

AUGUST PULMONARY PATHOLOGY JOURNAL CLUB

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Non-neoplastic

1. Late Complications of COVID-19: A Morphologic, Imaging, and Droplet Digital Polymerase Chain Reaction Study of Lung Tissue. Roden et al. Arch Pathol 2022; 146: 791-804

Case Report/Correspondence

1. Lung Disease and Subsequent COVID-19 Presenting With Worsening Dyspnea. Ng et al. Chest 2022; 162:e19-25
2. A subset of lung adenofibromas are morphological variants of solitary fibrous tumour. Laville et al. Histopathology 2022; 80:133- 136

Review articles

1. Algorithmic Approach to the Diagnosis of Organizing Pneumonia: A Correlation of Clinical, Radiologic, and Pathologic Features. Cherian et al. Chest 2022; 162:156-178
2. Medical and Surgical Care of Patients With Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations. Carbone et al. JTO 2022; 17: 873-89

I. ARTICLES FOR DISCUSSION

1. Primary NTRK-rearranged Spindle Cell Neoplasm of the Lung: A Clinicopathologic and Molecular Analysis of 3 Cases. Zhu and Wang. *Am J Surg Pathol* 2022; 46:1007-13

Discussed by Julian A. Villalba

Background NTRK-rearranged spindle cell neoplasm is an emerging entity spanning a wide spectrum of morphologies and clinical behavior with a predilection for superficial or deep soft tissues of the extremities, trunk, head and neck, with responsiveness to selective NTRK inhibitors. Primary lesions in the visceral organs are very rare. One case of *BPMS-NTRK3* rearranged primary lung tumor has been described.

Methods: Three cases of *NTRK1*-rearranged spindle cell neoplasm were retrieved from the files at Fudan University Shanghai Cancer Center. Tumors were evaluated histologically and cytomorphologically. IHC stains, FISH with *NTRK1* dual color break-apart fusion probes and RNA-sequencing on an Illumina NextSeq platform with Trusight RNA Fusion Panel (632 genes) were performed in all cases.

Result: The 3 tumors were discovered incidentally. Patients underwent lobectomy w/o adjuvant therapies. None had any prior h/o mesenchymal neoplasms. PET/CT: No metastatic disease elsewhere. The original pathDx: Inflammatory myofibroblastic tumor (2 cases) and spindle cell mesenchymal tumor NOS (1 case).

Case	Age/Sex	Location	Size	CD34	S-	Pan-	TrkA	FISH	Follow-up
1	31 M	RUL	1.7	+++	++	+++	+++	<i>NTRK1</i>	NED, 4
2	45 F	LUL	1.2	+++	+++	+++	+++	<i>NTRK1</i>	NED, 87
3	32 M	LLL	1.8	+++	+	+++	+++	<i>NTRK1</i>	NED, 9

Histologically: Irregular borders, pleural involvement (2 cases). Tumor cells grew around bronchi and encircled vessels. High power: monomorphic spindle cells arranged in haphazard fascicles or patternless, with pale eosinophilic cytoplasm, mild nuclear atypia, and low mitotic activity (<1/50 HPF). Prominent deposition of stromal collagen in 2 tumors, and thick keloid-like collagen bands focally in 1. Necrosis: absent in all cases. **IHC** (table), negative for all other markers (ALK, AE1/AE3, SMA, calponin, desmin, SOX10, STAT6). H3K27Me3 was retained. **FISH** showed rearrangement in all cases. **RNA-sequencing** identified *TPM3exon7-NTRK1exon10* fusion (2 cases), and *LMNAexon3-NTRK1exon11* (1 case).

