

PULMONARY PATHOLOGY JOURNAL CLUB (December 2019 Articles)

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February 17, 2020 (re-scheduled from January 27, 2020)

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Discussion articles

Naito T et al. Non-small cell lung cancer with loss of expression of the SWI/SNF complex is associated with aggressive clinicopathological features, PD-L1-positive status, and high tumor mutation burden. Lung Cancer 2019; 138:35-42.

Prepared and presented by Dr. Laurence Briski (Thoracic Pathology Fellow 2019/2020)

Purpose: To examine (1) the clinicopathologic features, (2) PD-L1 IHC expression, and (3) tumor mutation burden (TMB) in NSCLC with respect to loss of IHC expression of specific SWI/SNF proteins (SMARCA4, SMARCA2, ARID1A, and ARID1B)

- SWI/SNF = BAF, SMARCA4 = BRG1, SMARCA2 = BRM, SMARCB1 = INI1/BAF47

Methods:

- 1013 cases of NSCLC from one institution (744 ADCA, 254 SQCC, 7 ADSQ, 7 LCC, 1 PL)
- Clinicopathologic features analyzed: age, sex, smoking history, medical history, invasive tumor size, pleural invasion, vascular invasion, intrapulmonary metastasis, lymphatic permeation, lymph node metastasis, stage, tumor morphology, status of EGFR mutation, overall survival (OS), recurrence-free survival (RFS)
- For SWI/SNF, “loss” defined as complete absence of nuclear staining (“BAF-Loss” = loss of one or more subunits; “BAF-Intact” = retained expression of all four subunits)
- For PD-L1 (Dako, 22C3), the proportion of viable tumor cells exhibiting membranous staining of any intensity was evaluated (scores reported as <1% or ≥1%; <50% or ≥50%)
- Whole exome sequencing (WES) was performed on 10 cases to calculate TMB

Results:

- BAF-Loss was observed in 5.4% of cases (5.5% of ADCA, 4.7% of SQCC)
- Compared to BAF-Intact (n = 958), BAF-Loss (n = 55) was significantly associated with:
 - Younger age (median [range]: 66 [42–93] vs 70 [33–91] years; $p = 0.04$)
 - Male sex (80% vs 64%; $p = 0.01$)
 - Smoking history (87% vs 69%; $p < 0.01$)
 - Pulmonary emphysema or bulla (69% vs 26%; $p < 0.01$),
 - Larger invasive tumor size (median [range]: 3.2 [0.1–13.5] vs 2.4 [0.1–18.0] cm; $p < 0.01$)
 - Pleural invasion (55% vs 37%, $p = 0.01$),
 - Vascular invasion (67% vs 47%; $p < 0.01$)
 - Solid predominant histologic subtype (71% vs 40%; $p < 0.01$)
 - Absence of a lepidic growth component (69% vs 43%; $p < 0.01$)
- Overall, BAF-Loss was associated with shorter OS but there was no difference in RFS
 - Stage I (n = 588): shorter OS and RFS but multivariate analysis showed no differences
 - No differences in OS or RFS for stage II (n = 192), stage III (n = 218), or stage IV (n = 15)
- Higher proportion of PD-L1 ≥ 1% was observed among BAF-Loss (42% vs 26%; $p < 0.01$); no difference in proportion with PD-L1 ≥ 50% (13% vs 11%; $p = 0.64$)

- In the WES cohort, TMB was significantly higher in tumors with BAF-Loss (n = 3) than in tumors with BAF-Intact (n = 7) (median 437 vs 113 mutations/whole exome; $p = 0.02$)

Take home message: Loss of SWI/SNF IHC expression occurs in a small minority of NSCLC but may be more common in more poorly differentiated tumors. For conventional NSCLC, knowledge of SWI/SNF expression is not required for diagnosis (unlike for SMARCA4-deficient sarcomatoid tumors). While it may provide some prognostic value, it does not appear to be an independent prognostic factor and it is uncertain whether it could impact future clinical treatment strategies.

Chirieac LR et al. Diagnostic value of biopsy sampling in predicting histology in patients with diffuse malignant pleural mesothelioma. Cancer 2019; 125:4164-71.

