

**PULMONARY PATHOLOGY JOURNAL CLUB**  
**(March 2021 Articles)**

Presented by Kristine Konopka, M.D.

Michigan Medicine

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**List of review articles, case reports, and letters to the editor**

*Review articles*

Beasley MB et al. Pleural mesothelioma classification update. *Virchows Arch* 2021; 478:59-72.

Bohnenberger H et al. Recent advances and conceptual changes in the classification of neuroendocrine tumors of the thymus. *Virchows Arch* 2021; 478:129-35.

Bösmüller H et al. The pulmonary pathology of COVID-19. *Virchows Arch* 2021; 478:137-50.

Canberk S et al. Cytology samples and molecular biomarker testing in lung cancer – advantages and challenges. *Virchows Arch* 2021; 478:45-57.

Chatzopoulos K et al. Update on genetically defined lung neoplasms: NUT carcinoma and thoracic SMARCA4-deficient undifferentiated tumors. *Virchows Arch* 2021; 478:21-30.

Fernandez-Cuesta L et al. Challenges in lung and thoracic pathology: molecular advances in the classification of pleural mesotheliomas. *Virchows Arch* 2021; 478:73-80.

Marx A et al. Molecular pathology of thymomas: implications for diagnosis and therapy. *Virchows Arch* 2021; 478:101-10.

Metovic J et al. Morphologic and molecular classification of lung neuroendocrine neoplasms. *Virchows Arch* 2021; 478:5-19.

Oramas DM et al. Major pathologic response in patients treated for non-small cell carcinoma of the lung: is there a magic number in the histologic sections to be evaluated? *Adv Anat Pathol* 2021; 28:67-71.

Roden AC et al. Common and rare carcinomas of the thymus. *Virchows Arch* 2021; 478:111-28.

Smith ML et al. Vaping-related lung injury. *Virchows Arch* 2021; 478:81-8.

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Verleden SE et al. Molecular approach to the classification of chronic fibrosing lung disease – there and back again. *Virchows Arch* 2021; 478:89-99.

#### Case reports

Günther G et al. Pulmonary alveolar microlithiasis complicated by tuberculosis. *N Engl J Med* 2021; 384:e36.

Lazzaro MC et al. A potential case of asbestos-related granulomatosis due to adulterant contamination in a drug user. *Virchows Arch* 2021; 478:361-6.

Lee MH et al. Histopathological correlation of acute on chronic eosinophilic pneumonitis caused by vaporized cannabis oil inhalation. *CHEST* 2021; 153:e137-9.

#### Letters to the editor

Bain WG et al. Lower respiratory tract myeloid cells harbor SARS-CoV-2 and display an inflammatory phenotype. *CHEST* 2021; 159:963-6.

Edupuganti S et al. Organizing pneumonia as a manifestation of coronavirus disease 2019. *Pathol Int* 2021; 71:210-2.

Ren P et al. A novel TNIP2-RET fusion identified in a patient with mucinous adenocarcinoma of the lung. *Lung Cancer* 2021; 153:179-81.

Wang B et al. PLB1-ALK: A novel head-to-head fusion gene identified by next-generation sequencing in a lung adenocarcinoma patient. *Lung Cancer* 2021; 153:176-8.

Zhai X et al. OFCC1-ALK (Ointergenic: A20): A novel OFCC1 intergenic region-ALK fusion identified from a lung adenocarcinoma patient. *Lung Cancer* 2021; 153:171-3.

## Discussion articles

**Han YB et al. Tumor spread through air spaces (STAS): prognostic significance of grading in non-small cell lung cancer. *Mod Pathol* 2021; 34:549-61.**

*Prepared and presented by Dr. Rachael Fels Elliott (Thoracic Pathology Fellow 2020/2021)*

**Purpose:** To investigate the association of the extent of STAS (using a 2-tiered grading system) with clinicopathologic features and patient outcomes in surgically resected NSCLC.

