

## PULMONARY PATHOLOGY JOURNAL CLUB (April 2019 Articles)

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### Table of Contents

#### Discussion articles

- Page 3** Hernandez A et al. Assessment of programmed death-ligand 1 (PD-L1) immunohistochemical expression on cytology specimens in non-small cell lung carcinoma. *Am J Clin Pathol* 2019; 151:403-15.
- Page 4** Yoshimura M et al. Highly expressed EZH2 in combination with BAP1 and MTAP loss, as detected by immunohistochemistry, is useful for differentiating malignant pleural mesothelioma from reactive mesothelial hyperplasia. *Lung Cancer* 2019; 130:187-93.
- Page 5** Perret R et al. SMARC4-deficient thoracic sarcomas clinicopathologic study of 30 cases with an emphasis on nosology and differential diagnoses. *Am J Surg Pathol* 2019; 43:455-65.
- Page 6** Arora K et al. The histologic diagnosis of IgG4-related disease on small biopsies: challenges and pitfalls. *Histopathology* 2019; 74:688-98.

#### Articles for notation

- Page 7** *Neoplastic lung disease*  
Ahmadzada T et al. High BIN1 expression has a favorable prognosis in malignant pleural mesothelioma and is associated with tumor infiltrating lymphocytes. *Lung Cancer* 2019; 130:35-41.
- Doxtader EE. Displaced cartilage within lymph node parenchyma is a novel biopsy site change in resected mediastinal lymph nodes following EBUS-TBNA. *Am J Surg Pathol* 2019; 43:497-503.
- Edlund K et al. Prognostic impact of tumor cell programmed death ligand 1 expression and immune cell infiltration in NSCLC. *J Thorac Oncol* 2019; 14:628-40.
- Hermans BCM et al. Prevalence and prognostic value of PD-L1 expression in molecular subtypes of metastatic large cell neuroendocrine carcinoma (LCNEC). *Lung Cancer* 2019; 130:179-86.
- Kalhor N et al. Thymic epithelial neoplasms with sebaceous differentiation: a clinicopathological and immunohistochemical study of 8 cases. *Hum Pathol* 2019; 86:124-8.

Kervarrec T et al. Diagnostic accuracy of a panel of immunohistochemical and molecular markers to distinguish Merkel cell carcinoma from other neuroendocrine carcinomas. *Mod Pathol* 2019; 32:499-510.

Martinez-Terroba E et al. 5 protein-based signature for resected lung squamous cell carcinoma improves the prognostic performance of the TNM staging. *Thorax* 2019; 74:371-9.

Wang H et al. A study of ALK-positive pulmonary squamous-cell carcinoma: from diagnostic methodologies to clinical efficacy. *Lung Cancer* 2019; 130:135-42.

Zhang ML et al. Differential expression of PD-L1 and IDO1 in association with the immune microenvironment in resected lung adenocarcinomas. *Mod Pathol* 2019; 32:511-23.

**Page 9** *Non-neoplastic lung disease*

Hung YP et al. Incidental nonneoplastic parenchymal findings in patients undergoing lung resection for mass lesions. *Hum Pathol* 2019; 86:93-101.

**Page 9** *Review articles*

Regragui M et al. Primary malignant deciduoid mesothelioma: a challenging diagnosis. *Arch Pathol Lab Med* 2019; 143:531-3.

Savic Prince S et al. Predictive potential and need for standardization of PD-L1 immunohistochemistry. *Virchows Archiv* 2019; 474:475-84.

**Page 10** *Case report*

Tsuchiya K et al. Methotrexate-associated lymphoproliferative disorder with diffuse ground-glass opacities. *Am J Respir Crit Care Med* 2019; 199:1031-3.

**Page 10** *Letters to the editor*

Grosse A et al. PD-L1 expression in biphasic pleural mesothelioma with histiocytoid morphology and enrichment of CD8+/CD4+ lymphocytes. *Pathol Int* 2019; 69:180-2.

Li ZH et al. A case of cushing syndrome in ACTH-secreting thymic paraganglioma. *J Thorac Oncol* 2019; 14:e79-81.