Purpose: Assess the *concordance* between and *prognostic value* of the histologic subtype of pleural malignant mesothelioma diagnosed at initial biopsy and that observed in the paired surgical resection specimen, and correlate with the number and volume of the initial biopsies.

Methods:

- Retrospectively reviewed the patient characteristics, histologic subtypes, and outcomes for patients diagnosed with diffuse pleural mesothelioma and treated at Brigham and Women’s Hospital between 1988 and 2006
 - Inclusion criteria: Both biopsy and surgical resection material available for review
- Slides reviewed by 2 of 3 pathologists with consensus review performed for discrepant cases
- Tumors classified as: epithelioid, sarcomatoid, or biphasic

Results:

- 759 patients met inclusion criteria (clinical characteristics detailed in table 1)
 - Type of biopsy: 728 thorascopic; 31 core needle
 - Type of surgery: 519 extrapleural pneumonectomy; 240 pleurectomy/decortication
- Refer to table 2 for a detailed comparison histologic type in initial and surgical resections specimens
 - Overall, concordance between initial and resection typing 81.6% ($n = 613$)
 - Epithelioid type: initial biopsy $n = 575$; resection $n = 483$
 - Biphasic type: initial biopsy $n = 140$; resection $n = 243$
 - Sarcomatoid type: initial biopsy $n = 36$; resection $n = 33$
 - 8 cases “indeterminate” on initial biopsy and later typed as 5 epithelioid, 3 biphasic
 - 19% of both epithelioid and sarcomatoid initial biopsies subsequently classified at biphasic mesothelioma
 - 11% biphasic later diagnosed as epithelioid
 - 3% biphasic later diagnosed as sarcomatoid
- Small but statistically significant difference in the number of blocks examined in the initial biopsy and the concordance
 - 3.4 blocks (range 1-20) in concordant cases; 2.7 (range 1-9) in discordant cases
 - When more than 9 blocks examined ($n = 23$), there was 100% concordance
- No significant difference in volume of tissue examined and diagnostic accuracy
- Independent predictors of survival age, clinical stage, and histology in the resection specimen (see figure 2)

Take-home message: There is good concordance between initial biopsy and subsequent resection with most cases being reclassified to biphasic mesothelioma, and perhaps not surprisingly, the more tissue blocks we have to review, the more accurate we are at subclassifying mesothelioma. This is perhaps most meaningful in the context of survival implications in patients re-categorized from epithelioid to biphasic on final pathology.

Gagné A et al. Impact of specimen characteristics on PD-L1 testing in non-small cell lung cancer: validation of the IASLC PD-L1 testing recommendations. J Thorac Oncol 2019; 14:2062-70.

Purpose: Evaluate the impact of suboptimal specimen characteristic (i.e. fewer than 100 tumor cells and/or blocks older than 3 years) and cytologic cell blocks on PD-L1 testing results, using the 22C3 antibody.

Methods:

- Retrospective study of cases referred to the Quebec Heart and Lung Institute for PD-L1 testing
 - Inclusion criteria: Diagnosis of NSCLC and non-decalcified specimens
- PD-L1 expression scored as: <1%; 1-49%; and, \geq 50%

Results:

- 1249 cases met inclusion criteria (detailed in table 1)
 - 444 specimens had 1 or more characteristics for which PD-L1 testing not recommended
 - 40 blocks older than 3 years
 - 96 blocks with 1-100 tumor cells
 - 355 cytology specimens
- Refer to table 2 for detailed PD-L1 tumor proportion score
 - Decrease in antigenicity over time, particularly after 1 year
 - Specimens with fewer than 100 tumor cells associated with lower PD-L1 expression
 - No significant association between PD-L1 expression and specimen type
 - Lymph node and distant metastases showed higher expression when compared to the primary tumor

Take-home message: The IASLC testing recommendations for specimens older than 3 years and those comprised of fewer than 100 tumor cells have been validated, and this study supports the use of cell blocks for PD-L1 testing. If no other specimen is available, testing may be performed on suboptimal specimens with the acknowledgement that these patients are more likely to have a negative result.

Miyata-Morita K et al. Frequent appearance of club cell (Clara cell)-like cells as a histologic marker for ALK-positive lung adenocarcinoma. Pathol Int 2019; 69:688-96.

