and measured from 1.5 to 5.5 cm
- All cases were characterized by solid nests of large polygonal tumor cells containing atypical nuclei with abundant cytoplasm and sharp cell borders, adopting a pavement-like architecture that simulated squamous cell carcinoma
- Some cases demonstrated intracytoplasmic hyaline inclusions suggestive of keratinization
- The nests of tumor cells often showed central comedo-like areas of necrosis
- Intercellular bridges were not seen in any of the cases
- The tumors often displayed marked clearing of the cytoplasm enhancing their epidermoid appearance
- In 4 cases, the solid pseudosquamous areas were seen to merge with a focal lepidic adenocarcinoma component, and in 1 case, abortive microscopic foci of acinar differentiation were also noted within the tumor
- One case showed focal sarcomatoid spindle cell areas
- The tumor cells were negative for p40 and CK5/6 and labeled with TTF1 or Napsin-A, confirming an adenocarcinoma phenotype
- Clinical follow-up information was available in 8 patients; 6 patients died of their tumors between 6 months to 11 years after diagnosis (mean: 3.1 y)
- One patient died of complications related to surgery and one patient with a low-stage tumor died at 27 years from other causes

Conclusions:

- Solid pattern adenocarcinomas can be confused for squamous cell carcinoma and may require immunohistochemistry to determine their true phenotype.

Suster DI, Ronen N, Mejbel HA, …, Suster S. Non-small cell lung carcinoma with clear cell features: a clinicopathologic, immunohistochemical, and molecular study of 31 cases. Virchows Arch. 2024 Jul;485(1):83-96.

Background:

- Non-small cell lung carcinoma with predominantly clear cell features is a rare histologic presentation of lung carcinoma

Aims:

- To examine 31 cases of lung carcinomas showing extensive clear cell features

Results:

- The patients were 10 women, and 21 men aged 47-92 years (mean: 70 years)
- The tumors showed a predilection for the right upper and lower lobes and measured from 0.8 to 9.5 cm (mean: 4.2 cm)
- By immunohistochemistry
    - 9 cases were typed as adenocarcinoma (most cases showed a solid growth pattern)
    - 19 cases as squamous cell carcinoma
    - 3 cases as "null" phenotype (with complete loss of adenocarcinoma and squamous cell carcinoma markers)
- A subset of the solid adenocarcinoma cases showed a distinctive "pseudosquamous" morphology
- Next-generation sequencing was performed in 20 cases and showed a variety of molecular alterations
- The most common abnormalities were found in the TP53 gene (9 cases), FGFR gene family (8 cases), KRAS (5 cases), AKT1 (5 cases), and BRAF (3 cases)
- Clinical follow-up was available in 21 patients; 16/21 patients died of their tumors from 6 months to 12 years after initial diagnosis (mean: 4.2 years, median: 1.5 years)
- Four patients were alive and well from 4 to 27 years (mean: 11.5 years, median: 7.5 years); all were pathologic stage 1 or 2

Conclusions:

- NSCLC with clear cell features can display aggressive behavior and needs to be distinguished from various other tumors of the lung that can show clear cell morphology
- The identification of targetable molecular alterations in some of these tumors may be of value for therapeutic management

Hegedűs F, Zombori-Tóth N, Kiss S, Lantos T, Zombori T. Prognostic impact of the IASLC grading system of lung adenocarcinoma: a systematic review and meta-analysis. Histopathology. 2024 Jul;85(1):51-61.

Background:

- The International Association for the Study of Lung Cancer (IASLC) proposed a grading system for non-mucinous lung adenocarcinoma in 2020

Aims:

- To validate the prognostic impact of this novel grading system on overall survival (OS) and recurrence-free survival (RFS) based on literature data

Methods:

- The authors identified randomized or non-randomized controlled trials published after 2020 comparing different IASLC grade categories in Medline, Embase, and CENTRAL

Results:

- Ten articles were eligible for this review
- Regarding OS estimates, grade 1 lung adenocarcinomas were better than grade 3 both in univariate and multivariate analyses
- Regarding RFS estimates, grade 3 adenocarcinomas had a worse prognosis than grade 1 in multivariate analysis

Conclusions:

- The literature data and the result of our meta-analysis demonstrate the prognostic relevance of the IASLC grading system
- This supports the inclusion of this prognostic parameter in daily routine worldwide

Dong K, Zhu Y, Liu X, …, Lin D. Feasibility of two-step approach for screening NTRK fusion in two major subtypes of non-small cell lung cancer within a large cohort. Hum Pathol. 2024 Jul;149:39-47.

