PULMONARY PATHOLOGY JOURNAL CLUB
(April 2018 articles)
May 21, 2018
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I. Articles for Discussion

Churg A, et al. Cicatricial organsing pneumonia mimicking a fibrosing interstitial pneumonia. Histopathol 2018;72:846-854

Purpose: To describe the pathologic and radiologic features of cases demonstrating a variant of cicatricial organizing pneumonia (OP) different from that previously described by Yousem, in which there was organization of granulation tissue to much denser fibrous tissue still retaining the usual pattern of OP.

Methods: Cases were retrieved from consultation files that showed fibrotic OP in which there were linear bands and small nodular masses of dense collagen or densely organizing granulation in airspaces that did not resemble ordinary OP.

Results: There were 9 males and 1 female with a median age of 61 years, all of which were thought to have ILD on the basis of CT findings. Two patients had a history of hemoptysis. Fibrotic bands and nodules were mostly randomly distributed. Metaplastic bone was present in 4 cases, including a patient with Ehlers-Danlos syndrome, and occasionally the fibrotic process locally mimicked fNSIP. Small foci of loose granulation tissue at the edge of the fibrotic bands sometimes mimicked fibroblast foci. All cases had at least small amounts of conventional OP. CT findings were that of typical OP in some cases, but others showed only irregularly distributed linear opacities with or without calcification. Follow-up imaging of 6 cases showed improvement or stable disease with no cases progressing.

Discussion: This uncommon histological pattern can be confused with fNSIP both pathologically and radiographically. Importantly, patients with this pattern appear to follow a benign course. The history of hemoptysis in 2 cases raises the possibility that this pattern may represent organization of OP evoked by hemorrhage in some instances.

Take Home Message: The uncommon pattern of alveolar fibrosis does not imply progressive disease. Whether it should be considered a variant of OP or a distinct entity is debatable.

Ozkaya N, et al. The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. Mod Pathol 2018;31:581-597

Purpose: To comprehensively review the histopathological features in Erdheim-Chester disease (ECD).

Methods: Seventy-three biopsies from various sites of involvement in 42 patients were reviewed, including 6 lung specimens. All patients met consensus diagnostic criteria for ECD, which include xanthogranulomatous lesions composed of CD68-positive/CD1a-negative histiocytes, often with admixed inflammation and fibrosis, and bilateral and symmetric skeletal abnormalities in the long bones of the legs.

Results: Lung findings included characteristic subpleural, septal, and perivascular interstitial localization of histiocytes without nuclear grooves in an exquisitely lymphangitic distribution

with marked pleura and interlobular septal fibrosis. Eosinophils were rare and well-formed granulomas were lacking, as were emperipolesis and necrobiosis. All specimens were positive for one or more histiocytic marker (CD68, CD163, or FXIIIa) and negative for CD1a. S100 was positive in 30% of 40 samples from various sites. IgG4 immunostaining did not exceed 40% in 10 samples from various sites. The most common genetic alterations were somatic BRAF and MAPK pathway mutations.

Discussion: ECD is a clonal hematopoietic disorder associated with MAPK pathway mutations. In contrast to other organs, the histologic features of ECD in the lung are distinctive and characterized by a lymphangitic distribution. The histiocytes can be scarce in areas of fibrosis, posing a diagnostic challenge. Lesional cells typically show both nuclear and cytoplasmic FXIIIa expression, differentiating them from alveolar macrophages seen in UIP or adverse drug effect, which demonstrate only nuclear FXIIIa staining. Immunohistochemistry for BRAF using the VE1 antibody is not reliable in ECD and mutational analysis should be performed.

Take Home Message: A lymphangitic pattern of fibrosis should prompt consideration of ECD.

Rosen LE, et al. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. Mod Pathol 2018;31:598-606

Purpose: To validate a relatively recently described nuclear grading system for predicting survival in patients with epithelioid malignant pleural mesothelioma (eMPM) and identify additional prognostic factors.

Methods: Nuclear grade, as previously described by Kadota et al., was assigned I-III in each case by combining nuclear atypia and mitotic count scores. The presence or absence of necrosis and predominant growth pattern were also noted. The primary endpoint was median overall survival.

