PULMONARY PATHOLOGY JOURNAL CLUB
December 20, 2021
(November 2021 articles)
Kelly Butnor, MD
Professor
Department of Pathology & Laboratory Medicine
The University of Vermont Medical Center, Burlington, Vermont

Articles for Discussion

Agaimy A, et al. Recurrent *YAP1-TFE3* gene fusions in clear cell stromal tumor of the lung. Am J Surg Pathol 2021;45:1541-9

Purpose: To report the clinicopathologic and molecular findings in a series of clear cell (hemangioblastoma-like) stromal tumor of the lung (CCST-L), a recently described rare tumor of unknown histopathogenesis.

Methods: Cases were retrieved from the consultation files of the authors. Comprehensive immunohistochemical staining and NGS was performed.

Results: All four cases of CCST-L described in this study occurred in women ranging in age from 29-69 years. None had known von Hippel-Lindau or other genetic diseases. Three presented as a solitary lung nodule (ranging from 2.3-9.5 cm), while the fourth arise from the main bronchus. The tumors were characterized by relatively uniform medium-sized epithelioid to ovoid or slightly spindled cells with variably clear to focally foamy histiocytoid or flocculent cytoplasm and small round nuclei (see Figure 2 in paper). The stroma was hypervascular with predominantly thin-walled vascular spaces subtly resembling capillary hemangioblastoma and PEComa. Scattered larger hyperchromatic cells were seen in two cases. The intracytoplasmic material was PAS-diastase-sensitive. Two cases showed central ischemic-type necrosis. Immunohistochemically, all tumors showed nuclear TFE3 staining and were vimentin-positive, but were otherwise negative for lineage-specific markers, including keratin AE1/AE3, p63, desmin, SMA, HMB45, melan A, CD34, ERG, CD31, S100, SOX-10, PAX-8, NSE, TTF-1, Napsin A, calretinin, inhibin, GFAP, EMA, STAT6, and cathepsin K. *YAP1-TFE3* gene fusions were present in three cases. On follow-up, two patients are alive without disease at 12 and 36 months, one recent case has known metastases, and the case that lacked a *YAP1-TFE3* gene fusion has persistent disease over 4 years.

Discussion: Despite some morphologic overlap, CCST-L appears to be a different entity from conventional hemangioblastoma, PEComa, and *YAP1-TFE3*-rearranged epithelioid hemangioendothelioma. In contrast to conventional hemangioblastoma, CCST-L does not stain for NSE, inhibin, or S100, is less strikingly xanthomatous, and instead exhibits more granular to flocculant cytoplasm. CCST-L can be distinguished from PEComa by the lack of immunoreactivity for melanocytic markers. As CCST-L can have a vaguely nested pattern with vascularization, carcinoid tumor and paraganglioma also come into the differential, but can be separated on the basis of cytologic and immunohistochemical features. Metastatic RCC, epithelial-myoepithelial carcinoma (due to misinterpretation of focally entrapped alveolar

epithelium that can be seen CCST-L; see Figure 3 E in paper), and SFT are also considerations that can be excluded through immunohistochemistry. Care should be taken in interpreting TFE3 immunostaining, as it may be positive in non-*TFE3*-rearranged neoplasms.

Take Home Message: CCST-L is another tumor to add to the differential of epithelioid tumors with clear to flocculent cytoplasm in the lung.

Nandy S, et al. Diagnostic accuracy of endobronchial optical coherence tomography for the microscopic diagnosis of usual interstitial pneumonia. Am J Respir Crit Care Med 2021;204:1164-79

Purpose: To assess the diagnostic accuracy of endobronchial optical coherence tomography (EB-OCT) in the diagnosis of UIP. This minimally invasive technique uses endogenous tissue contrast to provide *in vivo* three-dimensional images of peripheral lung in real time through the working channel of a standard diagnostic bronchoscope. Prior studies suggest EB-OCT is a potentially lower risk method for diagnosing ILD than surgical lung biopsy without the removal of tissue. The authors of this study include journal club member Dr. Colby.

