

Pulmonary Pathology Journal Club

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Discussion Articles

Bunel V, et al. Pulmonary Arterial Histologic Lesions in Patients With COPD With Severe Pulmonary Hypertension. *Chest*. 2019 Jul;156(1):33-44.

OBJECTIVE:

- The development of pulmonary hypertension (PH) during the course of COPD is a well-known phenomenon, with the prevalence depending on the severity of airway obstruction.
- Cardiac index is a haemodynamic parameter that relates the cardiac output from left ventricle in one minute to body surface area (BSA), thus relating heart performance to the size of the individual. The unit of measurement is liters per minute per square meter (L/min/m²)
- When mean pulmonary pressure (mPAP) level at rest is ≥ 35 mm Hg or ≥ 25 mm Hg with low cardiac index, the term severe PH is used.
- For these patients, little is known on the underlying histologic lesions.
- The objective of this study was to describe these lesions.

METHODS:

- From the explants of patients undergoing lung transplantation, the authors compared retrospectively three groups of patients with COPD: severe PH-COPD (n = 10), moderate PH-COPD (mPAP between 25 and 34 mm Hg without low cardiac index) (n = 10), and no PH (mPAP < 25 mm Hg) (n = 10).
- Histologic analysis:
 - Wall thickness of muscular pulmonary arteries
 - Degree of microvascular muscularization (muscularization of pulmonary arterioles and venules on actin-stained slides)
 - Grade 0 (absence of muscle cells circumferentially),
 - Grade 1 (circumferential muscle cells, but on a single layer),
 - Grade 2 (circumferential and thick muscle cells with several layers), and
 - Grade 3 (presence of multiple layers of smooth muscle cells, and partial or complete obliteration of arterial lumen).
 - Degree of pulmonary capillary density
 - A ratio between the number of Erg-stained nuclei and the surface area.

RESULTS:

- No difference in the diameters of the medium-size arteries between the three groups was found.
- The microvessels were more muscularized in the severe PH group, as attested by a significantly higher remodeling score in this group than in the moderate PH group.
- The density of the capillary network was lower in the severe PH group than in the moderate PH group.
- The low level of Erg staining in the severe PH group is thought to be related to a loss of capillary network.

CONCLUSIONS:

- Patients with severe PH-COPD appear to have a specific histologic pattern, different from that observed in patients with COPD with moderate PH or without PH.

Dempsey TM, et al. Clinical Effectiveness of Antifibrotic Medications for Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2019 Jul 15;200(2):168-174.

OBJECTIVE:

- Since their approval, there has been no real-world or randomized trial evidence evaluating the effect of the antifibrotic medications pirfenidone and nintedanib on clinically important outcomes such as mortality and hospitalizations.
- The objective of this study was to evaluate the clinical effectiveness of the antifibrotic medications pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis.

METHODS:

- Using a large U.S. insurance database, the authors identified 8,098 patients with idiopathic pulmonary fibrosis between October 1, 2014 and March 1, 2018.
- A one-to-one propensity score-matched cohort was created to compare patients on antifibrotic medications (n = 1,255) no treatment (n = 1,255).
- The primary outcome was all-cause mortality.
- The secondary outcome was acute hospitalizations.
- Subgroup analyses were performed to evaluate mortality differences by drug.

RESULTS:

- The use of antifibrotic medications was associated with a decreased risk of all-cause mortality (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.62-0.98; P value = 0.034).
- However, this association was present only through the first 2 years of treatment.
- There was also a decrease in acute hospitalizations in the treated cohort (HR, 0.70; 95% CI, 0.61-0.80; P value <0.001).
- There was no significant difference in all-cause mortality between patients receiving pirfenidone and those on nintedanib (HR, 1.14; 95% CI, 0.79-1.65; P = 0.471).

CONCLUSIONS:

- Among patients with idiopathic pulmonary fibrosis, antifibrotic agents may be associated with a lower risk of all-cause mortality and hospitalization compared with no treatment.
- Future research should test the hypothesis that these treatments reduce early, but not long-term, mortality as demonstrated in this study.

Kadota K, et al. Limited Resection Is Associated With a Higher Risk of Locoregional Recurrence than Lobectomy in Stage I Lung Adenocarcinoma With Tumor Spread Through Air Spaces. Am J Surg Pathol. 2019 Aug;43(8):1033-1041.

