Journal Club
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Articles for Discussion

1. Syndrome of combined pulmonary fibrosis and emphysema: an official ATS/ERS/JRS/ALAT research statement. Cottin V, Selman M, Inoue Y, Wong AW, Corte TJ, Flaherty KR, Han MK, Jacob J, Johannson KA, Kitaichi M, Lee JS, Agusti A, Antoniou KM, Binachi P, Caro F, Florenzano M, Galvin L, Iwasawa T, Martinez FJ, Morgan RL, Myers JL, Nicholson AG, Occhipinti M, Poletti V, Salisbury ML, Sin DD, Sverzellati N, Tonia T, Valenzuela C, Ryerson CJ, Wells AU; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociacion Latinoamericana de Torax. Am J Respir Crit Care Med. 2022;206(4)e7-e41.

Background: The presence of emphysema in patients with fibrotic interstitial lung disease has been referred to as "combined pulmonary fibrosis and emphysema (CPFE)." Although CPFE has been around since 2005, there is no consensus regarding diagnostic criteria. The authors suggest that the lack of consensus has limited research. The objectives of the task force were to describe the features of CPFE through a review of the literature, to provide a consensus definition with diagnostic criteria, and to argue that CPFE represents a syndrome.

Methods: Review of all original research articles which included patients with both pulmonary fibrosis and emphysema dating back to January 1, 2000, yielding a total of 96 articles.

Results: The authors give a comprehensive description of the reported features of CPFE. Patients have mean age of 65-70 (similar to IPF and COPD) with a 73-100% male predominance. Two most common comorbidities are lung cancer and pulmonary hypertension. Epidemiological data are seen in table 2; the reported prevalence of CPFE is 8-67% in patients with IPF and 26-54% in patients with idiopathic interstitial pneumonias. The prevalence in the general population is unknown. Etiological factors can be seen in table 3. Almost all patients with CPFE report a history of smoking; with a notable exception being patients with CTD or fibrotic HP. CPFE can occur in nonsmokers, especially in CTD. For example, in a study of 116 never-smokers with RA-associated ILD, emphysema was present on HRCT in 27%. Emphysema reportedly occurs in 7-23% of patients with fibrotic HP.
Lung function characteristics are in table 4. Two important takeaways from this are 1) patients have relatively preserved airflow rates and lung volumes but severely limited DLco and transfer coefficient (perhaps masking the diagnosis) and 2) change in FVC, which is commonly used to monitor IPF progression, is not a reliable indicator of disease in patients with CPFE (which is an argument for why CPFE needs to be identified as a syndrome). No optimal parameter has been validated to monitor progression.
CT appearances vary (figures 1-9). Since many patients with CPFE have UIP pattern on HRCT, there is a challenge distinguishing admixed emphysema from honeycomb cysts. Admixed emphysema and fibrosis can also create an imaging pattern of thick-walled cystic lesions, thought to represent expansion of the emphysema by contracting fibrosing lung. The authors have proposed calling this "traction emphysema" given the similar mechanism as traction bronchiectasis. It is unknown whether thick-walled cystic lesions are specific for CPFE.
Similar to the radiology, the pathologic patterns of fibrosis seen in patients with CPFE are heterogenous. As the coexistence of emphysema and fibrotic ILD can be seen in biopsies, it is suggested that pathologists need to document the presence of emphysema in addition to the fibrotic ILD. UIP is the most commonly reported pattern of pulmonary fibrosis in patients with CPFE; other less commonly described patterns include fibrotic NSIP and DIP. Oddly, fibrotic HP is not mentioned in the pathology section. It's noted that CPFE cannot be diagnosed based on histopathology alone, but that supportive features include a combination of emphysema and a pattern of fibrosis other than SRIF or LCH. The authors state that SRIF has not been established as a cause of CPFE. However, the authors purport that a histologic feature unique to UIP in CPFE is the presence of thick-

walled cysts resulting from the combination of SRIF and emphysema (figure 13). The authors also later state in the paper that SRIF or AEF may represent a unique histopathologic pattern of CPFE.
The authors speculate that the poor prognosis of CPFE may relate to the presence of pulmonary hypertension; they note that vascular changes are more extensive in CPFE and IPF than in emphysema alone.
The proposed definitions of CPFE can be seen in table 11. The research definition is entirely based on HRCT confirming the presence of emphysema involving at least 5% of the lung by volume and lung fibrosis of any subtype. The classification criteria are intended to have clinical relevance and they add the requirement of emphysema involving at least 15% of the total lung volume in addition to criteria based on lung function and/or the presence of pulmonary hypertension.
Discussion: The authors favor that CPFE be considered a syndrome based on discrete clinical features, pathogenetic considerations including the clustering of pulmonary fibrosis and emphysema, and to facilitate further research.
Comment: From a clinical perspective, there may be some utility in defining this syndrome for diagnostic and management purposes but I'm skeptical that this line of research will uncover anything insightful about pathogenesis related to fibrosis and/or emphysema given the inclusion of all cases of fibrotic ILD. It's likely useful for pathologists to know what the term CPFE means for the purpose of communication with clinicians but I'm not sure there is anything in this statement directly applicable to a pathology practice.

2. MIXTURE of human expertise and deep learning: developing an explainable model for predicting pathological diagnosis and survival in patients with interstitial lung disease. Uegami W, Bychkov A, Ozasa M, Uehara K, Kataoka K, Johkoh T, Kondoh Y, Sakanashi H, Fukuoka J. Mod Pathol. 2022;35:1083-1091.

