Pulmonary Journal Club – February 2022

Andras Khoor, MD, PhD, Mayo Clinic Florida

Articles for Discussion

Loss of methylthioadenosine phosphorylase by immunohistochemistry is common in pulmonary sarcomatoid carcinoma and sarcomatoid mesothelioma

Terra S, Roden AC, Yi ES, Aubry MC, Boland JM
Am J Clin Pathol. 2022 Jan 6;157(1):33-39

Objectives:

- Differentiating malignant pleural mesothelioma from benign reactive mesothelial processes can be challenging
- Ancillary tests such as BRCA1-associated protein 1 (BAP1) immunohistochemistry and p16 fluorescence in situ hybridization (FISH) are helpful tools to aid in this distinction
- Immunohistochemistry for methylthioadenosine phosphorylase (MTAP) has recently been proposed as an effective surrogate marker for p16 FISH
- There are little data regarding the specificity of MTAP loss for mesothelioma or whether it may be useful to distinguish mesothelioma from the most common entity in the differential diagnosis, sarcomatoid carcinoma

Methods:

- The authors studied well-characterized cases of sarcomatoid carcinoma (n = 34) and sarcomatoid mesothelioma (n = 62), which were stained for MTAP (clone 2G4) and BAP1 (clone C-4)

Results:

- Pulmonary sarcomatoid carcinomas
    - Loss of MTAP expression was observed in 17 of 34 cases (50%)
    - BAP1 expression was retained in all cases in which it was performed (n = 31)
- Sarcomatoid mesotheliomas
    - MTAP expression was lost in 38 (61%) of 62 cases (61%)
    - BAP1 was lost in 6 of 62 (10%)
    - In the six cases with BAP1 loss, five also had loss of MTAP, while MTAP expression was retained in one

Conclusions:

- Loss of MTAP expression by immunohistochemistry is common in pulmonary sarcomatoid carcinoma, as it is present in half of cases
- This rate is similar to what is observed in sarcomatoid mesothelioma (61%)
- Therefore, this stain is not useful to distinguish between these two malignancies
- MTAP loss is more common than BAP1 loss in the setting of sarcomatoid mesothelioma (61% vs 10%, respectively)

The differential prognostic impact of spread through air spaces in early-stage lung adenocarcinoma after lobectomy according to the pT descriptor

Jung W, Chung JH, Yum S, Kim K, Lee CT, Jheon S, Cho S

J Thorac Cardiovasc Surg. 2022 Jan;163(1):277-284.e1

Objectives:

- The authors evaluated the differential prognostic impact of spread through air spaces (STAS) in early-stage lung adenocarcinoma after lobectomy according to the pT descriptor

Methods:

- The study population included 506 patients who underwent lobectomy with mediastinal lymph node dissection for pT1b, pT1c, and pT2a adenocarcinoma between 2011 and 2016
- The authors divided the study population into 2 groups according to STAS status, ie, STAS (+) versus STAS (–), and stratified them according to the pT descriptor
- A Cox proportional hazard model and inverse probability of treatment weight–adjusted Kaplan–Meier curves were used to evaluate the prognostic impact of STAS on recurrence-free survival (RFS) and its independency in each stratum

Results:

- Multivariable Cox proportional hazard regression analysis demonstrated that in pT1b and pT1c strata, STAS (+) patients had a 7.02-fold and 2.89-fold greater risk of recurrence than STAS (–) patients, respectively
- However, in the pT2a stratum, STAS did not affect RFS
- The RFS of the STAS (+) pT1b/c strata was similar to that of the pT2a stratum
- In the pT1b/c strata, inverse probability of treatment weighting-adjusted Kaplan-Meier curves also showed that RFS was significantly worse when STAS was present
- Furthermore, the risks for locoregional and distant recurrence were both greater when STAS was present

Conclusions:

- The presence of STAS increased the risk of recurrence independently from other poor prognostic factors in patients with pT1b/cN0M0 adenocarcinoma who underwent lobectomy, but not in pT2a patients
- The presence of STAS in pT1b/cN0M0 adenocarcinoma was associated with a similar risk of recurrence to that of pT2aN0M0 adenocarcinoma

Prognostic impact of the histologic lepidic component in pathologic stage IA adenocarcinoma

Okubo Y, Kashima J, Teishikata T, Muraoka Y, Yotsukura M, Yoshida Y, Nakagawa K, Watanabe H, Kusumoto M, Watanabe SI, Yatabe Y

J Thorac Oncol. 2022 Jan;17(1):67-75

Objectives:

- Because several articles have reported a prognostic association with the radiologic features of ground-glass opacity, the authors explored whether the histologic presence of a lepidic component had similar significance

Methods:

- The authors retrospectively evaluated 380 consecutive surgically resected lung adenocarcinomas (ADCs) of pathologic (p)stage IA
- The tumors were classified into lepidic-positive and lepidic-negative ADCs
- Clinicopathologic characteristics, radiographic ground-glass opacity status, and disease-free survival were compared between lepidic-positive and lepidic-negative ADCs and between part-solid and solid nodules on computed tomography images

Results:

- Of the 380 cases, 176 (46.3%) were lepidic-positive ADCs
- Of the overall patients with pT1, lepidic-positive ADCs were found to have significantly better recurrence-free survival (5 y, 95.4% versus 87.0%, p ¼ 0.005), but this significance was not reproduced in pT1 subcategories (pT1a, pT1b, and pT1c)
- Furthermore, the presence of the lepidic component was not an independent prognostic factor in the multivariate analysis (hazard ratio ¼ 0.46 [95% confidence interval: 0.19–1.14], p ¼ 0.09)
- The authors also analyzed the extent of the lepidic component with 10% incremental valuables
- Although they found that a 10% or greater extent of lepidic component made the recurrence-free survival difference the largest, a clear prognostic impact was not obtained with this cutoff point

Conclusions:

- Although lepidic-positive ADCs tended to have a favorable outcome, the lepidic component was not a clear independent prognostic factor in (p)stage I ADC

Cicatricial organising pneumonia associated with fibrosing interstitial pneumonia - a clinicopathological study

Zaizen Y, Tabata K, Yamano Y, Takei R, Kataoka K, Shiraki A, Nishimura K, Furuyama K, Bychkov A, Hoshino T, Johkoh T, Kondoh Y, Fukuoka J

Histopathology. 2022 Jan;80(2):279-290

Objectives:

- The recent recognition of cicatricial organizing pneumonia (ciOP) indicates that the ciOP may resemble or simulate fibrotic interstitial pneumonia
- In this study, the authors compared the characteristics of fibrotic interstitial pneumonia with and without ciOP

Methods/Results:

- The authors enrolled 121 patients whose pathological findings were fibrotic interstitial pneumonia and for whom follow-up clinical data were available
- They reviewed these cases histopathologically and classified them according to whether they showed ciOP
- They compared the clinicopathological features between the two groups
- CiOP, histopathologically characterized by deposition of dense collagenous fibers within alveolar spaces without destruction of the lung structure, was found in 48 patients (39.7%)
- None of the cases with ciOP experienced acute exacerbation during 12 months' follow-up
- The group with ciOP had more severe diffusion impairment but this, together with restrictive ventilatory impairment, improved significantly compared to the group without ciOP

Conclusions:

- CiOP is a histopathological finding commonly found in fibrotic interstitial pneumonia
- It does not relate to acute exacerbation or decrease in pulmonary function

Diffuse cystic lung disease in sickle cell anaemia: a series of 22 cases and a case-control study

Kort F, Habibi A, Lionnet F, Carette MF, Parrot A, Savale L, Nunes H, Maitre B, Schlemmer F, Naccache JM

Thorax. 2022 Jan;77(1):91-93

Objectives:

- Chronic interstitial lung abnormalities have been described in sickle cell disease (SCD) and attributed to repetitive episode of acute chest syndrome

Methods/Results:

- The authors report a series of 22 cases of diffuse cystic lung disease in SCD with a case–control study to hunt for mechanism
- On pathological analysis of a surgical lung biopsy of the index case, the bronchioles had the appearance of constrictive bronchiolitis
- Pulmonary function test results revealed lower forced expiratory flow from 25% to 75% of vital capacity in cases versus controls

Conclusions:

- These findings suggest a bronchiolar mechanism that was not associated with more acute chest syndrome

Articles for Notation

Neoplastic

Significance of p53 immunostaining in mesothelial proliferations and correlation with TP53 mutation status
Naso JR, Tessier-Cloutier B, Senz J, Huntsman DG, Churg A
Mod Pathol. 2022 Jan;35(1):77-81

Objectives:

- p53 immunohistochemistry has long been proposed for the separation of benign from malignant mesothelial proliferations, with the older literature suggesting that any degree of positivity supported a diagnosis of mesothelioma
- However, using modern immunohistochemistry platforms in other organ systems, notably gynecologic tumors, it has become clear that p53 staining can represent wild-type protein, and only specific staining patterns (absent, overexpression, or cytoplasmic expression) are indicative of a TP53 mutation

Methods:

- The authors applied these principles to two tissue microarrays containing 94 mesotheliomas and 66 reactive mesothelial proliferations

Results:

- 7/65 (11%) epithelioid mesotheliomas showed aberrant staining
    - Four absent and three overexpression patterns
- 5/29 (17%) sarcomatoid mesotheliomas showed aberrant staining
    - All overexpression patterns
- The authors sequenced the TP53 gene (exons 2–11) in 5 of the epithelioid and 3 of the sarcomatoid cases with aberrant staining as well as 12 epithelioid and eight sarcomatoid mesotheliomas with wild-type staining
    - All 3 sarcomatoid cases with aberrant staining showed mutated TP53, as did 3 of the epithelioid cases; in 2 of the epithelioid cases no mutation was detected, most likely because of large deletions not detected by this assay
    - In contrast, none of the 20 mesotheliomas with wild-type staining contained mutated TP53

Conclusions

- The authors conclude that absent or overexpression p53 staining patterns can be used as a marker of a malignant vs. a benign mesothelial proliferation
- The sensitivity of p53 staining by itself is low, but addition of p53 to BAP1/MTAP staining increased sensitivity from 72 to 81% for epithelioid and 38 to 50% for sarcomatoid mesotheliomas