Aims:

- To investigate a cost-effective approach to screen for NTRK fusion in the major subtypes of non-small cell lung cancer (NSCLC)
- To evaluate the concordance between
    - Immunohistochemistry (IHC) and next-generation sequencing (NGS)
    - Fluorescence in situ hybridization (FISH) and NGS

Methods:

- A cohort of 1654 patients with NSCLC underwent screening for NTRK fusion using whole slide IHC
- The positive cases were analyzed by both FISH and NGS

Results:

- Totally, 57 tested positive for pan-TRK, with positivity rates of 0.68% (10/1467) for lung adenocarcinoma (LADC) and 29.01% (47/162) for lung squamous cell carcinoma (LSCC)
- FISH showed separate NTRK1 and NTRK3 rearrangements in two pan-TRK-positive LADCs, while all LSCCs tested negative
- NGS confirmed functional NTRK fusion in two FISH-positive cases: one involving TPM3-NTRK1 and the other involving SQSTM1-NTRK3
- A non-functional fusion of NTRK2-XRCC1 was detected in LSCC, while FISH was negative
- According to this approach, the prevalence of NTRK fusion in NSCLC is 0.12%
- The concordance rate between IHC and RNA-based NGS was 20% (2/10) in LADC and 0% (0/162) in LSCC
- When the positive criteria increased over 50% of tumor cells showing strong staining, the concordance would be 100% (2/2)
- A concordance rate of 100% (2/2) was observed between FISH and RNA-based NGS in LADC
- The expression of pan-TRK was significantly correlated with the tumor proportion score (TPS) of PD-L1 ($p < 0.05$) and transcript per million (TPM) values of NTRK2 ($p < 0.05$)

Conclusions:

- The authors recommend using IHC with strict criteria to screen NTRK fusion in LADC rather than LSCC, confirmed by RNA-based NGS directly
- When the NGS results are inconclusive, FISH validation is necessary

Bielamowicz K, Dimitrion P, Abla O, …, Allen CE; North American Consortium for Histiocytosis. Langerhans cell histiocytosis: NACHO update on progress, chaos, and opportunity on the path to rational cures. Cancer. 2024 Jul 15;130(14):2416-2439.

Review:

- Langerhans cell histiocytosis (LCH) is a myeloid neoplastic disorder characterized by lesions with
    - CD1a-positive/Langerin (CD207)-positive histiocytes and
    - An inflammatory infiltrate that can cause local tissue damage and systemic inflammation
- Clinical presentations range from single lesions with minimal impact to life-threatening disseminated disease
- Therapy for systemic LCH has been established through serial trials empirically testing different chemotherapy agents and durations of therapy
- Fewer than 50% of patients who have disseminated disease are cured with the current standard-of-care vinblastine/prednisone/(mercaptopurine), and treatment failure is associated with long-term morbidity, including the risk of LCH-associated neurodegeneration
- Over the past 15 years, seminal discoveries have broadly defined LCH pathogenesis; specifically, activating mitogen-activated protein kinase pathway mutations (most frequently, BRAFV600E) in myeloid precursors drive lesion formation
- LCH therefore is a clonal neoplastic disorder, although secondary inflammatory features contribute to the disease
- These paradigm-changing insights offer a promise of rational cures for patients based on individual mutations, clonal reservoirs, and extent of disease
- The pace of clinical trial development lags the kinetics of translational discovery

Cittolin-Santos GF, Knapp B, Ganesh B, …, Morgensztern D. The changing landscape of small cell lung cancer. Cancer. 2024 Jul 15;130(14):2453-2461.