Discussion: The Dx of NTRK-rearranged mesenchymal tumor is challenging because of its nonspecific morphology. Deposition of stromal collagens and perivascular ring-like hyalinization may be clues but are non-specific. Most tumors show coexpression of CD34 and S-100. CD34 is usually diffuse, but the intensity of S-100 varies. Tumor cells are consistently (+) for a monoclonal pan-TRK (Abcam EPR17341) and strong immunoreactivity indicates NTRK rearrangement (inexpensive surrogate for screening). Sensitivity of pan-TRK IHC depends on the fusion involved: *NTRK1* (96%), *NTRK2* (100%), and *NTRK3* (79%). Metastatic disease must be excluded. Tumors with low-grade morphology tend to recur locally if incompletely excised.

Message: As most *NTRK*-rearranged tumors harbor *NTRK1* rearrangement, it may be recommended to use both pan-TRK and TrkA (Tropomyosin receptor kinase A) in routine practice in low-grade tumors with CD34/S-100 coexpression. Due to the overlapping morphology, the major differential diagnosis embraces IMT (can harbor ETV6-NTRK3 fusion), SFT (CD34+, rarely S-100+), and BRAF/RAF1/RET-rearranged spindle cell tumors (coexpress CD34/S-100, no reports in lung yet). 1% of NSCLC have NTRK fusions. Nevertheless, a conclusive Dx should be established on the detection of NTRK fusions by molecular studies and is often required in the aspect of determination of target therapy.

2. Thoracic SMARCA2-Deficient but SMARCA4-Preserved Tumors with Undifferentiated Morphology Combined with Claudin-4 Negativity. Iwakoshi A. et al. *Am J Surg Pathol* 2022; 46: 1000-1006 *Discussed by Jackie Chan*

Purpose To describe the clinical and histopathologic findings seen in thoracic undifferentiated tumors with isolated loss of SMARCA2 but retained expression of SMARCA4 and SMARCB1.

Methods

- Case identification (in-house database, 2017-2021):
 - Study cases: (n = 3) thoracic undifferentiated tumors fitting the WHO essential criteria for SMARCA4-deficient undifferentiated tumor (SMARCA4-UT), plus lack of claudin-4 expression (<5% membranous staining) but retained SMARCA4 expression.
 - Comparison cases (2017-2021): (n = 2) SMARCA4-UT with SMARCA4 loss
- Reviewed histology and clinical information on study cases
- Immunohistochemistry performed on study cases: SMARCA2, SMARCA4, SMARCB1, pan-keratin, claudin-4, CD34, SALL4, TTF-1 (8G7G3), p40, NUT, and other neuroendocrine, lymphoid, mesenchymal, melanoma, and germ cell tumor markers
 - Loss of SMARCA2, SMARCA4, and SMARCB1: defined as complete loss or diffuse severe loss compared to internal controls (e.g. fibroblasts, inflammatory cells)
- Mutation analyses: hotspot mutation analysis for EGFR, KRAS, and BRAF

Results

- Table 1: Clinical Findings:
 - Age 40-50, 2 males, 1 female; all current smokers (20-30 pack-years)
 - CT: emphysema and bullae; large primary lesions (5.7 – 9.3cm), locations: lung, mediastinum, lung>chest wall (Figure 1)
 - All cases were metastatic at presentation (adrenal gland, bone, brain)
 - Therapy: chemotherapy (3/3), immune checkpoint inhibitor (ICI) (1/3), radiation (2/3)
 - Outcomes: 1/3 responded to combined chemotherapy/ICI, stable on ICI for 7 months before passing at 10 months from complications of intestinal metastasis; 2/3 disease progressed despite chemo/radiotherapy, leading to deaths at 2 and 8 months
- Figure 2: All 3 cases were morphologically consistent with the WHO essential criteria (sheets of monotonous round discohesive cells). Rhabdoid cells and necrosis were also present in all cases.
- Table 2/Figure 3: Immunohistochemistry Findings:
 - All cases: SMARCA2 lost; SMARCA4 and SMARCB1 retained; claudin-4 negative.
 - 2/3 positive for CK AE1/AE3; 1/3 positive (focal/weak) for SALL4 and CD34
 - All negative for TTF-1, p40, NUT and almost all neuroendocrine markers
- Overall, in all 3 cases, the histology, immunophenotype, and clinical settings are consistent with SMARCA4-UT, except for their SMARCA4 retention.
 - Original diagnoses: high-grade malignancy
 - Two cases treated as NSCLC due to focal keratin positivity
 - One case treated as germ cell tumor due to focal SALL4 positivity