### **Methods:**

- Reviewed 2775 pathology reports of surgically resected lung cancers (2011-2018)
- Identified 1869 NSCLC cases: 1544 adenocarcinoma (ADC) and 325 squamous cell carcinoma (SCC)
  - Excluded: NE neoplasms, other malignancy, neoadjuvant therapy
- **Definition of STAS** (aerogenous spread): Micropapillary or solid clusters of or single tumor cells free floating within air spaces beyond the edge of the tumor
  - Excluded artifacts: Tumor clusters with jagged edges (knife cuts), linear strips lifted off the alveolar walls, isolated clusters at a distance rather than spreading continuously
- **Grading system (2-tiered):** Performed prospectively by a single pulmonary pathologist since 2011
  - I: distance from the edge of tumor < 2500  $\mu\text{m}$  (one 10x objective field)
  - II: distance from the edge of tumor  $\geq$  2500  $\mu\text{m}$  (one 10x objective field)

### **Results:**

#### *Clinicopathologic characteristics*

- **Table 1** (NSCLC): STAS in 41% (765 cases: 684 ADC, 81 SCC); 24% STAS I and 17% STAS II
  - Presence and extent of STAS associated with ADC (vs. SCC), pleural invasion, LVI, necrosis, higher pathologic stage, lobectomy (vs. limited resection)
  - No differences for clinical variables (sex, age, smoking) or surgical approach (VATS vs open)
- **Table 2** (ADC):
  - Presence and grade of STAS were associated with the predominant growth pattern (micropapillary > solid > papillary > acinar > lepidic)
  - Presence of micropapillary pattern (regardless of amount) was associated with STAS
  - STAS was more often found in *EGFR* wild-type tumors, but no association with grade

#### *Survival Analysis*

- **Figure 2:** In ADC, extent of STAS associated with shorter recurrence free survival, overall survival and lung cancer specific survival

- 5-year RFS: No STAS (91.8%), STAS1 (79%), STAS 2 (60.5%)
- 5-year OS: No STAS (95%), STAS1 (88%), STAS 2 (74%)
- No differences in survival for SCC
- **Subgroup analysis: Stage IA non-mucinous ADC**
  - STAS II associated with shorter recurrence free survival and lung cancer specific survival
  - STAS II was an independent risk factor for recurrence in limited and radical resection
  - STAS I had no bearing on recurrence in multivariate analysis

**Take-home message:** STAS II was an independent poor prognostic factor in low stage non-mucinous ADC, regardless of the extent of resection. This data suggests that including presence and grade of STAS in pathology reports could be useful; however, large-scale, multi-institutional studies are needed to establish a global standard for grading the extent of STAS.

**Li Y et al. Progression to fibrosing diffuse alveolar damage in a series of 30 minimally invasive autopsies with COVID-19 pneumonia in Wuhan, China. *Histopathology* 2021; 78:542-55.**

**Purpose:** Document the evolution of diffuse alveolar damage (DAD) in patients that die of COVID-19 pneumonia and correlate the progression to fibrosing DAD with patient age, duration of clinical course, hospitalization, and mechanical ventilation

**Methods:**

- Consecutively reviewed lung tissue and medical records on minimally invasive autopsies performed at a Wuhan, China, hospital from patients who tested positive for SARS-CoV-2 or had positive antibodies prior to death
  - Minimally invasive autopsy: Ultrasound-guided core needle biopsies performed on bilateral lungs to obtain at least 4 to 5 tissue samples
- Slides reviewed by 3 pathologists
- DAD classified as acute, organizing, or fibrosing based upon prominent component, and other pathologic findings noted (detailed in Supplemental Table 1)