Results: Of 776 cases from 17 institutions, 39% were nuclear grade I, 45% grade II and 16% grade III. Overall survival was 16 months. Adding necrosis to nuclear grade improved prognostic stratification, such that 4 distinct prognostic groups could be identified. An alternative scoring system employing mitotic count and necrosis also stratified patients by survival, but not as well as the combined necrosis and nuclear grade method.

Discussion: The Kadota nuclear grading system, which takes into account nuclear atypia and mitotic count, predicts survival in eMPM. Necrosis is an additional stratifying factor. The mitosis-necrosis score is a less subjective scoring system that avoids assessment of nuclear atypia and while not as robust, also stratifies patients into distinct prognostic groups.

Take Home Message: Reporting nuclear grade and the presence or absence of necrosis is prognostically useful in eMPM.

Hariri LP, et al. Endobronchial optical coherence tomography for low-risk microscopic assessment and diagnosis of idiopathic pulmonary fibrosis in vivo. Am J Respir Crit Care Med 2018;197(7):949-952

Purpose: To demonstrate the use of *in vivo* endobronchial optical coherence tomography (OCT), which is performed by passing a narrow catheter through a standard bronchoscope working channel out to the peripheral lung and conducting 3D helical scanning with a resolution of < 10 μm), as a minimally invasive method to microscopically assess and diagnosis UIP/IPF without tissue removal.

Methods: In this pilot study, endobronchial OCT was performed prior to lung biopsy in 5 sequential patients with ILD as part of a VATS procedure.

Results: Endobronchial OCT, which added < 6 minutes to each VATS, detected microscopic honeycombing and other UIP features in 4 patients with nondiagnostic HRCT, 1 of which also had an indeterminate surgical biopsy. The technique also differentiated traction bronchiectasis from microscopic honeycombing in 1 patient with a false-positive diagnosis of UIP/IPF by HRCT.

Discussion: Initial data from endobronchial OCT suggest it is a useful modality for accurately diagnosing UIP/IPF and non-UIP/IPF in patients with non-diagnostic or false-positive for UIP/IPF HRCT findings. Advantages of this technique are that it is minimally invasive, can be performed under conscious sedation, can be repeated over time to study disease progression, and has the ability to visualize larger volumes of tissue and more distinct locations than biopsy, thus potentially reducing sampling error.

Take Home Message: The questions implicitly raised by this study are who will be performing and/or interpreting these images and what is the role for pathologists?

II. Articles for Notation

Original Articles

Aherne EA, et al. What CT characteristics of lepidic predominant pattern lung adenocarcinoma correlated with invasiveness on pathology? Lung Cancer 2018;118:83-89

Purpose: To identify CT features associated with invasive growth in lung adenocarcinoma.

Methods: CT images from 63 patients with resected lepidic-predominant adenocarcinomas were evaluated retrospectively.

Results: Increasing maximum size of total lesion on CT and macroscopic examination significantly correlated with invasiveness, as did larger diameter of the solid component on CT.
Take Home Message: The larger the total size (ground glass and solid component) and the larger the solid component size on CT, the more likely a lung adenocarcinoma is to be invasive.

Baine MJ, et al. Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer. Lung Cancer 2018;118:20-26

Purpose: To evaluate the influence of histology of post-stereotactic body radiation therapy (SBRT) outcomes.

Methods: Records from 152 consecutive patients treated with SBRT for early-stage NSCLC at 2 academic medical centers were retrospectively reviewed.

Results: Patients with squamous cell carcinoma had increased risk of local, regional and distant failure at a median follow-up of 44 months and a shorter time to failure than those with adenocarcinoma. Squamous cell carcinoma was also independently associated with an increased risk of death with an overall 5-year survival of 26% versus 41% for adenocarcinoma.

Take Home Message: Patients with early-stage squamous cell carcinoma treated with SBRT fare worse than those with adenocarcinoma, raising the question whether the approach to treating early-stage NSCLC with SBRT should be modified based on histologic type.

