Journal Club
Andras Khoor, MD, PhD
Consultant and Associate Professor
Mayo Clinic, Jacksonville, Florida
October 26, 2020

Contents

Discussion Articles

Vanstapel A, et al. Late-onset "acute fibrinous and organising pneumonia" impairs long-term lung allograft function and survival. Eur Respir J 2020; in press.

- Background
  - Acute fibrinous and organizing pneumonia (AFOP) after lung transplantation is associated with a rapid decline in pulmonary function
  - However, the relationship between AFOP and chronic lung allograft dysfunction (CLAD) remains unclear
- Aim
  - To investigate the association between AFOP in lung allograft biopsies and clinically important endpoints
- Methods
  - Lung allograft biopsies from 468 patients were reviewed
  - AFOP was categorized as
    - *Early* new-onset (≤90 days post-transplant) or
    - *Late* new-onset (>90 days post-transplant)
  - CLAD-free survival, graft survival, donor-specific antibodies, airway eosinophilia and blood eosinophilia were also recorded
- Results
  - *Early* and *late* AFOP was detected in 24 (5%) and 30 (6%) patients, respectively
  - CLAD-free survival was significantly lower in patients with *late* AFOP (median survival 2.42y, p<0.0001) compared to patients with *early* or *without* AFOP and specifically associated with development of restrictive allograft syndrome (OR: 28.57; CI [11.34 – 67.88], p<0.0001)
  - Similarly, graft survival was significantly lower in patients with *late* AFOP (median survival 4.39y, p<0.0001) compared to patients with *early* AFOP or without AFOP
  - L*ate* AFOP was furthermore associated with detection of circulating donor-specific antibodies (OR: 4.75, CI [2.17-10.60], p=0.0004) compared to patients with *early* or *without* AFOP; and elevated airway and blood eosinophilia (p=0.043 and p=0.045, respectively) compared to *early* AFOP patients.
- Conclusions
  - *Late* new-onset AFOP is associated with a worse prognosis and high risk of CLAD development, specifically restrictive allograft syndrome
  - The findings indicate that *late* new-onset AFOP might play a role in the early pathogenesis of restrictive allograft syndrome.

Bösmüller H, et al. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Archiv 2020;477:349–357.

- Background
  - The pandemia of COVID-19 has caused more than 355,000 confirmed deaths worldwide.
  - However, publications on postmortem findings are scarce.
- Aim
  - To present the pulmonary findings in four cases of fatal COVID-19 infection with a spectrum of lung pathology reflecting disease course and duration, invasive therapies, and laboratory features
- Results
  - Early disease is characterized by neutrophilic, exudative capillaritis with microthrombosis and high levels of IL-1beta and IL-6.
  - Later stages are associated with diffuse alveolar damage and ongoing intravascular thrombosis in small to medium-sized pulmonary vessels, occasionally with areas of infarction, accompanied by laboratory features of disseminated intravascular coagulation
  - In late stages, organizing pneumonia with extensive intra-alveolar proliferation of fibroblasts and marked metaplasia of alveolar epithelium can be observed
  - Viral RNA is encountered in the lung, with virus particles in endothelial cells and pneumocytes
  - In many patients, multi-organ failure with severe liver damage sets in finally, possibly as consequence of an early-onset proinflammatory cytokine storm and/or thrombotic microangiopathy

Gordetsky J, et al. Non-necrotizing granulomatous pneumonitis and chronic pleuritis in soldiers deployed to Southwest Asia. Histopathology 2020, 77, 453–459.