OBJECTIVE:

- A growing number of independent studies have validated spread through air spaces (STAS) to be a predictor of worse prognosis in lung adenocarcinoma.
- The objective of this study was to investigate
 - The prognostic significance of STAS according to types of surgery and locations of recurrence and
 - The association between STAS and anti-anaplastic lymphoma kinase (ALK) expression.

METHODS:

- The authors analyzed a series of 735 Japanese patients with resected lung adenocarcinoma, which was restaged according to the 8th edition of TNM staging system.
- STAS was defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor.
- Tumors were classified according to the 2015 WHO lung tumor classification.
- Recurrence-free probability and overall survival were analyzed using the log-rank test and the Cox proportional hazards model.

RESULTS:

- STAS was observed in 247 patients.
- STAS was more frequently identified in ALK-positive tumors (P=0.020).
- STAS was an independent prognostic factor of a worse recurrence-free probability in all patients (hazard ratio [HR]=5.33, P<0.001) and in stage I patients (HR=6.87, P<0.001).
- STAS was an independent prognostic factor of a worse overall survival in all patients (HR=2.32, P<0.001) and in stage I patients (HR=2.85, P<0.001).
- In stage I patients with STAS, compared with lobectomy, limited resection was associated with a significantly higher risk of any recurrence (P=0.010) and locoregional recurrence (P=0.002).

CONCLUSION:

- The authors have demonstrated that, in lung adenocarcinoma with STAS, limited resection was associated with a significantly higher risk of recurrence (especially locoregional recurrence) than lobectomy was.

Kambouchner M, et al. Childhood pulmonary Langerhans cell histiocytosis: a comprehensive clinical-histopathological and BRAFV600E mutation study from the French national cohort. Hum Pathol. 2019 Jul;89:51-61.

OBJECTIVE:

- Childhood pulmonary Langerhans cell histiocytosis (PLCH) is a rare disease.
- Its pulmonary histopathology, according to comprehensive clinical-radiological findings and BRAFV600E mutation status, has not yet been thoroughly documented.

METHODS:

- From the 167 childhood PLCH cases entered in the French National Histiocytosis Registry (1983-2016), the authors retrieved lung biopsies from a consecutive retrospective series of 17 patients, diagnosed when they were 2 weeks to 16 years old (median, 9.4 years), and report the clinical and histopathological findings herein.

RESULTS:

- Histological analyses of biopsies (16 surgical and 1 postmortem) found the following features, alone or associated:
 - Langerhans cell (LC) nodules with cavitation (9/17),
 - Cysts (14/17),
 - Fibrotic scars (2/17),
 - Peribronchiolar topographic distribution of the lesions (10/17), and
 - “Accessory” changes, like stretch emphysema (7/17).
- Those characteristics closely resemble those describing adult PLCH.
- However, unusual findings observed were 2 large nodules and a diffuse interstitial LC infiltrate.
- BRAFV600E mutation was detected in 4 of 12 samples tested, notably in the 3 with unusual features.

CONCLUSIONS:

- In conclusion, childhood PLCH mostly shares the common histology features already described in adult PLCH, regardless of age.
- Because smoking is considered the major trigger in PLCH pathogenesis, the findings based on this series suggest other inducers of bronchiolar LC recruitment, especially in very young patients.

Kratz JR, et al. Incorporation of a Molecular Prognostic Classifier Improves Conventional Non-Small Cell Lung Cancer Staging. J Thorac Oncol. 2019 Jul;14(7):1223-1232.

OBJECTIVE:

- Despite adoption of molecular biomarkers in the management of NSCLC, the recently adopted eighth edition of the TNM staging system utilized only clinicopathologic characteristics and validated improvement in risk stratification of early-stage disease has remained elusive.
- The authors therefore evaluated the integration of a clinically validated molecular prognostic classifier into conventional staging.

METHODS:

- A novel staging system was developed by using data from 321 patients with NSCLC at the University of California, San Francisco.
- The TNMB (with the B denoting biology) system integrates a 14-gene molecular prognostic classifier into the 8th edition of the TNM staging system.
- The molecular prognostic classifier integrates expression levels of 11 cancer-related target genes against a background of three reference genes.
- The 11 cancer-related target genes included BCL2 associated athanogene gene [BAG1], BRCA1, DNA repair associated gene [BRCA1], DNA repair associated gene 2 [BRCA1], cell division cycle 6 gene [CDC6], cyclin dependent kinase 2 associated protein 1 gene [CDK2AP1], erb-b2 receptor tyrosine kinase 3 gene [ERBB3], fucosyltransferase 3 (Lewis blood group) gene [FUT3], interleukin 11 gene [IL11], LCK proto-oncogene, SRC family tyrosine kinase gene [LCK], Rho family GTPase 3 gene [RND3], SH3 domain binding glutamate rich protein gene [SH3BGR], and Wnt family member 3A gene [WNT3A].
- The TNMB staging system was subsequently validated in an independent, multicenter cohort of 1373 patients, and its implementation was compared with adoption of the seventh and eighth edition staging systems utilizing metrics of reclassification.