Ichikawa T, et al. The ratio of cancer cells to stroma within the invasive area is a histologic prognostic parameter of lung adenocarcinoma. Lung Cancer 2018;118:30-35

Purpose: To evaluate whether the prognosis of patients with lung adenocarcinoma is associated with the proportion of cancer cells to non-cancerous stroma with the invasive area.

Methods: Resected lung adenocarcinomas > 3cm in total size from 127 patients were classified into 3 categories based on the ratio of area occupied by cancer cells within the invasive area and clinicopathologic differences among the patients were analyzed.

Results: Tumors that had <10% cancer cells within the invasive area had a significant larger proportion of VVG-positive elastic fibers within the invasive area and demonstrated significantly longer recurrence-free survival than tumors with higher cancer cell-to-stroma ratios.

Take Home Message: Invasive adenocarcinomas with a large proportion of elastic fibers and sparse tumor cells in the area of invasion may have a better prognosis than their T category based on invasive size would suggest. In future staging iterations, the character of the invasive tumor area, in addition to invasive size, may become an important histologic parameter.

Kahlor N, Moran CA. Primary thymic adenocarcinomas: a clinicopathological and immunohistochemical study of 16 cases with emphasis on the morphological spectrum of differentiation. Hum Pathol 2018;74:73-82

Purpose: To summarize the spectrum of clinicopathologic features of primary thymic adenocarcinoma.

Methods: Resected cases from the MD Anderson Cancer Center surgical pathology files were retrospectively identified over a 16-year time period.

Results: Among 16 cases, the average age was 45 years. Patients presented with non-specific symptoms, including cough, chest pain and dyspnea. All had radiographic evidence of an anterior mediastinal mass. None of the tumors were encapsulated. Most were limited to the mediastinum and showed mixed growth pattern. Patterns included mucinous with features of "colloid carcinoma", non-mucinous and papillary/micropapillary. Adenocarcinoma was associated with conventional thymoma in 2 cases. All were negative for PAX8 and TTF-1. The mucinous tumors showed positivity for enteric markers (e.g. CK20, CDX-2), but were also CK7-positive. The non-mucinous and papillary tumors were positive for CD5 and largely positive for CD117. Seven of 10 patients with follow-up data were alive without recurrence.

Take Home Message: Practically, the diagnosis of thymic adenocarcinoma requires the presence of an anterior mediastinal mass in the absence of another extramediastinal carcinoma. The presence of nuclear atypia can aid in separating carcinoma from thymoma with a papillary or mucinous component.

Kobayashi M, et al. Prognostic significance of S100A16 subcellular localization in lung adenocarcinoma. Hum Pathol 2018;74:148-155

Purpose: To understand the prognostic significance of S100A16 expression in lung adenocarcinoma.

Methods: Immunoexpression of S100A16 and corresponding mRNA expression was evaluated in 170 surgically resected lung adenocarcinomas.

Results: Membrane-positive nucleus-negative S100A16 staining was significantly higher in males, smokers, node-positive cases, higher pTNM stage, larger tumors, poorly differentiated tumors, and those with vascular, lymphatic, and/or pleural invasion. This pattern of staining was an independent prognostic factor and was associated with significantly poorer survival than other staining patterns. This staining pattern correlated with MUC5B and TTF-1-negative expression. Higher S100A16 mRNA expression also correlated with poorer survival.

Take Home Message: S100A16 immunoexpression in a membranous but absent nuclear staining pattern may be a potential marker for risk-stratifying lung adenocarcinoma patients.

Lee HE, et al. Histopathologic findings in lungs of patients treated with extracorporeal membrane oxygenation. **Chest 2018;153(4):825-833**

Purpose: To evaluate the ECMO-related histopathologic findings of the lung.

Methods: Histologic findings in autopsy lungs of patients treated with ECMO for a cardiac reason were compared to those of an age- and sex-matched control group of patients without ARDS, pneumonia, or ECMO who died in the ICU.