Take Home Message:

Undifferentiated thoracic tumors with isolated SMARCA2 loss are not entirely uncommon. They share many clinical and pathologic similarities with SMARCA4-deficient tumors and should be considered in the differential diagnosis, given the potential therapeutic and prognostic implications.

3. 5-hmC loss is another useful tool in addition to BAP1 and MTAP immunostains to distinguish diffuse malignant peritoneal mesothelioma from reactive mesothelial hyperplasia in peritoneal cytology cell-blocks and biopsies. Alsugair et al. Virchows Archiv 2022; 481:23–29 Discussed by Julia Naso

Background

5-hydroxymethylcytosine (5-hmC) is a modified nucleotide, produced from 5-methylcytosine – produced as first step of DNA demethylation.

Loss of 5-hmC staining in greater than 50% of tumor nuclei had 100% specificity and 92% of sensitivity for pleural malignant mesothelioma – not yet studied in peritoneal disease or cytology

Aim: To assess the diagnostic accuracy of 5-hmC to distinguish diffuse peritoneal mesothelioma from reactive mesothelial hyperplasia in peritoneal small biopsies and cytology cell-blocks.

Methods

- 38 cytology specimens: 6 benign, 32 mesothelioma
- 37 tissue biopsies: 7 benign, 30 mesothelioma
- 87.2% were epithelioid mesothelioma, 9.6% were biphasic, and 3.2% were sarcomatoid
- BAP1, MTAP and 5-hmC (1:200;Active Motif, 39,679) IHC on whole sections of all cases
- Scoring by 2 pathologists blinded to diagnosis
Loss= absent in all nuclei for BAP1 and MTAP; absent in 50% of nuclei for 5-hmC

Results

Benign: 100% retained for all stains

Malignant:

5-hmC loss: 21.8% cytology, 30% biopsies

BAP1 loss: 71.9% cytology, 66.7% biopsies

MTAP loss: 40.6% cytology, 33.3% biopsies

The combination of BAP1, MTAP, and 5-hmC:

Cytology sensitivity = 0.84, Biopsy sensitivity = 0.90

(vs BAP and MTAP combined: Cytology sensitivity = 0.78, Biopsy sensitivity = 0.83)

Conclusions

The most sensitive combination is BAP1, MTAP, and 5-hmC.

5-hmC is useful on cytology and small biopsies of peritoneal mesothelioma, but less sensitive than in prior reports on pleural resections.

Still need data on sarcomatoid vs epithelioid, the number of cases near threshold, what cytology preparation was used, and how diagnoses were confirmed

Proposed sequential use of stains (also in Chapel et al., 2019) may delay turn-around time.

4. Molecular and immunohistochemical characterisation of mesothelioma of the tunica vaginalis. Anderson et al. *Histopathology* 2022; 81: 65-76

Background

- Mesothelioma of the pleura and peritoneum are well studied with known genomic alterations, involving common genes such as *CDKN2A*, *BAP1*, *NF2*, *TP53*, and relationship to asbestos.
- Some of these genomic alterations used to distinguish reactive from malignant mesothelial proliferation such as surrogate of *CDKN2A* MTAP and BAP1.
- Other novel markers to distinguish Mesothelioma from AD such as SOX6.
- Mesotheliomas of the tunica vaginalis are less well studied and as they don't have the same relationship to asbestos, could have genomic differences.

Aim

Study a cohort of mesothelioma of the tunica vaginalis, including so called mesothelioma of uncertain malignant potential (UMP).