RESULTS:

- Compared with staging according to the eighth edition of the TNM system, the TNMB staging system enhanced the identification of high-risk patients, with a net reclassification improvement of 0.33 (95% confidence interval [CI]: 0.24-0.41).
- It better predicted differences in survival, with a relative integrated discrimination improvement of 22.1% (95% CI: 8.8%-35.3%), and it improved agreement between observed and predicted survival, with a decrease in the reclassification calibration statistic of from 39 to 21.

CONCLUSIONS:

- Incorporation of a molecular prognostic classifier significantly improved identification of high-risk patients and survival predictions compared with when conventional staging is used.
- The TNMB staging system may lead to improved survival of early-stage disease through more effective application of adjuvant therapy.

Neoplastic Articles

Bott MJ, et al. Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non-small cell lung cancer. J Thorac Cardiovasc Surg. 2019 Jul;158(1):269-276.

OBJECTIVE:

- The authors conducted a phase I trial of neoadjuvant nivolumab, a monoclon antibody to the programmed cell death protein 1 checkpoint receptor, in patients with resectable non-small cell lung cancer.
- They analyzed perioperative outcomes to assess the safety of this strategy.

METHODS:

- Patients with untreated stage I-IIIa non-small cell lung cancer underwent neoadjuvant therapy with 2 cycles of nivolumab (3 mg/kg), 4 and 2 weeks before resection.
- Patients underwent invasive mediastinal staging as indicated and post-treatment computed tomography.
- Primary study end points were safety and feasibility of neoadjuvant nivolumab followed by pulmonary resection.
- Data on additional surgical details were collected through chart review.

RESULTS:

- Of 22 patients enrolled, 20 underwent resection.
- One was unresectable; another had small cell histologic subtype.
- There were no delays to surgical resection.
- Median time from first treatment to surgery was 33 (range, 17-43) days.
- There were 15 lobectomies, 2 pneumonectomies, 1 bilobectomy, 1 sleeve lobectomy, and 1 wedge resection.
- Of 13 procedures attempted via a video-assisted thoracoscopic surgery or robotic approach, 7 (54%) required thoracotomy.
- Median operative time was 228 (range, 132-312) minutes; estimated blood loss was 100 (range, 25-1000) mL; length of hospital stay was 4 (range, 2-17) days.
- There was no operative mortality.
- Morbidity occurred in 10 of 20 patients (50%).
- The most common postoperative complication was atrial arrhythmia (6/20; 30%).
- Major pathologic response was identified in 9 of 20 patients (45%).

CONCLUSIONS:

- Neoadjuvant therapy with nivolumab was not associated with unexpected perioperative morbidity or mortality.
- More than half of the video-assisted thoracoscopic surgery/robotic cases were converted to thoracotomy, often because of hilar inflammation and fibrosis.

Chan AW, et al. The Landscape of Actionable Molecular Alterations in Immunomarker-Defined Large-Cell Carcinoma of the Lung. J Thorac Oncol. 2019 Jul;14(7):1213-1222.

OBJECTIVE:

- Patients with pulmonary large-cell carcinoma (LCC) have poor prognosis and limited treatment options.
- The identification of clinically actionable molecular alterations helps to guide personalized cancer treatment decisions.

METHODS:

- A consecutive cohort of 789 resected NSCLC cases were reviewed.
- Fifty-nine NSCLC cases lacking morphologic differentiation, accounting for 7.5% of all resected NSCLCs, were identified and further characterized by immunohistochemistry according to the 2015 WHO lung tumor classification.
- Molecular alterations were investigated by multiple technologies including target capture sequencing, immunohistochemistry, and fluorescence in situ hybridizations.