Methods: This was a single-institution, prospective study of patients with fibrotic ILD on HRCT for whom the diagnosis was unclear. Immediately prior to surgical lung biopsy, EB-OCT was performed. Specifically, a flexible EB-OCT catheter was advanced beyond the visualized region of the bronchoscope until resistance was met in regions of subpleural lung that had been identified on HRCT as having interstitial abnormality. Helical cross-sections images were then acquired by rotating the inner optics of the catheter while pulling the it from distal to proximal over a distance up to 9 cm. A pathologist experienced in EB-OCT interpretation and ILD evaluated the images in real time to confirm placement and adequate data acquisition. Three pathologists without prior OCT imaging experience underwent training and testing on EB-OCT interpretation. They subsequently interpreted EB-OCT data from study patients without knowledge of the histopathology findings or the EB-OCT interpretation of the pathologist experienced in EB-OCT. Two thoracic pathologists blinded to the EB-OCT findings independently rendered a diagnosis on the lung biopsy slides and a clinical diagnosis for each study patient was arrived at independently by pulmonologists.

Results: The analysis included 27 patients. UIP was diagnosed in 12 and the other 15 had non-UIP ILD. EB-OCT was 100% sensitive and specific for both histopathologic UIP and clinical IPF. In contrast to normal alveolar parenchyma (see Figure 2 in paper), ECT-OCT imaging features of UIP included dense, homogeneous signal-intense subpleural tissue and irregularly shaped, signal-poor dilated cystic structures (see Figure 3 in paper). There was also a high level of agreement (weighted kappa = 0.87) between EB-OCT and corresponding surgical lung biopsy for other specific fibrotic ILD patterns, including mixed airway-centered fibrosis and NSIP (see Table 3 and Figures 6 and 7 in paper). Proficiency in EB-OCT interpretation could be acquired with minimal training (see Table 4 in paper).

Discussion: EB-OCT can accurately discriminate UIP/IPF from non-UIP ILD. It also is highly concordant with surgical lung biopsy in diagnosing specific fibrotic ILD patterns.

Take Home Message: Even in the absence of tissue, pathologists might retain usefulness, provided a desire to learn new tricks.

Ikezoe K, et al. Small airway reduction and fibrosis is an early pathology features of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2021;204:1048-59

Purpose: To better understand the morphology of IPF using ultra-high-resolution micro-computed tomography (microCT). Journal club member Dr. Colby is one of the authors on this study.

Methods: MicroCT was performed on inflated frozen explanted lungs from patients with IPF and donor control subjects (eight subject each) at a resolution of 13 microns for airway analysis and 7 microns for parenchymal analysis. Various small airway parameters (number, wall thickness, and luminal area) and aspects of parenchymal fibrosis (volume fraction of tissue, alveolar surface area, and septal wall thickness) were assessed stereologically.

Results: In IPF, there is a reduction in the number of the smallest airways (conducting terminal and respiratory transitional bronchioles) and thickening of the terminal bronchiolar walls in regions without histologic fibrosis (see Figure 2 A and B in paper). In areas with fibrosis, the remaining terminal bronchioles exhibit thicker walls and there is luminal distortion and dilation with resultant traction bronchiolectasis and the formation of honeycomb cysts (see Figure 3 A and B and Figure 4 G-J in paper).

Discussion: The data suggest that a reduction in and fibrosis of small airways are likely early events in IPF that precede the development of parenchymal fibrosis. The small airways may thus be a potential target for therapies to alter the course of IPF.

Take Home Message: Perhaps IPF is an airway-associated (or at least airway-incited) disease after all.

Yeh Y-C, et al. Whole-exome sequencing of Epstein-Barr virus-associated pulmonary carcinoma with low lymphocytic infiltration shows molecular features similar to those of classic pulmonary lymphoepithelioma-like carcinoma. Am J Surg Pathol 2021;45:1476-86

Purpose: To clarify the relationship between pulmonary EBV-associated pulmonary lymphoepithelioma-like carcinoma (LELC) and NSCLC associated with EBV that lacks significant lymphocytic infiltration.

