PULMONARY PATHOLOGY JOURNAL CLUB
(February 2018 Articles)

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Discussion articles

Pillappa R et al. Loss of BAP1 Expression in Atypical Mesothelial Proliferations Helps to Predict Malignant Mesothelioma. Am J Surg Pathol 2018; 42: 256-63.

Purpose: Assess how useful BAP1 immunohistochemistry and *CDKN2A (p16)* deletion are in predicting a diagnosis of malignant mesothelioma over reactive mesothelial proliferation in cases diagnosed as "atypical mesothelial proliferation."

Methods:
- Biopsy materials diagnosed as "atypical mesothelial proliferation" between 1993 and 2016 retrieved from the pathology archives of Mayo Clinic Rochester, MN ($n = 34$ with sufficient material)
  - Specimens: 21 pleura; 3 pericardium; 10 peritoneum
  - Initial procedure: 24 needle biopsies; 10 surgical biopsies
- Slides reviewed and confirmed diagnosis, which was rendered due to a) lack of definite invasion and b) no tumefactive growth
- BAP1 immunohistochemistry performed on selected blocks from those cases
- FISH for *CDKN2A* (9p21) deletion performed on 31 of 34 cases
  - 3 cases insufficient material

Results:
- 15 of 34 (44.1%) patients diagnosed with malignant mesothelioma (MM) in subsequent biopsy or resection ($n = 11$) or radiographic follow-up ($n = 4$)
  - Distribution of histologic subtype for cases where there was subsequent diagnostic pathology: 9 epithelioid MM; 1 biphasic; 1 desmoplastic; 1 sarcomatoid (*1 patient with B/L disease)
- 1 case of probable MM – Patient with lung adenocarcinoma and atypical mesothelioma proliferation that progressed radiographically to develop pleural thickening
- 10 of 16 patients died of disease (MM)
- 7 of 34 (20.6%) cases showed loss of BAP1 expression, including 6 of 15 (40%) cases of MM and 1 probable mesothelioma case
  - 5 cases of epithelioid MM
  - 1 case biphasic type
  - BAP1 sensitivity: 43.7% and specificity: 100%
  - Positive predictive value of BAP1 loss for MM: 100% and negative predictive value: 66.7%
- No cases showed homozygous deletion of *CDKN2A*
  - 2 cases of subsequent MM showed heterozygous *CDKN2A*
  - 1 reactive mesothelial proliferation showed heterozygous *CDKN2A*
  - Additional copies found in 2 cases: 1 MM; 1 reactive

Take-home message: Loss of BAP1 expression in atypical mesothelial proliferations is a useful adjunct test to predict subsequent diagnosis of malignant mesothelioma. FISH analysis for *CDKN2A* deletion was not found to be helpful in this setting.

Chou A et al. The epithelioid BAP1-negative and p16-positive phenotype predicts prolonged survival in pleural mesothelioma. Histopathology 2018; 72: 509-15.

*Prepared and presented by Dr. Kenny Hughes (Thoracic Pathology Fellow, University of Michigan)

Purpose: To predict survival differences among patients with mesothelioma using p16 IHC, alone and combined with other factors

Methods:
- 229 unselected cases of malignant pleural mesothelioma, from Jan '91 to Aug '14 in Australia
- All specimens were excisional pleural biopsies (excluded cases with effusion cytology alone)
- Diagnosis confirmed and subclassified by one pathologist
- TMA prepared for p16 IHC (21 cases excluded for lack of tumor cells on TMA)
- p16 IHC interpreted by two pathologists and scored as 2+ strong diffuse nuclear staining, 1+ patchy nuclear staining, 0 completely negative nuclear staining (see Figure 1)
- For survival analysis, scores 1+ and 2+ were combined as p16-positive, because there was no significant survival difference between these two groups
- BAP1 IHC previously studied in this cohort (reference 8)

Results:
- The median overall survival for the whole cohort was 9 months
- p16 scores: 153 (74%) were 0; 36 (17%) were 1+; 19 (9%) were 2+
- Table 1: summary of pathological findings: about half were epithelioid; BAP1 positive and negative cases were about equal in number; about a quarter were p16 positive (with significantly longer survival, 13.6 vs. 7.6 months)
- Table 2: multivariate analysis: increased hazard ratios for sarcomatoid or biphasic subtypes, BAP1-positivity, and p16-negativity
- Table 3: pts stratified into eight prognostic groups based on morphology, BAP1, and p16
- Figure 3B: Kaplan-Meier survival curves for epithelioid BAP-/p16+ group vs. all other groups

Take-home message: Patients with mesothelioma of epithelioid subtype and with IHC showing BAP1-negativity and p16-positivity showed significantly longer survival when compared to all other groups in a mesothelioma cohort (31.7 vs. 7.7 months).