- Background
  - During deployment to Southwest Asia, soldiers are exposed to various respiratory hazards, including dust storms, smoke from burn pits and industrial air pollutants
  - A few studies have reported increased rates of constrictive bronchiolitis and asthma in these patients
- Aim
  - To expand upon the pathological findings in this cohort
- Methods
  - Lung biopsies from veterans of Southwest Asia were identified and re-reviewed
  - All patients had undergone pulmonary function tests and chest high-resolution CT imaging with no significant findings
- Results
  - 59 patients with a history of inhalational exposure to at least one of the following were identified
    - Smoke from burn pit
    - Dust storm
    - Sulphur plant fire
  - Samples included (n=59)
    - 57 video-assisted thoracoscopic lung biopsies (96.6%) and
    - 2 cryobiopsies (3.4%)
  - Patients were predominantly male (54, 91.5%) with an age range of 24–55 years (mean and median = 35)
  - Non-necrotizing, poorly formed granulomas were identified in 22 cases (22 of 59, 37.2%)
  - The granulomas were mainly bronchiolocentric and were associated with chronic lymphoplasmacytic bronchiolitis, similar to hypersensitivity pneumonitis (HP)
  - Pleural reaction in the form of focal chronic lymphocytic pleuritis and/or focal pleural adhesions were seen in 43 of 57 (75.4%) biopsies
- Conclusions
  - This is the first study to report pleural reaction as well as features of HP in this population, suggesting that pleural reaction and HP may be part of the spectrum of Southwest Asia deployment-related lung diseases

Sazonova O, et al. Transcriptomic data helps refining classification of pulmonary carcinoid tumors with increased mitotic counts. Mod Pathol 2020;33:1712–1721.

- Background
  - NE tumors (2015 WHO)
    - Typical carcinoid (< 2 mitoses / 2 mm^2, lacking necrosis)
    - Atypical carcinoid (2 – 10 mitoses / 2 mm^2 or necrosis)
    - Large cell neuroendocrine carcinoma (LCNEC)
    - Small cell carcinoma
  - LCNEC with carcinoid morphology and low mitotic count is a gray zone within NE neoplasms
- Aim
  - To investigate clinicopathological and transcriptomic profiles of these tumors
- Methods
  - 18 cases
    - 7 carcinoids
    - 7 LCNECs
    - 4 borderline tumors (mitotic rate: 10 and 30 mitoses per 2 mm^2)
  - Methods
    - Histological and IHC evaluation
    - Tumor-based transcriptomic profiles were analyzed through unsupervised clustering
- Results
  - Histological and IHC features and molecular profiles of 3 of 4 borderline tumors were consistent with carcinoid
- Conclusion
  - These results support the emerging concept that NE tumors with carcinoid-like features and <20 mitoses per 2 mm^2 should be classified as carcinoids instead of LCNEC

Neoplastic Articles

Rokutan-Kurata M, et al. Discohesive growth pattern (Disco-p) as an unfavorable prognostic factor in lung adenocarcinoma: an analysis of 1062 Japanese patients with resected lung adenocarcinoma. Mod Pathol 2020;33:1722–1731.

- Background:
  - Disco-p was defined as an invasive growth pattern composed of single tumor cells, or trabeculae or small nests of tumor cells with desmoplastic fibrous stroma
  - According to the authors, Disco-p is often observed in lung adenocarcinoma (ADC) and mimics tumor budding, stromal invasive-type micropapillary pattern (SMPP), and complex glandular pattern
- Aim
  - To investigate the prognostic significance of Disco-p
- Methods
  - 1062 Japanese patients with resected lung ADC were studied
  - Percentage of Disco-p was recorded in 5% increments
- Results
  - Disco-p was observed in 203 tumors (19.1%)
  - It was significantly associated with male sex, smoking, lymph node metastasis, large tumor size, high TNM stage, lymphovascular and pleural invasion, spread through air spaces, and tumor budding (all, $p < 0.001$)
  - It was also associated with wildtype EGFR ($p < 0.001$) and ALK fusion ($p = 0.008$).
  - Patients harboring tumors with Disco-p had significantly worse prognoses (overall survival and disease free survival)
  - On multivariate analysis, Disco-p was an independent prognostic factor
- Conclusion
  - The authors proposed that Disco-p should be recognized as a new invasive pattern and accurately recorded for the better management of patients with lung ADCs

Trisolini R, et al. Pulmonary adenocarcinoma with psammoma bodies is associated with a specific endobronchial ultrasound pattern and a high prevalence of actionable driver mutations. Lung Cancer 2020;147:204–208.