Genetic and methylation status of *CDKN2A (p14^{ARF}/p16^{INK4A})* and *TP53* genes in recurrent respiratory papillomatosis

Chantre-Justino M, Gonçalves da Veiga Pires I, Cardoso Figueiredo M, Dos Santos Moreira A, Alves G, Faria Ornellas MH

Hum Pathol. 2022 Jan;119:94-104

Objectives:

- Recurrent respiratory papillomatosis (RRP) is a rare and chronic disease affecting the upper airway with papillomatous lesions caused by the human papillomavirus (HPV) infection, especially HPV-6 and/or HPV-11 types
- Little is known about the genetic and epigenetic drivers in RRP pathophysiology

Methods:

- The authors analyzed 27 papillomatous lesions from patients with RRP to evaluate somatic mutations and methylation status in CDKN2A (p14ARF/p16INK4A) and TP53, which are key tumor suppressor genes for the cell cycle control

Results:

- Sanger sequencing analysis revealed one somatic mutation in TP53 (c.733_734insA) and four mutations in CDKN2A (c.-30G > T, c.29_30insA, c.69delT, and c.300C > A)
- These mutations were observed in 10 patients, 6 of which carried double mutation
- Furthermore, 50% (5/10) of these patients carrying somatic mutations had RRP severity, representing 62.5% (5/8) of the severity cases in this study, albeit no significant association was found between somatic mutations and disease severity
- Methylation-specific polymerase chain reaction assays revealed p14ARF promoter hypermethylation in 100% of cases, followed by TP53 (96.3%) and p16INK4A (55.6%), suggesting the influence of HPV in the DNA methylation machinery

Conclusions:

- Somatic mutations were not common events identified in patients with RRP
- However, epigenetic modulation by high methylation rates, particularly for the p14ARF/TP53 pathway, seems to be in the course of RRP

The prognostic value of Kirsten rat sarcoma viral oncogene homolog mutations in resected lung adenocarcinoma differs according to clinical features

Ma Z, Zhang Y, Deng C, Fu F, Deng L, Li Y, Chen H

J Thorac Cardiovasc Surg. 2022 Jan;163(1):e73-e85

Objectives:

- The ninth edition of lung cancer staging system recommends that specific driver mutations should be considered as prognostic factors in survival models
- This study comprehensively investigated the prognostic value of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation in patients with resected lung adenocarcinomas according to different clinicopathologic and radiologic characteristics.

Methods:

- In total, 1464 patients with completely resected primary lung adenocarcinomas were examined for KRAS mutations from November 2008 to March 2015
- Age, sex, smoking status, performance status, tumor–node–metastasis stage, radiologic features, and histologic subtypes were collected
- Competing risk model was used to estimate the cumulative incidence rate of recurrence. Cox regression multivariable analyses on recurrence-free survival (RFS) and overall survival (OS) were performed

Results:

- KRAS mutations were more frequent in male subjects (P<.001), current/former smokers (P<.001), invasive mucinous adenocarcinoma (P<.001), and solid tumors (P<.001)
- In general, KRAS-mutated patients had greater cumulative recurrence rate (hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.23-3.08; P<.001) and worse overall survival (OS; HR, 1.88; 95% CI, 1.23-2.87; P<.001) than KRAS wild-type patients
- The OS (P<.001) of patients harboring KRAS-G12C/V mutations was shorter than that of other KRAS-mutated patients
- Cox multivariable analyses demonstrated that KRAS mutations were independently associated with worse RFS (HR, 5.34; 95% CI, 2.53-11.89; P ¼ .001) and OS (HR, 2.63; 95% CI, 1.03-6.76; P ¼ .044) in part-solid lung adenocarcinomas
- For stage I patients, Cox multivariable analyses revealed that KRAS mutation was an independent risk factor for RFS (HR, 2.05; 95% CI, 1.19-3.56; P ¼ .010) and OS (HR, 2.38; 95% CI, 1.29-4.40; P ¼ .005)

Conclusions:

- KRAS mutations was an independent prognostic factor in part-solid tumors and in stage I lung adenocarcinomas
- These findings may contribute to the ninth edition of lung cancer staging project

Comprehensive analysis of TP53 and KEAP1 mutations and their impact on survival in localized- and advanced-stage NSCLC

Saleh MM, Scheffler M, Merkelbach-Bruse S, Scheel AH, Ulmer B, Wolf J, Buettner R.

J Thorac Oncol. 2022 Jan;17(1):76-88.