Monaci N et al. Thymic carcinoma with thyroid transcription factor-1 expression: an insidious pitfall. *J Thorac Oncol* 2019; 14:e68-70.

Ravaglia C et al. Report standardization in transbronchial lung cryobiopsy. *Arch Pathol Lab Med* 2019; 143:416-7.

## Discussion articles

**Hernandez A et al. Assessment of programmed death-ligand 1 (PD-L1) immunohistochemical expression on cytology specimens in non-small cell lung carcinoma. Am J Clin Pathol 2019; 151:403-15.**

**Purpose:** Evaluate if non-small cell lung carcinoma (NSCLC) cytology specimens are reliable for PDL-1 testing by evaluating concordance with paired surgical specimens.

### **Methods:**

- Pathology database retrospectively reviewed for NSCLC surgical biopsies and resections that had undergone previous PD-L1 testing *and* had concurrent or subsequent cytology specimens that included a cell block
  - Cases with fewer than 50 tumor cells in cell block excluded
- Dako PD-L1 clone 22C3 applied to the cell blocks
- Tumor scored as: negative (<1%), low positive ( $\geq 1-49\%$ ), and high positive ( $\geq 50\%$ )
- Strength of agreement was assessed based upon concordance in the 3 expression levels between paired specimens

### **Results:**

- 52 cytology cases with paired surgical specimens identified (detailed in Table 3)
  - 47 adenocarcinomas; 2 squamous cell carcinomas; 2 poorly differentiated NSCLC; 1 sarcomatoid NSCLC
- Overall, there was agreement in 67% (35/52) of cases ( $\kappa = 0.51$ ; moderate agreement)
  - Highest concordance seen with samples obtained directly from the lung (83%;  $\kappa = 0.74$ )
  - Fair agreement in other sites sampled (lymph nodes and pleural fluid)
  - Cytology samples showed better agreement with excision samples than small biopsy specimens (12/14 [86%] vs. 23/38 [61%])
  - There was better concordance when 100 or more tumor cells were present in the cell block ( $\kappa = 0.63$ ) versus specimens with <100 tumor cells ( $\kappa = 0.19$ )
- Analyzing discordance:
  - Most commonly cell block was negative when the surgical specimen was positive (11/17)
  - 5/17 cases showed differences in expression (i.e. low vs. high)
  - 1 case showed low positive cytology, but negative surgical specimen (EBUS lung core biopsy)
  - Of the discordant cases, 8 were cytology specimens with <100 tumor cells

**Take-home message:** Cell blocks offer a good option PD-L1 testing, particularly in the context of positive expression, which seems reliable when compared to surgical specimens. Disagreement may be attributable to intratumoral heterogeneity and low cell block cellularity.

**Yoshimura M et al. Highly expressed EZH2 in combination with BAP1 and MTAP loss, as detected by immunohistochemistry, is useful for differentiating malignant pleural mesothelioma from reactive mesothelial hyperplasia. Lung Cancer 2019; 130:187-93.**

**Purpose:** Assess the sensitivity and specificity for EZH2 immunohistochemistry (IHC) for distinguishing malignant pleural mesothelioma (MPM) from reactive mesothelial hyperplasia (RMH), both alone and when used in combination with BAP1 and MTAP IHC and 9p21 FISH.

**Methods:**

- Cases of MPM (n = 38) and RMH (n = 29) retrieved from files between 2001 and 2015
  - 27 epithelioid, 6 biphasic, and 5 sarcomatoid mesotheliomas
- IHC for EZH2, BAP1, and MTAP and FISH for 9p21 performed on all specimens
  - EZH2 (nuclear) expression scored as low (<50%) or high (>50%)
  - BAP1 reported as lost if nuclear staining weaker than control in 50% of cells
  - MTAP (cytoplasmic and nuclear staining) reported as lost if weaker than control in 50% of cells