- Background
  - Pulmonary adenocarcinoma with psammoma bodies is a rare histological variant of lung adenocarcinoma
- Aim
  - To describe the molecular profile of these tumors
- Methods
  - 15 patients were identified based on a starry sky EBUS pattern
- Results
  - Pathological examination of the EBUS-TBNA specimens revealed
    - 12 cases of pulmonary adenocarcinoma
    - 2 cases of breast carcinoma
    - 1 case of colonic carcinoma
  - Molecular profiling was performed on 11 of the 12 pulmonary adenocarcinoma cases; 10 genetic alterations were detected in 7 cases
    - 4 BRAF mutations
    - 2 EGFR mutation
    - 1 ALK rearrangement
    - 1 RET rearrangement
    - 1 PIK3CA mutation
    - 1 CDK4 amplification 1
- Conclusion
  - The authors suggest that pulmonary adenocarcinoma with psammoma bodies is associated with a high prevalence of actionable driver mutations

Koike Y, et al. Machine learning-based histological classification that predicts recurrence of peripheral lung squamous cell carcinoma. Lung Cancer 2020;147:252–258.

- Background
  - Cancer tissue is composed of cancer cells, necrosis and stroma
- Aim
  - To investigate if the dominant component predicts the prognosis for lung squamous cell carcinoma (SqCC)
- Methods
  - 135 peripheral SqCC cases (tumor size: 3−5 cm) were enrolled in this study
  - The following areas were measured using machine learning
    - Cancer cell area
    - Necrotic area
    - Stromal area
  - Cases were divided into the following three subtypes
    - Predominant cancer cell subtype
    - Predominant necrosis subtype
    - Predominant stroma subtype
- Results
  - The number of cases per subtype was as follows
    - Predominant cancer cell subtype: 59
    - Predominant necrosis subtype: 6
    - Predominant stroma subtype: 70
  - Patients with the predominant stroma subtype had a significantly shorter recurrence free survival (RFS) than those with the predominant cancer cell subtype (5-yr RFS: 42.3 % vs. 84.3 %,$p<0.01$)
  - In the multivariate analysis of p-stage I patients, the predominant stroma subtype was confirmed to be an independent prognostic factor for RFS ($p<0.01$)
- Conclusion
  - Using machine learning, the study confirmed that the predominant stroma subtype was an independent factor for RFS, suggesting that the ratio of the stromal component correlates with the malignant potential of SqCC

Ben Dori S, et al. Spatial heterogeneity of PD-L1 expression and the risk for misclassification of PD-L1 immunohistochemistry in non-small cell lung cancer. Lung Cancer. 2020;147:91-98.

- Background
  - Intra-tumor heterogeneity for PD-L1 expression in non-small cell lung cancer (NSCLC) might lead to inaccurate classification of patients into immunotherapy groups
- Aim
  - To quantitate the effect of various risk factors leading to inaccurate assessment of PD-L1 expression
- Methods
  - MATLAB software was used to model the fraction, distribution and clustering of PD-L1 positive cells
- Results
  - The computer-based model showed
    - A significant increase in error rate when the fraction of PD-L1 positive cells was closer to the cut-off value
    - An association between larger clusters of PD-L1 positive cells and higher error rate and
    - A negative correlation between the biopsy size and error rate
  - Analysis of the clinical samples supported the findings of the computer-based model
  - Based on the computerized model and clinical analysis, the authors developed a model to predict the error rate based on biopsy size and the fraction of PD-L1 positive cells
- Conclusion
  - Analysis of small biopsies for PD-L1 expression might be associated with significant error rate
  - The model presented can be used to identify cases with increased risk for error

Da Cruz V, et al. Histopathological subtyping is a prognostic factor in stage IV lung adenocarcinoma. Lung Cancer. 2020;147:77-82.