Aim:

- The objective of this study was to examine the demographic trends and outcomes in SCLC

Methods:

- The authors queried the National Cancer Institute's Surveillance, Epidemiology, and End Results database to assess the trends in incidence, demographics, staging, and survival for SCLC from 1975 to 2019
- Trends were determined using joinpoint analysis according to the year of diagnosis

Results:

- Among the 530,198 patients with lung cancer, there were 73,362 (13.8%) with SCLC
- The incidence per 100,000 population peaked at 15.3 in 1986 followed by a decline to 6.5 in 2019
- The percentage of SCLC among all lung tumors increased from 13.3% in 1975 to a peak of 17.5% in 1986, declining to 11.1% by 2019
- There was an increased median age at diagnosis from 63 to 69 years and an increased percentage of women from 31.4% to 51.2%
- The percentage of stage IV disease increased from 58.6% in 1988 to 70.8% in 2010
- The most common sites of metastasis at diagnosis were
    - Mediastinal lymph nodes (75.3%)
    - Liver (31.6%)
    - Bone (23.7%)
    - Brain (16.4%)
- The 1-year and 5-year overall survival rate increased from 23% and 3.6% in 1975-1979 to 30.8% and 6.8% in 2010-2019

Conclusions:

- The incidence of SCLC peaked in 1988 followed by a gradual decline
- Other notable changes include
    - Increased median age
    - Increased percentage of women
    - Increased percentage of stage IV disease at diagnosis
- The improvement in 5-year overall survival has been statistically significant but clinically modest

Sun W, Qu L, Wu J, …, Lin D. "Percentage" and "size" of residual viable tumor in lymph node, the performance in estimating pathologic response of lymph node in non-small cell lung cancer treated with neoadjuvant chemoimmunotherapy. Hum Pathol. 2024 Jul;149:1-9.

Background:

- There is no universally accepted method for evaluating lymph node metastasis (LNM) in non-small cell lung cancer (NSCLC) after neoadjuvant chemoimmunotherapy
- Different protocols recommend evaluating the percentage of residual viable tumor (RVT%) and metastatic tumor size (MTS)

Aims:

- To determine the prognostic significance of RVT% and MTS
- To identify the more effective parameter for evaluating LNM

Methods:

- Two independent cohorts were collected (derivation, n = 84; external validation, n = 42)
- All patients exhibited metastatic cancer or treatment response in lymph nodes post-surgery
- In the derivation cohort, the authors assessed the mean and largest values of MTS and RVT% in LNM, estimating their optimal cutoffs for event-free survival (EFS) using maximally selected rank statistics
- Validation was subsequently conducted in the external validation cohort
- The quality of prognostic factors was evaluated using the Area Under Curve (AUC)

Results:

- A positive association was identified between RVT% and MTS, but an absolute association could not be conclusively established
- In the derivation cohort, neither the largest MTS (cutoff = 6 mm, p = 0.28), largest RVT% (cutoff = 75%, p = 0.23), nor mean RVT% (cutoff = 55%, p = 0.06) were associated with EFS
- However, mean MTS (cutoff = 4.5 mm) in lymph nodes was statistically associated with EFS (p = 0.018), validated by the external cohort (p = 0.017)
- The prognostic value of MTS exceeded that of ypN staging in both cohorts, as evidenced by higher AUC values

Conclusions:

- The mean value of MTS can effectively serve as a parameter for the pathological evaluation of lymph nodes, with a threshold of 4.5 mm, closely linked to EFS
- Its prognostic value outperforms that of ypN staging

Wankhede D, Grover S, Hofman P. SMARCA4 alterations in non-small cell lung cancer: a systematic review and meta-analysis. J Clin Pathol. 2024 Jun 19;77(7):457-463.