RESULTS:

- Of 59 NSCLC cases lacking morphologic differentiation, 20 (33.9%) were reclassified as adenocarcinoma (LCC-AD), 14 (23.7%) as squamous cell carcinoma (LCC-SqCC), and 25 (42.4%) as LCC-Null.
- Approximately 92% of LCC-Null, 95% of LCC-AD, and 86% of LCC-SqCC harbored clinically relevant alterations.
- Alterations characteristic of adenocarcinoma (EGFR, KRAS, ALK receptor tyrosine kinase [ALK], ROS1, and serine/threonine kinase 11 [STK11]) were detected in the LCC-AD subgroup but not in LCC-SqCC, whereas squamous-lineage alterations (phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit alpha [PIK3CA], SRY-box 2 [SOX2], fibroblast growth factor receptor 1 [FGFR1], and AKT1) were detected in the LCC-SqCC subgroup but not in the LCC-AD group.
- Although some LCC-Null tumors displayed a genetic profile similar to either adenocarcinoma or squamous-cell carcinoma, more than half of the LCC-Null group were completely devoid of recognizable lineage-specific genetic profiles. High programmed death ligand 1 expression and high frequency of cell cycle regulatory gene alterations were found in the LCC-Null group offering alternative options of targeted therapy.

CONCLUSIONS:

- This comprehensive molecular study provided further insight into the genetic architecture of LCC.
- The presence of clinically actionable alterations in a majority of the tumors allowed personalized treatment to emerge.

Dai J, et al. Optimal Lymph Node Examination and Adjuvant Chemotherapy for Stage I Lung Cancer. J Thorac Oncol. 2019 Jul;14(7):1277-1285.

OBJECTIVE:

- To determine the optimal number of lymph nodes (LNs) examined and the role of adjuvant chemotherapy in stage I lung cancer.

METHODS:

- The National Cancer Database was queried for surgically treated patients with pathologic stage I lung cancer between 2006 and 2014 (N = 65,438).
- The optimal LN numbers were determined in the multivariate Cox model and were further validated in the cohort with clinical stage I disease (N = 117,112) in terms of nodal upstaging and prognostic stratification.
- The role of adjuvant chemotherapy in patients with suboptimal staging (number of LNs examined was less than the optimum) was evaluated in each T stage.

RESULTS:

- The number of LNs examined correlated with tumor size ($p < 0.001$).
- There were increasing survival benefits with each additional LN examined-up to eight, nine, 10, and 11 nodes for patients with T1a, T1b, T1c, and T2a, respectively.
- Validation from the cohort with clinically staged disease showed that the threshold of eight to 11 LNs was an independent predictor of nodal upstaging (OR = 1.706, 95% confidence interval [CI] 1.608-1.779) and survival outcome (hazard ratio = 0.890, 95% CI: 0.865-0.916). After propensity matching, adjuvant chemotherapy was associated with improved survival in patients with stage T2a disease having suboptimal staging (hazard ratio = 0.841, 95% CI: 0.714-0.990), but not in patients with stage T1a to T1c disease.

CONCLUSION:

- LN evaluation was important for accurate staging and adequate treatment, and examinations of an increasing number of nodes for progressively higher T components (i.e., eight, nine, 10, and 11 nodes for T1a, T1b, T1c, and T2a tumors, respectively) seemed crucial to predict upstaging and survival outcomes.
- Adjuvant chemotherapy might be beneficial to patients with stage T2a disease who have suboptimal nodal staging.

Hofman V, et al. Multicenter Evaluation of a Novel ROS1 Immunohistochemistry Assay (SP384) for Detection of ROS1 Rearrangements in a Large Cohort of Lung Adenocarcinoma Patients. J Thorac Oncol. 2019 Jul;14(7):1204-1212.

OBJECTIVE:

- The detection of a ROS1 rearrangement in advanced and metastatic lung adenocarcinoma (LUAD) led to a targeted treatment with tyrosine kinase inhibitors with favorable progression-free survival and overall survival of the patients.
- Thus, it is mandatory to screen for the ROS1 rearrangement in all these patients.
- ROS1 rearrangements can be detected using break-apart fluorescence in situ hybridization (FISH), which is the gold standard; however, ROS1 immunohistochemistry (IHC) can be used as a screening test because it is widely available, easy and rapid to perform, and cost-effective.

METHODS:

- The authors evaluated the diagnostic accuracy and interpathologist agreement of two anti-ROS1 IHC clones, SP384 (Ventana, Tucson, Arizona) and D4D6 (Cell Signaling, Danvers, Massachusetts), in a training cohort of 51 positive ROS1 FISH LUAD cases, and then in a large validation cohort of 714 consecutive cases of LUAD from six routine molecular pathology platforms.