**Results:**

- 30 patients with COVID-19 underwent minimally invasive autopsy between February and March 2020
- Table 1 details clinical characteristics, duration of illness, hospitalization, treatment(s), and days of ventilatory support
  - Mean age 69 years (39-91 years)
  - 20 males; 10 females
  - Most patients had at least 1 significant underlying illness
    - Hypertension > malignancy > CAD; only 1 with respiratory disease (COPD)
  - Chest CT only available for 1 patient (refer to Supplemental Information)
- DAD diagnosed in 28 of 30 cases (93%)
  - DAD cause of death in 28 patients; acute pneumonia and gastric cancer in 2
  - Most cases showed multiple patterns, but predominant patterns were as follows:
    - Acute,  $n = 9$
    - Organizing,  $n = 7$
    - Fibrosing,  $n = 12$  (refer to Figure 2 for pattern of fibrosis)
- Table 2 details clinical correlations with predominant DAD patterns
  - Fibrosing DAD patients on average younger and ventilated longer than patients with acute or organizing DAD
  - Patients with organizing or fibrosing DAD had longer days of illness and hospitalization than those with acute DAD

**Take-home message:** Patients with prolonged hospitalization and ventilation, who die of COVID-19-related, may develop fibrosing DAD that is morphologically characterized by diffuse alveolar septal thickening by collagenous fibrosis. This begs the question – Will we see an increase in fibrosing lung disease as a result of the COVID-19 pandemic?

**Zhang Y et al. Excellent prognosis of patients with invasive lung adenocarcinomas during surgery misdiagnosed as atypical adenomatous hyperplasia, adenocarcinoma in situ, or minimally invasive adenocarcinoma by frozen section. CHEST 2021; 159:1265-72.**

**Purpose:** Investigate the prognosis of patients who undergo sublobar resection for intraoperatively diagnosed atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA), who are later reclassified as having invasive adenocarcinoma in their final pathology report.

**Methods:**

- Retrospectively reviewed the clinical characteristics, CT scans, tumor characteristics, and outcomes of patients who underwent frozen section and surgical resection for lung nodules between January 2012 and December 2018
  - Inclusion criteria: 1) Diagnosis of primary lung adenocarcinoma; 2) Intraoperative frozen section diagnosed as AAH, AIS, MIA; 3) Subtotal resection performed
- Frozen sections sampled 1 slice from largest diameter of tumor and interpreted by 2 pathologists, but if there was disagreement a 3<sup>rd</sup> pathologist also involved in diagnosis

**Results:**

- 3,031 cases met inclusion criteria
- 192 (6.3%) found to have a discrepancy between frozen section and final pathology
  - MIA ( $n = 183$ ) > AIS ( $n = 7$ ) > AAH ( $n = 2$ )
  - >98% of cases diagnosed as invasive lepidic, acinar, or papillary-predominant on final pathology (frozen section and final pathology detailed in Table 2)
  - Refer to Table 1 for detailed pathologic staging-related data
    - 97.4% of tumors  $\leq 2$  cm
    - 1 case had visceral pleural invasion
    - All case that underwent lymph nodes sampling ( $n = 148$ ) pN0
- 4 patients underwent subsequent completion lobectomy and lymph node dissection
- 100%, 5-year recurrence-free and overall survival
  - 5 patients who only underwent wedge resection developed a 2<sup>nd</sup> primary cancer in different lobes

**Take-home message:** If you are asked to differentiate between AAH/AIS/MIA and invasive adenocarcinoma on frozen section to guide surgical strategy, do not despair if you misclassify a lesion and the patient does not undergo completion lobectomy. In patients with small lung cancers ( $\leq 2$  cm), they will almost certainly still do well!



**Kunnath-Velayudhan S et al. Masson trichrome and sulfated Alcian blue stains distinguish light chain deposition disease from amyloidosis in the lung. Am J Surg Pathol 2021; 45:405-13.**

**Purpose:** 1) Evaluate the use of Masson trichrome (MT) and sulfated Alcian blue (SAB) stains to distinguish pulmonary light chain deposition disease (PLCDD) from amyloid; and 2) assess the presence of lymphoid or plasma cell neoplasms occurring in association with PLCDD

