**PULMONARY PATHOLOGY JOURNAL CLUB**
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**Table of Contents**

**Articles for Discussion**



**Articles for Notation**

Original Articles

## I. Articles for Discussion

### Tanizama K, et al. Significance of bronchiolocentric fibrosis in patients with histopathological usual interstitial pneumonia. Histopathology 2019;74:1088-1097

Purpose: To evaluate the clinical significance of bronchiolocentric fibrosis (BCF) in patients with histologic UIP and whether BCP would be associated with a clinical diagnosis other that IPF, an HRCT pattern inconsistent with UIP, *MUC5B* polymorphism, lack of shortened telomere length, and improved survival.

Methods: Patients with histologic UIP on surgical lung biopsy were identified from a single academic center database for whom a clinical diagnosis was established through multidisciplinary consensus (MDC) between 2000 and 2016. Those with connective tissue disease-associated interstitial lung disease were excluded, as were patients whose biopsies showed only microscopic honeycombing. BCF was considered present if there was peribronchiolar metaplasia (PBM) with prominent alveolar septal thickening (score 2) or bronchiolocentric septal thickening and architectural distortion (score 3) and absent if there were either no airway abnormalities (score 0) or PBM with only minimal to mild septal thickening (score 1) (see Figure 1). Severe BCF was distinguished from microscopic honeycombing by its central location adjacent to the pulmonary artery and the presence of normal alveolar septa between the fibrosis and the pleura.

Results: Of 252 patients identified, 215 (85%) had a multidisciplinary diagnosis of IPF. Among the entire cohort, 38% (96 of 252) had BCF, while BCF was seen in 33% (72 of 215) of those with IPF. Based on Figure 2, of the 37 with a non-IPF diagnosis, 24 (65%) had BCF. On multivariate analysis, the presence of BCF was significantly associated with a non-IPF diagnosis, but not with environmental exposures, GERD, smoking, radiologic patterns, MUC5B genotype, or telomere length, and did not impact survival time. The non-IPF diagnoses in the 24 patients with histologic UIP showing BCF included 13 cases of HP, 10 unclassifiable, and 1 “other.”

Discussion: The presence of BCF in histologic UIP is associated with a non-IPF diagnosis, most commonly HP. However, BCF is also seen in one-third of patients with an MDC diagnosis of PIF and therefore its presence cannot be used to necessarily exclude IPF. In patients with histologic UIP, BCF has no bearing on survival.

Take Home Message: While about one-quarter have an alternative diagnosis, such as HP, most patients with histologic UIP and BCF do end up having IPF as a multidisciplinary diagnosis.

### Kinoshita Y, et al. Distribution of emphysema and fibrosis in idiopathic pulmonary fibrosis with coexisting emphysema. Histopathology 2019;74:1103-1108

Purpose: Combined pulmonary fibrosis and emphysema (CPFE) was originally proposed by Cottin and colleagues in 2005 (Eur Respir J 2005;26:586-593) as a smoking-related condition featuring emphysema in the upper lobes and fibrosis in lower lobes characterized by subnormal spirometry measurements and severe gas exchange impairment. This study examines the

intrapulmonary distribution of emphysema and fibrosis in IPF patients who have coexisting emphysema.

Methods: In this single institution study, patients with a clinical diagnosis of IPF from whom both upper and lobe lower lung tissue had been procured either at explantation or autopsy and had CT evidence of emphysema occupying >25% of the lung were retrospectively identified.

Results: A total of 19 patients were identified. Upon histologic review, 9 had UIP, 8 had probable UIP, and 2 showed a pattern of interstitial fibrosis indeterminate for UIP. In 3 cases (16%), features of smoking-related interstitial fibrosis (SRIF) were also present, but only to a localized extent. No patients showed emphysema exclusively restricted to the upper lobes and fibrosis exclusively restricted to the lower lobes. In 15 (79%), coexisting fibrosis and emphysema was present in the upper and lower lobes. The emphysema and fibrosis were adjacent to or admixed with each other and the boundary between them was obscure.

Discussion: CPFE was originally proposed as a disease in which emphysema and fibrosis are considered to exist separately, with emphysema in the upper lobes and fibrosis in the lower lobes. In IPF patients with emphysema, coexistence of fibrosis and emphysema in the same lobe is common.