**Results:**

- Refer to table 1 for detailed look at sensitivity and specificity of individual markers and when used in combination
  - All markers showed 100% specificity for MPM
  - EZH2 immunohistochemistry alone is the least sensitive of all the individual markers tested at 44.7% (< MTAP < BAP1 < 9p21 FISH)
  - A combination of EZH2, BAP1, and 9p21 FISH captured the most cases of MPM (89.5%)
  - The combination of the 3 IHC stains was also very good (86.8% sensitivity)
  - BAP1 and 9p21 FISH performed very well together (81.6% sensitivity)
  - When EZH2 IHC used in combination with BAP1, sensitivity increases to 73.7% compared to 52.6% for BAP1 alone
- Survival analysis showed high EZH2 expression to be associated with significantly shorter overall survival in patients with epithelioid mesothelioma (Figure 4C)

**Take-home message:** If you would like to increase the sensitivity of your already available testing methods for differentiating MPM and RPM, you might consider implementing EZH2 IHC. BUT, if you are going to select just one testing method, EZH2 alone performs the worst.

**Perret R et al. SMARCA4-deficient thoracic sarcomas clinicopathologic study of 30 cases with an emphasis on nosology and differential diagnoses. Am J Surg Pathol 2019; 43:455-65.**

**Purpose:** 1) Describe the clinicopathologic features of SMARCA4-deficient thoracic sarcoma (SMARCA4-DTS), and 2) assess the specificity of a predicted immunohistochemical signature (co-loss of SMARCA4 and SMARCA2 and overexpression of SOX2)

**Methods:**

- 30 cases of SMARCA4-DTS identified and diagnosis confirmed by 2 pathologists
  - Diagnostic criteria: 1) Rhabdoid or poorly differentiated morphology; 2) Loss of SMARCA4 and SMARCA2 expression; 3) At least focal expression of 2 of the following: SOX2, CD34, SALL4
- Clinical information, demographics, and imaging reviewed
- All cases of SMARCA4-DTS underwent detailed immunohistochemical characterization and expression scored (-, +/-, +)
- Screening group tested for SMARCA4 ( $n = 431$ ), SMARCA2 ( $n = 220$ ), and SOX2 ( $n = 280$ ) expression

**Results:**

- Clinical features of patients with SMARCA4-DTS were consistent with other studies
  - Patient characteristics: Male > female (9 : 1); broad age range (28 to 90 years) with median age of 48 years; 87% current or former smokers
  - Tumors characteristics: Large, compressive masses involving mediastinum > pleura > lung; but many were multifocal, involving more than one of these sites; 77% of patients had metastases
  - Despite varied treatment strategies, all patients suffered disease progression (median OS 6 months)
- Pathologic features in keeping with previous descriptions of sheets of discohesive, pleomorphic epithelioid cells with rhabdoid features and abundant necrosis
  - 2 cases described as reminiscent of desmoplastic small round cell tumor (Fig 3)
  - 2 cases showed focally myxoid/edematous stroma (Fig 3)
- All SMARCA4-DTS showed loss of SMARCA4 and SMARCA2 and 96% showed staining for SOX2 (Table 2)
  - CD34 seen in 96% of cases
  - SALL4 often negative (67%)
  - 54% of cases positive for AE1/AE3; 96% positive for AE1/AE3 or EMA
  - Pitfall: TTF-1 focally positive in 1 case
- SMARCA4 lost in a surprising number of screening group carcinomas
- SMARCA4 and SMARCA2 lost in small cell carcinoma of the ovary hypercalcemic type
- SOX2 expressed in 37.5% ( $n = 18/48$ ) squamous cell carcinomas

**Take-home message:** Co-loss of SMARCA4 and SMARCA2 and expression of SOX2 by immunohistochemistry is helpful and specific for the diagnosis of SMARCA4-DTS. Cases that show loss of SMARCA4 and express epithelial markers, but do not fulfill the other diagnostic criteria (above) are classified by these authors as “SMARCA4-deficient carcinoma.”

**Arora K et al. The histologic diagnosis of IgG4-related disease on small biopsies: challenges and pitfalls. *Histopathology* 2019; 74:688-98.**

**Purpose:** Assess the histologic spectrum of findings in small biopsies from a prospective series of patients with presumptive clinical diagnoses of IgG4-related disease (IgG4-RD) to understand the relative importance of current pathologic criteria used for diagnosis (Table 1). A minor objective, using retrospective and control groups, appears to be validation of ISH assay for IgG and IgG4.