Results: As compared to 47 control patients, the lungs of 76 ECMO patients more frequently showed pulmonary hemorrhage (63.2%), DAD (60.5%), thromboembolic disease (47.4%),

hemorrhagic infarct (21.1%), pulmonary calcifications (28.9%), fibrinous pleuritis (25%) and vascular changes (21.1%). Pulmonary hemorrhage was associated with longer ECMO duration.

Take Home Message: Not surprisingly, pulmonary hemorrhage and thromboembolic disease are common in ECMO patients, as they receive systemic anticoagulation as part of their management. The findings from this study suggest that ECMO may cause or at least contribute to the development of acute lung injury.

Morisset J, et al. Identification of diagnostic criteria for chronic hypersensitivity pneumonia. Am Rev Respir Crit Care Med 2018;197(8):1036-1044

Purpose: There are no widely accepted criteria or international guidelines for the diagnosis of chronic hypersensitivity pneumonia (cHP). The authors sought to identify diagnostic criteria for cHP that reach consensus among international experts.

Methods: A 3-round online Delphi survey of 45 experts representing 14 countries was conducted in which diagnostic items were identified and rated in terms of their importance. Consensus was defined as 75% or more experts rating a diagnostic item as very important or important.

Results: Consensus was achieved for 18 of the 40 diagnostic items. Items of highest importance were identification of a causative antigen, temporal relationship between exposure and disease, air trapping and mosaic attenuation on HRCT, and poorly formed non-necrotizing granulomas on lung biopsy. The only scenario experts considered sufficient to establish a diagnosis of cHP without lung biopsy was an identified exposure combined with HRCT features of cHP and BAL lymphocytosis > 40%. Experts highlighted the need for lung biopsy in patients with HRCT patterns less suggestive of cHP or lacking an identified exposure. However, experts lacked unanimity regarding the method of biopsy.

Take Home Message: Pathologists still have value in the diagnosis of cHP.

Pelosi G, et al. Most high-grade neuroendocrine tumours of the lung are likely to secondarily develop from pre-existing carcinoids: innovative findings skipping the current pathogenesis paradigm. Virchows Arch 2018;472:567-577

Purpose: To test the hypothesis that aggressive lung neuroendocrine tumors evolve from different histologic subtypes through acquiring genetic alterations using molecular classification of a large cohort of lung neuroendocrine tumors.

Methods: Two-way clustering analysis of previously reported NGS data on 148 surgically resected lung neuroendocrine tumors (including the spectrum of carcinoids, LCNEC, and SCLC) was performed.

Results: Six histology-independent clusters accounting for 68% of tumors were identified. Low-grade neuroendocrine tumors were likely to evolve into high-grade tumors following 2 smoking-related paths. The findings support that typical carcinoid can evolve to LCNEC, SCLC to LCNEC, and atypical carcinoid to SCLC.

Take Home Message: The majority of lung neuroendocrine tumors exhibit widely shared genetic alterations. As Dr. Weissferdt posits in the accompanying editorial (Virchows Arch 2018;472:579-580), perhaps it is time to replace the terms "carcinoid tumor" and "atypical carcinoid" with nomenclature that better highlights the malignant nature of the tumors, such as low grade and intermediate grade NE carcinoma and focus on features other than cytomorphology to classify such tumors.

Sakakura N, et al. The eighth TNM classification system for lung cancer: a consideration based on the degree of pleural invasion and involved neighboring structures. Lung Ca 2018;118:134-138

Purpose: To assess the impact of involvement of neighboring structures and degree of visceral pleural invasion on NSCLC prognosis.

Methods: The pathologic stage data of 2756 resected NSCLC patients was analyzed with consideration of degree of visceral pleural invasion and involvement of neighboring structures.

Results: T2a tumors with PL2 visceral pleural invasion (invasion through the visceral pleura to the visceral pleural surface) had significantly worse prognosis than those with PL1 visceral pleural invasion (invasion into visceral pleura without involvement of visceral pleural surface), such that they behaved like T2b tumors. T3 tumors that invaded structures beyond the parietal pleura had significantly worse prognosis than T3 tumors than only invaded the parietal pleura (PL3 pleural invasion).