Take Home Message: Unsurprisingly, given the smoking-association for both, IPF and emphysema commonly coexist and they usually do so in proximity to one another. What this study does not address is whether IPF with concomitant emphysema and CPFE are one in the same or distinct entities and their relationship to the ever-expanding potpourri of smoking-related fibrotic processes that includes RB-ILD with fibrosis, SRIF, and airspace enlargement with fibrosis.

**Grondahl V, et al. Characteristics of 252 patients with bronchopulmonary neuroendocrine tumours treated at the Copenhagen NET Centre of Excellence. Lung cancer 2019;132:141-149**

Purpose: To comprehensively compare the clinicopathologic characteristics of typical carcinoid (TC), atypical carcinoid (AC), and large cell neuroendocrine carcinoma (LCNEC).

Methods: Clinicopathologic data from a neuroendocrine tumor database at a single European institution were collected.

Results: Among 252 patients, there were 162 TC, 29 AC, and 61 LCNEC. Differences in median age at diagnosis (68 years of TC, 72 for AC, and 69 for LCNEC) were significant, as was gender distribution (73% females for TC, 72% for AC, 54% for LCNEC), and smoking status (44% never smokers for TC, 38% for AC, and 12% for LCNEC). Fifty-eight percent of TC were centrally located, while 52% of AC and 64% of LCNEC were in the periphery of the lung. FDG-PET positivity was observed in 95% of all cases tested and was not significantly different among tumor types. The percentage of patients with metastatic disease at presentation was also statistically significant, occurring in 4% of TC, 27% of AC, and 58% of LCNEC. Only 28% of patients with LCNEC underwent surgical resection, while 87% of patients with TC and 72% of

those with AC did. Resected patients had better survival irrespective of tumor type (87% versus 26% 5-year overall survival for operated and non-operated patients). Five-year overall survival (OS) was 88% for TC, 63% for AC, and 20% for LCNEC. Patients with node-negative TC had significantly longer OS than those with nodal metastasis, but OS among patients with AC was similar irrespective of stage and was also the case for patients with LCNEC. TTF-1 positivity was seen in 69% of TC, 84% of AC, and 78% of LCNEC. Nearly all carcinoids stained for synaptophysin, but 8% of LCNEC were negative. Significant differences in mean Ki67 index using hot spot counting method were observed (5% in TC, 16% in AC, and 69% in LCNEC). In the TC group, 20% had a Ki67 index of 5-10%. Mitotic count, necrosis, or Ki67 index were not individually prognostic for separating TC from AC, but were able to provide accurate risk stratification when used in combination.

Discussion: There was a female predominance not only among carcinoids, but also LCNEC, which contrasts with the male predominance of LCNEC reported in prior studies. Another novel finding of this study is the high proportion of TC and AC that show FDG-PET avidity.

Take Home Message: Surgical resection appears to be beneficial even in patients with N2 stage TC. FDG-PET may be better at delineating the extent of disease in patients with carcinoid tumors than existing literature would suggest. The majority of carcinoids and LCNEC are positive for TTF-1, at least according to this study.

**Lindholm KE, et al. Xanthomatous thymoma. Am J Clin Pathol 2019;151:593-597**

Purpose: To describe the clinicopathologic features of thymomas in which an extensive xanthomatous component is present.

Methods: Thymectomy specimens were identified from the files of a single academic cancer center containing over 500 thymomas. Each case had 9-14 H&E slides of tumor available for review.

Results: Ten cases were from 5 men and 5 women, ranging in age from 47 to 64 years. Frequent presenting symptoms were chest pain and/or dyspnea. All of the tumors were solid, 8 of which were encapsulated and 2 minimally invasive, ranging from 2.5 to 4.5 cm. Each tumor exhibited an extensive xanthomatous component comprising 50 to 80% of the tumor. Identifiable areas of thymoma showed spindle cell WHO type A thymoma in 5 cases (see Image 1), 1 case was mixed spindle and lymphocytic WHO type A/B1 thymoma, 3 cases were lymphocytic and epithelial WHO type B1/B2 thymoma, and 1 case was atypical WHO type B3 thymoma. None had a cystic component, necrosis, or hemorrhage. Of the 9 patients with follow-up, all are alive without recurrence at 12 to 22 months.

