Journal Club
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Articles for Discussion

1. De Giacomi F, Vassallo R, Yi ES, Ryu JH. Acute eosinophilic pneumonia: causes, diagnosis and management. Am J Respir Crit Care Med. 2018;197(6):728-36.

Background: Acute eosinophilic pneumonia (AEP) is currently diagnosed according to the Philit criteria as:
1. Acute respiratory illness of less than or equal to one month.
2. Pulmonary infiltrates on imaging.
3. Pulmonary eosinophilia greater than 25% in BAL or eosinophilic pneumonia on biopsy.
4. Absence of other specific eosinophilic pulmonary diseases, e.g., ABPA.

Methods/Results: Article summarizes recent literature on causes, diagnosis, and management. The three main categories of underlying etiologies include inhalational exposures, drugs, and infections.

- Tobacco smoking is probably the most significant and frequent. AEP is particularly associated with first time smoking or in those who resume smoking. Of note, evidence for a causal relationship between smoking and AEP is derived from studies reporting that exposure of individuals with a history of smoking-related AEP to tobacco smoke induces lung eosinophilia with or without the development of respiratory symptoms, imaging abnormalities, or abnormalities on PFTs.
- Numerous medications have also been implicated, some of them more common being antibiotics, nonsteroidal anti-inflammatories, and selective serotonin reuptake inhibits.
- Infections include parasitic, fungal, and viral including HIV, H1N1, and influenza vaccination.

Pathogenesis: Incompletely understood. Likely an acute type 1 HP reaction by alveolar macrophages. Certain pathogens appear to be able to interact with pulmonary epithelial cells and elicit activation of signals, e.g., IL33, which results in recruitment of eosinophils and TH2 cytokines. Figure 1 shows a proposed model. Mechanism for drug and tobacco smoke-induced AEP is even less well understood. As incidence of AEP very low compared with the prevalence of cigarette smoking, it strongly suggests an underlying genetic predisposition.

Pathology: Pathologic description has not changed much with most cases showing a pattern of diffuse alveolar damage with prominent eosinophils.

Clinical Features: Typically acute and associated with systemic symptoms, e.g., night sweats, chills, myalgias, and fever. Extra pulmonary organ involvement should make one consider other diagnoses. AEP may be mild and resolve spontaneously or end up producing ARDS. Smoking-related AEP seems more likely to present with severe disease than AEP cases not related to smoking. Peripheral eosinophilia may or may not be present and its absence may be more common in smoking-related AEP than idiopathic or medication-related AEP. BAL usually shows significant eosinophilia, therefore the eosinophilia criteria for BAL seems relatively sensitive. Treatment: for those cases clearly related to an exogenous agent, cease exposure. Systemic steroids also, but the length of treatment is not clear. Relapse is rare but reported in patients who resume smoking.

Discussion: AEP can be fatal if not promptly diagnosed and managed. Clinical response is typically prompt and complete without long-term consequences.

Comment: Nice recent review summarizing an unusual disease mostly reported in the form of case reports or very small series.

2. Antonescu CR, Agaram NP, Sung YS, Zhang L, Swanson D, Dickson BC. A distinct malignant epithelioid neoplasm with GLI1 gene rearrangements, frequent S100 protein expression, and metastatic potential: expanding the spectrum of pathologic entities with ACTB/MALAT1/PTCH1-GLI1 fusions. Am J Surg Pathol. 2018;42:553-60.

Background: Recurrent ACTB-GLI1 Fusions (Actin Beta-Glioma-Associated Oncogene Homolog 1) have been described in a distinctive mesenchymal neoplasm with a pericytic phenotype (tongue, stomach, bone). The present study investigates a cohort of malignant mesenchymal neoplasms with frequent S-100 protein expression, recurrent GLI1 fusions with ACTB, MALT1 (metastasis-associated lung adenocarcinoma transcript 1), or PTCH1 (patched 1 protein).

Methods: Cases from the author searched for tumors harboring GLI1 gene abnormalities identified by either FISH or targeted RNA sequencing. Study group was analyzed for clinical and pathologic features including immunohistochemical profile.