Methods: In this single-institution retrospective study, 28 lung carcinomas that were positive for EBER ISH, along with 58 SCC and 30 solid adenocarcinomas surgically resected between 2005-2018 were stained with CD45 and subjected to digital image analysis. EBV-associated cases with low lymphocytic infiltration were defined those with CD45 staining falling within the 90th percentile range of SCC and adenocarcinoma. Whole-exome sequencing was performed.

Results: Five EBV-associated lung carcinomas with low lymphocytic infiltration that had enough tissue for sequencing were analyzed. While these tumors morphologically and immunohistochemically resembled nonkeratinizing lung SCC (see Figure 1 A, E, and F in

paper), their propensity to occur in female nonsmokers was similar to LELC, as were their molecular profiles. In contrast to SCC, EBV-associated lung carcinomas with low lymphocytic infiltration exhibited APOBEC-related mutations, low tumor mutational burden, and were enriched for CD274 (PD-L1) amplification. Differences in survival from SCC did not reach statistical significance.

Discussion: EBV-associated lung carcinomas with low lymphocytic infiltration and LELC appear to part of a single disease entity.

Take Home Message: Consider performing EBER ISH in female never-smokers with tumors resembling nonkeratinizing squamous cell carcinoma that show large vesicular nuclei and prominent eosinophilic nucleoli and are positive for squamous lineage markers, as they may be part of the spectrum of EBV-associated pulmonary carcinoma that have distinct molecular alterations.

Notation Articles - Neoplastic

Anderson WJ, et al. Loss of expression of YAP1 C-terminus as an ancillary marker for epithelioid hemangioendothelioma variant with *YAP1-TFE3* fusion and other YAP1-related vascular neoplasms. Mod Pathol 2021;34:2036-42

Purpose: A small subset (<5%) of epithelioid hemangioendotheliomas (EHE) harbor a *YAP1-TFE3* fusion. These tumors typically affect younger patients and may have a better prognosis than conventional EHE. Morphologically, they show vasoformative growth and voluminous eosinophilic cytoplasm (see figure 1 in paper), which are features that overlap with a variety of endothelial neoplasms. While TFE3 immunohistochemistry is positive in EHE with *YAP1-TFE3* fusion, this marker lacks specificity. This study examines the role of YAP1 C-terminus immunohistochemistry in discriminating EHE with *YAP1-TFE3* fusion from other epithelioid vascular neoplasms.

Methods: Immunoexpression of a rabbit monoclonal anti-YAP1 C-terminus antibody (Cell Signaling Technology) was assessed.

Results: Complete loss of expression was observed in 10 of 13 (77%) of EHE with *YAP1-TFE3* fusion. One of the 13 tumors was from the pleura, but the results as presented in the paper do not specify which anatomic sites had retained or lost expression.

Take Home Message: YAP1 C-terminus has the potential to be useful in cases with variant EHE morphology that are positive for TFE3 and negative for CAMTA1 by immunohistochemistry.

Gross DJ, et al. Spread through air spaces (STAS) in non-small cell lung carcinoma: evidence supportive of an in vivo phenomenon. Am J Surg Pathol 2021;45:1509-15

Purpose: To further examine whether STAS is an *ex vivo* artifact or *in vivo* phenomenon.

Methods: Cases of NSCLC showing STAS on limited resection that underwent additional resection at a single institution and were grossed at different times using a different knife were retrospectively identified.

Results: Of the 10 cases included in the study, all exhibited STAS in both the limited and the additional resection specimens. The authors contend the presence of STAS in specimens grossed at a different time supports STAS is an *in vivo* phenomenon.

Take Home Message: Will there ever be STAS-isfactory evidence to put this debate to rest?

Li Y, et al. Morphologic, immunohistochemical, and genetic differences between high-grade and low-grade fetal adenocarcinomas of the lung. Am J Surg Pathol 2021;45:1464-75

Purpose: To examine the clinicopathologic, immunohistochemical, and molecular genetic differences between low- and high-grade fetal adenocarcinoma of the lung (FLAC).

Methods: A single-institution retrospective search for cases between 2013-2020 was undertaken and the tumors were subjected to NGS. The literature on FLAC was also reviewed.