   Background: The interobserver reproducibility of ILDs diagnosis is low. The authors propose an original method named "MIXTURE" (huMan-In-the-loop eXplainable artificial intelligence Through the Use of REcurrent training), to develop deep learning models for extracting pathological findings based on an expert pathologist's perspective, which can predict the pathological diagnosis and survival in patients with ILDs.

   Methods: The procedure of MIXTURE consisted of different steps (see Figure 2, and below) in a single center study. All included cases were diagnosed by one expert pulmonary pathologist and reviewed in multidisciplinary discussion (MDD) with clinicians and radiologists. There were 3 sets of cases.

   1- Elementary feature extraction (ElEx): The authors had a principal pretraining set of 53 cases – 151 whole slide images (WSIs) from patients with IPF/UIP, RA-ILD, SSc-ILD, DAD, PPFE, OP, and sarcoid. The WSIs were tiled into 280×280-pixel images at 3 different magnifications (2.5x, 5x, 20x). The tiles were used by a convolutional neural network (CNN) to automatically extract morphological features without the need of a human (self-supervised learning).
   2- Clustering of Tiles: The authors used an algorithm that clustered similar tiles. 120 tiles were randomly selected from each cluster and a montage was created (see Figure S1).
   3- Cluster integration: Two pathologists reviewed the montages and grouped them by pathologically synonymous findings into separate classes. The morphological classes varied based on the magnification (see Figure S2).
   4- Supplemental pretraining set: As clusters for fibroblastic foci were not created with the initial set, the authors selected WSIs from a supplemental pretraining set (15 cases of UIP with prominent fibroblastic foci) to obtain clusters of "purer findings" at a 20x magnification only.
   5- Transfer learning: The pathologist's integrated classes were used to create a CNN classifier
   6- Tile classification and mapping: The authors used the classifier to categorize tiles as from a "utility set" of 180 consecutive surgical lung bx cases for which follow-up data were available. The results were mapped (see Figures 4 and S3), compared with the original WSIs by two pathologists. Findings were aggregated, and the number of tiles predicted as each finding was totaled.
   7- UIP prediction: In the utility set, the authors defined UIP as cases diagnosed with "definite UIP" or "probable UIP" in the pathology report and non-UIP as all other cases according to the international

2011 guidelines. They separated the set in a training set of 126 cases and a validation set of 54 cases. They developed 2 models (random forest and support vector machine) to predict UIP/non-UIP diagnosis based on the frequency of each finding. The performance was evaluated with ROC curves, and they tested if the models could predict the overall survival by using the log-rank test.

8- Comparison of non-integrated model and MIXTURE: The authors created a model without human derived cluster integration, and they compared it with MIXTURE.
9- Factors associated with survival: The authors examined the histological risk factors for overall survival in a cox proportional hazard model.

Results: Using these extracted findings, the model was able to predict the diagnosis of UIP at 5x with high accuracy (AUC 0.90 in validation set and AUC 0.86 in test set). The accuracy for 25x models was also high, but lower for 2.5x. The most important findings for prediction in the model were cellular interstitial pneumonia/NSIP and acellular fibrosis (see Table 3). There was marginal improvement of the model when all the magnifications were used (see Table 2, Figure 5). The cases predicted to be UIP had a poorer prognosis (5-year overall survival [OS]: 55.4%) than the non-UIP ones (OS: 95.2%) (See Figure 5c), suggesting that the model effectively predict the UIP as a poor prognostic factor. The high accuracy could not be achieved in the non-integrated model, which had a significantly lower performance ($p = 0.0002$) compared to MIXTURE. The Cox proportional hazards model for each microscopic finding and prognosis pointed out fibroblastic foci, dense fibrosis, elastosis, and lymphocyte aggregation as independent risk factors.

Discussion: MIXTURE is pathologist-centered as it leaves room for the expert's judgment in model creation. The model alone does not form pathologically meaningful clusters. Clustering reduces the burden of labeling each individual tile and makes it easier to maintain the consistency of the training data (pathological findings occur in a spectrum). The authors propose MIXTURE may serve as a model approach to different diseases evaluated by medical imaging, including pathology and radiology.

Comment: The method to integrate the clusters depends on the insights of the experts, which may affect the final model. The model does not include clinical or radiological data into account; therefore, it only identifies patterns based on histopathological information alone. This is far from the real-life diagnoses of ILDs. The Cox proportional hazard models did not correct for covariates that may affect the survival (demographics, number og slides, etc). The spatial relationship of each finding was not considered. External validation is needed. UIP with acute exacerbation (only one case) with low score

3. Integrating clinical probability into the diagnostic approach to idiopathic pulmonary fibrosis: an international working group perspective. Cottin V, Tomassetti S, Valenzuela C, Walsh SLF, Antoniou KM, Bonella F, Brown KK, Collard HR, Corte TJ, Flaherty KR, Johannson KA, Kolb M, Kreuter M, Inoue Y, Jenkins RG, Lee JS, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nathan SD, Poletti V, Quadrelli S, Raghu G, Rajan SK, Ravaglia C, Remy-Jardin M, Renzoni E, Richeldi LK, Spagnolo P, Troy L, Wijsenbeek M, Wilson KC, Wuyts W, Wells AU, Ryerson CJ. Am J Respir Crit Care Med. 2022;206(3)247-259.

Background: The authors propose to fill a gap they identify in the diagnosis of IPF. Guidelines exist for the probable likelihood of a diagnosis of IPF based on HRCT and pathology, but none exist for the clinical features that help differentiate IPF from other fibrosing ILDs (fILD).