Results: Tumors were from four females and two males, ages 16 to 79 years, mean 32 yrs.
Locations: Thigh, foot, retroperitoneal, **chest wall**, head and neck, and bone. All tumors had a monomorphic appearance of round epithelioid cells arranged in nests, cords, and reticular patterns associated with a rich capillary network. Two tumors showed tubular cribriform growth or a sieve-like pattern admixed with solid sheets of epithelioid cells (refer figure 1). Two tumors had a myxoid stroma. All cases had solid growth and one had cystic areas. Mitotic activity was low and none showed necrosis in the primary.

S-100 protein--4/6.
SOX10, EMA, SMA, HMB 45 negative.
ACTB-GLI1 Fusion: Four cases.
MALT1-GLI1 Fusion: Two cases.

In one case, the tumor metastasized to the lung; although despite metastases, occasional patients still seem to do well.

Discussion and comment. New tumor, worth knowing about. Brandon Larsen, M.D., just made me aware of one of these cases as he received it as a chest wall tumor consult. So in addition to the tumors which may metastasize to the lung, be on the lookout for these in the chest wall. The tumors definitely have a distinctive appearance so the figures are worth a glance.

3. Xing D, Banet N, Sharma R, Vang R, Ronnett BM, Illei PB. Aberrant Pax-8 expression in well-differentiated papillary mesothelioma and malignant mesothelioma of the peritoneum: a clinicopathologic study. Hum Pathol. 2018;72:160-6.

Background: It is typically not so difficult to distinguish well-differentiated papillary mesothelioma (WDPM) and malignant mesothelioma (MM) from high-grade serous carcinoma. Recently PAX8 has been used in challenging cases, its reactivity having been used to support the diagnosis of an ovarian epithelial tumor. However, the authors began to notice frequent staining of PAX8 in WDPM and therefore undertook the current study.

Methods: Cases from JHH and consultation files.
Peritoneal WDPM- 33 cases (6 with invasive foci).
Peritoneal MM-34 cases
Adenomatoid tumors: 11 cases
Peritoneal inclusion cysts: 5 cases
Benign reactive mesothelium: 51 cases
Additional MM microarrays-48 cases

IHC for PAX8 performed; + = nuclear PAX8 staining (weak, moderate strong, 0, negative; focal, <50%; diffuse, >50%). Other stains were done to confirm mesothelial differentiation.

Results: Table below summarizes results.

Pax-8, Calretinin and BerEP4/MOC31 staining

Diagnosis	Pax-8			Calretinin +/total (%)	BerEP4/MOC31 +/total (%)
	+/Total (%)	Diffuse (n)	Focal (n)		
WDPM	61%	17	3	100%	7%
Perit MM	12%	3	1	100%	10%
Pleural MM	4%	0	2	100%	N/A
Aden. tumor	0%	0	0	100%	N/A
Mes Incl. cyst	0%	0	0	100%	N/A
Reactive meso	4%	0	2	100%	N/A

Discussion: Nuclear PAX8 reactivity was quite common in WDPMs (61%). Therefore caution should be used in using this to distinguish between serous tumors and mesothelial proliferations. It is probably best used for distinguishing malignant mesothelioma from gynecologic malignancies but the authors suggest that by using PAX8 along with staining for calretinin as well as Ber-EP4 or MOC31 may help in the distinction between WDPM/benign mesothelial proliferations and superficial epithelial proliferations of Mullerian origin, although they do not actually present the data on the utility of Ber-EP4 and MOC31 in this setting. ER can also be helpful, although again this study did not analyze this specific question.

Comment: Use PAX8 with caution, particularly in the peritoneum when your differential includes WDPM, especially those with invasion, the ones more likely to be confused with serous tumors.

4. Li R, Li X, Xue R, Yang F, Wang S, Li Y, Shen D, Sun K, Chen K, Weng W, Bai F, Wang J. Early metastasis detected in patients with multifocal pulmonary ground-glass opacities (GGOs). Thorax. 2018;73:290-2.

Background: The 8th edition of the AJCC Staging System indicates that multiple foci of ground-glass opacities (GGOs) should be regarded as separate tumors; however, data on this is relatively limited as the AJCC staging manual admits. This report calls that assumption into question.

Methods: Two nonsmokers with multiple GGOs were identified and their multiple tumors were subjected exome sequencing.

Results:

- Pt. #1. A 62-year-old woman--nine GGOs. All were resected and eight diagnosed as adenocarcinomas, T1-pT1-2.
- Pt. #2. A 44-year-old woman with eight GGOs, six of which were removed and diagnosed as adenocarcinoma (or AHH).