Nicholson AG et al. Interobserver Variation among Pathologists and Refinement of Criteria in Distinguishing Separate Primary Tumors from Intrapulmonary Metastases in Lung. J Thorac Oncol 2018; 13: 205-17.

Purpose: Assess reproducibility of distinguishing second primary lung cancer from intrapulmonary metastasis, using "comprehensive histologic assessment," which includes: a) assessment of predominant and minor histologic patterns, and b) evaluation of cytologic features. A second objective was to identify the most useful histologic features in separating second primary lung cancers and intrapulmonary metastasis.

Methods:
- One representative scanned slide of 126 tumors from 48 patients reviewed by 17 members of the multiple nodules subgroup and other invited participants of the International Association for the Study of Lung Cancer
  - 31 cases with 2 tumors; 17 cases with more than 2 tumors
- Tumor site provided, but not nodal status, immunohistochemical, or molecular data
- Using an online survey, reviewers assessed the following for each tumor (21 questions):
  - Primary lung cancers, intrapulmonary metastasis, or a combination of both
  - Provided a histologic diagnosis for each nodule with additional subtyping
  - Scored presence or absence of histologic features in each tumor (e.g. lepidic growth)
  - Compared tumors as being similar or significantly different for various morphologic features (e.g. mitotic rate, nuclear pleomorphism)
- Statistical analysis then conducted to assess level of agreement of pathologist's answer to a reference diagnosis

Results:
- 81% overall agreement (κ 0.596) between primary lung cancer and intrapulmonary metastasis status between panelist and reference diagnosis
- Refer to table 4 for analysis of summed data of histologic features for the tumor pairs with regard to primary versus metastatic
- Table 5 reflects features found to be most informative for differentiation of primary versus metastatic

Take-home message: There is good agreement among pathologists for the determination of primary lung cancers from intrapulmonary metastasis when using comprehensive histologic analysis. The most useful criteria found for separating the two include: main histologic type and predominant pattern, cell size, nucleolar appearances, acinus formation, nuclear pleomorphism, and mitoses.

Schneider F et al. Pulmonary Pathologic Manifestations of Anti-Alanyl-tRNA Synthetase (Anti-PL-12)-Related Inflammatory Myopathy. Arch Pathol Med 2018; 142: 191-7.

Purpose: Describe the clinical, radiographic, and pulmonary histologic findings in anti-aminoacyl-tRNA synthetase syndrome (ARS) patients with the anti-PL-12 antibody and clinical evidence of interstitial lung disease.

Methods:
- University of Pittsburgh's Idioathic Inflammatory Myopathy registry searched for patients with anti-PL-12 antibodies, seen between January 1985 and December 2012
  - Patients included regardless of their connective tissue diagnosis
  - Only patients for whom histology slides were available for review were included
- Charts retrospectively reviewed for organ involvement and noted presence or absence of: myositis, skin disease (rash or sclerodactyly), Raynaud, arthritis, "Mechanic's hands," dysphagia, and fever
- Chest imaging studies reviewed by the institution's thoracic radiologists
- Glass slides reviewed, assessing main pattern of disease and secondary histologic features