- Aim
    - To evaluate the prognostic role of histopathological subtypes in lung adenocarcinoma metastases
- Methods
    - This was a retrospective study of 253 patients
- Results
    - The presence of the solid subtype was related to overall survival; the median overall survival was 6.8 months when present and 11.1 months when absent
    - TTF-1 immunohistochemistry was also related to overall survival; the median overall survival was 11.2 months when positive and 4 months when negative
    - On multivariate analysis, the presence of solid subtype, TTF-1 positivity, age<60 years at the time of resection, performance status<2, treatment by chemotherapy, and treatment by tyrosine kinase inhibitor or immunotherapy were related to overall survival
- Conclusion
    - Evaluation of architectural pattern of metastases in stage IV patients provides further information for physicians about the prognosis

Kidokoro Y, et al. Gene expression profiling by targeted RNA sequencing in pathological stage I lung adenocarcinoma with a solid component. Lung Cancer 2020;147:56–63.

- Background
  - Solid predominant adenocarcinoma is considered an independent predictor of an unfavorable prognosis in patients with stage I lung adenocarcinoma (LUAD)
- Aim
  - To elucidate differentially expressed genes (DEGs) between solid component (SC) and acinar component (AC) within the same tumor tissue in pathological (p)-stage I LUAD patients
- Methods
  - LUAD tissue samples containing both SC and AC were obtained from 8 patients with p-stage I LUAD and each component was microdissected
  - Targeted RNA sequencing was performed by a high-throughput chip-based approach
- Results
  - In total, 1272 DEGs were identified, including 677 upregulated genes and 595 downregulated genes in SC compared with AC
  - The most highly upregulated gene was TATA binding protein associated factor 7 (TAF7) and the most highly downregulated gene was homeobox B3 (HOXB3), which acts as a metastasis suppressor
  - The staining score for PD-L1 in SC was significantly higher than that in AC by immunohistochemistry
- Conclusion
  - The results revealed several new DEGs and key PPI network in SC compared to AC, contributing to understanding the biological features of SC and providing therapeutic targets for early-stage LUAD with SC in the future

Roberts JM, et al. Radiological-pathological correlation of subsolid pulmonary nodules: A single centre retrospective evaluation of the 2011 IASLC adenocarcinoma classification system. Lung Cancer 2020;147:39–44.

- Background
  - The 2011 IASLC classification system proposes guidelines for radiologists and pathologists to classify adenocarcinomas spectrum lesions as
    - Preinvasive minimally invasive adenocarcinoma (MIA), or
    - Invasive adenocarcinoma (IA)
  - Imaging distinction between MIA and IA is controversial
- Methods
  - Subsolid pulmonary nodules resected by microcoil localization over a three-year period were retrospectively reviewed by three chest radiologists and a pulmonary pathologist
  - Nodules were classified radiologically based on preoperative computed tomography (CT), with the solid nodule component measured on mediastinal windows applied to high-frequency lung kernel reconstructions, and pathologically according to 2011 IASLC criteria
  - Radiology interobserver variability and radiological-pathological variability of nodule classification, and potential reasons for nodule classification discordance were assessed
- Results
  - 71 subsolid nodules in 67 patients were included
  - The average size of invasive disease focus at histopathology was 5mm
  - Radiology interobserver agreement of nodule classification was good (Cohen's Kappa=0.604, 95 % CI: 0.447 to 0.761)
  - Agreement between consensus radiological interpretation and pathological category was fair (Cohen's Kappa=0.236, 95 % CI: 0.054−0.421)
  - Radiological and pathological nodule classification were concordant in 52 % (37 of 71) of nodules
  - The IASLC proposed CT solid component cut-off of 5mm to distinguish MIA and IA yielded a sensitivity of 59 % and specificity of 80 %
  - Common reasons for nodule classification discordance included multiple solid components within a nodule on CT, scar and stromal collapse at pathology, and measurement variability
- Conclusion
  - Solid component(s) within persistent part-solid pulmonary nodules raise suspicion for invasive adenocarcinoma
  - Preoperative imaging classification is frequently discordant from final pathology, reflecting interpretive and technical challenges in radiological and pathological analysis

Gachechiladze M, et al. Prognostic value of tumor-infiltrating lymphocytes (TILs) and their association with PD-L1 expression and DNA repair protein RAD51 in patients with resected non-small cell lung carcinoma. Lung Cancer 2020;147:30-38.