RESULTS:

- In the two cohorts, the SP384 and D4D6 clones show variable sensitivity and specificity rates on the basis of two cutoff points greater than or equal to 1+ (all % tumor cells) and greater than or equal to 2+ (>30% stained tumor cells).
- In the validation cohort, the D4D6 yielded the best accuracy for the presence of a ROS1 rearrangement by FISH. Interpathologist agreement was moderate to good (interclass correlation 0.722-0.874) for the D4D6 clone and good to excellent (interclass correlation: 0.830-0.956) for the SP384 clone.

CONCLUSIONS:

- ROS1 IHC is an effective screening tool for the presence of ROS1 rearrangements.
- However, users must be acutely aware of the variable diagnostic performance of different anti-ROS1 antibodies before implementation into routine

Kondoh C, et al. Anaplastic lymphoma kinase expression in small-cell lung cancer. *Histopathology*. 2019 Jul;75(1):20-28.

OBJECTIVE:

- Anaplastic lymphoma kinase (ALK) immunohistochemistry has shifted from being a screening tool to being a sole determinant for ALK-targeted therapy.
- Recent articles have referred to small-cell lung cancer (SCLC) transformation as a resistance mechanism after ALK inhibitor treatments, but few reports have addressed ALK expression in treatment-naïve SCLC in a comprehensive manner.
- Therefore, we examined ALK expression and the mechanisms in treatment-naïve SCLCs.

METHODS AND RESULTS:

- The authors examined ALK expression in a consecutive series of SCLC tumours, and the expression mechanism was analysed regarding gene rearrangement, copy number changes, and point mutations.
- The authors also examined whether SCLC with ALK expression can be suppressed by crizotinib treatment in vitro. Immunohistochemical results revealed that ALK was expressed in 16 of 142 (11.3%) SCLCs.
- The expression was focal and less intense, which is in contrast to strong and uniform expression in adenocarcinoma with ALK rearrangement.
- Two combined SCLCs showed a positive reaction restricted to the SCLC component.
- None of the known genetic alterations, including rearrangement, amplification, copy number gain, or point mutations, were associated with ALK expression.
- A SCLC cell line, SKLC2, which expressed ALK without known genetic alterations, was not inhibited by a practically achievable serum concentration of crizotinib.

CONCLUSIONS:

- Anaplastic lymphoma kinase immunohistochemistry for treatment-naïve SCLCs should not be used as a predictive biomarker for ALK inhibitor therapy, because the positive reactions were due to intrinsic expression of normal ALK transcript.

Muppa P, et al (including Aubry MC). Immune Cell Infiltration May Be a Key Determinant of Long-Term Survival in Small Cell Lung Cancer. J Thorac Oncol. 2019 Jul;14(7):1286-1295.

OBJECTIVE:

- Although most patients with SCLC die within a few months of diagnosis, a subgroup of patients survive for many years. Factors determining long-term survivorship remain largely unknown.
- The authors present the first comprehensive comparative genomic and tumor microenvironment analyses of SCLC between patients with long-term survivorship and patients with the expected survivorship.

METHODS:

- The authors compared surgically resected tumors of 23 long-term SCLC survivors (survival >4 years) and 18 SCLC survivors with the expected survival time (survival ≤2 years).
- There were no significant differences in clinical variables, including TNM staging and curative- versus non-curative-intent surgery between the groups.
- Gene expression profiling was performed by using microarrays, and tumor microenvironment analyses were performed by immunohistochemistry of prominent immune-related markers.

RESULTS:

- Immune-related genes and pathways represented the majority of the differentially overexpressed genes in long-term survivorship compared with in expected survivorship.
- The differences in the immunological tumor microenvironment were confirmed by quantitative immunostaining. Increased numbers of tumor-infiltrating and associated lymphocytes were present throughout tumors of long-term survivors of SCLC.
- Several differentiating patterns of enhanced antitumor immunity were identified.
- Although some areas of the tumors of long-term survivors of SCLC also harbored higher numbers of suppressive immune cells (monocytes, regulatory lymphocytes, and macrophages), the ratios of these suppressive cells to CD3-positive lymphocytes were generally lower in the tumors of long-term survivors of SCLC, indicating a less tumor-suppressive microenvironment.