Discussion: An extensive xanthomatous component can hamper accurate diagnosis of thymoma, particularly if not adequately sampled or in the setting of a small mediastinoscopic biopsy, as it may obscure the tumor and/or be misinterpreted as an inflammatory or infectious process. Other thymic lesions that can show xanthomatous inflammation include multiloculated thymic cyst that has breakdown of the cyst wall, but macrophages are usually less conspicuous and accompanied by other inflammatory cells and sometimes lymphoid hyperplasia or pseudoepitheliomatous

hyperplasia. Xanthomatous inflammation can also be seen in cystic thymomas undergoing breakdown, as well as following neoadjuvant chemotherapy of a mediastinal lesion. Thymic cholesterolomas are also characterized by an extensive xanthomatous component, but additionally include cholesterol clefs and giant cells.

Take Home Message: An extensive xanthomatous component does not appear to affect the outcome of thymomas that show this uncommon feature, but can be diagnostically problematic, especially in small specimens. Adequate sampling is necessary, as is exclusion of infection and multilocular thymic cyst.

## II. Articles for Notation

### Original Articles

**Distler O, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518-2528**

Purpose: Evaluate the efficacy and safety of the anti-fibrotic drug nintedanib in patients with interstitial lung disease (ILD) and systemic sclerosis.

Methods: This was a randomized, double-blind, placebo-controlled trial with a primary end point of annual rate of decline in forced vital capacity (FVC). ILD was identified on the basis of HRCT showing fibrosis affecting at least 10% of the lungs.

Results: Among 576 participants, the annual rate of FVC decline was 52.4 ml in the nintedanib group versus 93.3 ml in the placebo group (P=0.04).

Take Home Message: Nintedanib-treated patients with systemic sclerosis and ILD have lower annual rates of FVC decline than those treated with placebo.

**Jurmeister P, et al. DNA methylation profiling reliably distinguishes pulmonary enteric adenocarcinoma from metastatic colorectal cancer. Mod Pathol 2019;32:855-865**

Purpose: Pulmonary enteric adenocarcinoma is difficult to distinguish from metastatic carcinoma of gastrointestinal origin through routine morphological and immunohistochemical assessment. The aim of this study is to develop a DNA methylation-based algorithm to better distinguish these entities.

Methods: Publically available genome-wide methylation profiles of 600 primary pulmonary and gastrointestinal adenocarcinomas were used as a training set for a machine-learning algorithm that subsequently correctly classified all 680 samples from a validation cohort. Methylation data of 15 pulmonary enteric adenocarcinomas, 4 metastases to the lung, and 4 primary colorectal adenocarcinomas were then analyzed.

Results: The algorithm reliably classified all 23 cases correctly as originating from the lung or gastrointestinal tract. The pulmonary enteric adenocarcinomas did not form a separate

methylation subclass from other primary lung carcinomas. All 15 pulmonary enteric adenocarcinomas were positive for CDX2 and slightly over half (53%) were also positive for CK20, while about one-quarter (27%) were negative for CK7, and all but 2 were negative for TTF-1 (see Table 1 of paper).

Take Home Message: Interestingly, while primary pulmonary enteric adenocarcinoma has different morphologic and immunohistochemical characteristics from "standard" lung adenocarcinoma, their molecular features are largely similar. Methylation analysis could become a useful tool to distinguish pulmonary enteric adenocarcinoma from metastases of gastrointestinal origin.

**Negrao M, et al. PD-L1 expression, tumor mutational burden, and cancer gene mutations are stronger predictors of benefit from immune checkpoint blockade than *HLA* class I genotype in non-small cell lung cancer. J Thorac Onc 2019;14:1021-1031**

Purpose: Only about 15% of NSCLC patients experience a durable benefit with immune checkpoint blockade. Recent data have suggested human leukocyte antigen (*HLA*) class I heterozygosity might mediate this benefit. This study examines the impact of *HLA* class I genotype on outcomes of NSCLC patients receiving immune checkpoint inhibitors

Methods: Genomic, *HLA*, and clinical data were collected from patients with advanced NSCLC treated with immune checkpoint inhibitors.