- Background
    - DNA repair proteins have emerged as potential predictors for immunotherapy response alongside PDL1 expression, tumor-infiltrating lymphocytes (TILs) and tumor mutational burden.
- Aim
    - To analyze expression of PD-L1, TIL count and expression of the homologous recombination (HR) protein RAD51, as potential prognostic factors in patients with resected non-small-cell lung carcinoma (NSCLC)
- Methods
    - Discovery set included 96 NSCLC patients from the University Hospital Olomouc (Czech Republic) and a replication set included 1109 NSCLC patients from University Hospital Zurich (Switzerland)
    - Tissue microarrays (TMAs) were stained using the automated staining platform Ventana Benchmark Ultra with antibodies against RAD51, CD3, CD8, CD68 and PD-L1.
- Results
    - Loss of nuclear RAD51 protein was associated with high TILs and PD-L1 status in patients receiving neoadjuvant chemo-/radiotherapy (CT/RT).
    - High TILs status was significantly associated with improved OS in the replication set
- Conclusions
    - RAD51 nuclear loss is weakly associated with increased TILs and high PD-L1 at the time of surgery in curatively resected NSCLC and after prior exposure to neoadjuvant chemo- or radiotherapy
    - Both high TILs and RAD51 nuclear loss were confirmed as independent prognostic factors in curatively resected NSCLC

Hermelijn SM, et al. Early KRAS oncogenic driver mutations in nonmucinous tissue of congenital pulmonary airway malformations as an indicator of potential malignant behavior. Hum Pathol. 2020;103:95-106.

- Background
    - The potential for malignant degeneration is the most common reason for some practitioners to resect asymptomatic congenital pulmonary airway malformations (CPAMs)
- Aim
    - To investigate the potential of various immunohistochemical (IHC) and genomic biomarkers to predict the presence of mucinous proliferations (MPs) in CPAM
- Methods
    - Archival CPAM tissue samples were re-assessed and underwent IHC analysis using a panel of differentiating markers (TTF1/CDX2/CC10/MUC2/MUC5AC/p16/p53/DICER1)
    - In each sample, intensity of IHC staining was assessed separately in normal lung tissue, CPAM, and MP tissue, using a semiquantitative approach
    - Likewise, next-generation targeted sequencing of known adult lung driver mutations, including KRAS/BRAF/EGFR/ERBB2, was performed in all samples with MP and in control samples of CPAM tissue without MP
- Results
    - We analyzed samples of 25 CPAM type 1 and 25 CPAM type 2 and found MPs in 11 samples
    - They were all characterized by strong MUC5AC expression, and all carried a KRAS mutation in the MP and adjacent nonmucinous CPAM tissue, whereas the surrounding normal lung tissue was negative
    - By contrast, in less than half (5 out of 12) control samples lacking MP, the CPAM tissue also carried a KRAS mutation
- Conclusion
    - KRAS mutations in nonmucinous CPAM tissue may identify lesions with a potential for malignant degeneration and may guide histopathological assessment and patient follow-up

Hayashi T, et al. Clinicopathological characteristics of lung adenocarcinoma with compound EGFR mutations. Hum Pathol. 2020;103:42-51.

- Background
  - It is becoming clearer that some EGFR-mutated lung adenocarcinomas possess more than one type of EGFR mutations (compound mutations)
  - However, clinicopathological impacts of these compound EGFR mutations in lung adenocarcinoma remain unclear
- Aim
  - To evaluate clinicopathological characteristics of lung adenocarcinomas with compound EGFR mutations in comparison with cases with common or uncommon single mutations
- Results
  - Among 64 compound EGFR mutations, L858R/E709G (9%) was the most frequent mutation type, followed by L858R/S768I (8%), L858R/T790M (8%), and L858R/L833V (6%)
  - Both single and compound mutations were frequently observed in women, never or light smokers; their adenocarcinomas showed thyroid transcription factor-1 immunoreactivity
  - In contrast, compound mutations were significantly associated with lymph node metastases and the presence of tumor cells with clear cytoplasm
  - Furthermore, patients with compound mutations had significantly poorer prognoses than cases with single EGFR mutations
- Conclusions
  - Overall, clinicopathological features of common, uncommon, and compound EGFR mutations are similar; however, tumors with compound mutations may be characterized by aggressive behavior and histological findings of clear cell features

Perrotta F, et al. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for PD-L1 Testing in Non-small Cell Lung Cancer. CHEST 2020; 158:1230-1239.