CONCLUSIONS:

- Our data demonstrate that long-term survivorship of patients with SCLC is strongly influenced by the presence of the immune cells in the tumor microenvironment. Characterization of the antitumor immune responses may identify opportunities for individualized immunotherapies for SCLC.

Penault-Llorca F, et al. Testing algorithm for identification of patients with TRK fusion cancer. J Clin Pathol. 2019 Jul;72(7):460-467.

- The neurotrophic tyrosine receptor kinase (NTRK) gene family encodes three tropomyosin receptor kinases (TRKA, TRKB, TRKC) that contribute to central and peripheral nervous system development and function.
- NTRK gene fusions are oncogenic drivers of various adult and paediatric tumours.
- Several methods have been used to detect NTRK gene fusions including immunohistochemistry, fluorescence in situ hybridisation, reverse transcriptase polymerase chain reaction, and DNA- or RNA-based next-generation sequencing. For patients with TRK fusion cancer, TRK inhibition is an important therapeutic target.
- Following the FDA approval of the selective TRK inhibitor, larotrectinib, as well as the ongoing development of multi-kinase inhibitors with activity in TRK fusion cancer, testing for NTRK gene fusions should become part of the standard diagnostic process.
- In this review the authors discuss the biology of NTRK gene fusions, and they present a testing algorithm to aid detection of these gene fusions in clinical practice and guide treatment decisions.

Savic S, et al. PD-L1 testing of non-small cell lung cancer using different antibodies and platforms: a Swiss cross-validation study. *Virchows Arch.* 2019 Jul;475(1):67-76.

- With the approval of pembrolizumab for first- and second-line treatment of PD-L1+ non-small cell lung cancer (NSCLC), PD-L1 testing by immunohistochemistry (IHC) has become a necessity.
- However, the DAKO autostainer ASL48 for the FDA approved DAKO 22C3 pharmDx assay is not broadly available in Switzerland and other parts of Europe.
- The primary goal of this study was to cross-validate the 22C3 anti-PD-L1 antibody on Benchmark Ultra (VBMU) and Leica Bond (LBO) immunostainers.
- IHC protocols were developed for 22C3 on both platforms with the 22C3phDx using ASL48 as reference.
- A tissue microarray (TMA) was constructed from 23 NSCLC specimens with a range of PD-L1 staining results.
- Empty TMA sections and the 22C3 antibody were distributed to 16 participants for staining on VBMU (8 centers) and/or LBO (12 centers) using the centrally developed protocols.
- Additionally the performance of the Ventana SP263 assay was tested in five centers. IHC scoring was performed centrally.
- Categorical PD-L1 staining (0-49% vs. 50-100%) did not significantly differ between centers using VBMU, whereas data from LBO were highly variable ($p < 0.001$). The SP263 assay was well concordant with 22C3 on VBMU and with 22C3 pharmDx. PD-L1 IHC using a standardized 22C3 protocol on VBMU provides satisfactory results in most centers.
- The SP263 assay is confirmed as a valid alternative to 22C3 pharmDx. 22C3 PD-L1 IHC on LBO shows major staining variability between centers, highlighting the need for local validation and adjustment of protocols.

Nonneoplastic Articles

Al-Mutairy EA, et al. An atypical pulmonary fibrosis is associated with co-inheritance of mutations in the calcium binding protein genes S100A3 and S100A13. Eur Respir J. 2019 Jul 18;54(1).

OBJECTIVE:

- Pulmonary fibrosis is one of the leading indications for lung transplantation.
- The disease, which is of unknown aetiology, can be progressive, resulting in distortion of the extracellular matrix (ECM), inflammation, fibrosis and eventual death.

METHODS:

- 13 patients born to consanguineous parents from two unrelated families presenting with interstitial lung disease were clinically investigated.
- Nine patients developed respiratory failure and subsequently died.
- Molecular genetic investigations were performed on patients' whole blood or archived tissues, and cell biological investigations were performed on patient-derived fibroblasts.

RESULTS:

- The combination of a unique pattern of early-onset lung fibrosis (at 12-15 years old) with distinctive radiological findings, including
 - Traction bronchiectasis,
 - Intralobular septal thickening,
 - Shrinkage of the secondary pulmonary lobules mainly around the bronchovascular bundles and
 - Early type 2 respiratory failure (elevated blood carbon dioxide levels), represents a novel clinical subtype of familial pulmonary fibrosis.
- Molecular genetic investigation of families revealed a hypomorphic variant in S100A3 and a novel truncating mutation in S100A13, both segregating with the disease in an autosomal recessive manner.
- Family members that were either heterozygous carriers or wild-type normal for both variants were unaffected.
- Analysis of patient-derived fibroblasts demonstrated significantly reduced S100A3 and S100A13 expression.
- Further analysis demonstrated aberrant intracellular calcium homeostasis, mitochondrial dysregulation and differential expression of ECM components.