Results: Four low-grade and two high-grade FLAC were assessed. High-grade FLAC was seen in predominantly elderly male smokers with advanced stage disease. Low-grade FLAC was characterized by a pure pattern of tumor cells with sub- and supranuclear vacuoles resembling developing fetal lung with a complex glandular architecture, whereas high-grade cases had both conventional adenocarcinoma and fetal lung-like components (see Figures 1 and 2 in paper). High-grade cases lacked morule formation but showed multifocal necrosis. Low-grade FLAC exhibited nuclear/cytoplasmic β-catenin staining, while a membranous staining pattern was seen in high-grade cases. Both high- and low-grade FLAC stained diffusely for TTF-1. Strong p53 staining was seen in high-grade FLAC. Some SALL-4 and synaptophysin staining was present in low-grade FLAC. NGS detected *CTNNB1* and *DICER1* mutations in all and *MYCN* P44L in half of the low-grade cases. In contrast, testing of the fetal lung-like components of the high-grade cases did not show these mutations, but rather genetic alterations that overlapped with conventional adenocarcinoma.

Take Home Message: Based on clinicopathologic and molecular data, high-grade FLAC is probably best considered a subtype of conventional lung adenocarcinoma. The significance of the mutational alterations in low-grade FLAC remains unclear.

Liu X, et al. Major pathologic response assessment and clinical significance of metastatic lymph nodes after neoadjuvant therapy for non-small cell lung cancer. Mod Pathol 2021;34:1990-8

Purpose: To examine the pathologic assessment of primary tumor and metastatic lymph node responses and their prognostic significance in cases of neoadjuvantly treated NSCLC.

Methods: The pathologic treatment response in both the primary tumor and lymph node metastases was assessed in resected cases of neoadjuvantly-treated NSCLC. The relationship between response and survival was retrospectively analyzed.

Results: Of 336 patients, 208 had lymph node metastases. The optimal residual viable tumor (% RVT) cutoff for overall survival in the primary tumor was 12% for squamous cell carcinoma and 58% for adenocarcinoma. The optimal %RVT in lymph node metastases was 8% for both disease-free and overall survival. In rare cases, treatment response substantially differed between sites with the primary tumor showing near complete response and nearly negligible response in the lymph node metastases. %RVT in the primary tumor correlated with long-term prognosis, while %RVT in lymph node metastases correlated with short-term recurrence.

Take Home Message: Inconsistencies between %RVT in lymph node metastases and primary tumor, albeit rare, suggest careful pathologic assessment of both may be prognostically important. In practice, ≤10% RVT in the primary tumor and lymph node metastases appears prognostically useful for squamous cell carcinoma. The %RVT threshold that portends an adverse prognosis appears to be substantially higher for adenocarcinoma.

Naso JR, et al. Deep-learning based classification distinguishes sarcomatoid malignant mesotheliomas from benign spindle cell mesothelial proliferations. Mod Pathol 2021:34:2028-35

Purpose: To determine whether a deep learning approach can distinguish between benign and malignant spindle cell mesothelial proliferations.

Methods: A convolutional neural network was trained to classify spindle cell mesothelial proliferations as benign or malignant using a training set of whole slide images from 58 malignant sarcomatoid mesotheliomas and 81 benign spindle cell mesothelial proliferations. Accuracy was assessed on a set of 40 cases of spindle cell mesothelial proliferations referred for expert opinion and 25 cases from other institutions by comparing to the diagnoses of three experienced pathologists.

Results: Diagnostic accuracy of the neural network on the referral set of cases (92.5%) was comparable to that of three experienced pathologists (91.7%).

Take Home Message: Another reminder that we are becoming increasingly superfluous. Though in the words of Voltaire, “Le superflu, chos très necessaire” (“The superfluous, a very necessary thing”).

Salisbury T, Churg A. CD146 immunohistochemical staining for the separation of benign from malignant mesothelial proliferations. Virchow Archiv 2021;479:1047-50

Purpose: To assess the diagnostic utility of CD146 immunostaining in separating benign and malignant mesothelial proliferations.