- Background
    - Programmed death-ligand 1 (PD-L1) expression on cancer cells is a clinically important biomarker to select patients with non-small cell lung cancer (NSCLC) for treatment with programmed death-1/PD-L1 inhibitors
    - Clinical trials of immunotherapy in patients with NSCLC require histologic PD-L1 testing
- Aim
    - To investigate whether endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) samples are adequate for PD-L1 testing in NSCLC
- Methods
    - 577 NSCLC specimens were analyzed from consecutive patients with NSCLC across six centers in the United Kingdom and one center in the United States between January 2015 and December 2016
- Results
    - In the EBUS-TBNA group (189 specimens), the overall percentage of patients with successful PD-L1 testing was 94.7%
    - There was no significant difference in sampling adequacy with other methods of tissue acquisition.
    - Older patients had higher failure rates of PDL1 testing
    - In multivariate analysis, advanced N-stage and presence of brain metastasis were associated with high PD-L1 expression.
- Conclusion
    - This large multicenter study shows that EBUS-TBNA provides samples adequate for PD-L1 testing and that advanced N stage and the presence of brain metastasis are associated with high PD-L1 expression

Dermawan JKT, et al. Malignancies in Pleural, Peritoneal, and Pericardial Effusions. Arch Pathol Lab Med. 2020;144:1086–1091.

- Background
  - The incidence and types of malignancies in effusion cytology are largely limited to studies performed in the 1970s through the 1990s
- Aim
  - To examine how the incidence of different types of malignancies in effusions has changed with time
- Methods
  - A computerized search for fluid cytology from 2000 through 2016 (database included age, gender, cytologic diagnosis, and type of malignancy) was performed, and all cases were reviewed.
- Results
  - Of 30 085 effusion specimens, 3285 (11%) were positive for malignancy
    - 2175 pleural
    - 955 peritoneal
    - 155 pericardial
  - Malignancy was more common in females than males in both pleural (15% versus 9%) and peritoneal (14% versus 5%) effusions
  - The most common metastatic tumors
    - In pleural fluid were
      - Lung for males
      - Breast for females
    - In peritoneal fluid
      - Hematolymphoid for males
      - Mullerian tumors for females
    - In pericardial fluid
      - Lung for both genders
  - Among invasive mammary carcinomas, lobular carcinoma tended to metastasize to peritoneal fluid, whereas ductal carcinoma tended to metastasize to pleural fluid
  - Plasma cell neoplasms metastasized to pleural and pericardial but not peritoneal fluid
- Conclusions
  - Although pulmonary and Mullerian tumors continue to be the most common origin of metastasis in pleural and peritoneal fluid for males and females, respectively, the frequencies for other malignancies have changed

Zhang YZ. Et al. Presence of pleomorphic features but not growth patterns improves prognostic stratification of epithelioid malignant pleural mesothelioma by 2-tier nuclear grade. Histopathology 2020, 77, 423–436.

- Background
    - Nuclear grade has been recently validated as a powerful prognostic tool in epithelioid malignant pleural mesothelioma (E-MPM)
- Aims
    - To validate the prognostic role of pleomorphic features in EMPM and
    - To investigate if evaluating growth pattern in addition to 2-tier nuclear grade improves prognostication
- Methods
    - 614 consecutive cases of E-MPM over a period of 15 years were retrospectively reviewed
- Results
    - 51 showed pleomorphic features.
    - E-MPM with pleomorphic features showed significantly worse overall survival compared to those without (5.4 versus 14.7 months)
    - Tumours with predominantly micropapillary pattern showed the worst survival (6.2 months) followed by solid (10.5 months), microcystic (15.3 months), discohesive (16.1 months), trabecular (17.6 months) and tubulo-papillary (18.6 months)
    - Sub-classification of growth patterns into high grade (solid, micropapillary) and low grade (all others) led to good separation of overall survival (10.5 versus 18.0 months) but did not predict survival independent of 2-tier nuclear grade
    - A composite score comprised of growth pattern and 2-tier nuclear grade did not improve prognostication compared with nuclear grade alone
    - Intra-tumoral heterogeneity in growth patterns is extensive
- Conclusions
    - The findings support the incorporation of E-MPM with pleomorphic features in the epithelioid subtype as a highly aggressive variant distinct from 2-tier nuclear grade
    - E-MPM demonstrates extensive heterogeneity in growth pattern but its evaluation does not offer additional prognostic utility to 2-tier nuclear grade