Objectives:

- TP53 and KEAP1 are frequently mutated in NSCLC, but their prognostic value is ambiguous, particularly in localized stage tumors

Methods:

- This retrospective cohort study included a total of 6297 patients with NSCLC who were diagnosed between November 1998 and February 2020
- The primary end point was overall survival. Patients were diagnosed in a central pathology laboratory as part of the Network Genomic Medicine collaboration, encompassing more than 300 lung cancer-treating oncology centers in Germany
- All patients underwent molecular testing, including targeted next-generation panel sequencing and in situ hybridization

Results:

- A total of 6297 patients with NSCLC were analyzed
- In 1518 surgically treated patients (Union for International Cancer Control [UICC] I–IIIA), truncating TP53 mutations and KEAP1 mutations were independent negative prognostic markers in multivariable analysis (hazard ratio [HR]TP53truncating ¼ 1.43, 95% confidence interval [CI]: 1.07–1.91, p ¼ 0.015; HRKEAP1mut ¼ 1.68, 95% CI:1.24–2.26, p ¼ 0.001)
- Consistently, these mutations were associated with shorter disease-free survival
- In 4779 patients with advanced-stage (UICC IIIB– IV) tumors, TP53 mutations did not predict outcome in univariable analysis
- In contrast, KEAP1 mutations remained a negative prognostic factor (HRKEAP1mut ¼ 1.40, 95% CI: 1.23–1.61, p < 0.001) in patients with advanced-stage tumors
- Furthermore, those with KEAP1- mutant tumors with co-occurring TP53 missense mutations had longer overall survival than those with KEAP1-mutant tumors with wild-type or truncating TP53 mutations

Conclusions:

- This study found that TP53 and KEAP1 mutations were prognostic for localized and advanced-stage NSCLC
- The increased relative hazard of harboring TP53 or KEAP1 mutations was comparable to an increase in one UICC stage
- The data suggest that molecular stratification on the basis of TP53 and KEAP1 mutation status should be implemented for localized and advanced-stage NSCLC to optimize and modify clinical decision-making.

Tumor and tumor-associated macrophage programmed death-ligand 1 expression is associated with adjuvant chemotherapy benefit in lung adenocarcinoma

Gross DJ, Chintala NK, Vaghjiani RG, Grosser R, Tan KS, Li X, Choe J, Li Y, Aly RG, Emoto K, Zheng H, Dux J, Cheema W, Bott MJ, Travis WD, Isbell JM, Li BT, Jones DR, Adusumilli PS

J Thorac Oncol. 2022 Jan;17(1):89-102

Objectives:

- Patients with stage II to III lung adenocarcinomas are treated with adjuvant chemotherapy (ACT) to target the premetastatic niche that persists after curative-intent resection
- The authors hypothesized that the premetastatic niche is a scion of resected lung tumor microenvironment and that analysis of tumor microenvironment can stratify survival benefit from ACT

Methods:

- Using tumor and tumoral stroma from 475 treatment-naive patients with stage II to III lung adenocarcinomas, the authors constructed a tissue microarray and performed multiplex immunofluorescent staining for immune markers (programmed death-ligand 1 [PD-L1], tumor-associated macrophages [TAMs], and myeloid-derived suppressor cells) and derived myeloid-lymphoid ratio
- The association between immune markers and survival was evaluated using Cox models adjusted for pathologic stage

Results:

- Patients with high PD-L1 expression on TAMs or tumor cells in resected tumors had improved survival with ACT (TAMs: hazard ratio [HR] ¼ 1.79, 95% confidence interval [CI]: 1.12–2.85; tumor cells: HR ¼ 3.02, 95% CI: 1.69– 5.40)
- Among patients with high PD-L1 expression on TAMs alone or TAMs and tumor cells, ACT survival benefit is pronounced with high myeloid-lymphoid ratio (TAMs: HR ¼ 3.87, 95% CI: 1.79–8.37; TAMs and tumor cells: HR ¼ 2.19, 95% CI: 1.02–4.71) or with high stromal myeloid-derived suppressor cell ratio (TAMs: HR ¼ 2.53, 95% CI: 1.29–4.96; TAMs and tumor cells: HR 3.21, 95% CI: 1.23–8.35)
- Patients with low or no PD-L1 expression on TAMs or tumor cells had no survival benefit from ACT

Conclusions:

- The observation that PD-L1 expression on TAMs or tumor cells is associated with improved survival with ACT provides rationale for prospective investigation and developing chemoimmunotherapy strategies for patients with lung adenocarcinoma

Molecular subtypes of primary SCLC tumors and their associations with neuroendocrine and therapeutic markers

Qu S, Fetsch P, Thomas A, Pommier Y, Schrump DS, Miettinen MM, Chen H

J Thorac Oncol. 2022 Jan;17(1):141-153

Objectives:

- To validate the new molecular subtype classification of SCLC in primary tumors by immunohistochemical (IHC) staining and to define its clinical relevance

Methods:

- The authors used IHC to assess four subtype markers (ASCL1, NEUROD1, POU2F3, and YAP1) in 194 cores from 146 primary SCLCs
- The profiles of tumor-associated CD3+ and CD8+ T-cells, MYC paralogs, SLFN11, and SYP were compared among different subtypes
- Validation was performed using publicly available RNA sequencing data of SCLC

Results:

- ASCL1, NEUROD1, POU2F3, and YAP1 were the dominant molecular subtypes in 78.2%, 5.6%, 7%, and 2.8% of the tumors, respectively; 6.3% of the tumors were negative for all four subtype markers
- Substantial intratumoral heterogeneity was observed, with 17.6% and 2.8% of the tumors being positive for two and three subtype markers, respectively
- The non-ASCL1/NEUROD1 tumors had more CD8+ T-cells and manifested more frequently an “inflamed” immunophenotype
- L-MYC and MYC were more often associated with ASCL1/NEUROD1 subtypes and non-ASCL1/NEUROD1 subtypes, respectively
- SLFN11 expression was absent in 40% of the tumors, especially those negative for the four subtype markers
- SYP was often expressed in the ASCL1 and NEUROD1 subtypes and was associated with less tumor-associated CD8+ T-cells and a “desert” immunophenotype