Sequencing: On fourteen tumors, methodologic details can be found in the paper (and are beyond my ability to summarize).

But, six out of eight lesions in P1 had no shared mutations and could be assumed to be independent primaries but two showed genetic profiles indicating they likely represented tumors with intrapulmonary metastases. P2—two lesions also shared same genetic makeup, indicating they were best regarded as intrapulmonary metastases.

Discussion: Whether metastases among GGOs influences prognosis is not known. This study had "moderate exome coverage" and so conclusions may be limited, i.e., authors could not rule out that these clonally unrelated GGOs could actually be clonally related under higher exome coverage depth.

Comment: Interesting observation, especially in light of the new staging rules. We knew this was not as easy as assumed.

Neoplastic Lung

1. **Hoton D, Humblet Y, Libbrecht L. Phenotypic variation of an ALK-positive large-cell neuroendocrine lung carcinoma with carcinoid morphology during treatment with ALK inhibitors. Histopathology. 2018;72:707-12.**

Background: ALK rearrangement and overexpression only rarely occur in neuroendocrine lung tumors.

Methods: Case report of large cell neuroendocrine carcinoma with carcinoid morphology with ALK gene rearrangements.

Results: A 69-year-old woman.

FNA of lymph node diagnosed as adenocarcinoma (TTF positive, ALK strong) confirmed by FISH. H&E stains not performed. Patient received cisplatin-pemetrexed, then crizotinib.

Hepatic mets—treated with ceritinib.

Patient underwent cholecystectomy and hilar lymph node showed features most consistent with LCNEC (supported by IHC—also ALK positive).

Liver metastases diagnosed as LCNEC with carcinoid morphology.

Discussion: ALK testing may be considered in LCNECs and LCNECs with carcinoid morphology.

Comment: Morphology and genetic testing are not the same thing!

2. **Letovanec I, Finn S, Zygoura P, Smyth P, Soltermann A, Bubendorf L, Speel EJ, Marchetti A, Nonaka D, Monkhorst K, Hager H, Martorell M, Sejda A, Cheney R, Hernandez-Losa J, Verbeken E, Weder W, Savic S, Di Lorito A, Navarro A, Felip E, Warth A, Baas P, Meldgaard P, Blackhall F, Dingemans AM, Dienemann H, Dziadziuszko R, Vansteenkiste J, O'Brien C, Geiger T, Sherlock J, Schageman J, Dafni U, Kammler R, Kerr K, Thunnissen E, Stahel R, Peters S, on behalf of the European Thoracic Oncology Platform Lungscape Consortium. Evaluation of NGS and RT-PCR methods for ALK rearrangement in European NSCLC patients: results from the European Thoracic Oncology Platform Lungscape Project. J Thorac Oncol. 2018;13(3):413-25.**

Background: FISH is the primary diagnostic method for diagnosis of ALK gene rearrangements although IHC, RT-PCR, and NGS are other platforms which can be used. This study compares these four techniques in resected NSCLCs from a large European cohort.

Methods: Ninety-six cases from the European Thoracic Oncology platform, Lungscape iBiobank, with any ALK immunoreactivity were examined by FISH, RT-PCR, and NGS.

Results: See tables 1 and 2.

If concordance of any two techniques is considered true positive, instead of concordance between IHC and FISH (the usual gold standard), the study showed that none of the techniques exhibit 100% sensitivity or specificity.

NGS provided results in 77/95.

RT-PCR provided results for 77/96.

Concordance occurred in 55/60 cases with all 4 methods.

Using ALK positivity by IHC plus FISH as gold standard, RT-PCR had sensitivity and specificity of 70% and 87.1% while NGS had a specificity of 85% and specificity of 79%.

Discussion: While ICH is currently approved and inexpensive, these results show that NGS and RT-PCR based approaches on FFPE are possible.

Comment: The study did not address cost issues but this may well factor into which test may be best (NGS clearly the most expensive).

3. **Lozano MD, Echeveste JI, Abengozar M, Mejias LD, Idoate MA, Calvo A, de Andrea CE. Cytology smears in the era of molecular biomarkers in non-small cell lung cancer: doing more with less. Arch Pathol Lab Med. 2018;142:291-8.**

Background: Cytology samples provide high quality material for molecular testing but samples are underutilized. This report summarizes many new advances on molecular cytopathology and suitability and utility of cytology samples for genetic testing of NSCLC.

Methods: Peer review literature and author experience.