Results: No significant correlations between *HLA* class I zygosity and either progression-free or overall survival were observed.

Take Home Message: Tumor genomic and immune markers would appear to be more important than *HLA* status in predicting immune checkpoint blockade benefit in NSCLC.

**Ngo C, et al. C4d detection and histological patterns in the diagnosis of antibody-mediated rejection after lung transplantation: a single-centre study. Histopathology 2019;74:988-996**

Purpose: While endothelial deposition of C4d and microvascular inflammation are indicators of antibody-mediated rejection (AMR) in renal and cardiac transplant, their role in lung AMR is not well-established. This study aims to assess C4d IHC and histologic patterns for diagnosing lung AMR.

Methods: C4d staining was scored, microvascular inflammation was assessed, and the presence of acute lung injury was recorded in 158 transbronchial biopsies, 85 of which were clinically-indicated and 73 were taken for surveillance purposes from 48 lung transplant recipients.

Results: Three-quarters of biopsies showed no C4d staining. Microvascular inflammation and acute lung injury were rare, but more frequent in biopsies with C4d staining. C4d staining ranging from 10-50% was frequently observed with concomitant infection. No surveillance biopsies showed either acute lung injury or >50% C4d. An association between histopathologic

findings and donor-specific antibodies was not seen. The 4 patients with > 50% C4d could be retrospectively diagnosed with AMR and developed chronic lung allograft dysfunction (CLAD).

Take Home Message: Diffuse C4d deposition appears to be a useful tool in the diagnosis of acute lung AMR.

**Reyfman PA, et al. Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. Am J Respir Crit Care Med 2019;199:1517-1536**

Purpose: To determine whether single-cell RNA sequencing can disclose disease-related changes in individual cell populations within the lung tissue of patients with pulmonary fibrosis that may be important to pathogenesis.

Methods: Single-cell RNA sequencing was performed on lung tissue from 8 lung transplant donors and 8 recipients with pulmonary fibrosis, as well as 1 cryobiopsy sample from an IPF patient.

Results: A novel distinct population of profibrotic alveolar macrophages was identified only in lung tissue from patients with pulmonary fibrosis, as well as a few other subtler differences in the epithelial cells, as compared to donor lung tissue.

Take Home Message: Next-generation sequencing may prove useful in identifying therapeutically exploitable signaling pathways in pulmonary fibrosis.

**Stevens TM, et al. *NUTM1*-rearranged neoplasia: a multi-institution experience yields novel fusion partners and expands the histologic spectrum. Mod Pathol 2019;32:764-773**

Purpose: NUT carcinomas, which are generally poorly differentiated and show variable squamous differentiation, usually have *BRD4* as a *NUTM1* fusion partner. Some undifferentiated soft tissue tumors have been found to also harbor *NUTM1* fusions. This study attempts to expand understanding of *NUTM1*-rearranged neoplasms.

Methods: The databases of three institutions were searched for neoplasms in which *NUTM1*-rearrangements were identified by NGS ± FISH.

Results: A total of 26 *NUTM1*-rearranged neoplasms were identified (20 NUT carcinomas, 4 sarcomas, and 2 neoplasms of uncertain lineage), 24 of which had fusion partner data. Three-quarters (18/24) had *BRD4* as a fusion partner, *NSD3* was present in 2 cases, *BRD3* in 1 case, and two novel fusion partners were seen, including *MGA* in 1 myxoid spindle cell sarcoma and 1 undifferentiated sarcoma and *MXD4* in 1 round cell sarcoma. All 11 cases tested for NUT IHC were positive, including those with the novel fusion partners.

Take Home Message: As if recognizing NUT carcinoma was not challenging enough, *NUTM1*-rearrangements can also be seen in sarcomas, albeit rarely. The susceptibility of newly recognized *NUTM1* fusion partners to bromodomain inhibitor therapy is unknown. Therefore,

detecting a *NUTM1*-rearrangement may not be sufficient and determining the specific fusion partner by FISH or NGS may be necessary.