Conclusions:

- The authors validated the new molecular subtype classification in primary SCLC tumors by IHC and identified several intriguing associations between subtypes and therapeutic markers
- The new subtype classification may potentially assist treatment decisions in SCLC

Solid papillary mesothelial tumor

Churg A, Le Stang N, Dacic S, Pissaloux D, Begueret H, Dartigues P, Giusiano-Courcambeck S, Sequeiros R, Pairon JC, Tirode F, Galateau-Sallé F

Mod Pathol. 2022 Jan;35(1):69-76

Objectives/Methods:

- The authors report nine examples of a previously undescribed type of peritoneal circumscribed nodular mesothelial tumor characterized by nests or sheets of mesothelial cells with sharp cell borders and extremely bland, sometimes grooved, nuclei
- In some cases, nests were separated by fibrous bands

Results:

- All patients were women, age range 30–72 years (median 52 years)
- All tumors were incidental findings during surgery and grossly were either solitary nodules or a few small nodules on the peritoneal surface
- Referring pathologic diagnoses included diffuse malignant mesothelioma, localized malignant mesothelioma, well-differentiated papillary mesothelioma, and adenomatoid tumor
- No tumor showed BAP1 loss by immunohistochemistry nor deletion of CDKN2A by FISH
- RNA-seq revealed that these tumors clustered together and were distinct from peritoneal diffuse malignant mesotheliomas. Very few mutations or translocations were found, none of them recurrent from tumor to tumor, and no tumor showed an abnormality in any of the genes typically mutated/deleted in diffuse malignant mesothelioma
- Array CGH on three cases revealed two with a completely flat profile and one with a small deletion at 3q26–3q28. On follow-up (range 5–60, median 34 months), there were no deaths, no recurrences, and no evidence of metastatic disease nor local spread; one case that initially had scattered nodules on the pelvic peritoneum had the same pattern of nodules at a second look operation 2 years later

Conclusions:

- The authors propose the name solid papillary mesothelial tumor for these lesions
- These appear to be either benign or very low-grade tumors that need to be separated from malignant mesotheliomas

Molecular characterization of pleomorphic mesothelioma: a multi-institutional study
Roy S, Galateau-Sallé F, Le Stang N, Churg A, Lyons MA, Attanoos R, Dacic S
Mod Pathol. 2022 Jan;35(1):82-86

Objectives:

- The molecular alterations of pleomorphic mesotheliomas are largely unknown

Methods:

- In the present study, we performed whole-exome sequencing (WES) on 24 pleomorphic mesotheliomas in order to better characterize the molecular profile of this rare histologic variant
- BAP1 protein expression and CDKN2A deletion by FISH were also evaluated

Results:

- Significantly mutated genes included BAP1 (35%), NF2 (13%), LATS2 (8%), TP53 (5%), and LATS1 (3%)
- BAP1 alterations most frequently co-occurred with deletions of chromosomes 4, 9, and 13
- Other important genetic alterations in pleomorphic mesotheliomas included truncating mutations in NF2 (3 of 24; 12.5%), LATS2 (2 of 24; 8%), TP53 (1 of 24; 4%), and PBRM1 (1 of 24; 4%)
- Focal losses of chromosome 9p21 were most common copy number alterations (11 of 24 cases; 46%), and were assessed by WES and targeted FISH
- The second most common were deletions of chromosome 4 (8 of 24; 33% pleomorphic mesotheliomas)
- Three cases of pleomorphic mesothelioma did not show any mutations, copy number alterations, or LOH

Conclusions:

- This first WES analysis of pleomorphic mesotheliomas did not identify novel or unique mutations
- In contrast to transitional mesothelioma that was reclassified as sarcomatoid variant based on transcriptome data, pleomorphic mesotheliomas are molecularly heterogeneous and therefore their reclassification into single subtype is more difficult

Non-Neoplastic

Antemortem vs postmortem histopathologic and ultrastructural findings in paired transbronchial biopsy specimens and lung autopsy samples from three patients with confirmed SARS-CoV-2

Gagiannis D, Umathum VG, Bloch W, Rother C, Stahl M, Witte HM, Djudjaj S, Boor P, Steinestel K

Am J Clin Pathol. 2022 Jan 6;157(1):54-63

Objectives:

- Respiratory failure is the major cause of death in coronavirus disease 2019 (COVID-19)
- Autopsy-based reports describe diffuse alveolar damage (DAD), organizing pneumonia, and fibrotic change, but data on early pathologic changes and during progression of the disease are rare

Methods:

- The authors prospectively enrolled three patients with COVID-19 and performed full clinical evaluation, including high-resolution computed tomography
- They took transbronchial biopsy (TBB) specimens at different time points and autopsy tissue samples for histopathologic and ultrastructural evaluation after the patients' death