Results: Molecular testing can be performed on cytologic specimens, especially direct smears.

Mutational profiling of NSCLC using NGS can be performed using very small amounts of DNA.

FISH can be used to detect ALK and ROS1 rearrangements with cytology specimens, allowing assessment of the entire nucleus.

Use of cytology for PD-L1 expression currently not ready for primetime.

Discussion and Comment: Clearly we can do more with less. Nice summary article with lots of detail.

4. **Larque AB, Kradin RL, Chebib I, Nielsen GP, Selig MK, Thiele EA, Stemmer-Rachamimov A, Bredella MA, Kurzawa P, Deshpande V. Fibroma-like PEComa: a tuberous sclerosis complex-related lesion. Am J Surg Pathol. 2018;42:500-5.**

Background: A range of fibromas have been described in patients with TSC. The authors describe a TSC-related neoplasm resembling a soft tissue fibroma with immunophenotypic features of PEComa.

Methods: Three cases identified from the institutional and consultation files of the authors. They were compared to other tumors in TSC patients including six periungual fibromas, one oral, and one odontogenic.

Results: Tumors occurred in three women from 4 to 51 years of age. Tumors occurred on wrist, in chest wall, and foot.

All three TSC-related fibromas are comprised of densely collagenized stroma resembling "collagenous fibroma." In some cases, perivascular accentuation of epithelioid cells was appreciated. Cases showed variable reactivity for HMB 45, MART-1, MiTF, Desmin, smooth muscle actin, but did not react with antibodies to S-100 protein.

Discussion: Given the strong association with TSC, the authors recommend that a diagnosis of fibroma-like PEComas should prompt thorough evaluation for TSC.

Comment: Just thought it was worth mentioning another tumor that might be seen in someone with lymphangiomyomatosis.

5. **Thunnissen E, Allen TC, Adam J, Aisner DL. Beasley MB, Borczuk AC, Cagle PT, Capelozzi VL, Cooper W, Hariri LP, Kern I, Lantuejoul S, Miller R, Mino-Kenudson M, Radonic T, Raparia K, Rekhtman N, Roy-Chowdhuri S, Russell P, Schneider F, Sholl LM, Tsao MS, Vivero M, Yatabe Y. Immunohistochemistry of pulmonary biomarkers: a perspective from members of the Pulmonary Pathology Society. Arch Pathol Lab Med. 2018;142:408-19.**

Background: Yet another in a series from "members of the Pulmonary Pathology Society."

Methods: Review article, likely with input from authors' experience.

Results: Topics discussed include:

Pre-analytic, analytic, and post-analytic variables.
Validation.
ALK.
ROS1.
PD-L1.
Other.

Discussion: Although the lung oncology community is somewhat suspicious of IHC biomarkers, the authors support their use when performed well.

Comment: None.

6. **Martini M, Capodimonti S, Cenci T, Bilotta M, Fadda G, Larocca LM, Rossi ED. To obtain more with less: cytologic samples with ancillary molecular techniques – the useful role of liquid-based cytology. Arch Pathol Lab Med. 2018;142:299-307.**

Background: Review of use of liquid-based cytology preparations for molecular techniques.

Methods: Authors' experience on the topic.

Results: Following organ systems covered:

Thyroid.
Head and neck.
Lung.
Lymph node.

Discussion: Ancillary studies can clearly be performed on liquid biopsy cytologic samples.

Comment: None

7. **Laggner U, Khiroya R, Wotherspoon AC, Desai SR, Nicholson AG. Lesson of the month: MALT lymphoma arising on the background of reactive pulmonary lymphoid hyperplasia in a patient with systemic lupus erythematosus. Histopathology. 2018;72:704-6.**

Background and methods: Case report.

Results: A 57-year-old woman with SLE.

CT showed multiple thin-walled cysts. Surgical lung biopsy showed cystic LIP (reactive pulmonary lymphoid hyperplasia) with amyloid; other areas showed features of MALT lymphoma.

Discussion: While the association of amyloid, lymphoid hyperplasia, and cystic lung disease is well described in Sjogren's, this pattern should also be added to the differential for those with SLE.