Purpose: Report the histologic features of papillary adenocarcinoma in *ALK*+ lung cancers.

Methods:

- Analyze the histologic patterns of 18 *ALK*+ lung adenocarcinoma compared to a control group (22 *EGFR*+ adenocarcinomas and 40 *ALK*-/*EGFR*- adenocarcinomas)
- Assess the presence of “club cell-like cells”(CLCs) in the papillary portions of these adenocarcinomas (see figure 1 for representative histology)
 - Perform immunohistochemistry for surfactant protein and perilipin 2 to investigate production of these proteins in the CLCs in *ALK*+ cases only

Results:

- Solid signet ring cell and mucinous cribriform patterns almost exclusively seen in *ALK*+ cases (table 2) and seen in all but 1 *ALK*+ case
- Papillary pattern observed in 95% of all cases and was more commonly seen in *EGFR*+ and *ALK*-/*EGFR*- cases than in *ALK*+ (83%)
 - Represented predominant pattern in 5 of 18 *ALK*+ cases
- Micropapillary pattern *ALK*+ (83%) > *EGFR*+ (73%) > *ALK*-/*EGFR*- (33%)
- CLCs seen with greater frequency in *ALK*+ cases (table 4) and observed in all cases that showed papillary pattern

Take-home message: In the absence of solid ring cell and mucinous cribriform patterns, the presence of club cell-like cells in a papillary arrangement may be a histologic clue that you are dealing with an *ALK*+ lung adenocarcinoma.

Articles for notation

Neoplastic lung disease

Chatzopoulos K et al. Loss of succinate dehydrogenase B immunohistochemical expression distinguishes pulmonary chondromas from hamartomas. *Histopathology* 2019; 75:825-32.

Take-home message: Immunohistochemistry for succinate dehydrogenase (SDH) B was applied to 6 pulmonary chondromas, which included 4 patients with established clinical diagnoses of Carney triad, and 33 cases of pulmonary hamartoma. Cytoplasmic SDHB expression was lost in 5 chondromas (4 of 4 Carney triad), but retained in all hamartomas. In conclusion, SDHB immunohistochemistry may be a helpful marker in the differential diagnosis of chondroma versus hamartoma, particularly in small biopsies, and may assist in identification of patients with SDH-deficiency syndromes (e.g. Carney triad).

Forest F et al. Impact of delayed fixation and decalcification on PD-L1 expression: a comparison of two clones. *Virchows Arch* 2019; 475:693-9.

Take-home message: The expression of two PD-L1 antibodies, 22C3 and E1L3N, was tested on placenta ($n = 7$) and tumor ($n = 5$) control tissues using varied pre-analytic conditions. The proportion of cells staining and intensity of staining were not significantly affected by delayed fixation, up to 24 hours at room temperature. When using the 22C3 antibody, decalcification with DC3 decalcifier significantly and rapidly reduced expression of PD-L1 (non-decalcified control: $92\% \pm 14.8$ versus decalcified for 24 hours: $13.6\% \pm 13.1$), while EDTA decalcification only resulted in decreased intensity but no significant decline in expression; the E1L3N antibody showed no change in expression or intensity during the first 24 hours.

Jurmeister P et al. Next generation sequencing of lung adenocarcinoma subtypes with intestinal differentiation reveals distinct molecular signatures associated with histomorphology and therapeutic options. *Lung Cancer* 2019; 138:43-51.

Take-home message: Here, the authors take a comprehensive look at the immunophenotype (TTF-1, CK7, CK20, CDX2, Ki-67, ALK, and PD-L1) and tumor mutation burden by next-generation sequencing, using a 404 cancer-related gene panel, of: 6 invasive mucinous carcinomas, 7 pulmonary enteric adenocarcinomas (PEAD), and 6 colloid adenocarcinomas. Immunophenotypically, all cases were similar with the majority positive for CK7 and CDX2, but negative for TTF-1, CK20, and ALK; PD-L1 was only expressed in 3 cases of PEAD, while all others were negative; Ki-67 was variable. Invasive mucinous adenocarcinomas showed the fewest chromosomal alterations, while PAED had the most.