**Methods:**

- Identified lung specimens diagnosed as PLCDD or had features typical for light chain deposition disease at Columbia University and Mayo Clinic between 2010 and 2020
  - Diagnostic algorithm detailed in Figure 1
  - Immunohistochemistry, in situ hybridization, +/- immunoglobulin heavy chain gene rearrangement performed to characterize the inflammatory infiltrate
- 10 cases pulmonary amyloid used as controls

**Results:**

- 11 cases of PLCDD identified (patient characteristics detailed in Table 1)
  - 4 cases originally not recognized as having PLCDD
  - Mean age ~60 years; female > male
  - Most patients asymptomatic
  - Radiographic nodules seen most commonly
    - 1 case cystic lung disease; 1 case nodules and cysts
  - Pathologic assessment detailed in Table 2
    - Congo red negative / MT bright red / SAB salmon pink (Figure 3 illustrative)
    - Light chain deposits: kappa ( $n = 10$ ) > lambda ( $n = 1$ )
    - 10 cases of MALT lymphoma with extensive plasmacytic differentiation; 1 case of multiple myeloma
- Refer to Table 3 for diagnostic characteristics of PLCDD versus amyloid

**Take-home message:** A combination of Congo red, MT, and SAB are helpful in distinguishing non-amyloid light chain deposition from amyloid, and establishing a diagnosis of PLCDD with more confidence than simply relying on a negative Congo red.

## **Articles for notation**

### *Neoplastic lung disease*

**Alidousty C et al. Prevalence and potential biological role of TERT amplifications in ALK translocated adenocarcinoma of the lung. *Histopathology* 2021; 78:578-85.**

**Take-home message:** In this study, 109 ALK-translocated lung adenocarcinomas were screened for *TERT* amplification using FISH. Five cases (4.6%) showed *TERT* amplification and 4 of these subsequently underwent genetic further interrogation, which showed genetic instability. The histologic patterns associated with *TERT* amplification included papillary ( $n = 2$ ) and solid ( $n = 3$ ) growth patterns.

**Amemiya R et al. Prognostic impact of the tumor immune microenvironment in pulmonary pleomorphic carcinoma. *Lung Cancer* 2021; 153:56-65.**

**Take-home message:** Immunohistochemical stains for E-cadherin, vimentin, PD-L1, CA-IX, CD204, Foxp3, CD8, and CD20 were applied to 80 cases of pleomorphic carcinoma to characterize the immune microenvironment. The aim was to correlate the scores of these immunostains with patient outcomes. High ( $\geq 50\%$ ) PD-L1 expression in adenocarcinomas and large cell carcinomas was associated with longer 5-year overall survival and recurrence-free survival; however, this did not hold true for squamous cell carcinomas and PD-L1 showed no prognostic significance.

**Boland JM et al. Molecular genetic landscape of sclerosing pneumocytomas: evidence of aberrant mTOR pathway signaling and lack of recurrent translocations. *Am J Clin Pathol* 2021; 155:397-404.**

**Take-home message:** In this work from the Mayo Clinic, 10 cases of sclerosing pneumocytoma from 8 patients (1 with two tumors; 1 with multiple, bilateral tumors) underwent next-generation sequencing and RNA-seq. Mutations in *AKT* were identified in 7 of 9 specimens and 1 had mutations in both *PTEN* and *PIK3RI*, suggesting that abnormal activation of PIK3/AKT/mTOR pathway is a consistent oncologic events in sclerosing pneumocytomas. No recurrent fusion genes were identified.

**Chia PL et al. Expression of EGFR and conformational forms of EGFR in malignant pleural mesothelioma and its impact on survival. *Lung Cancer* 2021; 153:35-41.**

**Take-home message:** To expand on the title, the aim of this study was to determine the prevalence of wtEGFR expression and *EGFR* amplification, including conformational forms, by immunohistochemistry and FISH, and correlate those findings with survival in 329 tissue microarrays from patients with malignant mesothelioma. EGFR overexpression was most common in epithelioid mesothelioma; however, overexpression was not associated with true *EGFR* amplification. A conformational form of EGFR was detected in 8.2% of cases, 84.6% of which were the epithelioid subtype, and seemed to be associated with poorer outcomes; however, this finding was not statistically significant.