Method

- Total 17 cases : 13 mesothelioma and 4 of UMP, limited to the tunical vaginalis
- NGS with panel of 447 cancer related genes (OncoPanel) on 7 meso and 2 UMP
- IHC on the study cohort and control of 13 adenomatoid tumors and 2 mesothelial hyperplasia: WT1, calretinin, D2-40, MTAP, SOX6 and BAP-1

Results

- Med age 79 yo, right sided 92%, asbestos exposure in 1 (unknown exposure in 7), radiation history in 1. No sarcomatoid variant.
- All UMP ANED (med 29 mos). In meso, many DOD or AWD (up to 74 mos) but 3 ANED at 6, 16 and 47 mos
- NGS results in Figure 5
 - In Meso group (n=7)
 - *NF2* alteration most common (71%), *CDKN2A* (43%), *BAP1* (29%)
 - 1 case with *PTCH1* mutation and 1 in *TSC1*
 - In UMP group (n=2) no alterations of meso. 1 case with *TRAF7* mutation
- IHC results in Table 2
 - In Meso group, only 2 with BAP1 or MTAP loss. 82% SOX6+
 - In UMP group no loss of BAP1, MTPA and 0% SOX6 +
 - In benign control SOX6 neg in all adenomatoid tumors and + in both hyperplasia

Conclusion

- Differences are noted with clinical implication with less common genomic alterations of *BAP1* and *CDKN2A* and enriched for *NF2* mutations
- Identified of rare alterations in *PTCH1* and *TSC1*
- SOX6 relatively sensitive marker for mesothelial differentiation but still distinctively negative in adenomatoid tumors.

II. Articles for notation

Neoplastic

1. Validation of multiplex immunofluorescence and digital image analysis for programmed death ligand 1 expression and immune cell assessment in non-small cell lung cancer: comparison with conventional immunohistochemistry. Wu et al. Am J Clin Pathol 2022; 75:452-58

Study that compares conventional IHC to multiplex IF for the staining and scoring of PD-L1 as well as co-localization of PD-L1 to tumor cells and immune cells using CK, CD8 and CD68. There was an excellent correlation overall. And the added value of being to better co-localize using multiplex IF, as well as the advantages of multiplexing like decrease tissue use, ease of biomarker analysis, less interobserver variability. Although there is a cost to this in terms of equipment and expertise required.

2. Prognostic phenotypes of early-stage lung adenocarcinoma. Lamort et al. Eur Respir J 2022; 60: 2101674

Small cohort of 200 patients with AD, looking at many clinical, histologic, molecular parameters, as well as specific IHC including p53, NF1, CD45, PD1, PCNA, TUNEL, FVIII. Not clear why these markers were specifically targeted. Looking at survival, there are so many parameters that can influence survival, yet there wasn't any mention of multivariate analysis and so forth. This being said, they identified 2 profiles of patients, that would have been equal for all usual clinicopathologic parameters, one called "proliferative" and one "apoptotic" with the "apoptotic" profile showing a 5-yr survival of 70% vs 50% for the other group.

3. Identification of filigree pattern increases the diagnostic accuracy of micropapillary pattern on frozen section for lung adenocarcinoma. Zhao et al. Histopathology 2022; 81: 119-27

The authors studied the sensitivity and specificity of diagnosing micropapillary architecture in stage I AD on frozen section as their prior studies and other studies have shown a worse outcome for patients with sublobar resection for these cases. 5 pathologists reviewed FS and regular H&E in an initial study cohort and a second more recent validation cohort. They looked at what they called the conventional MP pattern vs adding the more recently described filigree pattern. They showed in this current study that indeed, MP architecture conveys a worse outcome. And they showed significant improvement in their sensitivity of recognizing MP pattern on FS over time and by adding the filigree features. They, however, lose some specificity. The kappa for intraobserver variability was excellent. So feasible to recognize on FS but no perfect accuracy. Still not sure if good enough to make a decision of sublobar resection or not on this feature alone.