Results:

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed by reverse transcription polymerase chain reaction and/or fluorescence in situ hybridization in all TBBs
- Lung histology showed reactive pneumocytes and capillary congestion in one patient who died shortly after hospital admission with detectable virus in one of two lung autopsy samples
- SARS-CoV-2 was detected in two of two autopsy samples from another patient with a fulminant course and very short latency between biopsy and autopsy, showing widespread organizing DAD
- In a third patient with a prolonged course, autopsy samples showed extensive fibrosis without detectable virus

Conclusions:

- The authors report the course of COVID-19 in paired biopsy specimens and autopsies, illustrating vascular, organizing, and fibrotic patterns of COVID-19–induced lung injury
- Their results suggest an early spread of SARS-CoV-2 from the upper airways to the lung periphery with diminishing viral load during disease

Lung microenvironments and disease progression in fibrotic hypersensitivity pneumonitis

De Sadeleer LJ, McDonough JE, Schupp JC, Yan X, Vanstapel A, Van Herck A, Everaerts S, Geudens V, Sacreas A, Goos T, Aelbrecht C, Nawrot TS, Martens DS, Schols D, Claes S, Verschakelen JA, Verbeken EK, Ackermann M, Decottignies A, Mahieu M, Hackett TL, Hogg JC, Vanaudenaerde BM, Verleden SE, Kaminski N, Wuyts WA

Am J Respir Crit Care Med. 2022 Jan 1;205(1):60-74

Objectives:

- Fibrotic hypersensitivity pneumonitis (fHP) is an interstitial lung disease caused by sensitization to an inhaled allergen
- To identify the molecular determinants associated with progression of fibrosis

Methods:

- Nine fHP explant lungs and six unused donor lungs (as controls) were systematically sampled (4 samples/ lung)
- According to microcomputed tomography measures, fHP cores were clustered into mild, moderate, and severe fibrosis groups
- Gene expression profiles were assessed using weighted gene co-expression network analysis, xCell, gene ontology, and structure enrichment analysis
- Gene expression of the prevailing molecular traits was also compared with idiopathic pulmonary fibrosis (IPF)
- The explant lung findings were evaluated in separate clinical fHP cohorts using tissue, BAL samples, and computed tomography scans

Results:

- The authors found six molecular traits that associated with differential lung involvement
- In fHP, extracellular matrix and antigen presentation/sensitization transcriptomic signatures characterized lung zones with only mild structural and histological changes, whereas signatures involved in honeycombing and B cells dominated the transcriptome in the most severely affected lung zones
- With increasing disease severity, endothelial function was progressively lost, and progressive disruption in normal cellular homeostatic processes emerged
- All six were also found in IPF, with largely similar associations with disease microenvironments
- The molecular traits correlated with in vivo disease behavior in a separate clinical fHP cohort

Conclusions:

- The authors identified six molecular traits that characterize the morphological progression of fHP and associate with in vivo clinical behavior
- Comparing IPF with fHP, the transcriptome landscape was determined considerably by local disease extent rather than by diagnosis alone

Proteomic analysis of human lung development

Clair G, Bramer LM, Misra R, McGraw MD, Bhattacharya S, Kitzmiller JA, Feng S, Danna VG, Bandyopadhyay G, Bhotika H, Huyck HL, Deutsch GH, Mariani TJ, Carson JP, Whitsett JA, Pryhuber GS, Adkins JN, Ansong C.

Am J Respir Crit Care Med. 2022 Jan 15;205(2):208-218

Objctives:

- The current understanding of human lung development derives mostly from animal studies
- Although transcript-level studies have analyzed human donor tissue to identify genes expressed during normal human lung development, protein-level analysis that would enable the generation of new hypotheses on the processes involved in pulmonary development are lacking
- To define the temporal dynamic of protein expression during human lung development

Methods:

- The authors performed proteomics analysis of human lungs at 10 distinct times from birth to 8 years to identify the molecular networks mediating postnatal lung maturation

Results:

- The authors identified 8,938 proteins providing a comprehensive view of the developing human lung proteome
- The analysis of the data supports the existence of distinct molecular substages of alveolar development and predicted the age of independent human lung samples, and extensive remodeling of the lung proteome occurred during postnatal development
- Evidence of post-transcriptional control was identified in early postnatal development
- An extensive extracellular matrix remodeling was supported by changes in the proteome during alveologenesis
- The concept of maturation of the immune system as an inherent part of normal lung development was substantiated by flow cytometry and transcriptomics

Conclusions:

- This study provides the first in-depth characterization of the human lung proteome during development, providing a unique proteomic resource freely accessible at Lungmap.net
- The data support the extensive remodeling of the lung proteome during development, the existence of molecular substages of alveologenesis, and evidence of post-transcriptional control in early postnatal development

Reviews

The highlights of the 15th international conference of the international mesothelioma interest group - Do molecular concepts challenge the traditional approach to pathological mesothelioma diagnosis?
Klebe S, Galateau Salle F, Bruno R, Brcic L, I Chen-Yost H, Jaurand MC.
Lung Cancer. 2022 Jan;163:1-6.

