Pulmonary Pathology Journal Club – Feb 4, 2019

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Articles for Notation:

Neoplastic

5. Kalhor N, Moran CA. Thymic epithelial neoplasms with Rhabdomyomatous component: a Clinicopathological and Immunohistochemical study of 7 cases. Hum Pathol. 2018 Sep 11. pii: S0046-8177(18)30353-8.

6. Mukhopadhyay S, et al. Insulinoma-associated protein 1 (INSM1) is a sensitive and highly specific marker of neuroendocrine differentiation in primary lung neoplasms: an immunohistochemical study of 345 cases, including 292 whole-tissue sections. Mod Pathol. 2019 Jan;32(1):100-109.

7. Pogoriler J, et al. Congenital Cystic Lung Lesions: Redefining the Natural Distribution of Subtypes and Assessing the Risk of Malignancy. Am J Surg Pathol. 2019 Jan;43(1):47-55.

8. Munari E, et al. Expression of programmed cell death ligand 1 in non-small cell lung cancer: Comparison between cytologic smears, core biopsies, and whole sections using the SP263 assay. Cancer Cytopathol. 2019 Feb;127(1):52-61.

9. Cavic M, et al. TP53 and DNA-repair gene polymorphisms genotyping as a low-cost lung adenocarcinoma screening tool. J Clin Pathol. 2019 Jan;72(1):75-80.

10. Thompson JC, et al. Measurement and immunophenotyping of pleural fluid EpCAM-positive cells and clusters for the management of non-small cell lung cancer patients. Lung Cancer. 2019 Jan;127:25-33.

11. Ogata S, et al. Expressions of ATF6, XBP1, and GRP78 in normal tissue, atypical adenomatous hyperplasia, and adenocarcinoma of the lung. Hum Pathol. 2018 Aug 16. pii: S0046-8177(18)30314-9.

12. Villaruz LC, et al. Comparison of PD-L1 immunohistochemistry assays and response to PD-1/L1 inhibitors in advanced non-small-cell lung cancer in clinical practice. Histopathology. 2019 Jan;74(2):269-275.

13. Qin A, et al. Detection of Known and Novel FGFR Fusions in Non-Small Cell Lung Cancer by Comprehensive Genomic Profiling. J Thorac Oncol. 2019 Jan;14(1):54-62.

14. Eguchi T, et al. Lobectomy Is Associated with Better Outcomes than Sublobar Resection in Spread through Air Spaces (STAS)-Positive T1 Lung Adenocarcinoma: A Propensity Score-Matched Analysis. J Thorac Oncol. 2019 Jan;14(1):87-98.

15. Machado-Rugolo J, et al. Usefulness of complementary next-generation sequencing and quantitative immunohistochemistry panels for predicting brain metastases and selecting a treatment outcomes of non-small cell lung cancer. Hum Pathol. 2018 Sep 12. pii: S0046-8177(18)30352-6.

16. Chen X, et al. Overexpression of RCN1 correlates with poor prognosis and progression in non-small cell lung cancer. Hum Pathol. 2018 Aug 30. pii: S0046-8177(18)30329-0.

17. Yu H, et al. Correlation of PD-L1 Expression with Tumor Mutation Burden and Gene Signatures for Prognosis in Early-Stage Squamous Cell Lung Carcinoma. J Thorac Oncol. 2019 Jan;14(1):25-36.

18. Pepe F, et al. Performance analysis of SiRe next-generation sequencing panel in diagnostic setting: focus on NSCLC routine samples. J Clin Pathol. 2019 Jan;72(1):38-45.

19. Ferrer L, et al. A Brief Report of Transformation From NSCLC to SCLC: Molecular and Therapeutic Characteristics. J Thorac Oncol. 2019 Jan;14(1):130-134.

20. Kumar N, et al. Retrospective response analysis of BAP1 expression to predict the clinical activity of systemic cytotoxic chemotherapy in mesothelioma. Lung Cancer. 2019 Jan;127:164-166.