Methods: The committee identified factors that influence the likelihood of a diagnosis of IPF. These were categorized as a pretest clinical probability of IPF into high (70-100%), intermediate (30-70%), or low (0-30%). After integration of HRCT and pathology, post-test probability of a diagnosis was categorized as definite (90-100%), high confidence (70-89%), low confidence (51-69%), or low (0-50%) probability of IPF. "Probabilities are subjective estimations based on the inference of data integrated into the dynamic scenario of the multi-disciplinary discussion of cases". A Bayesian framework was utilized i.e., updating diagnostic confidence as new information became available.

The proposed factors (see Figure 2) that increase the likelihood of a diagnosis of IPF include male sex, age greater than 60 yrs, Ex- or current smoking history, velcro crackles, clubbing with an absence of significant antigens associated with HP, family aggregation of fibrotic ILD, restrictive physiology and chronic onset, Idiopathic no plausible differential.

Additional information that may "modulate the estimated probability of IPF" include BAL, genetic tests, and the immediate classifier. The final result was based on voting by committee members in addition to several discussions.

Results: *proposed framework*: the authors propose beginning with clinical likelihood of IPF (Figure 2), list and estimating the diagnostic likelihood of IPF as high, intermediate, or low. Then integrating the radiologic assessment into the four patterns: definite, probable, indeterminate, or patterns suggesting an alternative diagnosis (see Figure 3). Figure 4 lists additional factors which would increase the likelihood of an IPF diagnosis if available including progression over months or years despite treatment, BAL less than 15%, the presence of single-nucleotide polymorphisms (e.g., MUC5B), pathogenic variants related to surfactant metabolism and telomere maintenance and syndromic ILD (e.g., short telomere syndrome), *a molecular classifier that is positive for UIP* and an absence of a short-term response to glucocorticoids or immunosuppression. Finding: pathology assessment is considered. Glucocorticoid guidelines if there is a definite or high confidence provisional diagnosis of IPF no biopsy is warranted. See Figure 5 for the remaining approach.

The authors then present three potential case examples.

Discussion: *The authors comment that the clinical assessment of probability of IPF as proposed does not substitute for an expert clinical gestalt* but is a way of attempting to generalize how committee members make the diagnosis and may help delineate IPF in a more reproducible fashion. They also hope that this approach may help those less familiar with this diagnosis. Future work involves developing clinical scores which could include scores for radiology and pathology.

Limitations, in terms of availability, is always a problem and not all likelihood ratios are known for the tests considered, probabilities are necessarily coarse estimates.

Comment: I found it interesting that this group of experts concluded that their overall gestalt might still be better than this approach! On the other hand, this may be helpful for clinicians who do not see these patients on a regular basis.

4. Clear cell stromal tumour of the lung with YAP1::TFE3 fusion: four cases including a case with highly aggressive clinical course. Dehner CA, Sadegh D, Boulos F, Messias N, Wang WL, Demicco EG, Chrisinger JSA. Histopathology. 2022;81:239-245.

Background: Clear cell stromal tumour of the lung (CCST-L) was recently recognized and expresses TFE3 and harbors a YAP::TF3 fusion. Initial reports suggested this might be a benign tumour but there is one report of this tumour showing distant metastases. The authors wanted to present additional cases.

Methods: Files at Wash U, MD Anderson and Mount Sinai (Toronto) were searched for cases of CCST-L or tumors with YAP1::TFE3 fusions. Available slides including immunohistochemistry were re-reviewed and clinicopathologic features recorded.

Results: Four tumors were identified, all in women age range 24-69, median 61 years.

Median tumour size 1-9.5cm, median 4.4.

One tumour was multifocal.

Case 1: bilateral multiple PET-positive enhancing lesions, confined to lung. Unresectable treated chemotherapy, patient died of disease at 7 months; case 2 alive at 43 months; cases 3 and 4 no follow-up.

Case 2: 10-cm mass identified following hysterectomy.

Case 4: patient had a remote hysterectomy.

Pathology: tumors composed of epithelioid to spindled cells were eosinophilic to clear cytoplasm growing in sheets, vague nests and short fascicles.

Table 2. Pathological, immunohistochemical and molecular features

Case	Initial diagnosis	Nuclear atypia	Mitotic count (/2 mm^2)	Necrosis	TFE3 expression	YAP1::TFE3
1	Malignant spindle cell neoplasm	Present	6	Present	Diffuse	Exon4::Exon7
2	Synovial sarcoma	Absent	< 1	Absent	Diffuse	Exon4::Exon7
3	Favour PEComa	Focal	< 1	Absent	Diffuse	Exon4::Exon7
4	PEComa	Absent	2	Absent	Diffuse	Exon4::Exon7

See Figures 1-4 for pathology

Molecular findings: RNA sequencing showed the YAP1::TFE3 fusion in all four cases. FISH from case 2 identified an abnormal deletion of the 5′TFE3 gene while case 3 showed no MDM2 amplification.

Discussion: This brings the total number of cases of CCST-L reported to 17 among which 3 patients had aggressive disease.

CCST-L with YAP1::TFE3 fusion is a growing family of tumors associated with TFE3 expression and YAP1::TFE3 fusions including epithelioid haemangioendothelioma and cutaneous low-grade fibromyxoid neoplasm.

Differential includes metastases and other low-grade pulmonary neoplasms including a PEComa which can also express TFE3 but not myelomelanocytic markers. It should be noted, however, that their case 4 had very rare HMB45 and MART1 positive cells with weak SMA [reactivity].

Comment: Another tumour to keep in mind.