Take Home Message: Although the presence of visceral pleura invasion does not impact the T category of T2-size tumors in the 8th edition AJCC, this study suggests that upcategorization of T2a-sized tumors with visceral pleural surface extension to T2b should be considered for future staging iterations, as might separating T3-PL3 tumors into 2 categories based on the presence or absence of invasion beyond the parietal pleura into neighboring deeper structures.

Song Z, et al. Clinicopathological characteristics of *POLE* mutation in patients with non-small-cell lung cancer. Lung Ca 2018;118:57-61

Purpose: To evaluate the frequency of *POLE* gene mutation in NSCLC. Limited data suggest tumors with *POLE* mutations are particularly sensitive to immune checkpoint (PD-1/PD-L1) therapy.

Methods: NGS was used to assess for *POLE* mutation in 319 patients with NSCLC.

Results: *POLE* mutation was identified in 2.8% of patients, all of who had adenocarcinoma. Median tumor mutational burden (TMB) was significantly higher in patients with *POLE* mutation than those with wild-type *POLE*. No microsatellite instability (MSI) was detected in patients with *POLE* mutation. Over 50% of patients with *POLE* mutation had >25% PD-L1 staining and high levels of CD8-positive tumor infiltrating lymphocytes (TILs). Patients with *POLE* mutation had significantly longer overall survival than patients with wild-type *POLE*.

Take Home Message: *POLE* mutation may be a candidate biomarker for response to immunotherapy in a very small subset of NSCLC patients.

Case Reports

Callahan S, et al. Two siblings with interstitial lung disease. Chest 2018;153(4):e75-e79

Case Summary: Report of a 52-year-old women and her 61-year-old brother presenting separately with worsening dyspnea on exertion and cough. Imaging showed bilateral interlobular septal thickening in the female sibling and paraseptal emphysema, basilar reticulations/ honeycombing, traction bronchiectasis and GGO in the male sibling. Both siblings had abundant foamy alveolar macrophages with fibrosis and chronic interstitial inflammation on biopsy and genetic testing disclosed homozygosity for the R610del mutation of the *SMPD1* gene, confirming acid sphingomyelinase deficiency (Niemann-Pick disease type B).

Take Home Message: Niemann-Pick disease type B is 1 of 2 lysosomal storage disorders that present as ILD in adults, the other being Gaucher disease. Symptoms and radiographic findings are not specific and can be highly variable. Lower lobe reticulation, honeycombing, and GGO are most common. The histologic hallmark is lipid-laden alveolar macrophages, which can also affect the liver, spleen and lymphatics. The differential diagnosis includes Gaucher disease, Erdheim-Chester disease, chronic aspiration, lipoid pneumonia, fat embolism, CF and amiodarone therapy. This report includes a nice table summarizing familial ILDs.

Letters to the Editor

Miller ER, et al. Histopathology of interstitial lung abnormalities in the context of lung nodule resection. Am J Respir Crit Care Med 2018;197(7):949-952

Purpose: To evaluate the histopathologic findings of interstitial lung abnormalities (ILAs) detected on CT in patients undergoing lung nodule resection.

Methods: Retrospective blinded histopathologic examination of sections of non-neoplastic lung was performed on 424 patients with no history of interstitial lung disease who had undergone lung nodule resection.

Results: The majority (61%) of patients did not have ILA, 6% had ILA, and 33% had indeterminate ILA. Patients with ILA were more likely to have subpleural fibrosis, fibroblastic foci, and atypical adenomatous hyperplasia (AAH) than those without ILA. ILA was centrilobular in 12%, subpleural in 65%, and mixed in the remainder. Among the ILA cohort, UIP was present in 8% and AAH was seen in 35%. AAH was noted in the original pathology report in only one-third of patients in which it was identified retrospectively and no mention of UIP was made in the original report in the 2 patients with UIP. The association with AAH appeared limited to patients with centrilobular ILA.

Take Home Message: ILA in some cases represents an early stage and/or mild form of pulmonary fibrosis. Additional study is needed to determine the clinical outcome of ILAs detected on CT.