Results:
- 12 patients met inclusion criteria
  - 9 women and 5 men; age ranging from 17 to 64 years at time of biopsy/resection
  - Clinical diagnosis: 5 undifferentiated connective tissue disease; 4 polymyositis; 2 systemic sclerosis; 1 Sjogren syndrome
- Dyspnea most common presenting complaint (9 of 12)
- 11 of 12 patients showed radiographic features of usual interstitial pneumonia (UIP), including bibasilar reticulations, traction bronchiectasis, and honeycomb change; the last patient (17 yrs) had subpleural fibrosis, bronchiectasis, and consolidation
- Primary histologic findings:
  - 8 of 12 patients confirmed to have UIP on surgical lung biopsy/lung explant
  - 2 patients with radiographic UIP diagnosed with NSIP on lung biopsy; in both cases, only 1 lobe was sampled (lower lobe samples)
  - 2 patients with organizing pneumonia, which included 1 patient with radiographic UIP – In that patient, only 1 lobe was sampled (site not specified)
- Secondary histologic findings:
  - Tissue eosinophilia most common secondary finding (10 of 12)
  - 8 of 12 cases noted to have interstitial lymphoplasmacytic inflammation and lymphoid aggregates with and without germinal centers
  - 3 of 8 cases of UIP thought to have prominent NSIP-like areas
  - 3 patients had scattered non-necrotizing granulomas, including the patient with clinical diagnosis of Sjogren syndrome

Take-home message: UIP is the most common form of interstitial lung disease found in patients with anti-PL-12 ARS. There are no pathopneumonic features to allow for a definitive diagnosis of anti-PL-12 ARS on the basis of histology alone.

Articles for notation

Neoplastic lung disease
Kubouchi Y et al. Podoplanin expression in cancer-associated fibroblasts predicts unfavourable prognosis in patients with pathological stage IA lung adenocarcinoma. Histopathology 2018; 72: 490-9.

  Take-home message: Podoplanin (D2-40 clone) expression in cancer-associated fibroblasts (CAFs) had previously been shown to be a poor prognostic indicator in squamous cell carcinoma of the lung; therefore, this group set out to evaluate expression in stage IA lung adenocarcinomas ($n = 158$). Podoplanin expression in greater than 10 percent of CAFs was considered a positive result and was found in 41 cases. Of those podoplanin-positive cases, expression was found to significantly correlate with lymph-vascular invasion, presence of high grade component (solid/micropapillary subtypes), and shorter disease-free survival.

Scheel AH et al. Interlaboratory concordance of PD-L1 immunohistochemistry for non-small-cell lung cancer. Histopathology 2018; 72: 449-59.

  Take-home message: In this German study, interlaboratory (10 testing sites) and interassay concordance was assessed for commercially available assays (28-8, 22C3, SP263, and SP142) and "laboratory-developed tests" of PD-L1 immunohistochemistry, using tissue microarrays, containing 21 non-small cell lung cancer (NSCLC) specimens, and further validated using 11 cell lines with defined PD-L1 expression. The commercially available assays showed no qualitative or significant quantitative difference in results with high concordance rate for the clinically approved cut-offs of ≥1 percent and ≥50 percent, while the laboratory developed tests were similar to commercially available stains about 50 percent of the time. These findings support that staining patterns can be reproducibly produced at different testing sites when using commercially available assays, and laboratory-developed tests should be carefully validated.

Stoy SP et al. Programmed Death-Ligand 1 Testing of Lung Cancer Cytology Specimens Obtained With Bronchoscopy. Cancer Cytopathol 2018; 126: 122-8.

  Take-home message: This study looked at PD-L1 testing by immunohistochemistry in endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) cell blocks from non-small cell lung carcinoma specimens to determine overall success rate and if needle size affected adequacy for testing. Twenty-two specimens were tested (4, 19-gauge needles, 2, 21-gauge, 9, 22-gauge, and 5, 25-gauge), of which twenty were adequate; the two unsuccessful cases, using 22 and 25-gauge needles, had less than 100 cells, and therefore, deemed inadequate. The authors conclude that PD-L1 testing is feasible on EBUS-TBNA cell blocks, and success rate is not affected by needle size.

Tandon RT et al. Immunohistochemistry in Peritoneal Mesothelioma – A Single-Center Experience of 244 Cases. Arch Pathol Lab Med 2018; 142: 236-42.

  Take-home message: In this study, 17 immunohistochemical markers used in the differential diagnosis of mesothelioma were applied to 244 cases of peritoneal mesothelioma. Of

the markers tested, 100 percent of cases were positive for calretinin with the majority of cases positive for other mesothelial markers (WT-1, CK 5/6, D2-40, and mesothelin), and BAP1 loss in 55 percent of cases. The presence of CK 7 staining in the majority of cases (93%) and positivity for Ber-EP4 (8%), CEA (5%), B72.3 (3%), PAX8 (6%), p63 (5%), and CK 20 (4%) remind us that there is no definitive marker to rule out mesothelioma.