**Hashemi S et al. Surprising impact of stromal TIL's on immunotherapy efficacy in a real-world lung cancer study. *Lung Cancer* 2021; 153:81-9.**

**Take-home message:** Here, the authors retrospectively assessed the impact of various clinicopathologic variables in patients with metastatic non-small cell lung cancer, who were treated with immunotherapy agents, nivolumab or pembrolizumab. The entire cohort comprised 366 patients all of whom had PD-L1 testing on their tumors, while 141 of these also had PD-L1 expression reported in the stroma and assessment of the CD8+ infiltrate in the tumor and stroma. The strongest pathologic predictor of progression free survival and overall survival was the presence of CD8+ stromal lymphocytes.

**Ikeda T et al. The epithelial-mesenchymal transition phenotype is associated with the frequency of tumor spread through air spaces (STAS) and a high risk of recurrence after resection of lung carcinoma. *Lung Cancer* 2021; 153:49-55.**

**Take-home message:** The authors retrospectively assessed 635 lung resections for adenocarcinoma and squamous cell carcinoma and discovered that STAS was present in 44% of cases, more commonly seen in adenocarcinomas, particularly those with micropapillary and solid types, and patients with higher pathologic stage, lymphovascular invasion, and pleural invasion. Immunohistochemistry for markers of EMT (E-cadherin, vimentin, and  $\beta$ -catenin) were applied to the tumors to evaluate the associated between an epithelial (E-cadherin+/vimentin-), intermediate (E-cadherin+/vimentin+ or E-cadherin-/vimentin-, and mesenchymal E-cadherin-/vimentin+) phenotype and the presence of STAS. STAS was associated with nuclear translocation of  $\beta$ -catenin and more often observed in tumors with an intermediate or mesenchymal phenotype than an epithelial phenotype, and the mesenchymal phenotype was found to be an independent predictor of high risk for recurrence.

**Li R et al. Pseudo-small cell transformation in EGFR-mutant adenocarcinoma. *Lung Cancer* 2021; 153:120-5.**

**Take-home message:** For purposes of this study, small cell transformation is defined by the authors as patients originally diagnosed as *EGFR*-mutant adenocarcinoma on lung biopsy or resection, who went on to have small cell carcinomas identified on re-biopsy of the lung or biopsies of distant metastases, indicating that the tumor transformed to small cell carcinoma. Fourteen cases of "small cell transformation" were identified, including 1 case reported as combined adenocarcinoma and small cell carcinoma on initial biopsy; however, re-review of the initial biopsies revealed previously not identified small cell components in the majority of these cases (up to 90%) and those cases were re-categorized as "pseudo-small cell transformation." The authors also found that mutated *EGFR* expression by immunohistochemistry was limited to the adenocarcinoma component, leading them to conclude that only the adenocarcinoma component would respond to *EGFR* tyrosine kinase inhibitors.

**Suzuki J et al. Relationship between podoplanin-expressing cancer-associated fibroblasts and the immune microenvironment of early lung squamous cell carcinoma. *Lung Cancer* 2021; 153:1-10.**

**Take-home message:** The authors investigated the relationship between podoplanin-expressing tumor-associated fibroblasts and the tumor microenvironment in stage I lung squamous cell carcinoma through gene expression profiles and the use of immunohistochemistry. *In vitro* studies of podoplanin-high squamous cell carcinoma fibroblasts showed higher secretion of immunosuppressive cytokines. Patient sample testing also seemed to suggest that podoplanin-expression resulted in an immunosuppressive tumor microenvironment.