- Pathology plays an important role in diagnosing mesothelioma since radiological and clinical findings alone cannot distinguish mesothelioma reliably from its many mimics
- The long-held gold standard for pathological diagnosis requires a tissue biopsy that, in addition to mesothelial phenotype, demonstrates invasion, but this is challenged by the WHO recognition of mesothelioma in situ (MIS) and concurrent acknowledgement of all mesotheliomas as malignant
- Tumor sampling and ancillary techniques are of paramount importance for diagnosis of MIS
- Standardization of these techniques, cut-off points and terminology, and an updated staging system are urgently required
- These clinically relevant issues and the impact of new developments were illustrated at the pathology session of 15th meeting of the International Mesothelioma Interest Group
- It was reported that combination of losses in p16 nuclear expression, with cut-off ≤ 1%, and cytoplasmic MTAP with cut-off ≥ 30% demonstrated increased specificity (96%) and high sensitivity (86%) for CDKN2A HD detection
- Otherwise, the combination of p16 IHC and CDKN2A HD may improve prognosis
- The potential usefulness of pleural effusions for early diagnosis was demonstrated in a retrospective study investigating pleural effusions had been diagnosed as benign prior to mesothelioma diagnosis
- Alterations of BAP1 (IHC) and CDKN2A (FISH) were detectable 2 or more years prior diagnosis
- Moreover, analysis of gene expression profiles in cytology samples by principal component analysis discriminated reactive hyperplasia from epithelioid mesothelioma
- Early diagnosis, including cytology diagnosis, is being actively investigated
- Since no treatment recommendations exist for MIS, pathologists recognize the need for international collaborations to fully characterize this rare entity
- Clear communication with the clinical teams is required to ensure optimum patient care
- The data reported in this meeting are encouraging and open avenues for further work that will allow even earlier diagnosis and better characterization of mesothelioma progression, based on changes in gene expression, including epigenetic changes

DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma

González IA, Stewart DR, Schultz KAP, Field AP, Hill DA, Dehner LP

Mod Pathol. 2022 Jan;35(1):4-22

- DICER1 syndrome (OMIM 606241, 601200) is a rare autosomal dominant familial tumor predisposition disorder with a heterozygous DICER1 germline mutation
- The most common tumor seen clinically is the pleuropulmonary blastoma (PPB), a lung neoplasm of early childhood which is classified on its morphologic features into four types (IR, I, II and III) with tumor progression over time within the first 4–5 years of life from the prognostically favorable cystic type I to the unfavorable solid type III
- Following the initial report of PPB, its association with other cystic neoplasms was demonstrated in family studies
- The detection of the germline mutation in DICER1 provided the opportunity to identify and continue to recognize a number seemingly unrelated extrapulmonary neoplasms: Sertoli-Leydig cell tumor, gynandroblastoma, embryonal rhabdomyosarcomas of the cervix and other sites, multinodular goiter, differentiated and poorly differentiated thyroid carcinoma, cervical-thyroid teratoma, cystic nephromaanaplastic sarcoma of kidney, nasal chondromesenchymal hamartoma, intestinal juvenile-like hamartomatous polyp, ciliary body medulloepithelioma, pituitary blastoma, pineoblastoma, primary central nervous system sarcoma, embryonal tumor with multilayered rosettes-like cerebellar tumor, PPB-like peritoneal sarcoma, DICER1-associated presacral malignant teratoid neoplasm and other non-neoplastic associations
- Each of these neoplasms is characterized by a second somatic mutation in DICER1
- In this review, the authors have summarized the salient clinicopathologic aspects of these tumors whose histopathologic features have several overlapping morphologic attributes particularly the primitive mesenchyme often with rhabdomyoblastic and chondroid differentiation and an uncommitted spindle cell pattern
- Several of these tumors have an initial cystic stage from which there is progression to a high grade, complex patterned neoplasm
- These pathologic findings in the appropriate clinical setting should serve to alert the pathologist to the possibility of a DICER1-associated neoplasm and initiate appropriate testing on the neoplasm and to alert the clinician about the concern for a DICER1 mutation

Case Reports

Amyloid nodules masquerading as multifocal lung cancer
Kristo S, Zou T, Dexter EU, Pokharel S
Am J Respir Crit Care Med. 2022 Jan 1;205(1):e1-e3

A 63-year-old man

- Underwent a computed tomography (CT) scan of the chest revealing multiple lung nodules
- A positron emission tomography (PET)-CT scan showed standardized uptake value up to 5.5 Biopsy showed necro-inflammatory debris worrisome for malignancy
- Bronchoscopy before surgery was normal. A wedge resection revealed well-circumscribed, friable, 3.2-cm and 1.9-cm lesions composed of amorphous eosinophilic material and patchy aggregates of T and B lymphocytes and clonal plasma cells
- Congo red staining showed apple green birefringence under polarized light, compatible with nodular amyloidosis
- Mass spectrometry detected amyloid light chain (lambda type) amyloidosis, prompting workup for systemic disease
- Bone marrow biopsy and serum electrophoresis showed no evidence of monoclonal gammopathy of undetermined significance or multiple myeloma
- Abdominal fat pad biopsy, cardiac imaging, and kidney function test were normal
- A PET-CT scan 14 months after surgery showed no residual hypermetabolic disease in the lung
- The patient is doing well 20 months after the surgery