21. Roca E, et al. Outcome of EGFR-mutated adenocarcinoma NSCLC patients with changed phenotype to squamous cell carcinoma after tyrosine kinase inhibitors: A pooled analysis with an additional case. Lung Cancer. 2019 Jan;127:12-18.

22. Terra SBSP, et al. Heterogeneity of programmed death-ligand 1 expression in thymic epithelial tumours between initial specimen and synchronous or metachronous metastases or recurrences. Histopathology. 2019 Jan;74(2):364-367.

23. Hsu KH, et al. High PD-L1 expression correlates with primary resistance to EGFR-TKIs in treatment naïve advanced EGFR-mutant lung adenocarcinoma patients. Lung Cancer. 2019 Jan;127:37-43.

24. Park S, et al. Histologic transformation of ALK-rearranged adenocarcinoma to squamous cell carcinoma after treatment with ALK inhibitor. Lung Cancer. 2019 Jan;127:66-68.

25. Sakai H, et al. Impact of cytotoxic chemotherapy on PD-L1 expression in patients with non-small cell lung cancer negative for EGFR mutation and ALK fusion. Lung Cancer. 2019 Jan;127:59-65.

26. Bian T, et al. Lepidic component at tumor margin: an independent prognostic factor in invasive lung adenocarcinoma. Hum Pathol. 2018 Aug 29. pii: S0046-8177(18)30332-0.

Case Reports

27. Smith-Hannah A, Naous R. Primary peritoneal Epithelioid mesothelioma of clear cell type with a novel VHL gene mutation: a case report. Hum Pathol. 2018 Aug 14.

28. Ninan N, et al. Polypoid Endobronchial Cavernous Venous Hemangioma. Am J Respir Crit Care Med. 2019 Jan 1;199(1):113-114.

29. Suster D, et al. Selected Case From the Arkadi M. Rywlin International Pathology Slide Seminar: Atypical Thymoma With Rhabdomyomatous Differentiation. Adv Anat Pathol. 2019 Jan;26(1):64-68.

Reviews and Consensus statements

30. Lu YW, Yeh YC. Ciliated Muconodular Papillary Tumors of the Lung. Arch Pathol Lab Med. 2019 Jan;143(1):135-139.

31. Chapel DB, et al. Molecular pathways and diagnosis in malignant mesothelioma: A review of the 14th International Conference of the International Mesothelioma Interest Group. Lung Cancer. 2019 Jan;127:69-75.

32. Wick MR. Hamartomas and other tumor-like malformations of the lungs and heart. Semin Diagn Pathol. 2019 Jan;36(1):2-10.

<u>Non-neoplastic</u>

33. Raparia K, Raj R. Tissue continues to be the issue: Role of histopathology in the context of recent updates in the radiologic classification of interstitial lung diseases. Arch Pathol Lab Med. 2019 Jan;143:30-33.

34. Myc LA, et al. Necrobiotic Pulmonary Nodules of Crohn's Disease in a Patient Receiving Vedolizumab. Am J Respir Crit Care Med. 2019 Jan 1;199(1):e1-e2.

35. Abe N, et al. Disseminated Cryptococcosis with Bronchiolitis and Cellulitis. Am J Respir Crit Care Med. 2019 Jan 15;199(2):235-236.

Articles for Discussion

1. Larsen BT, et al. Molecular and Ultrastructural Features of Diffuse Intrapulmonary Malignant Mesothelioma. Am J Surg Pathol. 2019 Jan;43(1):147-150.

Aims/Background:

Better establish the mesotheliomatous nature of diffuse intrapulmonary malignant mesothelioma (DIMM), a rare variant of MM that simulates interstitial lung disease. Mesothelial origin has been based on morphology and conventional immunophenotype.