8. **Lindeman NI, Cagle PT, Aisner DL, Arcila ME, Beasley MB, Bernicker EH, Colasacco C, Dacic S, Hirsch FR, Kerr K, Kwaitkowski DJ, Ladanyi M, Nowak JA, Sholl L, Temple-Smolkin R, Solomon B, Souter LH, Thunnissen E, Tsao MS, Ventura CB, Wynes MW, Yatabe Y. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Thorac Oncol. 2018;13(3):323-58. (also published in APLM)**

Background: In 2013, evidence-based guidelines from CAP/IASLC and AMP set standards for molecular analysis of patients with lung cancer. New evidence has prompted an update.

Methods: Literature review, expert panel opinion.

Results: Eighteen new recommendations drafted and three recommendations updated.

1. Importance of ROS testing.
2. The value of IHC for ALK testing.
3. Importance of testing for T790M mutation in patients who progress on anti-EGFR therapy.

Authors also discuss emerging and promising molecular alterations including BRAF, MET, ERBB2 (HER-2 and RET).

Discussion and Comment: None.

9. Mehrad M, Roy S, Bittar HT, Dacic S. Next-generation sequencing approach to non-small cell lung carcinoma yields more actionable alterations. Arch Pathol Lab Med. 2018;142:353-7.

Background: Different testing algorithms and platforms for evaluation of adenocarcinoma EGFR and ALK rearrangements exist. The multistep approach has been challenged by the use of NGS. The authors attempted to determine the best algorithm for their patients in clinical practice.

Methods: Two testing approaches were compared : Reflex testing for 8-gene panel composed of DNA Sanger sequencing for EGFR, K-Ras, PIK3CA, and BRAF; and FISH for ALK, ROS1, MET, and RET, AND 50 gene ion AmpliSEQ cancer panel.

Results: Forty-six cases of ADCA, NSCLC NOS tested by non-NGS 8-gene panel and subsequently subjected to ion AmpliSEQ cancer panel.

Seventeen tumors had mutations by 8-gene panel.

Twenty-nine were wild type on 8-gene panel.

Of those 29, 9 actionable or investigational mutations and/or variants were identified by NGS (31%).

Discussion: The authors showed the benefit of NGS in identifying more targetable mutations than a stepwise approach. This has the potential to increase therapeutic options for patients with advanced NSCLC.

Comment: Our local oncologists routinely order the 600-gene panel from a nearby reference laboratory!

10. Kythreotou A, Siddique A, Mauri FA, Bower M, Pinato DJ. PD-L1. J Clin Pathol. 2018;71:189-94.

Background: Review of PD-L1 significance in tumor biology.

Topics Covered:
NSCLC.
Melanoma.
Ovarian carcinoma.
Breast cancer.
Gastrointestinal malignancy.
Other malignancies.

11. Hendry S, Byrne DJ, Wright GM, Young RJ, Sturrock S, Cooper WA, Fox SB. Comparison of four PD-L1 immunohistochemical assays in lung cancer. J Thorac Oncol. 2018;13(3):367-76.

Background: Four PD-L1 IHC assays are approved or in development as companion or complimentary diagnostics to different immunotherapeutic agents in lung cancer. Authors compared the performance characteristics of four antibodies.

Methods: Microarray study from 368 cases of resected lung cancer stained with antibodies to 22C3 and 28-8 (DOCO) and SP142 and SP263 (Ventana).

Results: Differences in mean tumor cell and a mean cell staining were observed between the four assays ($P < 0.001$).

Differences between 22C3 and 28-8 were not statistically significant. Concordance of tumor cell scores was good when SP142 was excluded as an outlier.

Highest concordance was between 22C3 and 28-8. Concordance was poor for immune cell staining.

Discussion: Concordance between the four PD-L1 IHC assays when performed and scored as intended show that apart from 28-8 and 22C3 they cannot be used interchangeably.

Comment: PD-L1 testing is complicated.

12. Tseng YH, Ho HL, Lai CR, Luo YH, Tseng YC, Whang-Peng J, Lin YH, Chou TY, Chen YM. PD-L1 expression of tumor cells, macrophages, and immune cells in non-small cell lung cancer patients with malignant pleural effusion. J Thorac Oncol. 2018;13(3):447-53.

Background: There have been a few studies determining whether PD-L1 expression in cells in pleural effusion could predict response to immunotherapy.

Methods: Retrospective review from 2014 to 2016 of pleural fluid cell block preparations stained with clone SP142 and 22C3 scoring a PD-L1 on tumor and inflammatory cells was performed.

Results: PD-L1 expression on tumor cells was associated with PD-L1 expression on macrophages and immune cells.