Acute presentation of a high-grade myxofibrosarcoma originating in the thoracic wall: A case report

D'Angelo LA, Arora Y, Carrillo RG

Chest. 2022 Jan;161(1):e1-e4

The authors report the first case of a patient with myxofibrosarcoma (MFS) who presented acutely with a rib fracture and developed a rapidly expanding loculated hemothorax after chest trauma

- The patient was taken to the operating room for evacuation of hemothorax, and samples and biopsy specimens were taken for cytologic and pathologic examination
- Final report with immunohistochemical staining showed a high-grade MFS
- After the procedure, there was clinical and radiological improvement, and the patient was followed up as an outpatient

67-year-old male patient with COVID-19 With worsening respiratory function and acute kidney failure

Melchers M, Festen B, den Dekker BM, Mooren ERM, van Binsbergen AL, van Bree SHW, Heusinkveld M, Schellaars R, Buil JB, Verweij PE, van Zanten ARH. A
Chest. 2022 Jan;161(1):e5-e11.

A 67-year-old obese man (BMI 38.0)

- With type 2 diabetes mellitus (DM), chronic atrial fibrillation, and chronic lymphocytic leukemia stage II, stable for 8 years after chemotherapy, and a history of smoking presented to the ED with progressive dyspnea and fever due to SARS-CoV-2 infection
- He was admitted to a general ward and treated with dexamethasone (6 mg IV once daily) and oxygen
- On day 3 of hospital admission, he became progressively hypoxemic and was admitted to the ICU for invasive mechanical ventilation
- Dexamethasone treatment was continued, and a single dose of tocilizumab (800 mg) was administered
- On day 9 of ICU admission, voriconazole treatment was initiated after tracheal white plaques at bronchoscopy, suggestive of invasive Aspergillus tracheobronchitis, were noticed
- However, his medical situation dramatically deteriorated

Diagnosis:

- The patient was diagnosed with COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated disseminated mucormycosis (CAM) with pulmonary and renal involvement

A 65-Year-Old Man With Weight Loss, Peripheral Neuropathy, and Lower Extremity Swelling

Lane T, Hountras P

Chest. 2022 Jan;161(1):e29-e34

A 65-year-old man

- With no past medical history sought treatment at the hospital with lower extremity swelling, pain, tingling in a stocking-glove distribution, and syncope
- He reported a 23-pound unintentional weight loss
- He felt unsteady walking with a couple of falls, and his exercise tolerance was limited to several hundred feet
- He did not report vision changes, dysphagia, bowel or bladder problems, tremor, orthopnea, lightheadedness, or chest pain
- He did not report any history of substance misuse, high-risk sexual behavior, or concerning exposures
- The patient was admitted for further workup.

Diagnosis:

- Pulmonary hypertension (group 5) secondary to polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome

A 71-year-old man with diffuse waxing and waning multifocal lung lesions, empyema, and episodic fevers reveals a rare diagnosis

Morin JA, Gooch CR, Stowell JT, Mallea JM, Jiang L, Thomas M.
Chest. 2022 Jan;161(1):e35-e41

A 71-year-old man

- With history of gastroesophageal reflux disease, chronic sinusitis, arthritis, hypothyroidism, and anemia of chronic disease initially sought treatment with a recurrent left pleural effusion along with other abnormal lung findings on chest CT scan
- Before his referral, he was being managed for 3 years at his local hospital for waxing and waning fevers, fatigue, productive cough, chills, and night sweats
- He did not report any hemoptysis or chest pain, but reported weight loss of 13 kgs in 15 months
- During those 3 years, he was treated with multiple courses of antibiotics and steroids with temporary relief of symptoms
- At that time, his chronic sinusitis was suspected to be the cause of his symptoms and he underwent balloon sinuplasty
- He was receiving daily sublingual immunotherapy for inhaled respiratory allergens for the previous year after showing positive test results for 17 inhaled allergens
- The patient had no other known immunologic workup before our evaluation

Diagnosis:

- Lymphomatoid granulomatosis, grade 3

A 33-Year-Old Man With Chest Pain

Ballenberger M, Vojnic M, Indaram M, Machnicki S, Harshan M, Novoselac AV, Singh A, Mina B
Chest. 2022 Jan;161(1):e43-e49.

A 33-year-old man

- Was admitted with a 4-week history of intermittent, right-sided chest pain
- Two weeks before the incident, he had completed a 10-day course of levofloxacin for a presumed right-sided pneumonia without much improvement
- He denied any dyspnea, cough, sputum production, hemoptysis, night sweats, or weight loss
- He was an active smoker with a 20-pack-year smoking history and 1-year history of vaping nicotine

Diagnosis:

- Thoracic NUT-midline carcinoma

COVID-19 vaccine-related interstitial lung disease: a case study
Park JY, Kim JH, Lee IJ, Kim HI, Park S, Hwang YI, Jang SH, Jung KS
Thorax. 2022 Jan;77(1):102-104