Xing D et al. Aberrant Pax-8 expression in well-differentiated papillary mesothelioma and malignant mesothelioma of the peritoneum: a clinicopathologic study. Hum Pathol 2018; 72: 160-6.

Take-home message: This study sought to determine the diagnostic value of Pax-8 in distinguishing mesothelial lesions from gynecologic malignancies. Pax-8 was expressed in 61% (20/33) of well-differentiated papillary mesotheliomas (WDPMs), 12% (4/34) of peritoneal mesotheliomas, 4% (2/48) of pleural mesotheliomas, 4% (2/51) of benign/reactive mesothelial proliferations, and no adenomatoid tumors (0/11) or peritoneal inclusion cysts (0/5). Given these results, Pax-8 might be helpful in the setting of malignant mesothelioma, but not useful in distinguishing WDPMs from borderline or low-grade gynecologic lesions.

Yang C-H et al. Pulmonary sclerosing pneumocytoma remains a diagnostic challenge using frozen sections: a clinicopathological analysis of 59 cases. Histopathology 2018; 72: 500-8.

Take-home message: The aim of this study was to identify the most frequently misdiagnosed histologic patterns of sclerosing pneumocytoma to highlight potential diagnostic pitfalls at the time of frozen section. Of 59 cases of sclerosing pneumocytoma, 26 cases were correctly diagnosed at the time of frozen section, 14 were given benign diagnoses (including: chronic inflammation, fibrosis, granulomatous inflammation, hemangioma, reactive hyperplasia, and pneumonia), 10 were assigned as malignant with adenocarcinoma being the most common diagnosis, and in nine cases, a diagnosis was deferred. Cases in which the solid pattern of sclerosing pneumocytoma predominated were the commonly missed with only 23% accurately diagnosed, and represented the biggest diagnostic pitfall at the time of frozen section.

Zhang J et al. Protein overexpression and gene amplification of cellular mesenchymal-epithelial transition factor is associated with poor prognosis in micropapillary-predominant subtype pulmonary adenocarcinoma. Hum Pathol 2018; 72: 59-65.

Take-home message: Eighty-six cases of micropapillary predominant adenocarcinoma were studied. Immunohistochemistry demonstrated cellular mesenchymal-epithelial transition factor (c-MET) protein overexpression in 62.8 percent of cases, and 10.5 percent were found to have c-MET gene amplification by FISH. While both c-MET overexpression and gene amplification were significantly associated with lymph-vascular invasion and higher T stage, only c-MET gene amplification was found to be an independent predictor of poor survival.

Zhao X et al. Combined Small Cell Carcinoma of the Lung: Is it a Single Entity? J Thorac Oncol 2018; 13: 237-45.

Take-home message: The design of the study was to describe the clinicopathologic features of 10 cases of combined small cell lung carcinoma (CSCLC) and perform next generation sequencing on three of the cases, comparing mutations in the small cell (SCLC) and non-small cell (NSCLC) components. There was no significant difference in patient demographics between the CSCLC and SCLC ($n = 160$) cohorts; however, overall survival was much shorter in the CSCLC group with median survival of 26 months, as compared to 58 months for SCLC patients. NGS revealed a significant number (75%) of all mutations were present in the SCLC and NSCLC components of all three cases sequenced, leading the investigators to conclude that CSCLC may be derived from a common precursor with divergent differentiation.

Zhou F et al. Distinct clinicopathologic features, genomic characteristics and survival of central and peripheral pulmonary large cell neuroendocrine carcinoma: From different origin cells? Lung Cancer 2018; 30-7.

Take-home message: Clinicopathologic features, genomic characteristics, and survival outcomes were investigated in 126 cases of large cell neuroendocrine carcinoma (LCNEC), which included 81 peripheral and 45 centrally-located tumors. Peripheral tumors were more commonly seen in non-smokers, exclusively found to have EGFR mutations, and presented with earlier TNM stage, the latter resulting in significantly better survival (mean 4.04 years) than the patients with central tumors, who had a mean survival of 1.51 years. The finding that anatomic location is independently associated with prognosis leads the authors to conclude that this may be due to differences in cell of origin and pathogenesis.