PD-L1 expression of immune cells was not associated with that of macrophages.

PD-L1 expression of tumor cells correlated with gender, smoking status, and performance status.

PD-L1 expression of immune cells was associated with overall survival ($P = 0.004$).

Discussion: There was overall low PD-L1 expression in immune cells in the pleura which may be correlated with the poor survival of patients with malignant pleural effusions.

13. Wick MR. Primary lesions that may imitate metastatic tumors histologically: a selective review. Semin Diagn Pathol. 2018;35:123-42.

Background: Review.

Methods: Literature review and author experience.

Results: There is a section on primary pleural pulmonary tumors that may simulate metastases, including:

Clear cell carcinoma of the lung.

Special types of primary pulmonary adenocarcinoma including enteric, mucinous, signet ring cell, and those with psammoma bodies. Figure 9 is an algorithm for IHC evaluation of clear cell tumors.

Primary pulmonary salivary duct carcinoma.

Pleural mesothelioma.

14. Miyake A, Okudela K, Matsumura M, Hideaki M, Arai H, Umeda S, Yamanaka S, Ishikawa Y, Tajiri M, Ohashi K. Update on the potential significance of psammoma bodies in lung adenocarcinoma from a modern perspective. Histopathology. 2018;72:609-18.

Background: Only one previous study (1972) systematically described as significance of psammoma bodies in lung adenocarcinoma. The aim of the study was to update the literature.

Methods and Results: 822 adenocarcinomas reviewed among which 7.2% had psammoma bodies.

Papillary (20.3%, 12/59), acinar (44%, 26/59) were dominant.

Adenocarcinomas with psammoma bodies were preferentially associated with targetable driver mutations.

EGFR—69.8%.
ALK—13.2%.
ROS1—1.9%.

Multivariate analysis indicated that psammoma bodies may constitute an independent predictor for these mutations, particularly EGFR and ALK.

Discussion: Psammoma bodies may predict a favorable response of lung adenocarcinomas to TKIs. These results corroborate other studies which have suggested that psammoma bodies may be used to predict response to targeted molecular therapies.

Comment: Interesting observation but likely of little clinical utility in current climate.

15. Kawai H, Takayashiki N, Otani H, Sakashita S, Noguchi M. A case of microscopic, multiple sclerosing pneumocytoma. Pathol Int. 2018;68:196-201.

Background and Methods: Case report of multiple pneumocytomas.

Results: A 19-year-old woman. CT showed dozens of small nodules in upper and middle lobes. Images fairly convincing. Authors do an extensive immunohistochemical workup and apotheosize about the nature of the cells of origin.

16. Inoue T, Nakazato Y, Karube Y, Maeda S, Kobayashi S, Chida M. Mitosis count and number of cancer cells in cases of primary pulmonary adenocarcinoma: correlations among phosphorylated histone 3, number of cancer cells, nuclear grade, pathologic features and prognosis. Pathol Int. 2018;68:159-66.

Background: Phosphorylated histone 3 (PHH3) has been found to be a reliable mitosis-specific marker and has been useful in multiple tumors (gliomas, meningiomas, pulmonary neuroendocrine carcinomas, etc.). The current study correlates PHH3 stained mitotic figures (PHMFs) and survival in lung carcinoma.

Methods: 113 pulmonary adenocarcinomas (less than 2 cm) stained with PHH3. Results compared this to Ki-67 index and nuclear grade.

Results: PHH3 index was defined as number of PHH3 positive cells within 1 mm^2.

Cases with PHH3 index greater than or equal to 0.27 had worse relapse-free survival compared to value less than 0.27, and OS multi-variate analysis demonstrated that the PHH3 to cancer cell index was correlated with prognosis but not Ki-67 index.

Authors stressed the importance of their finding in estimating malignant potential in small size adenocarcinomas.

Non-neoplastic Lung

1. Jain D, Tamm M, Savic S, Bubendorf L. Alveolar herniation in transbronchial lung biopsy: a newly recognized diagnostic pitfall. Histopathology. 2018; 72:710-12.

Background and Methods: Letter to the editor

Results: 8 cases of previously unrecognized artifact of displacement of alveolar pneumocytes and macrophages into bronchial mucosa. The authors label this " bronchial alveolar herniation".

Thought to be an artifact of alveolar tissue telescoping into bronchial wall.