Background:

- A mutation in the SMARCA4 gene which encodes BRG1, a common catalytic subunit of switch/sucrose non-fermentable chromatin-remodeling complexes, plays a vital role in carcinogenesis
- SMARCA4 mutations are present in approximately 10% of non-small cell lung cancers (NSCLC), making it a crucial gene in NSCLC, but with varying prognostic associations

Aims:

- To explore this, the authors conducted a systematic review and meta-analysis on the prognostic significance of SMARCA4 mutations in NSCLC

Methods:

- Electronic database search was performed from inception to December 2022
- Study characteristics and prognostic data were extracted from each eligible study
- Depending on heterogeneity, pooled HR and 95% CI were derived using the random-effects or fixed-effects models

Results:

- 8 studies (11 cohorts) enrolling 8371 patients were eligible for inclusion
- Data on overall survival (OS) and progression-free survival (PFS) were available from 8 (10 cohorts) and 1 (3 cohorts) studies, respectively
- Comparing SMARCA4-mutated NSCLC patients with SMARCA4-wild-type NSCLC patients, the summary HRs for OS and PFS were 1.49 (95% CI 1.18 to 1.87; I2=84%) and 3.97 (95% CI 1.32 to 11.92; I2=79%), respectively
- The results from the trim-and-fill method for publication bias and sensitivity analysis were inconsistent with the primary analyses
- Three studies reported NSCLC prognosis for category I and II mutations separately; category I was significantly associated with OS

Conclusions:

- The findings suggest that SMARCA4 mutation negatively affects NSCLC OS and PFS
- The prognostic effects of SMARCA4-co-occurring mutations and the predictive role of SMARCA4 mutation status in immunotherapy require further exploration

ARTICLES FOR NOTATION: NON-NEOPLASTIC

Tepp JA, Remotti F, Szabolcs MJ, Saqi A. Histological characterisation of pulmonary monkeypox virus infection in a patient with AIDS. Histopathology. 2024 Jul;85(1):193-195. (Case report)

Nossent EJ, Smits JA, Seegers C, …, Vonk Noordegraaf A. Clinical correlates of a nonplexiform vasculopathy in patients with a diagnosis of Idiopathic pulmonary arterial hypertension. Chest. 2024 Jul;166(1):190-200.

Background:

- The clinical phenotype of patients with idiopathic pulmonary arterial hypertension (IPAH) has changed
- Whether subgroups of patients with IPAH have different vascular phenotypes is a subject of debate

Aim:

- To examine histologic patterns of IPAH and their clinical correlates

Methods:

- In this this cross-sectional registry study, lung histology of 50 patients with IPAH was assessed qualitatively by two experienced pathologists
- In addition, quantitative analysis by means of histopathologic morphometry using immunohistochemistry was performed
- Histopathologic characteristics were correlated with clinical and hemodynamic parameters

Results:

- In this cohort of 50 patients with IPAH, a plexiform vasculopathy was observed in 26 of 50 patients (52%), whereas 24 of 50 patients (48%) showed a nonplexiform vasculopathy
- The nonplexiform vasculopathy was characterized by prominent pulmonary microvascular (arterioles and venules) remodeling and vascular rarefaction
- Although hemodynamic parameters were comparable in plexiform vs nonplexiform vasculopathy, patients with nonplexiform vasculopathy were older, more often were male, more often had a history of cigarette smoking, and had lower diffusing capacity of the lungs for carbon monoxide at diagnosis
- No mutations in established pulmonary arterial hypertension genes were found in the nonplexiform group

Conclusions:

- This study revealed different vascular phenotypes within the current spectrum of patients with a diagnosis of IPAH, separated by clinical characteristics (age, sex, history of cigarette smoking, and diffusing capacity of the lungs for carbon monoxide at diagnosis)
- Potential differences in underlying pathobiological mechanisms between patients with plexiform and nonplexiform microvascular disease should be considered in future research strategies unravelling the pathophysiologic features of pulmonary hypertension and developing biology-targeted treatment approaches

Sarver E, Keles C, Lowers H, …, Cohen R. In situ lung dust analysis by automated field emission scanning electron microscopy with energy dispersive x-ray spectroscopy: A method for assessing inorganic particles in lung tissue from coal miners. Arch Pathol Lab Med. 2024 Jul 1;148(7):e154-e169.