**Verleden SE, et al. Phenotypical diversity of airway morphology in chronic lung graft vs. host disease after stem cell transplantation. Mod Pathol 2019;32:817-829**

Purpose: To compare airway architecture in chronic lung allograft dysfunction (CLAD) and pulmonary graft versus host disease (GVHD) following allogenic hematopoietic stem cell transplantation.

Methods: Small airways pathology in explanted inflated lungs from GVHD patients, patients with CLAD, and controls (n = 6 per group) was analyzed by a combination of CT, microCT (imaging of tissue cores), and histology.

Results: Among the stem cell transplant patients, 3 had bronchiolitis obliterans syndrome (BOS) and 3 showed interstitial changes and restriction. CT findings were similar in patients with BOS post-lung transplant or post-stem cell transplant. In comparison, the degree of airway obstruction was lower in stem cell transplant patients with restrictive/interstitial changes and was similar to lung transplant patients with restrictive allograft syndrome, who showed decreased numbers of terminal bronchioles per lung and parenchymal fibrosis. Airway and parenchymal morphometric changes were similar in lung GVHD and CLAD.

Take Home Message: The pathophysiologic mechanisms underlying lung GVHD and CLAD may be similar and this paper has a lot of fancy photos and reconstructions attempting to show that.

## Review Articles

**Boone PM, et al. The genetics of pneumothorax. Am J Respir Crit Care Med 2019;199:1344-1357**

A thorough review of the clinical and genetic aspects of spontaneous pneumothorax that includes a useful table and montage of clinical and CT images. As many as 10-12% of patients with spontaneous pneumothorax have a family history of pneumothorax.

## Case Reports

**Kunimasa K, et al. Patients with SMARCA4-deficient thoracic sarcoma and severe skeletal-related events. Lung Cancer 2019;132:59-64**

Case Summary: Two male smokers, both 45-years-old, presented with orthopedic complaints, one with upper leg pain and impending pathologic femoral fracture and the other with back pain resulting from spine cord compression. Both had a large lung mass adjacent to the mediastinum that on biopsy were undifferentiated tumors, one with rhabdoid morphology, showing identical immunoprofiles (TTF-1 negative, p40 rare positive, pan-CK patchy positive, SMARCA4 diffuse

loss of expression, SOX positive, claudin-4 negative, SALL4 positive, CD34 negative, p53 overexpressed).

Take Home Message: Severe skeletal-related events requiring emergent intervention appear, not surprisingly given its aggressive clinical course, to be a feature of SMARCA4-DTS. According to the authors of this report, negative staining for claudin-4 and expression of SOX2 supports a diagnosis of SMARCA4-DTS rather than SMARCA4-mutated carcinoma.

**Van Treeck BJ, et al. A 52-year-old woman with an abdominal mass, bilateral pulmonary nodules, and mediastinal and hilar lymphadenopathy. Chest 2019;155:e175-e178**

Case Summary: A very nicely presented case of pulmonary talcosis published by several members and an alumnus of this journal club, complete with energy dispersive x-ray spectroscopy data.

Take Home Message: Pulmonary talcosis resulting from excessive use of talcum powder can resemble sarcoidosis both clinically and histologically. Before making a a diagnosis of sarcoidosis, polarize those well-formed non-necrotizing epithelioid granulomas to look for the needle-shaped crystals of talc, which contrast with the generally more rounded oxalate crystals that are an occasional endogenous manifestation of sarcoidosis!

## Letters to the Editor

**Finkelstein MM. Malignant mesothelioma and its nonasbestos causes. Arch Pathol Lab Med 2019;143:659-660**

A previously reported study (see Attanoos RL, et al. Arch Pathol Lab Med 2018;142:753-760) concluded most mesotheliomas not clearly attributable to asbestos exposure are spontaneous (idiopathic). The writer of this letter takes issue with this conclusion without providing countering evidence that talcum powder causes malignant mesothelioma. The disclosure statement indicates the writer has served as a consultant to plaintiff's lawyers in asbestos and talc litigation. A rebuttal letter by the authors of the original study will be forthcoming in the August issue of the same journal.

## Images in Clinical Medicine

**Katz MG, et al. Injury from e-cigarette explosion. N Engl J Med 2019;380:2460**

In addition to the physiologic dangers of e-cigarettes, there are physical ones as well, as this photograph dramatically illustrates.