**Methods:**

- Prospective cohort comprised of 55 patients seen at Massachusetts General Hospital, who underwent needle or small biopsy (defined as size <10 mm)
  - Retroperitoneum and salivary gland biopsies comprised the most common sites
  - Clinical characteristics evaluated: tumefactive lesions, organ involvement, serum levels of IgG4, and response to immunosuppressive therapy
- IHC and ISH for IgG and IgG4 applied to retrospective and control groups
  - Retrospective cohort comprised of 71 resection specimens from patients diagnosed with IgG4-RD
  - Control cohort of histologic mimics of IgG4-RD

**Results:**

- Prospective study:
  - 26 (47%) of patients categorized as “definite IgG4-RD” on biopsy using current diagnostic criteria
  - 29 patients (53%) categorized as “borderline IgG4-RD” on biopsy, based upon lack of 1 or more histologic criteria or immunohistochemical findings
    - 20 cases lacked both storiform fibrosis and obliterative phlebitis
    - 8 or 9 cases did not have enough IgG4-positive plasma cells
  - 99% of patients in both definite and borderline groups showed IgG4 to IgG ratio >40%
  - Clinical characteristics of definite and borderline cases detailed in Table 3
    - Borderline group slightly younger (48 vs. 53)
    - Borderline cohort had higher peripheral and tissue eosinophilia
    - No significant difference in organ involvement or serum IgG4
    - Borderline patients less responsive to steroid therapy; 17% non-responsive compared to 6% of definite cases
- Similar to previous studies the IgG4 to IgG ratio needed to distinguish IgG4-RD from its histologic mimics is 40% for IHC
- A lower ratio is required for ISH with >30% deemed the acceptable threshold (Figure 5)

**Take-home message:** IgG4 to IgG ratio is the most sensitive histologic feature in small biopsies from patients with presumptive IgG4-RD. Patients with presumptive clinical diagnoses of IgG4-RD, but lacking all the classic histologic features are clinically similar to those who fulfill of the pathologic criteria.

## Articles for notation

### Neoplastic lung disease

**Ahmadzada T et al. High BIN1 expression has a favorable prognosis in malignant pleural mesothelioma and is associated with tumor infiltrating lymphocytes. Lung Cancer 2019; 130:35-41.**

**Take-home message:** The aim of this work was to assess BIN1 and IDO1 expression in 67 cases of malignant mesothelioma, including 33 epithelioid and 34 “non-epithelioid.” BIN1 expression was frequently observed with only 4 cases showing no expression and 51% of patients having a high ( $\geq 89\%$ ) expression, while IDO1 was more often negative (70%). IDO1 showed no significant association between survival and expression, but high BIN1 expression was associated with tumoral inflammation and increased overall survival of 12 versus 6 months when compared to the low expression group.

**Doxtader EE. Displaced cartilage within lymph node parenchyma is a novel biopsy site change in resected mediastinal lymph nodes following EBUS-TBNA. Am J Surg Pathol 2019; 43:497-503.**

**Take-home message:** A perhaps surprisingly large and diverse group of pathologists (22 participants from 14 institutions in 5 countries) collaborated on this work, made possible by Twitter. These various institutions submitted a total of 297 mediastinal lymph node resections from patients who previously underwent EBUS-TBNA. Of these, 34 patients (11.4%) were discovered to have previous biopsy site-related changes that included cartilage fragments in 26 cases, which was the most common findings, followed by nodal scar ( $n = 7$ ) and hemosiderin ( $n = 1$ ).

**Edlund K et al. Prognostic impact of tumor cell programmed death ligand 1 expression and immune cell infiltration in NSCLC. J Thorac Oncol 2019; 14:628-40.**

**Take-home message:** Immunohistochemistry for CD3, CD8, FOXP3, CD20, CD79a, IGKC and PD-1 was applied to tissue microarrays for a total of 705 patients that included a combination of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The authors found that tumors with greater inflammatory infiltrates of cytotoxic T-cells had better overall survival independent of PD-L1 status.