Non-Neoplastic Notations

1. The proteomic profile of interstitial lung abnormalities. Axelsson GT, Gudmundsson G, Pratte KA, Aspelund T, Putman RK, Sanders JL, Gudmundsson EF, Hatabu H, Gudmundsdottir V, Gudjonsson A, Hino T, Hida T, Hobbs BD, Cho MH, Silverman EK, Bowler RP, Launer LJ, Jennings LL, Hunninghake GM, Emilsson V, Gudnason V. Virchows Archiv. 2021;479:827-833.

Background: Interstitial lung abnormalities (ILAs) are radiologic changes which may represent the presence of early interstitial lung disease. Knowledge of biomarker abnormalities in patients with ILAs may allow early intervention if found to be sufficiently robust. This study sought to uncover blood proteins associated with ILAs using a large-scale proteomic method.

Methods: Data from two prospective cohort studies (the AGES-Reykjavik/Age, Gene/Environment Susceptibility-Reykjavik) study, (N=5,259) for biomarker discovery and the COPDGene (Genetic Epidemiology of COPD), study (N=4,899) were used. Blood proteins were measured using DNA aptamers targeting more than 4,700 protein analytes. The association of proteins with ILAs and ILA progression was assessed with regression modeling as were associations with genetic risk factors.

Results: Of 287 associations surfactant protein B (SFTPB), secretoglobin family 3A1 (SCGB3A1), and WAP four-disulfide core domain protein 2 (WFDC2) were most significantly associated with ILA in both studies. In the AGES-Reykjavik study, elevated concentrations of SFTPB were associated with MUC5B promoter polymorphisms.

SFTPB and WFDC2 have the strongest associations with ILA progression.

Discussion: Novel replicated associations of ILA, its progression and genetic risk factors with numerous blood proteins were demonstrated. These proteins may be potential markers of early fibrotic lung disease.

2. Acute exacerbations in children's interstitial lung disease. Seidl E, Schwerk N, Carlens J, Wetzke M, Emiralioglu N, Kiper N, Lange J, Krenke K, Szepfalusi Z, Stehling F, Baden W, Hammerling S, Jerkic SP, Proesmans M, Ullmann N, Buchvald F, Knoflach K, Kappler J, the child EU collaborators, Griese M. Thorax. 2022;77:799-804.

   Background: Little is known about the characteristics and impact of acute exacerbation on children with interstitial lung disease.

   Methods: Characteristics of AEs were obtained from the Kids Lung Register of rare pediatric lung diseases.

   Results: Data from 2,822 AEs and 2,887 register visits of 719 patients with chILD were recorded.

   AEs were characterized by increased levels of dyspnea, elevated respiratory rate and increase in oxygen demand.

   Infections (94.4%) were the most suspected cause of AE.

   During the median observation period of 2.5 years, 81 of the 719 patients died and 49 of these patients (60.5%) mortalities were associated with an AE.

   Discussion: This is the first comprehensive study analyzing the characteristics and impact on the clinical course of AEs in chILD patients.

3. Characterization of immunopathology and small airway remodeling in constrictive bronchiolitis. Gutor SS, Richmond BW, Du RH, Wu P, Lee JW, Ware LB, Shaver CM, Novitskiy SV, Johnson JE, Newman JH, Rennard SI, Miller RF, Blackwell TS, Polosukhin VV. Am J Respir Crit Care Med. 2022;206(3):260-270.

   Background: Constrictive bronchiolitis (ConB) is an understudied form of lung disease whose underlying immunopathology remains incompletely defined. This study was designed to quantify specific pathologic

features that differentiate ConB from other diseases affecting the small airways and to investigate the underlying immune and inflammatory phenotype present in Con B.

Methods: Authors did a comparative histomorphologic analysis of small airways and lung biopsy samples collected from 50 soldiers with postdeployment ConB, 8 with sporadic ConB, 55 with COPD and 25 nondiseased control subjects.

Immune and inflammatory gene expression was identified using NanoString nCounter Immunology Panel from six controls, six soldiers and six patients with sporadic ConB.

Results: Shared pathologic changes in small airways from soldiers and sporadic ConB were identified including increased thickness of bronchiolar smooth muscle, increased collagen deposition in the subepithelium, and increased lymphocyte infiltration. ConB pathology was clearly separable from control lungs and from patients with small airway disease in the setting of COPD.

NanoString gene expression analysis revealed T-cell activation in both groups of ConB patients with upregulation of proinflammatory pathways, including cytokine-cytokine with receptor interactions, nuclear factor-κB (NF-κB, toll-like receptor (TLR) signaling, and T-cell receptor signaling, and antigen processing and presentation.

The authors show some very nice images highlighting the somewhat subtle pathologic changes one can frequently see in patients with ConB. (see Figure 1)

Discussion: These findings indicate shared immunopathology among different forms of ConB.

They suggest an ongoing T-helper cell type 1 adaptive immune response may be responsible for airway wall remodeling in this group of patients.

Neoplastic Notations

1. NUT carcinoma, an under-recognized malignancy: a clinicopathologic and molecular series of 6 cases showing a subset of patients with better prognosis and a rare ZNF532::NUTM1 fusion. Abreu RF, de Oliveira TB, Hertzler H, Toledo RN, D'Almeida F, Lopes Pinto CA, Nunes WA, Nascimento AF, French CA, Nascimento AG. Hum Pathol. 2022;126:87-99.

   Background: NUT carcinoma is a rare aggressive subtype of carcinomas genetically defined by rearrangements involving the NUT midline carcinoma family member 1 (NUTM1) gene locus. The tumor can arise in a wide variety of locations including the thorax, head and neck but also bladder, pancreas, and kidney. This study aimed to explore morphologic characteristics and the genetic profile highlighting variable outcomes and alerting pathologists to its recognition for more accurate diagnosis and better management.