Methods: Immunoexpression was assessed in TMAs containing a spectrum of mesothelial proliferations.

Results: Ten of 43 (23%) of epithelioid and 10 of 31 (33) of sarcomatoid mesotheliomas showed CD146 staining that was generally weak and focal. Among reactive mesothelial proliferations, 2 of 32 (6%) epithelioid and 4 of 17 (24%) spindled cases were positive. Sensitivity and specificity

were 23% and 94% for epithelioid and 33% and 76% for sarcomatoid mesothelioma, respectively. CD146 immunoexpression did not correlate with BAP1 or MTAP loss or expression.

Take Home Message: CD146 stains fibroblasts and endothelial cells, making it a challenge to interpret. Given its low sensitivity for mesothelioma, this marker is unlikely to be of added benefit in the distinction of benign and malignant mesothelial proliferations

Shang Z, et al. Challenging of [sic] frozen diagnoses of small sclerosing pneumocytoma. J Clin Pathol 2021;74:730-4

Purpose: To examine the frozen section features of small (≤ 1 cm) sclerosing pneumocytomas (SP).

Methods: The clinicopathologic features of small SP that were surgically resected between January 2015 and March 2019 at a single institution were retrospectively reviewed.

Results: Seventy-six cases were identified, 54 of which were evaluated by frozen section intraoperatively. The intraoperative misdiagnosis rate was 11.1% (6/54). A single dominant growth pattern was present in 78.9% of cases. Solid and papillary growth patterns were the most misdiagnosed. Among the entities SP was misdiagnosed as on frozen section were invasive adenocarcinoma, carcinoid, inflammatory lesions, and hemangioma. Difficulty in identifying the two cellular components was noted as a source of frozen section error.

Take Home Message: Helpful clues to the diagnosis of SP on frozen section include foam cells in the glandular cavity, hypercellular or collagenous rather than fibrovascular cores, and hemorrhage and hemosiderin at the periphery. Gross features can also be helpful in that SP is often well-circumscribed, grayish yellow or dark red with a hard texture, smooth borders on imaging, and exhibits a tendency to shell out at surgery.

van den Broek MFM, et al. Well-differentiated bronchopulmonary neuroendocrine tumors: more than one entity. J Thorac Onc 2021;16:1810-20

Purpose: To compare survival of sporadic well-differentiated bronchopulmonary neuroendocrine tumors (WDNETs) to those arising in the setting of MEN1 or DIPNECH.

Methods: Records of all patients with histologically confirmed MEN1-associated WDNETs in the DutchMEN Study Group database, as well as patients with resected sporadic or DIPNECH-associated WDNETs referred to a Dutch European NET Society center were retrospective reviewed for disease-specific mortality.

Results: The study included 112 patients with sporadic WDNETs, 29 with MEN1-associated WDNETs, and 27 with DIPNECH-associated WDNETs. No patients with MEN1 or DIPNECH died due to NET during the study period (1990-2017), whereas death due to NET was observed in 18% of sporadic cases. Median follow-up was 4.8 years.

Take Home Message: Disease-specific mortality is significantly higher among patients with sporadic WDNET than those with MEN1 or DIPNECH-associated WDNET, suggesting distinctive underlying biological mechanisms may be at play.

Vrana JA, et al. SATB2 is expressed in a subset of pulmonary and thymic neuroendocrine tumors. Am J Clin Pathol 2021;156:853-65

Purpose: Immunohistochemical expression of SATB2 in colorectal carcinoma has been associated with a good prognosis. Staining for this marker has also been reported in well-differentiated neuroendocrine tumors (NETs) of colorectal and appendiceal origin but has not been well-studied in those of thoracic origin. This study assesses the staining characteristics and prognostic import of SATB2 in thoracic neuroendocrine tumors. Among the authors of this study are two journal club members, Drs. Boland and Roden.

Methods: Immunoexpression of SATB2 (clone EP281) in whole tissue sections of 150 thoracic NETS (64 typical and 40 atypical lung carcinoids, 39 SCLC, 4 thymic atypical carcinoids, 2 thymic small cell carcinomas, and 1 thymic large cell carcinoma) was assessed.