4. Prognostic impact of tumor-infiltrating lymphocytes and neutrophils in resected non-small cell lung carcinoma. Ishikawa et al. Hum Pathol 2022; 125: 87-96

TILs have been shown to be good prognosis in many cancer types. Neutrophils in peripheral blood has been associated with outcome but only rare study have looked at TIN. In a large cohort of almost 1000 patients with stage I and II NSCLC, doing multivariate analysis, the authors showed that for AD TIN predicted for worse outcome but TIL not prognostic, and for SQCC nor TIN and TIL were prognostic.

5. BAP1 Loss by Immunohistochemistry Predicts Improved Survival to First-Line Platinum and Pemetrexed Chemotherapy for Patients With Pleural Mesothelioma: A Validation Study. Louw et al. JTO 2022; 17:921-30

Based on the premise that BAP1, as a tumor suppressor that plays a role in DNA repair and other mechanisms that may alter response to the standard of care chemotherapy, and that patients with BAP1 germline mutations have a better outcome than patients without, the authors studied 114 patients from a Danish cohort and 234 from an Australian cohort to assess the role of BAP1 loss as a prognostic marker. Sarcomatoid mesothelioma represented 10% of the overall cohort, and 38% were biphasic in the Danish cohort. Loss of BAP1 was noted in 60% of cases, in over 65% of epithelioid, and 33 or less in sarcomatoid. Not surprisingly cohorts with BAP1 loss did better as mostly epithelioid mesothelioma but also did better in the non-epithelioid mesothelioma. Perhaps BAP1 should be done routinely on our mesothelioma cases.

6. Tumour cell budding and spread through air spaces in squamous cell carcinoma of the lung – Determination and validation of optimal prognostic cut-offs. Stogbauer et al. Lung Cancer 2022; 169: 1-12

As SQCC lack well-established prognostic and targets as compared to AD, the authors looked at features such as tumor budding, STAS (# of foci and distance) and TILs, in both the TCGA cohort and separate in house cases for validation. In the TCGA cohorts, in multivariate, high number of TB, STAS and TILs were significant for OS and only stage for PFS. In their validation cohort, age, stage, TB, STAS were significant for OS and Disease specific survival, not TILs. Not sure if there is added value to count tumor budding....

7. SMARCA4-deficient lung carcinoma is an aggressive tumor highly infiltrated by FOXP3+ cells and neutrophils. Velut et al. Lung cancer 2022; 169: 13-21

SD-NSCLC have a poorer prognosis and, although some contradicting studies, seems overall to show no response to immunotherapy. In this study, the authors studied the immune environment of 63 SD-NSCLC and compared to 28 non SD-NSCLC, with similar [but not identical clinicopathologic parameters (more smokers, COPD, higher grade AD, Stage III, PDL1 0%)]. Multiplex IF was used to assess immune environment. The SD-NSCLC had more neutrophils and FOXP3+ and less CD8+ lymphocytes than non SD-NSCLC. But this was not prognostic. Only stage was an independent marker.

8. Neuroendocrine transformation from EGFR/ALK-wild type or TKI-naïve non-small cell lung cancer: An under-recognized phenomenon. Chu et al. Lung cancer 2022; 169:22-30

The premise of this study is that transformation from AD to NE carcinoma does not occur only in TKI treated cancers. The authors identified 8 cases of AD or SQCC not treated with TKA that had a pre and post tx usually chemotherapy biopsy for sequencing and IHC studies, that transformed into a NE carcinoma (although one was atypical carcinoid?). All had mutations that are more typical of AD exception two that had a *RBI* mutation in the initial tumor. Although most did not have mutations in RB/p53 many had lost of the IHC staining? There were no images or explanation on how the initial diagnosis were made on the treatment naïve cases. So not clear if this transformation does occur in NSCLC not treated with TKI.