**Takagi H et al. Delta-like 1 homolog (DLK1) as a possible therapeutic target and its application to radioimmunotherapy using <sup>125</sup>I-labelled anti-DLK1 antibody in lung cancer models (HOT1801 and FIGHT004). *Lung Cancer* 2021; 153:134-42.**

**Take-home message:** The expression of DLK1 was evaluated in 112 cases of small cell lung carcinoma (SCLC) and 101 cases of non-small cell lung carcinoma (NSCLC) and examined to learn if there is prognostic significance. Twenty-one percent of SCLC and 17% of NSCLC expressed DLK1; however, expression was only associated with lymph node metastases in NSCLC and therefore perhaps not surprisingly poorer recurrence-free survival, but was otherwise of no special significance. The authors further showed that DLK1 might serve as a novel therapeutic target for immunotherapy using *in vitro* and animal models.

#### Non-neoplastic lung disease

**Barisione E et al. Fibrotic progression and radiologic correlation in matched lung samples from COVID-19 post-mortems. *Virchows Arch* 2021; 478:471-85.**

**Take-home message:** In this Italian study, 8 patients who were ventilated and SARS-CoV2-positive, underwent cyrobiopsy immediately after death with the aim of correlating histologic findings with duration of illness and radiographic findings. Two patients with groundglass opacities had early diffuse alveolar damage (DAD) and positive SARS-CoV-2 immunostains. The remaining 6 patients had proliferative ( $n = 3$ ) or fibrotic ( $n = 3$ ) DAD, negative immunostains, and died 24 to 42 days after symptom onset; however, I suspect that at least 1 of the cases of fibrotic DAD was potentially a patient with underlying UIP - - This patient was a 75-year-old male with lower lobe honeycombing on chest CT and microscopic honeycomb change on biopsy.

**Gallob F et al. Senescence and autophagy in usual interstitial pneumonia. *Virchows Arch* 2021; 478:479-506.**

**Take-home message:** As the title implies, the aim of this study was to evaluate the presence or absence of senescence and autophagy in usual interstitial pneumonia (UIP) through the use of immunohistochemistry. The cohort included 23 patient samples, including 10 cases of idiopathic pulmonary fibrosis (IPF) and 13 cases of connective tissue disease-associated UIP (CTD-UIP). There was no difference in the staining patterns between IPF and CTD-UIP cases with both groups showing expression of cell cycle arrest (senescence) markers and upregulation of autophagy markers, the latter being particularly prominent in fibroblastic foci.

**McMullen PD et al. A descriptive and quantitative immunohistochemical study demonstrating a spectrum of platelet recruitment patterns across pulmonary infections including COVID-19. Am J Clin Pathol 2021; 155:354-63.**

**Take-home message:** CD61 immunohistochemical staining was quantitated in lung tissue obtained from autopsy cases ( $n = 27$ ) to assess platelet deposition. The cohort comprised 3 cases with histologically normal lungs, 4 cases of DAD without primary lung infections, 9 patients with COVID-19, 2 with influenza, 4 each with different types of bacterial and invasive fungal pneumonias, and 1 with bilateral pulmonary thromboembolic disease. Infectious causes of lung disease resulted in increased CD61 expression compared to controls and the level of staining in COVID-19 was similar to that seen in non-infectious causes of DAD.

**Valdivia-Mazeyra MF et al. Increased number of pulmonary megakaryocytes in COVID-19 patients with diffuse alveolar damage: an autopsy study with clinical correlation and review of the literature. Virchows Arch 2021; 478:487-96.**

**Take-home message:** In this observational study, the authors compare the number of megakaryocytes seen in lung tissue from COVID-19 patients who underwent autopsy ( $n = 18$ ) to a control group comprised of patients with diffuse alveolar damage (DAD) who died of other causes ( $n = 14$ ) and a second control group of histologically normal lung tissue obtained from lobectomy specimens performed for tumor resection ( $n = 14$ ). The number of megakaryocytes counted in 25 HPF in COVID-19 patients was elevated ( $7.61 \pm 5.59$ ) compared to non-COVID-19 DAD ( $4 \pm 4.17$ ) and normal ( $1.14 \pm 0.86$ ) controls. The authors propose that the increase in pulmonary megakaryocytes may be implicated in the thrombotic events seen in patients with severe COVID-19.