Materials and methods:

- 4 cases of DIMM (incl. 3 from original series) – 2 epithelioid, 2 biphasic
- BAP1 immunohistochemistry
- FISH of *CDKN2A* (p16) gene
- Ultrastructure (transmission electron microscopy)

Results:

- 4 of 4 - BAP1 loss (incl. sarcomatoid component)
- 1 of 4 – Heterozygous loss of p16 (epithelioid DMM)
- TEM: Numerous long microvilli, well-formed desmosomes, intracytoplasmic tonofilaments

Conclusions:

- DIMM shows molecular characteristics of typical MM and ultrastructural characteristics of mesothelium
- Immunohistochemistry sufficient to establish mesothelial nature of DIMM
- Other take-home points (more generally):
    - Retention of BAP1 does not exclude malignancy
    - Normal or heterozygous p16 FISH does not exclude malignancy

2. Kinoshita Y, et al. Pleuroparenchymal fibroelastosis as a histological background of autoimmune diseases. Virchows Arch. 2019 Jan;474(1):97-104.

Aims/Background:

1) Evaluate the prevalence of PPFE in patients with autoimmune disease-related interstitial lung disease (AID-ILD). 2) Verify the increase in elastic fibers

Materials and methods:

- Case selection and definitions
    - Retrospective review of autopsies and lung explants from 1974-2018
    - Patients with diagnoses of "interstitial pneumonia" and "autoimmune disease" (CTD or vasculitis)
    - Excluded if upper or lower lobe not available
    - 24 patients with → "AID-ILD"
    - Comparison groups
        - 49 "IPF or probable IPF" patients (autopsy or lung explant)
        - 9 non-pulmonary patients (autopsy)
    - "Interstitial pneumonia" – multidisciplinary approach using consensus classification criteria
    - "Histological patterns of fibrosis"
        - Definite UIP or probable UIP
        - NSIP
        - PPFE
            - Increased elastic fibers with septal elastosis in the subpleural area
            - Intraalveolar collagen deposition associated with septal elastosis
            - Collagenous thickening of visceral pleura

        (NB – did they exclude ILD with incidental apical cap? Or elastotic-rich UIP?)

        - "Unclassified fibrosis" (when predominant pattern did not fit)
        - "Undetermined fibrosis"
            - End-stage fibrosis, superimposed acute lung injury, "end-stage infection"
    - Quantification of elastic/collagen fibers using virtual slide software of EVG and Masson-stained section (in at least 1 section from each of the upper and lower lobes)
    - "Intralobar distribution" (subpleural vs diffuse)

Results:

- 24 AID-ILD: rheumatoid arthritis (8), poly/dermatomyositis (6), microscopic polyangiitis (4), systemic sclerosis (3), SLE (2), Sjogren's (1)

	AID-ILD (n=24)	IPF (n=49)	*p* value
Clinical info			
Age	67.3	69.4	ns
Female	11(46%)	9 (18%)	0.024
Smoking (curr/form)	15 (53%)	40 (82%)	<0.01
FVC (% pred)	65	50	ns
Histologic pattern			
UIP	13 (51%)	--	
NSIP	4 (17%)	--	
Undeterm/unclassif	5 (20%)	--	
PPFE	2 (8%)	--	
"histologic PPFE"	12 (50%)	11 (22%)	
Elastic fiber score			
Whole lung	17.3	11.6	<0.01
Upper lobes	16.6	11.2	<0.01
Lower lobes	18.0	12.0	<0.01
Upper/lower	1.07*	1.03*	ns

* not sure how number arrived at

- 22 of 24 AID-ILD had above-average (vs normal lung) elastic fiber scores on whole lung analysis ("AID-ILD with elastosis")
    - 10 upper-lobe predominant elastosis ("ratio >= 1")
    - 12 lower-lobe predominant (ratio < 1)
        - 5 UIP, 2 NSIP, 2 undetermined fibrosis

Conclusions:

- Increased lung elastosis generally and PPFE specifically may be a marker for underlying autoimmune disease, irrespective of final histologic diagnosis

Problems:

- Methods of diagnosis (multidisciplinary consensus vs pathologic, diagnoses vs patterns etc.)
- "Garbage in = garbage out'
- Convoluted (non-practical) way of measuring elastosis
- So is apical cap a marker of autoimmune disease?