Zombori T et al. Evaluation of grading systems in stage I lung adenocarcinomas: a retrospective cohort study. Thorax 2018; 71: 135-40.

Take-home message: This study compares overall survival (OS) and disease-free survival (DFS) in 261 stage I adenocarcinomas, using three different grading schemes: 1) the WHO classification, using predominate pattern, 2) Kadota grade, which uses predominant pattern and mitotic index, and 3) Sica grade – a scoring system that takes into account the predominant and second most common patterns. According to this study, the WHO classification is the most predictive of OS and DFS, since architectural grade was identified as the only independent prognostic factor.

Review articles
Batra K et al. Pathology and radiology correlation of idiopathic interstitial pneumonias. Hum Pathol 2018; 72: 1-17.

Take-home message: This review article by the people at UT Southwestern (Dallas) is a review that gives a very brief introduction to each entity, followed by a summary of the radiographic and histologic features. The following are covered: idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial

pneumonia, idiopathic lymphoid interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis, hypersensitivity pneumonitis, and smoking-related interstitial fibrosis.

Jain D et al. Rapid On-Site Evaluation of Endobronchial Ultrasound-Guided Transbronchial Needle Aspirations for the Diagnosis of Lung Cancer – A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med 2018; 142: 253-62.

Take-home message: In this review, the authors advocate the use of rapid on-site evaluation (ROSE) as a means to increase adequacy rate, diagnostic yield, and accuracy of the procedure for targeted, endobronchial ultrasound-guided transbronchial biopsy needle aspirates. The article details the procedure, specimen handling, and assessment for ROSE, as well as the diagnostic pitfalls.

Case reports
Alsaad KO et al. Histopathology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection – clinicopathological and ultrastructural study. Histopathology 2018; 72: 516-24.

Take-home message: This is an autopsy case report of a 33-year-old man with T-cell lymphoma, who acquired MERS-CoV infection. On histologic examination, no viral cytopathic changes were seen, but the lungs were remarkable for a hemorrhagic necrotizing pneumonia and diffuse alveolar damage. Electron microscopy localized viral particles within the cytoplasm of pneumocytes and alveolar macrophages.

Kimura N et al. SMARCB1/INI1/BAF47-deficient pleural malignant mesothelioma with rhabdoid features. Pathol Int 2018; 68: 128-32.

Take-home message: The patient was a 62-year-old male, who presented with chest pain, was discovered to have a large left-sided pleural effusion and left lower lobe lung/posterior pleural tumor, and died during the course of his hospitalization. Autopsy revealed pleural and left lower lobe lung nodules comprised of loosely cohesive, rhabdoid-appearing tumor cells that were found to be positive for calretinin and D2-40, establishing the diagnosis of malignant mesothelioma with rhabdoid features. Interestingly, tumor cells showed loss of SMARCB1/INI1/BAF47 by immunohistochemistry, retained expression of BAP1, and no *p16* deletion by FISH.

Letters to the editor
Stephanov O et al. Mucinous adenocarcinoma with lepidic pattern and with K-RAS mutation in a newborn with antenatal diagnosis of congenital pulmonary airway malformation. Histopathology 2018; 72: 530-1.

Take-home message: The title essentially tells the whole story; for further clarification, it was a type 1 CPAM.

Taylor MS et al. Delayed Alveolar Epithelialization: A Distinct Pathology in Diffuse Acute Lung Injury. Am J Respir Crit Care Med 2018; 197: 522-3.

      Take-home message: The authors present two previously health, young patients who suffered idiopathic acute lung injury, requiring extracorporeal membrane oxygenation. The patients underwent lung wedge biopsy less than seven days after intubation, and both were found to have virtually absent hyaline membranes, alveolar denudation, macrophages lining the alveolar septa, and peribronchiolar squamous metaplasia that the authors refer to as "peribronchiolar basaloid pods." The authors conclude that type 2 pneumocyte proliferation was delayed in these cases, and these cases represent a unique histologic subtype and propose to term this pattern "diffuse alveolar injury with delayed epithelialization."