   Methods: All cases of NC from the A.C. Camargo Cancer Center in Sao Paulo, Brazil, from 2013-2022. Clinical features and all slides were reviewed. FISH was performed at BWH.

   Results: Authors identified six cases (head and neck, thoracic, and femur).

   Authors highlight the variable histologic features with some cases having only a minor rhabdoid component, some with clear cytoplasm. In many cases cytoplasm was inconspicuous.

In IHC all tumors expressed a NUT but also INI1 and cytokeratins. Five cases had BRD4::NUTM1 fusions while one tumor had ZNF532::NUTM1 fusions.

Patients with the longest survivals in this subset were patients with tumors in the parotid and lacrimal glands possibly due to earlier diagnosis.

Discussion: Authors expand on the histologic spectrum of NUT carcinomas.

ZNF532::NUTM1 fusion has been previously described so although they highlight this, it is not new information.

High-grade undifferentiated malignancies/carcinomas should probably always be evaluated for the possibly of NUT carcinoma.

2. Cytomorphologic features of SMARCA4-deficient non-small cell lung carcinoma and correlation with immunohistochemical and molecular features. Sun T, Gilani SM, Podany P, Harigopal M, Zhong M, Wang H. Cancer Cytopathol. 2022;130:620-629.

Background: In addition to SMARCA4/BRG1-deficient undifferentiated thoracic tumors, this article and the article by Velut Lung Cancer 2022;169:13-21 (one of the notation articles from last month) highlights the presence of a subset of NSCLCs with SMARCA4 deficiencies. This article describes the cytomorphologic features of this group of tumors.

Methods: Cases were identified by molecular studies and were further studied by immunohistochemistry.

Results: Twelve cases from different anatomic sites were included. All showed variable expression of cytokeratin.

Glandular features identified in one-half while other tumors had squamous or poorly differentiated features. Most common cytologic features included sheets or tumors with papillary architecture, round or oval cell shapes, nuclear enlargement, moderate to marked pleomorphism, and coarse chromatin. Two cases consisted predominantly of single cells, scant cytoplasm and macronucleoli. TP53 was the most frequently co-mutated gene in this group of tumors.

Discussion: This study demonstrates that SMARCA4 deficient NSCLCs can have wide cytologic features or relatively well differentiated adenocarcinoma to poorly differentiated/undifferentiated carcinomas.

Comment: Dr. Nassar presented this paper as part of her discussion on cytologic features on of lung cancer at the recent Mayo thoracic workshop. I have to admit I was a bit confused at the time because I had not heard of this class of tumors. In the article by Velut, et al., they noted that these tumors also had other targetable mutations including KRAS, G12C and met amplification. The tumors also appeared to have a high density of neutrophils. In discussions with Drs. Boland and Roden, the SMARCA4 deficient NSCLCs may look like ordinary carcinomas and have diffuse keratin reactivity. The SMARCA4 loss may represent a passenger mutation and may not be a strong oncogenic driver for the tumor. In their opinion the SMARCA4-deficient undifferentiated thoracic tumors should not be used for those easy to recognize carcinomas per the WHO recommendations.

3. Clinicopathologic and genomic features of high-grade pattern and their subclasses in lung adenocarcinoma. Ahn B, Yoon S, Kim D, Chun SM, Lee G, Kim HR, Jang SJ, Hwang HS. Lung Cancer. 2022;170:176-184.

Background: The authors wanted to evaluate the clinicopathologic and genomic characteristics associated with high-grade patterns (HGP) as defined by the IASLC.

Methods: 174 patients who underwent surgical resection of lung adenocarcinomas from January through December 2015.

Proportions of HGPs, including solid, micropapillary, cribriform, and complex glandular patterns, were individually quantified.

Prognostic implications of HGP proportions as a continuous variable and as subclasses divided by cutoffs of 20%, 50%, and 90% (low-intermediate grade/LIG, HGP <20%; high grade 1/HG1, 20-<50%, HG2, 50-<90%; HG3 >90%) were evaluated. Clinicopathologic factors and genomic alterations were assessed.

Results: Relative hazards of HGP gradually elevated as its proportion increased over 20% and the cancer-specific overall survival of HG1 subclass was not significantly decreased compared to the LIG subclass on univariate analysis.

Further subgrouping showed significantly increased frequencies of male, advanced stage, lymphovascular invasion, and STAS in higher HGP subclasses.

Common adenocarcinoma driver mutations, particularly EGFR were less frequent in this group, whereas, alterations in TP53 and cell cycle pathway-related genes were more frequent.

Higher HGP subclasses and TP53 alterations were associated with shorter cancer-specific and RFS in multivariate survival analysis.

Discussion: HGP subclasses of adenocarcinoma displayed distinct clinicopathological characteristics with genomic alterations including TP53 and cell cycle pathway mutations.

Authors emphasize the clinical value of these subclasses and indicate that alterations in TP53 may be markers of poor post-operative survival.

4. Understanding factors associated with anaplastic lymphoma kinase testing delays in patient with non-small cell lung cancer in a large real-world oncology database. Bernicker EH, Xiao Y, Croix DA, Yang B, Abraham A, Redpath S, Engstrom-Melnyk J, Shah R, Allen TC. Arch Pathol Lab Med. 2022;146:975-983.

   Background: The authors wanted to assess factors impacting ALK test ordering and time to result delivery.

   Methods: A retrospective study using de-identified EMR database.

   Post-diagnosis ALK tests (n=14,657) were analyzed from 14,197 patients with advanced NSCLC diagnosed 1/2015-5/2019. Time from diagnosis to ALK sample receipt was a surrogate for test order time.