3. Stevers M, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42. Mod Pathol. 2019 Jan;32(1):88-99.

Aims/Background:

Perform genomic analysis on WDPM of peritoneum (WDPM-P) in order to determine neoplastic nature of the lesion and assess molecular pathogenesis

- TRAF – tumor necrosis factor alpha receptor-associated factor (E3 ubiquitin ligase)
    - TRAF7 mutation – adenomatoid tumor, perineurioma, meningioma
- CDC42 – Rho family GTPase

Materials and methods:

- 10 WDPM-P from pathology archives (1993-2014)
- Targeted next-gen DNA sequencing
- Immunohistochemistry for Bap1 and L1CAM
    - L1CAM – marker of NF-kB pathway activation, + in adenomatoid tumor

Results: Clinical -

- 3 males, 7 females; all incidental discoveries at surgery for another indication
- 8 solitary (2- 12 mm), 1 two nodules (5 mm), 1 "several" nodules (2-10 mm)
- No specific therapy
- No recurrences (3.1 year median f/u)

Histological – simple papillary structures, fibroedematous core, no atypia, no invasion

Genomic –

- 7 cases (TRAF7 mutation), 3 cases (CDC42 mutation) – verified somatic (tumor-specific)
- All missense mutations (1 also had focal gene amplification (TRAF), 1 also multiple missense (TRAF))
- CDC42 mutations not previously known but equivalent to very common NRAS/HRAS/KRAS mutation (homologous proteins)
- Allele frequencies (all <50%) suggest clonal heterozygous alteration
- No anomalies in genes (*BAP1, CDKN2A, NF2, DDX3X, SETD2 TP53, ALK*) altered in DMM

IHC – Positive BAP1 and L1CAM (9 of 9)

Normal mesothelium – Positive BAP1, Negative L1CAM

DMM – Negative BAP1, Negative L1CAM

Conclusions:

- WDPM-P is clonal and neoplastic; defined by TRAF7 or CDC42 mut
- WDPM-P and adenomatoid tumor of genital tract may be related/ morphologic variants (though 31 adenomatoid tumor of genital tract did not show CDC42 mut)

4. Histopathological and molecular analysis of idiopathic pulmonary fibrosis lungs from patients treated with pirfenidone or nintedanib. *Histopathology* 2019, 74, 341–349.

Purpose: To quantify the impact of pirfenidone or nintedanib treatment on lung histopathology and molecular mediators of fibrosis in patients with idiopathic pulmonary fibrosis (IPF).

Methods:

- 28 IPF patients who underwent lung tansplantation at UCSF, 11 of whom were treated with pirfenidone and seven with nintedanib.
- P16 and P21 expression levels as senescence makers were quantified with immunoblot by densitometry from lung lysates and *in vitro* induced cellular injury.
- P16 and P21 expression levels were compared by immunohistochemistry under microscope and confocal microscope.
- Levels of p-SMAD as marker of TGF-β signaling pathway were quantified by immunoblot in untreated and treated IPF patients.

Results:

- There were no significant differences in age, smoking history, FVC or diffusion capacity of carbon monoxide (DLCO) between groups. Eight patients were found to have histopathological evidence of acute lung injury.
- Quantification of the senescence markers p16 and p21 expression in lung lysates and *in vitro* demonstrated no difference in the lungs of untreated or treated IPF patients.
- Lung sections were immunostained for p16 and p21 of alveolar type II cells in the lungs demonstrated similar immunoreactive to p16 and p21 among untreated or treated IPF patients.
- IPF patients treated either with pirfenidone or nintedanib tended to have higher levels of p-SMAD than untreated controls.

Take-home message:

- Pirfenidone and nintedanib do not modulate expression of senescence markers, levels of p-SMAD3 or the amount of fibrosis in IPF lungs.
- Treated patients have less histopathological evidence of acute lung injury at the time of lung transplantation.
- Limitations of the study include small number of sample, variable length of treatment, fixed evaluation time at the transplantation.