CONCLUSION:

- The data demonstrate that digenic inheritance of mutations in S100A3 and S100A13 underlie the pathophysiology of pulmonary fibrosis associated with a significant reduction of both proteins, which suggests a calcium-dependent therapeutic approach for management of the disease.

Moore C, et al. Resequencing Study Confirms That Host Defense and Cell Senescence Gene Variants Contribute to the Risk of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2019 Jul 15;200(2):199-208.

OBJECTIVE:

- Several common and rare genetic variants have been associated with idiopathic pulmonary fibrosis, a progressive fibrotic condition that is localized to the lung.
- The objective of this study was to develop an integrated understanding of the rare and common variants located in multiple loci that have been reported to contribute to the risk of disease.

METHODS:

- The authors performed deep targeted resequencing (3.69 Mb of DNA) in cases (n = 3,624) and control subjects (n = 4,442) across genes and regions previously associated with disease.
- The authors tested for associations between disease and
 - Individual common variants via logistic regression and
 - Groups of rare variants via sequence kernel association tests.

RESULTS:

- Statistically significant common variant association signals occurred in all 10 of the regions chosen based on genome-wide association studies.
- The strongest risk variant is the MUC5B promoter variant rs35705950, with an odds ratio of 5.45 (95% confidence interval, 4.91-6.06) for one copy of the risk allele and 18.68 (95% confidence interval, 13.34-26.17) for two copies of the risk allele ($P = 9.60 \times 10^{-295}$).
- In addition to identifying for the first time that rare variation in FAM13A is associated with disease, The authors confirmed the role of rare variation in the TERT and RTEL1 gene regions in the risk of IPF, and found that the FAM13A and TERT regions have independent common and rare variant signals.

CONCLUSIONS:

- A limited number of common and rare variants contribute to the risk of idiopathic pulmonary fibrosis in each of the resequencing regions, and these genetic variants focus on biological mechanisms of host defense and cell senescence.

Roberts DJ, et al. Comparison of Minimally Invasive Tissue Sampling With Conventional Autopsy to Detect Pulmonary Pathology Among Respiratory Deaths in a Resource-Limited Setting. Am J Clin Pathol. 2019 Jun 5;152(1):36-49.

OBJECTIVES:

- The authors compared minimally invasive tissue sampling (MITS) with conventional autopsy (CA) in detection of respiratory pathology/pathogens among Kenyan children younger than 5 years who were hospitalized with respiratory disease and died during hospitalization.

METHODS:

- Pulmonary MITS guided by anatomic landmarks was followed by CA.
- Lung tissues were triaged for histology and molecular testing using TaqMan Array Cards (TACs).
- MITS and CA results were compared for adequacy and concordance.

RESULTS:

- Adequate pulmonary tissue was obtained by MITS from 54 (84%) of 64 respiratory deaths.
- Comparing MITS to CA, full histologic diagnostic concordance was present in 23 (36%) cases and partial concordance in 19 (30%), an overall 66% concordance rate.
- Pathogen detection using TACs had full concordance in 27 (42%) and partial concordance in 24 (38%) cases investigated, an overall 80% concordance rate.

CONCLUSIONS:

- MITS is a viable alternative to CA in respiratory deaths in resource-limited settings, especially if combined with ancillary tests to optimize diagnostic accuracy.

Yousem SA, et al. Pulmonary pathologic alterations associated with biopsy inserted hydrogel plugs. Hum Pathol. 2019 Jul;89:40-43.

- The prevention of pneumothorax after percutaneous lung biopsy is a major patient safety concern.
- The insertion of hydrogel plugs into biopsy sites to mitigate this complication is a new intervention.
- The histology of the plug has not been previously reported, and in this study the histologic reaction is reported in 13 cases.
- The hydrogel plug forms a spherical basophilic matrix pool with an adjacent foreign body giant cell reaction and patchy eosinophilia.
- No extension to the pleural surface is present.
- The potential diagnostic errors related to the presence of the plug are discussed.