   Test ordering was considered delayed if order time was more than 20 days.

   TAT from sample received to test result was calculated and considered delayed if more than 10 days.

   Multivariable logistic regression analysis was used to assess factors associated with order time and TAT delays.

   Results: Median ALK test order time was 15 days among which 36.4% were delayed.

Factors associated with delays include non-FISH testing, send-out laboratories, testing prior to 2018, nonadenocarcinoma histology, and smoking history.

Median TAT was 9 days and 40.3% of all tests were delayed.

Non-FISH testing, tissue sample, and orders combined with ALK, and other biomarkers were associated with delayed reporting.

Discussion: This study provides a snapshot of real-world ALK testing and reporting in US community practices.

Multiple factors impacted both test ordering time and test results, revealing opportunities for improvement.

Comment: With wide performance of NGS testing, perhaps this article is less relevant than it would have been in the past.

5. Pulmonary Langerhans cell histiocytosis and lymphangioleiomyomatosis have circulating cells with loss of heterozygosity of the TSC2 gene. Elia D, Torre O, Vasco C, Geginat J, Abrignani S, Bulgheroni E, Carelli E, Cassandro R, Pacheco-Rodrigues G, Steagall WK, Moss J, Harari S. Chest. 2022;162(2):385-393.

   Background: LAM and PLCH are both cystic lung diseases in which a neoplastic cell is thought to be responsible for disease pathogenesis. Authors sought to evaluate whether TSC2 loss of heterozygosity (LOH) was specific to LAM or might also be found in PLCH.

   Methods: Patients with LAM (n=53), healthy volunteers (n=22), and PLCH (n=12) were evaluated for the presence of TSC2 LOH in blood and urine.

   Results: Using FACS (fluorescence activated cell sorting)
   Healthy volunteers had no cells with TSC2 LOH
   LAM patients did have evidence of TSC2 LOH (42/52 informative cases, 92%)
   Patients with PLCH showed some TSC2 LOH (11/12, 93%)

   Urine samples were less informative than blood samples.

   Discussion: The presence of TSC2 LOH in circulating cells is not specific for LAM. The significance of TSC2 LOH in blood and urine from patients with PLCH is difficult to explain but the LOH is consistent with the neoplastic characteristics of the diseases.

6. Thymic mucoepidermoid carcinoma: a clinicopathologic and molecular study. Murase T, Nakano S, Sakane T, Domen H, Chiyo M, Nagasaka S, Tanaka M, Kawahara Y, Toishi M, Tanaka T, Nakamura S, Sawabata N, Okami J, Mukaida H, Tzankov A, Szolkowska M, Porubsky S, Marx A, Roden A, Inagaki H. Am J Surg Pathol 2022;46:1160-1169.

   Background: Authors present 20 cases of thymic MEC.

   Methods: Cases were collected from Nagoya City University Hospital and DLMP MCR. Histology and molecular profiles were performed.

   Results: Median age 56 years (range 19 to 80 y).

3:2 male:female ratio

Tumors were evaluated according to multiple grading schemes.

Numerous histologic variants noted (70% of cases), including concurrent multilocular thymic cysts, sclerosing, oncocytic, clear cell, orphan like, and with prominent mucinous features).

MAML2 rearrangement identified in 56% of cases; fusion partner was CRTC1 and CRTC1-MAML2 was associated with lower level of pT classification of lower TMN stage.

Overall survival was 69% and 43% at five and ten years.

None of the patients with these CRTC1-MAML2 fusion died during follow-up.

Discussion: A MAML2 evaluation of thymic MECs routinely may have clinical significance and should be considered in their work up.

Mesothelioma

1. Asbestos lung burden does not predict survival in malignant pleural mesothelioma: a necropsy-based study of 185 cases. Barbieri PG, Consonni D, Somigliana A. J Thorac Oncol. 2022;17(8):1042-1049.

   Background: Some studies have suggested that a higher asbestos lung burden is associated with reduced survival in mesothelioma. This study sought to evaluate this hypothesis.

   Methods: Two series of autopsy patients with mesothelioma in the Brescia province, and workers or persons living with them employed in Monfalcone shipyards. Asbestos fibers and asbestos bodies in lung samples were counted using a scanning EM and optical microscopy.

   In the two series, median survival time and fitted multivariate Cox regression models adjusted for sex, period and age at diagnosis and histopathologic diagnosis were evaluated to calculate hazard ratios in 95% confidence intervals for three levels of asbestos fiber counts.

   Results: 185 necropsies (83 in Brescia, 102 in Monfalcone) were evaluated.

   Despite a much higher lung asbestos burden in Monfalcone patients, the median survival was slightly lower in Brescia (8.3 months) versus (10.2 months).

   Discussion: No relationship between asbestos burden and survival was found. Histologic subtype of mesothelioma was the strongest prognostic determinant.

2. Pulmonary asbestos fiber burden is related to patient survival in malignant pleural mesothelioma. Laaksonen S, Kettunen E, Sutinen E, Ilonen I, Vehmas T, Tormakangas T, Rasanen J, Wolff H, Myllarniemi M. J Thorac Oncol. 2022;17(8):1032-1041.

   Background: The authors sought to retrospectively determine whether there was an association between asbestos fiber burden and all-cause mortality in patients with malignant pleural mesothelioma.

   Methods: National registry of the Finnish Cancer Registry was merged with pulmonary asbestos fiber analysis results from the Finnish Institute of Occupational Health.

   Results: 590 patients

Multivariant analysis showed that total asbestos fiber concentration was associated with increased mortality but no differences were noted between different fiber types

Comment: These authors did not control for mesothelioma subtype.