**Hermans BCM et al. Prevalence and prognostic value of PD-L1 expression in molecular subtypes of metastatic large cell neuroendocrine carcinoma (LCNEC). Lung Cancer 2019; 130:179-186.**

**Take-home message:** This study investigated the prevalence of PD-L1 expression in 98 cases of stage IV large cell neuroendocrine carcinoma (LCNC), a group that was further subdivided based upon molecular subtype as co-mutated *TP53* and *STK11/KEAP1* or *TP53* and *RBI*. Tumor cells were positive ( $\geq 1\%$  staining) in 16% of cases; no *STK11* mutated tumors expressed PD-L1. Overall survival was marginally better in PD-L1 positive cases with median of 8.9 months, as compared to 6.6 months in patients with PD-L1 negative tumors.

**Kalhor N et al. Thymic epithelial neoplasms with sebaceous differentiation: a clinicopathological and immunohistochemical study of 8 cases. Hum Pathol 2019; 86:124-8.**

**Take-home message:** MD Anderson again digs into their files to report 8 cases, including 7 thymomas and 1 thymic carcinoma, with sebaceous differentiation. While an interesting finding, the presence of sebaceous differentiation is of no special clinical significance nor as the authors acknowledge, does it make the primary diagnosis more difficult.

**Kervarrec T et al. Diagnostic accuracy of a panel of immunohistochemical and molecular markers to distinguish Merkel cell carcinoma from other neuroendocrine carcinomas. Mod Pathol 2019; 32:499-510.**

**Take-home message:** Occasionally, Merkel cell carcinoma can be negative for cytokeratin (CK) 20, the marker most used in distinguishing Merkel cell carcinoma from other neuroendocrine carcinomas. In this study, other ancillary methods were investigated for differentiating Merkel cell carcinoma ( $n = 103$ ) from extracutaneous neuroendocrine carcinoma ( $n = 70$ ). The authors found that immunohistochemistry for SATB2 and NF and Merkel cell polyomavirus qPCR were the most helpful in identifying CK 20-negative cases as Merkel cell carcinoma with 97-8% specificity.

**Martinez-Terroba E et al. 5 protein-based signature for resected lung squamous cell carcinoma improves the prognostic performance of the TNM staging. Thorax 2019; 74:371-9.**

**Take-home message:** This interesting study details how the authors generated a protein-based classifier to predict survival in patients with squamous cell carcinoma, from gene selection to signature development and validation of concept. From 12 proteins evaluated, five were selected (RAE1, RRM2, SLC2A1, SRSF1, and STC1) and complex algorithm created to calculate prognostic index. This method was then applied to two cohorts of patients ( $n = 42$  and  $n = 117$ ) and showed significant association with disease free survival and overall survival, leading the authors to conclude that the use of these prognostic markers could be complementary to the current TNM system to improve risk stratification.

**Wang H et al. A study of ALK-positive pulmonary squamous-cell carcinoma: from diagnostic methodologies to clinical efficacy. Lung Cancer 2019; 130:135-42.**

**Take-home message:** The primary aim of this study was to assess concordance between ALK immunohistochemistry (IHC) versus FISH in squamous cell carcinoma. Of the 2403 cases of squamous cell carcinoma, 37 cases (1.5%) were identified as ALK-positive for IHC, but only 4 of these (28 tested) showed ALK rearrangement by FISH. The 14.3% concordance between IHC and FISH led the authors to conclude that IHC is an unreliable guide for targeted therapy in this setting.



**Zhang ML et al. Differential expression of PD-L1 and IDO1 in association with the immune microenvironment in resected lung adenocarcinomas. *Mod Pathol* 2019; 32:511-23.**

**Take-home message:** PD-L1 and IDO1 expression were investigated in 261 lung adenocarcinomas using tissue microarrays, and expression correlated with various parameters, including: clinical features, tumor-infiltrating lymphocytes, driver mutations, and patient outcomes. PD-L1 and IDO1 expression were both associated with smoking and abundant CD8+ T-cells; PD-L1 expression was seen in association with *KRAS* mutation, while isolated IDO1 expression was observed in 69% of *EGFR* mutants. PD-L1 expression correlated with poorer progression-free and overall survival, but IDO1 showed no significant association with survival.