Brcic L, et al. Pleuropulmonary blastoma type I might arise in congenital pulmonary airway malformation type 4 by acquiring a Dicer 1 mutation. Virchows Archiv 2020;477:375–382.

- Background
  - Congenital pulmonary airway malformation (CPAM) occurs most commonly in infants; it is divided into 5 types.
    - Type 0 presents as bronchial buds without alveolar tissue, most likely corresponding to alveolar dysgenesis
    - Types 1 and 2 (most common types) are cystic
    - Type 3 is composed of branching bronchioles and appears as a solid lesion
    - Type 4 is a peripheral cystic lesion with a thin cyst wall covered by pneumocytes; it has been confused with pleuropulmonary blastoma (PPB) type I and some authors question its existence.
- Aim
  - To investigate 5 cases of CPAM type 4 for the presence or absence of rhabdomyoblasts, and for markers associated with CPAM development
  - In addition, all cases were evaluated for mutations within the Dicer gene and for mutations of the RAS family of oncogenes
- Results
  - All 5 cases showed smooth muscle actin and desmin-positive cells; however, only one case showed a few cells positive for MyoD
  - The same case showed a mutation of Dicer 1
  - All cases were negative for mutations of the RAS family of genes
  - Fibroblast growth factor 10 was similarly expressed in all cases, and thus cannot be used to differentiate CPAM4 from PPB-I
  - Low expression of the proliferation marker Ki67 was seen in CPAM 4 cases and the probable PPB-I case
- Conclusion
  - YingYang-1 protein seems to play an active role in the development of PPB-I
  - CPAM4 can be separated from PPB-I based on the presence of rhabdomyoblasts and mutations in Dicer 1 gene
  - These cells might not be numerous; therefore, all available tissue has to be evaluated
  - As CPAM 4 morphologically looks very similar to PPB-I, it might be speculated, that there exists a potential for progression from CPAM 4 to PPB-I, by acquiring somatic mutations in Dicer 1

Non-Neoplastic Articles

Tanabe N, et al. Pathological Comparisons of Paraseptal and Centrilobular Emphysema in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2020;202:803–811.

- Background
  - Paraseptal emphysema (PSE) refers to a morphological subtype of pulmonary emphysema located adjacent to the pleura and septal lines with a peripheral distribution within the secondary pulmonary lobule; the affected lobules are almost always subpleural and demonstrate small focal lucencies up to 10 mm in size
  - Although centrilobular emphysema (CLE) and PSE are commonly identified on multidetector computed tomography (MDCT), little is known about the pathology associated with PSE compared with that of CLE
- Aims
  - To assess the pathological differences between PSE and CLE in COPD
- Methods
  - Air-inflated frozen lung specimens (n = 6) obtained from patients with severe COPD treated by lung transplantation were scanned with MDCT
  - Frozen tissue cores were taken from central (n = 8) and peripheral (n = 8) regions of each lung, scanned with micro–computed tomography (microCT), and processed for histology
  - microCT-based volume fractions of CLE and PSE allowed classifying cores into
    - Mild emphysema
    - CLE-dominant
    - PSE-dominant
- Results
  - The percentages of PSE measured on MDCT and microCT were positively associated
  - The number of terminal bronchioles per milliliter of lung and cross-sectional lumen area were significantly lower and wall area percentage was significantly higher in CLE-dominant regions compared with mild emphysema and PSE-dominant regions
  - Immunohistochemistry showed significantly higher infiltration of neutrophils, but not of macrophages, CD4, CD8, or B cells, in PSE compared with CLE regions
- Conclusions
  - The terminal bronchioles are relatively preserved, whereas neutrophilic inflammation is increased in PSE-dominant regions compared with CLE-dominant regions in patients with COPD