3. Bilateral pleural mesothelioma in situ and peritoneal mesothelioma in situ associated with BAP1 germline mutation: a case report. MacLean A, Churg A, Johnson ST. JTO Clinical and Research Reports. 2022;3(8):100356.

   Summary: Case report of a 43-year-old woman who developed bilateral in situ pleural and peritoneal in situ mesotheliomas in the setting of a BAP1 germline mutation.

   This is the first report of mesothelioma in situ involving multiple body cavities.

4. Update of pathological diagnosis of pleural mesothelioma using genomic-based morphological techniques, for both histological and cytological investigations. Nabeshima K, Hamasaki M, Kinoshita Y, Matsumoto S, Sa-ngiamwibool P. Pathol Int. 2022;72:389-401.

   Summary: Review article outlining how one establishes the diagnosis of pleural mesothelioma.

   A reasonable review which includes a number of useful tables, diagrams, and approach for cytology specimens.

5. Sarcomatoid mesothelioma originating from mesothelioma in situ: are methylthioadenosine phosphorylase loss and CDKN2A homozygous deletion poor prognostic factors for preinvasive mesothelioma? Nishikubo M, Jimbo N, Tanaka Y, Tachihara M, Itoh T, Maniwa Y. Virchows Archiv. 2022;481:307-312..

   Summary: Case report of a 73-year-old man diagnosed with mesothelioma in situ with progression to sarcomatous mesothelioma. The authors believe that this is the first example of a patient with mesothelioma in situ progressing to sarcomatous as opposed to epithelial mesothelioma.

   Since that patient had MTAP loss and CDKN2A deletions, they hypothesized that this molecular profile might be a high-risk factor for developing invasive, possibly sarcomatous mesothelioma. BAP1 in this patient was retained.

6. Does the amount of asbestos exposure influence prognosis? Yang H, Gaudino G, Bardelli F, Carbone M. J Thorac Oncol. 2022;17(8):949-952.

   Summary: The editorial reviews the two papers noted above by Laaksonen, et al and Barbieri, et al. They highlight the prominence of missing information which might be useful in determining the discrepancy between the two studies.

Case Reports, Editorials and Reviews

1. Bronchiectasis: a clinical review. O'Donnell AE. N Engl J Med. 2022;387:533-545.

Summary: This is a very nice clinical review of pathophysiology, underlying causes, and treatment of patients with bronchiectasis. Some very nice diagrams and images. Figure 1 may be particularly worthwhile for medical school teaching.

2. Diagnostic aspirations. Chen HX, Cernadas M, Vargas SO, Levy BD, Loscalzo J. N Engl J Med. 2022;387:452-458.

   Summary: Clinical case study of a patient with endogenous lipoid pneumonia. Interestingly, the patient had been vaping, but the authors don't contribute her disease to vaping, but rather mineral oil.

3. Diffuse "tree-in-bud" pattern on high-resolution computed tomography in severe vaping-induced lung injury. Collins PD, Meadows CIS, Lams BEA, Agarwal S, Wyncoll DLA. Am J Respir Crit Care Med. 2022;206(4):501-502.

   Summary: This is an images and critical care imaging in pulmonary medicine in which an 18-year-old patient with EVALI had widespread tree-in-bud abnormalities. Radiology images are striking but no pathology included.

4. Post-coronavirus disease 2019 smoldering interstitial pneumonia/pulmonary fibrosis (Letter to the Editor). Ichihara S, Nakatani Y, Tanino M, Fujimori K, Cho Y, Otsuka M, Kitamura C, Murao K, Taya T, Mori M, Ichimura T, Muraoka S. Pathol Int. 2022;72:419-422.

   Summary: Case report of a 71-year-old patient with severe COVID. Her bilateral, multilobar ground glass opacities improved but she had some residual parenchymal band-like changes on imaging that she had for follow-up of a nodule that had been identified on her initial presentation. A lobectomy was performed. A carcinoma was identified but, in addition, changes of cicatricial organizing pneumonia as well as other acute and chronic interstitial changes were noted (similar to those our group identified). Not much new here but the authors were surprised about the prominence of the findings in someone with very few imaging abnormalities.

5. Histopathologic insights into distal lung injury an inflammation following military deployment (Editorial). Krefft SD, Rose CS. Am J Respir Crit Care Med. 2022;206(3):233-246.

   Summary: This is an editorial to accompany the article on constrictive bronchiolitis. The editor lauds the work and emphasize the importance of histopathologic study of patients with constrictive bronchiolitis, particularly those with airway injury due to deployment.

6. A 54-year-old man with migratory pulmonary consolidation and progressive dyspnea. Ma JY, Chuang CH. Chest. 2022;162(2)e85-e88.

   Summary: Vaccine induced immune thrombotic thrombocytopenia (VITT) is an emerging disease, reported increasingly among individuals who receive certain adenoviral-vectored COVID-19 vaccinations. Case report of a 54-year-old man with hepatitis B and recurrent pneumonias. The ultimate diagnosis was vaccine-induced immune thrombotic thrombocytopenia related bilateral multiple pulmonary emboli and infarcts. He reported experiencing intermittent fever, dyspnea on exertion, and relapsing pleuritic chest pain after his first does of the ChAdOx1 nCoV-19 vaccine.

7. Biomarkers for interstitial lung abnormalities: a stepping-stone toward idiopathic pulmonary fibrosis prevention? (Editorial). Maher TM. Am J Respir Crit Care Med. 2022;206(3):244-246.

   Summary: This is an editorial that accompanies the article on looking for biomarkers in ILA. Generally favorable.