Krencz I et al. Correlation between immunohistochemistry and RICTOR fluorescence in situ hybridization amplification in small cell lung carcinoma. *Hum Pathol* 2019; 93:74-80.

Take-home message: This collaboration between authors from Semmelweis University in Hungary and Mayo Clinic – Jacksonville assessed *RICTOR* FISH and Rictor and p-Akt immunohistochemistry in 100 cases of small cell carcinoma. *RICTOR* amplification was observed in 15% of cases, while immunoreactivity for Rictor and p-Akt were 37% and 43%,

respectively. With a sensitivity of 93% and specificity of 73%, Rictor immunohistochemistry is considered a good screening tool for the assessment of *RICTOR* overexpression and may be useful in the identification of patients who could benefit from mTORC1/2 inhibitor therapy.

Zugazagoitia J et al. Quantitative assessment of CMTM6 in the tumor microenvironment and association with response to PD-L1 pathway blockade in advanced-stage non-small cell lung cancer. J Thorac Oncol 2019; 14:2084-96.

Take-home message: In this study, quantitative multiplexed immunofluorescence for CMTM6 and PD-L1 were performed on tissue microarrays from 438 NSCLCs. Most (70%) cases showed tumor and stromal CMTM6 expression, which significantly correlated with PD-L1 expression. Neither CMTM6 or PD-L1 alone predicted for immunotherapy outcomes, but stromal co-expression was associated with longer overall survival in patients who received immune checkpoint inhibitors.

Non-neoplastic lung disease

Ryu AJ et al. Clinico-radiologic features of lung disease associated with aspiration identified on lung biopsy. CHEST 2019; 156:1160-6.

Take-home message: This work out of the Mayo Clinic takes a retrospective look at the clinical and radiographic features of 52 patients diagnosed with aspiration on surgical or transbronchial biopsy. Interestingly, aspiration was clinically suspected in only about one-third of cases, but 90% of subjects had at least one identifiable risk factor with gastroesophageal reflux disease being the most common (62%).

Case reports

Watanabe H et al. A rare case of pulmonary typical carcinoid with prominent acinic cell differentiation, resembling acinic cell carcinoma. Pathol Int 2019; 69:721-6.

Take-home message: To expand on the title, approximately 40% of the resected tumor resembled acinic cell carcinoma (ACC) with positive staining for α -1-antichymotrypsin and zymogen-type granule on electron microscopy, while the remainder of the tumor was morphologically, immunophenotypically, and ultrastructurally consistent with typical carcinoid tumor. The authors ultimately concluded that the entire tumor was a carcinoid tumor, since the acinic cell component was negative for NR4A3 by immunohistochemistry, which is a nuclear marker that is reportedly highly specific and sensitive for ACC.

Letters to the editor

Fels Elliott DR et al. Giant cell interstitial pneumonia secondary to cobalt exposure from e-cigarette use. Eur Respir J 2019; 54:1901922.

Take-home message: This letter is a case report of a 49-year-old woman who presented with progressive exertional dyspnea, associated with dry cough, moderately severe restrictive defect and severe diffusion impairment on pulmonary function tests, and bilateral groundglass opacities with ill-defined centrilobular nodules. The liquid from her marijuana e-cigarette (ZenPen personal vaporizer) that she used for six months prior to presentation was analyzed by

mass spectrometry and shown to contain cobalt. The findings in her lung wedge biopsy were consistent with giant cell interstitial pneumonia, but elemental analysis of the tissue by electron microscopy energy dispersion X-ray spectrometry failed to detect cobalt.

Geyer SJ. Malignant mesothelioma and its nonasbestos causes: talcum powder does not create occult asbestos exposure. Arch Pathol Lab Med 2019; 143:1439.

Take-home message: This is a fiery retort to Finkelstein's letter to the editor, published in the June 2019 edition of *Archives of Pathology & Laboratory Medicine*, where he contends talcum powder is a nonasbestos cause of malignant mesothelioma. Of note, Finkelstein serves as a consultant to plaintiff's lawyers in asbestos and talc litigation, while Greyer serves as an expert witness to parties involved in the same type of litigation cases.