Reviews

Sholl LM, et al. The Promises and Challenges of Tumor Mutation Burden as an Immunotherapy Biomarker: A Perspective from the International Association for the Study of Lung Cancer Pathology Committee. J Thorac Oncol 2020;15:1409-1424.

Pal P, Chetty R. Multiple sclerosing pneumocytomas: a review. J Clin Pathol 2020;73:531–534.

Calabrese F, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. Virchows Archiv 2020;477:359–372.

Aquila I, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic: Review of the Literature and Proposal for Safe Autopsy Practice. Arch Pathol Lab Med. 2020;144:1048–1056.

Yang F, et al. Cribriform growth pattern in lung adenocarcinoma: More aggressive and poorer prognosis than acinar growth pattern. Lung Cancer 2020;147:187–192.

Editorial

Tzankov A, Jonigk D. Unlocking the lockdown of science and demystifying COVID-19: how autopsies contribute to our understanding of a deadly pandemic. Virchows Archiv 2020;477:331–333.

Commentary

Rossi G. Pleuropulmonary blastoma type I and congenital pulmonary airway malformation type 4: distinct entities or sides of the same coin? Virchows Archiv 2020;477:373–374.

Case Reports

Heinrich F, et al. Germany's first COVID-19 deceased: a 59-year-old man presenting with diffuse alveolar damage due to SARS-CoV-2 infection. Virchows Archiv (2020) 477:335–339.

Pezzuto F, et al. Lesson of the Month: Immunohistochemical neuroendocrine marker expression in primary pulmonary NUT carcinoma: a diagnostic pitfall. Histopathology 2020, 77, 508–510.

Yan L, et al. COVID-19 in a Hispanic Woman: Autopsy Report with Clinical-Pathologic Correlation. Arch Pathol Lab Med. 2020;144:1041–1047.

Konopka KE, … Myers JL. Postmortem Lung Findings in a Patient with Asthma and Coronavirus Disease 2019. CHEST 2020; 158:e99-e101

Yap V. An Older Woman With Transient Cough, Mild Airway Obstruction, and Lung Nodules. CHEST 2020; 158(3):e111-e115.

- Diagnosis: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, carcinoid tumorlets, carcinoid tumors, occurring concurrently

Dodge DL, et al. A 35-Year-Old Woman with Progressive Dyspnea and Cough. CHEST 2020; 158(3):e103-e106.

- Diagnosis: Pulmonary alveolar microlithiasis

Tzilas V, et al. A 77-Year-Old Woman with Sjogren Syndrome Experiencing Progressive Dyspnea on Exertion and Nonproductive Cough. CHEST 2020; 158(3):e117-e121.

- Diagnosis: Marginal zone B-cell bronchus associated lymphoid tissue lymphoma, fibrotic nonspecific interstitial pneumonia in the context of Sjögren syndrome

Papan C, et al. A 71-Year-Old Man With Chest Pain and a Solitary Pulmonary Mass. CHEST 2020; 158(3):e123-e126.

- Diagnosis: Localized pulmonary mucormycosis caused by Rhizopus arrhizus (synonymous: Rhizopus oryzae)

Kamp JC, et al. Recurrent Life-threatening Pneumonitis in a 37-Year-Old Woman. CHEST 2020; 158:e127-e132.

- Diagnosis: Primary Sjögren syndrome with lung involvement

Oyama T, et al. Squamous Cell Carcinoma of the Lung with Micropapillary Pattern. J Thorac Oncol. 2020;15:1541-1544.

Hibino M, et al. Localized Tracheal Cryptococcosis Misdiagnosed as Severe Refractory Asthma. Am J Respir Crit Care Med 2020;202:e92–e94.