8. Case 26-2022: a 48-year-old woman with cystic lung disease. Reddy KP, Price MC, Barnes JA, Rigotti NA, Crotty RK. N Engl J Med. 2022;387:738-747.

   Summary: Case records of MGH.

   Patient is a 48-year-old woman with cystic lung disease found to have Langerhans-cell histiocytosis. Nice transbronchial biopsy diagnosis was established.

9. Outbreak of silicosis in worker producing artificial stone skirting boards: a novel application of silica-based composites. Ronsmans S, Goeminne P, Jerjir N, Nowe V, Vandebroek E, Keirsbilck S, Weynand B, Hoet PHM, Vanoirbeek JAJ, Wuyts WA, Yserbyt J, Nemery B. Chest. 2022;162(2):406-408.

   Summary: Four patients with silicosis reported from the production of artificial stone skirting boards. Pathology images are present but are a bit suboptimal.

10. A young child with recurrent pneumonia and hemoptysis during the COVID-19 pandemic. Zhao Z, Kim RC, Tavernier F, Choksi R, Van Brunt T, Davis JE, Kevill K, Hsieh H. Chest. 2022;162(2):e77-e80.

    Summary: Case report of a 6-year-old boy with mucoepidermoid carcinoma. No pathology shown.

11. What are the long-term pulmonary sequelae of COVID-19 infection? Elicker BM. Radiology. 2022;304:193-194.

    Summary: This is an editorial that accompanies a radiology study. It briefly outlines the changes seen with persistent symptoms after COVID-19 including prominent air trapping.

12. The role of genetic testing in pulmonary fibrosis: a perspective from the Pulmonary Fibrosis Foundation Genetic Testing Work Group. Newton CA, Oldham JM, Applegate C, Carmichael N, Powell K, Dilling D, Schmidt SL, Scholand MB, Armanios M, Garcia CK, Kropski JA, Talbert J; and the Pulmonary Fibrosis Foundation Genetic Testing Work Group. Chest. 2022;162(2):394-405.

    Summary: Nice summary on guidance of genetic testing in patients with pulmonary fibrosis. This is a concise review of the proceedings of the Pulmonary Fibrosis Foundation Work Group on Genetic Testing. Table 1 lists clinical features within pathways or families that suggest a possible genetically driven process stratified by three gene pathways (telomere, surfactant, and Hermansky-Pudlak). Table 2 lists clinical scenarios in which clinicians may consider genetic testing and the potential yield for identifying a variant. Overall, a nice summary with info that may be useful in updating a talk.

13. Organ manifestations of COVID-19: what have we learned so far (not only) from autopsies? Jonigk D, Werlein C, Acker T, Aepfelbacher M, Amann KU, Baretton G, Barth P, Bohle RM, Buttner A, Buttner R, Dettmeyer R, Eichhorn P, Elezkurtaj S, Esposito I, Evert K, Evert M, Fend F, Gabler N, Gattenlohner S, Glatzel M, Gobel H, Gradhand E, Hansen T, Hartmann A, Heinemann A, Heppner FL, Hilsenbeck J, Horst

D, Kamp JC, Mall G, Markl B, Ondruschka B, Pablik J, Pfefferle S, Quaas A, Radbruch H, Rocken C, Rosenwald A, Roth W, Rudelius M, Schirmacher P, Slotta-Huspenina J, Smith K, Sommer L, Stock K, Strobel P, Strobl S, Titze U, Weirich G, Weis J, Werner M, Wickenhauser C, Wiech T, Wild P, Welte T, von Stillfried S, Boor P. Virchows Arch. 2022;481:139-159.

Background: This article summarizes the published literature and consented experience of a nationwide (German) autopsy centers who saw more than 1200 COVID-19 autopsies.

Results: Autopsy tissue revealed SARS-CoV-2 infection can be found in virtually all human organs and tissues and in the majority of cells.

Autopsies revealed organ and tissue tropism of SARS-CoV-2.

Confirmed that in the lungs diffuse alveolar damage associated with angiocentric changes including endothelial abnormalities, vascular inflammation, thrombosis, and "intussusceptive" angiogenesis were common.

Extra-respiratory organs, pathologic changes were often non-specific and it was unclear to what extent these changes were due to direct infection versus secondary mechanisms of organ injury or a combination.

Discussion: The authors highlight the importance of autopsies in the evaluation of human disease.

14. An airway-centric view of idiopathic pulmonary fibrosis. Stancil IT, Michalski JE, Schwartz DA. Am J Respir Crit Care Med. 2022;206(4):410-416.

    Summary: This is a listed as a "pulmonary perspective" on the airway-centric structural and functional defects inherent in IPF, genetic risks in the context of distal airway changes involved in the pathogenesis of IPF, and they present a working model of airway-driven IPF. It is an interesting read.

15. First report of thoracic carcinoma with DEK::AFF2 rearrangement: a case report. Savari O, Chang JC, Bishop JA, Sakthivel MK, Askin FB, Rekhtman N. J Thorac Oncol. 2022;17(8):1050-1053.

    Summary: DEK::AFF2 carcinomas have been recorded in the head and neck region and have an aggressive clinical behavior. The authors present the case of a 26-year-old with morphologic and molecular features of the DEK::AFF2 carcinoma identified from the head and neck region. The tumor was a head and endobronchial exophytic component with basaloid features, focal keratin pearl production in the absence of overt keratinization. Interestingly, the tumor co-expressed p40 and TTF1 as well as CK5/6. See Figure 2 for a peek at the histology. Since this tumor had squamous features, they suggest testing for this fusion should be initiated in every smoker's who develop squamous carcinomas.