Background:

- Overexposure to respirable coal mine dust can cause severe lung disease including progressive massive fibrosis (PMF)
- Field emission scanning electron microscopy with energy dispersive x-ray spectroscopy (FESEM-EDS) has been used for in situ lung dust particle analysis
- Automating such work can reduce time, costs, and user bias

Aims:

- To develop and test an automated FESEM-EDS method for in situ analysis of inorganic particles in coal miner lung tissue

Methods:

- The authors programmed an automated FESEM-EDS procedure to collect particle size and elemental data, using lung tissue from 10 underground coal miners with PMF and 4 control cases
- A statistical clustering approach was used to establish classification criteria based on particle chemistry
- Data were correlated to PMF/non-PMF areas of the tissue, using corresponding brightfield microscopy images
- Results for each miner case were compared with a separate corresponding analysis of particles recovered following tissue digestion

Results:

- In situ analysis of miner tissues showed higher particle number densities than controls and densities were generally higher in PMF than non-PMF areas
- Particle counts were typically dominated by aluminum silicates with varying percentages of silica
- Compared to digestion results for the miner tissues, in situ results indicated lower density of particles (number per tissue volume), larger size, and a lower ratio of silica to total silicates-probably due to frequent particle clustering in situ

Conclusions:

- Automated FESEM-EDS analysis of lung dust is feasible in situ and could be applied to a larger set of mineral dust-exposed lung tissues to investigate specific histologic features of PMF and other dust-related occupational diseases

Zeder K, Marsh LM, Avian A, Brcic L, …, Kovacs G. Compartment-specific remodeling patterns in end-stage chronic obstructive pulmonary disease with and without severe pulmonary hypertension. J Heart Lung Transplant. 2024 Jul;43(7):1090-1101.

Background:

- In patients with end-stage chronic obstructive pulmonary disease (COPD), severe pulmonary hypertension (PH) is frequently associated with less severe airway obstruction as compared to mild or no PH
- However, the histologic correlate of this finding is not clear

Aim:

- To quantify remodeling of pulmonary arteries, airways, and parenchyma in random samples of explanted end-stage COPD lungs

Methods:

- The authors quantified remodeling of small pulmonary arteries, small airways, and the degree of emphysema (mean interseptal distance [MID]) with dedicated software
- As primary objective, they compared COPD patients with severe PH (SevPH-COPD) with age- and sex-matched MildPH-COPD. For comparison, they also investigated COPD lungs with no PH (NoPH-COPD), idiopathic PAH (IPAH), and healthy donors

Results:

- The authors included n = 17 SevPH-COPD (mPAP = 43 [39-45]mm Hg), n = 17 MildPH-COPD (mPAP = 28 [24-31]mm Hg), n = 5 NoPH-COPD (mPAP = 18 [16-19]mm Hg), n = 10 IPAH (mPAP = 72 [65-91]mm Hg), and n = 10 healthy donor lungs
- SevPH-COPD versus MildPH-COPD was characterized by better preserved forced vital capacity (51% vs 40% predicted, $p < 0.05$), less emphysema (MID 169 µm vs 279 µm, $p < 0.001$), and less PAS-positive and CD45-positive mucosa cells (15% vs 22%, $p = 0.063$% and 5% vs 7%, $p = 0.058$) suggesting less airway inflammation
- In COPD patients, intimal and medial thickening were strongly correlated with mPAP ($r = 0.676$, $p < 0.001$ and $r = 0.595$, $p < 0.001$)
- MID was negatively correlated with mPAP ($r = -0.556$, $p < 0.001$) and was highest in NoPH-COPD (mean 281 µm), suggesting that emphysema per se is not associated with PH

Conclusion:

- End-stage COPD with severe PH is characterized by pronounced pulmonary vascular remodeling, less inflammation of small airways, and less emphysema as compared to COPD with mild PH or no PH, suggesting that COPD with severe PH may represent a unique phenotype of COPD

EDITORIAL

Barberà JA, Peinado VI, Blanco I. Untangling severe pulmonary hypertension in chronic obstructive pulmonary disease. J Heart Lung Transplant. 2024 Jul;43(7):1102-1104.