Reviews and Letters

Ahadi MS, Gill AJ. SMARCA4 Loss Is Very Rare in Thoracic Mesothelioma. Am J Surg Pathol. 2019 Aug;43(8):1154-1155.

Culver DA, et al. Patient Registries in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2019 Jul 15;200(2):160-167.

- Over the past decade, several large registries of patients with idiopathic pulmonary fibrosis (IPF) have been established.
- These registries are collecting a wealth of longitudinal data on thousands of patients with this rare disease.
- The data collected in these registries will be complementary to data collected in clinical trials because the patient populations studied in registries have a broader spectrum of disease severity and comorbidities and can be followed for a longer period of time.
- Maintaining the quality and completeness of registry databases presents administrative and resourcing challenges, but it is important to ensuring the robustness of the analyses.
- Data from patient registries have already helped improve understanding of the clinical characteristics of patients with IPF, the impact that the disease has on their quality of life and survival, and current practices in diagnosis and management. In the future, analyses of biospecimens linked to detailed patient profiles will provide the opportunity to identify biomarkers linked to disease progression, facilitating the development of precision medicine approaches for prognosis and therapy in patients with IPF.

Hamasaki M, et al. Cytoplasmic MTAP expression loss detected by immunohistochemistry correlates with 9p21 homozygous deletion detected by FISH in pleural effusion cytology of mesothelioma. Histopathology. 2019 Jul;75(1):153-155.

Hamza A, Weissferdt A. Non-Neoplastic and Benign Tumoral Lesions of the Thymic Gland: A Review and Update. Adv Anat Pathol. 2019 Jul;26(4):257-269.

- The thymus is a dynamic organ that undergoes changes throughout life and can demonstrate a myriad of pathologic alterations.
- A number of benign entities of the thymus prove to be diagnostic dilemmas owing to their resemblance and association with true thymic tumors.
- These are usually discovered incidentally on routine imaging and most patients are either asymptomatic or present with signs and symptoms of compression of adjacent organs. The radiologic appearance of these lesions varies from simple cysts to complex masses that are suspicious for malignancy.

- The diagnosis is usually made purely on morphologic grounds, however, immunohistochemical stains can help rule out possible differential diagnoses.
- Surgical removal is usually curative in these lesions and recurrences are rare.
- The prognosis is excellent, however, some of these lesions may be associated with myasthenia gravis and/or thymomas.
- In this review, we describe non-neoplastic lesions and benign tumoral lesions of the thymus, with emphasis on the clinical, radiologic, and pathologic features.
- The differential diagnosis of each entity is also discussed.

Lindholm KE, de Groot P, Moran CA. Fibrosing/Sclerosing Lesions of the Mediastinum: A Review. *Adv Anat Pathol.* 2019 Jul;26(4):235-240.

- Fibrosing lesions of the mediastinum represent a small but challenging group of lesions that range in etiology from infectious to idiopathic to neoplastic.
- The diagnosis of such lesions becomes more challenging in the setting of mediastinoscopic biopsies.
- In addition, over the years, there has been further accumulation of knowledge of the clinical aspects of these lesions that needs to be incorporated into their evaluation.
- Therefore, it is essential that in the general evaluation of these fibrosing processes, one not only carefully examines the histopathologic features of the lesion, that of a fibroinflammatory process with the appropriate histochemical and immunohistochemical studies, but also carefully evaluates the clinical presentation and imaging findings.
- Needless to say, as will be illustrated in this review, determining a definitive unequivocal diagnosis on a small mediastinoscopic biopsy may be difficult, and often one needs to provide guidance on the perspective of the histologic features present.
- In some cases, mainly tumoral conditions with extensive fibrosis, a conclusive diagnosis can be made; however, it is those cases in which the extensive fibrosis is the only histopathologic feature where more appropriate guidance is required.
- While this review will focus more on the non-neoplastic fibroinflammatory lesions of the mediastinum, within the discussion of differential diagnoses, we will discuss some neoplastic conditions that commonly show extensive fibrosing features.

Stearman RS, et al. Familial Pulmonary Fibrosis and Hermansky-Pudlak Syndrome Rare Missense Mutations in Context. *Am J Respir Crit Care Med.* 2019 Jul 15;200(2):253-256.

van den Berge M, et al. Differential lung tissue gene expression in males and females: implications for the susceptibility to develop COPD. *Eur Respir J.* 2019 Jul 18;54(1).