*Non-neoplastic lung disease*

**Hung YP et al. Incidental nonneoplastic parenchymal findings in patients undergoing lung resection for mass lesions. *Hum Pathol* 2019; 86:93-101.**

**Take-home message:** This study retrospectively looked at the types and prevalence of nonneoplastic findings incidentally discovered in 397 patients, who underwent lung resection for localized lesions (78% malignant). Of these patients, 25 percent were discovered to have incidental parenchymal findings for which smoking-related interstitial fibrosis was the most common diagnosis. Diffuse fibrotic disease (usual interstitial pneumonia, nonspecific interstitial pneumonia, and unclassifiable) was identified in 11 patients (~3%), and only recognized by experts upon retrospective review.

*Review articles*

**Regragui M et al. Primary malignant deciduoid mesothelioma: a challenging diagnosis. *Arch Pathol Lab Med* 2019; 143:531-3.**

**Take-home message:** This review article describes the clinical characteristics, histologic features, immunophenotype, and prognostic implications of the rare (<5%) deciduoid variant of malignant mesothelioma. The differential diagnosis is also covered.

**Savic Prince S et al. Predictive potential and need for standardization of PD-L1 immunohistochemistry. *Virchows Archiv* 2019; 474:475-84.**

**Take-home message:** In this review, the authors provide the biologic background for PD-L1 biomarker testing in non-small cell lung cancer, clinical indications for testing and initiation of targeted immunotherapy. The article details the confusion surrounding PD-L1 reporting that is largely the result of various antibodies and assays, and their links to clinical drug trials that used varied scoring systems and cutoffs to stratify patients.

Case reports

**Tsuchiya K et al. Methotrexate-associated lymphoproliferative disorder with diffuse ground-glass opacities. Am J Respir Crit Care Med 2019; 199:1031-3.**

**Take-home message:** The patient is a 53-year-old woman with history of rheumatoid arthritis and Sjogren's syndrome, managed with methotrexate (MTX) for eight years, who presents with three-month history of fever, lymphadenopathy, and discovered to have diffuse ground glass opacities on chest CT. A lymph node biopsy revealed a diffuse infiltrate of atypical T-cells, ultimately diagnosed as MTX-associated angioimmunoblastic T-cell lymphoma-like lymphoproliferative disorder. Her symptoms resolved after stopping MTX therapy.

Letters to the editor

**Grosse A et al. PD-L1 expression in biphasic pleural mesothelioma with histiocytoid morphology and enrichment of CD8+/CD4+ lymphocytes. Pathol Int 2019; 69:180-2.**

**Take-home message:** The title pretty much says it all; this tumor resembled the "lymphohistiocytic variant" of malignant mesothelioma and there was 100% expression of PD-L1 in neoplastic cells and tumor-associated/infiltrating lymphocytes.

**Li ZH et al. A case of cushing syndrome in ACTH-secreting thymic paraganglioma. J Thorac Oncol 2019; 14:e79-81.**

**Take-home message:** The title essentially tells the whole story.

**Monaci N et al. Thymic carcinoma with thyroid transcription factor-1 expression: an insidious pitfall. J Thorac Oncol 2019; 14:e68-70.**

**Take-home message:** This letter is a case report of a right apical/supraclavicular lung mass, initially diagnosed as non-small cell carcinoma, based upon positive staining for TTF-1 by immunohistochemistry. Upon resection, the tumor was reclassified as a thymic carcinoma with aberrant TTF-1 expression.

**Ravaglia C et al. Report standardization in transbronchial lung cryobiopsy. Arch Pathol Lab Med 2019; 143:416-7.**

**Take-home message:** This letter makes a proposal for lengthy and detailed reporting of lung cryobiopsy samples with each separate sample including: site, size of sample, whether the tissue appears to be central or peripheral lung, description of histologic pattern, including your level of confidence in the diagnosis as high or low... *Then*, you can offer a unifying diagnosis for all separate tissue diagnoses, also including your level of confidence for each separate diagnosis (high/low). Oh – And, if you want to diagnosis usual interstitial pneumonia, you should indicate the presence or absence of all of the following: patchy fibrosis, fibroblastic foci, and honeycomb change (Phew!).