Results: Small cell carcinoma showed higher SATB2 expression and staining intensity than carcinoid. SATB2 expression did not correlate with progression-free or overall survival in patients with lung NETs.

Tumor type	**% cases with ≥ 5% SATB2 staining**
Lung typical carcinoid	40.6%
Lung atypical carcinoid	22.5%
SCLC	74.4%
Thymic atypical carcinoid	100%
Thymic LCNC	100%
Thymic small cell carcinoma	0%

Take Home Message: SATB2 is not specific for NETs of the lower GI tract. As SATB2 is also seen in a proportion of thoracic NETs, it is not useful for determining site of origin for neuroendocrine tumors (SATB2 does however appear to be generally useful in separating pulmonary adenocarcinoma from colorectal adenocarcinoma [3% vs. 87% SATB2 positive] – see article from earlier this year in Am J Clin Pathol 2021;155:124-32)

Notation Articles - Non-Neoplastic

Crespo MM, et al. ISHLT consensus document on lung transplantation in patients with connective tissue disease: part I: epidemiology, assessment of extrapulmonary conditions, candidate evaluation, selection criteria, and pathology statements. J Heart Lung Transplant 2021;40:1251-66

Purpose: To standardize the evaluation and listing of patients with connective tissue disease (CTD) for lung transplantation, which has varied widely across lung transplantation centers.

Results: Numerous tables outline relative and absolute contraindications for lung transplantation in different connective tissue diseases.

Take Home Message: Absolute contraindications to transplantation include any other organ dysfunction or medical problem that would substantially jeopardize transplant outcome. Early referral for transplantation is recommended due to complexity of medical issues in this patient population.

Review Articles

Wang M, et al. Salivary gland-type tumors of the lung: a distinct group of uncommon lung tumors. Arch Pathol Lab Med 2021;145:1379-86

Contemporary review of salivary gland-type tumors of the lung that includes a nice table of diagnostic features and differential diagnoses of the different entities.

Case Reports

Manglani R, et al. Pulmonary involvement in Sweet's syndrome. Am J Respir Crit Care Med 2021;204:1222-3

Describes a case of Sweet's syndrome (acute febrile neutrophilic dermatosis) with lung involvement. Surgical lung biopsy was reported to show alveolar blood and early interstitial fibrosis with interstitial edema, fibrin, and inflammation that was predominantly neutrophilic without evidence of vasculitis.

Take Home Message: Lung involvement, which is rare in Sweet's syndrome, may precede dermatologic manifestations. Based on the provided photomicrographs, it seems this would be difficult to separate from capillaritis. Would be interested to know if anyone in the club has seen a case.

Letters to the Editor

Churg A, et al. Fibroblast foci and patchy fibrosis do not separate usual interstitial pneumonia from fibrotic hypersensitivity pneumonitis in transbronchial cryobiopsies. Arch Pathol Lab Med 2021;145:1325-6

The authors assessed "cryobiopsies" created by outlining circles on slides of VATS biopsy specimens from patients with a high probability of fibrotic HP for the presence of features described in the COLDICE study as favoring UIP, namely fibroblast foci and patchy fibrosis (Cooper WA, et al. Cryobiopsy for identification of usual interstitial pneumonia and other interstitial lung disease features: further lessons from COLDICE, a prospective multicenter study. Am J Respir Crit Care Med 2021;203:1306-13). The combination of fibroblast foci and patchy fibrosis was found in 47% of cases when four "cryobiopsies" were reviewed, suggesting

that almost half of patients with fibrotic HP have the potential to be misclassified as UIP on cryobiopsy.

In reply, Cooper and colleagues point out that when the absence of alternative diagnostic features, such as giant cells/granuloma or peribronchiolar metaplasia, is also included in the assessment, 14% or less of Churg and colleageues' cases in which four mock cryobiopsies were reviewed would be erroneously classified as UIP. They go on to emphasize that while UIP and fibrotic HP can have overlapping histologic features, multidisciplinary discussion (MDD) is essential to establishing a final diagnosis.