9. Atypical thymomas with squamoid and spindle cell features: clinicopathologic, immunohistochemical and molecular genetic study of 120 cases with long-term follow-up. Suster et al. Mod Pathol 2022; 35:875-894

The authors describe of group of 120 “atypical thymoma”. While the majority of these seem to be the run of the mill WHO B3, the authors want to make the point that there are some that don’t fit in as they have a spindle cell morphology rather than epithelioid. And a smaller subset with mixed morphology. The authors make the point that therefore atypical type A thymoma are basically in the same category as B3 but because of their cell morphology they get a separate classification marker as “atypical” type A. And the mixed morphology doesn’t fit in nicely in the current WHO. I think we can all agree that the WHO classification of thymomas remains complex and despite this does not encompass neatly all the morphologic variants. Otherwise, this study did not provide any novel information in regards to immunohistochemistry or genomics of these tumors.

10. Utility of secretogin as a marker for the diagnosis of lung neuroendocrine carcinoma. Baykara et al, Virchows Archiv 2022; 481: 31-39

The authors evaluated the sensitivity of secretogin, in comparison to other neuroendocrine markers including synaptophysin, chromogranin, CD56 and INSM1 in 71 NEC (combination of SCLC, LCNEC, combined SCLC and combined LCNEC) and 20 carcinoid tumors. Secretogin is of no added value to existing markers. It did perform slightly better than chromogranin. As expected, CD56 and synaptophysin were the 2 most sensitive markers.

Non-neoplastic

1. Late Complications of COVID-19: A Morphologic, Imaging, and Droplet Digital Polymerase Chain Reaction Study of Lung Tissue. Roden et al. Arch Pathol 2022; 146: 791-804

Largest series of cases focused on pulmonary histologic findings > 28 days from onset of COVID with 44 specimens in 43 cases. The majority had a least focal ALI (DAD, OP, AFOP) up to 10 months after the initial diagnosis. SARS-coV-2 could still be identified by RT-ddPCR nearly 6 months later. About 75% of patients had fibrosis, mostly evolving from the ALI, including fibrotic DAD and cicatricial OP. Some had pre-existing fibrotic ILD, determined by clinical history and imaging prior to COVID infection. Up to 25% of patients had persistent recent thrombi. Few (<10%) cases showed organized thrombi suggesting mostly resolution. There was not a good correlation between CT Scan imaging and pathology, probably because of lag between when imaging was done and procedure performed.

Case Report/Correspondence

1. Lung Disease and Subsequent COVID-19 Presenting With Worsening Dyspnea. Ng et al. Chest 2022; 162:e19-25

Interesting case of acid sphingomyelinase deficiency (ASMD) a.k.a. Nieman-Pick disease with a great discussion, differential diagnosis and lovely histologic picture (by Mary Beth Beasley).

A subset of lung adenofibromas are morphological variants of solitary fibrous tumour. Laville et al. Histopathology 2022; 80:133- 136

Interesting case report of a case that morphologically had a component classic for SFT and a component that looked more like what has been described as adenofibroma. Both components showed STAT6 and confirmed *NAB2:STAT6* fusion suggesting that maybe some of these so-called adenofibromas are in fact SFT with entrapped benign pneumocytes. Furthermore, they also described a *FGFR2* mutation in their case, which seems to be novel to SFT and would have potential therapeutic implications.

Review articles

1. Algorithmic Approach to the Diagnosis of Organizing Pneumonia: A Correlation of Clinical, Radiologic, and Pathologic Features. Cherian et al. Chest 2022; 162:156-178

Nice review on OP, with exhaustive clinical, radiologic and pathologic descriptions of a very heterogeneous disease with a very broad differential diagnosis. The authors put forth an algorithmic approach to making the diagnosis.

2. Medical and Surgical Care of Patients With Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations. Carbone et al. JTO 2022; 17: 873-89

Nice review on BAP1 cancer syndrome with focus on mesothelioma, screening, clinical management, genetic testing, differences with mesothelioma with somatic mutation in terms of survival, and new clinical trials targeting BAP1 mutation.