Discussion/Comment: Do not miss this one!

2. Pierry C, Caumont C, Blanchard E, Brochet C, Dournes G, Gros A, Bandres T, Verdon S, Marty M, Begueret H, Merlio JP. Assessment of $BRAF^{V600E}$ mutation in pulmonary Langerhans cell histiocytosis in tissue biopsies and bronchoalveolar lavages by droplet digital polymerase chain reaction. Virchows Arch. 2018;472:247-58.

Background: The neoplastic nature of PLCH is still debated. The aim of this study was to evaluate digital droplet polymerase chain reaction (DDPCR) in PLCH.

Methods: Forty-two PLCH biopsies and 18 BAL studied by IHC high resolution melting PCR (HRM) and NGS, and DDPCR.

Results: Table 1 has a detailed breakdown of results of four methods.

18/41 positive by DDPCR.
10/36 positive by HRM PCR.
16/31 positive by NGS.

BRAF IHC 94% sensitive and 79% specific.

HRM PCR 59% sensation, 100% specific.

NGS 100% sensitivity, 100% specificity for interpretable cases.

BAL by DDPCR positive in small number of patients confirming utility of the method.

Conclusion: Their data confirm the neoplastic nature of a large subset of PLCH cases.

Discussion and Comment: Methods a bit beyond me. Confirms results of other studies.

3. Daccord C, Latovanec I, Yerly P, Block J, Ogna A, Nicod LP, Aubert JD. First histopathological evidence of irreversible pulmonary vascular disease in dasatinib-induced pulmonary arterial hypertension. Eur Respir J. 2018;51(3).

Background: Dasatinib has been associated with pulmonary arterial hypertension but no pathology has been reported.

Methods: Case report of patient who developed dasatinib-induced PAH and underwent lung transplantation.

Results: Variety of lesions identified.

- Medial hypertrophy in concentric nonlaminar intimal thickening.
- Plexiform lesions.
- Dilatation lesions

Discussion and comment: Severe vascular pathology in this patient, although the images are not entirely convincing for these specific lesions. The plexiform lesion looks more like an organizing thrombus to me

4. **Tsakok M, Addala D, Bradley C, Gleeson F. Subpleural cystic change in a patient with multiple rib exostoses. Thorax. 2018;73:300-1.**

Background: Chest wall exostoses have been associated with pneumothoraces, hemothoraces, pleural effusions, diaphragmatic lacerations, and pericardial and pleural thickening.

Methods: Case report.

Results: A 75-year-old patient with multiple hereditary exostoses was found to have widespread subpleural cystic change adjacent to the rib exostoses.

No pathology shown, but the CT images are quite remarkable.

Discussion/Comment: Be on the lookout for such a case being associated with a pneumothorax. You hit a home run if you suggest this possibility correctly.

5. **Fernandez Perez ER, Kong AM, Raimundo K, Koelsch TL, Kulkami R, Cole AL. Epidemiology of hypersensitivity pneumonitis among an insured population in the United States: a claims-based cohort analysis. Ann Am Thorac Soc. 2018;15(4):460-9. AND Salisbury ML. Powers and pitfalls of using administrative data to study the epidemiology of interstitial lung diseases. Ann Am Thorac Soc. 2018;15(4):424-5. Editorial.**

Background: Limited data exists regarding epidemiology of hypersensitivity pneumonitis in the United States.

Methods: Claims-based coding algorithm to identify patients with hypersensitivity pneumonitis using a large commercial and Medicare healthcare claim database.

Results: 7498 cases were identified (2004 to 2013). Prevalence and incidence are explored by state and degree of fibrosis. In the US, H&P incidence and prevalence rates remained stable from 2004 to 2013. It affects women more than men and increases with age, particularly among those 65 years and older. Cases with pulmonary fibrosis died at significantly faster rates than those without fibrosis.

Discussion and Comment: Interesting approach. Typically don't think of HP as an old person's disease, but it is increasing in this age group (true in our consult practice also).

6. **Griese M, Seidl E, Hengst M, Reu S, Rock H, Anthony G, Kiper N, Emiralioglu N, Snijders D, Goldbeck L, Leidl R, Ley-Zaporozhan J, Kruger-Stollfuss I, Kammer B, Wesselak T, Eismann C, Schams A, Neuner D, MacLean M, Nicholson AG, Lauren M, Clement A, epaud R, de Blic J, Ashworth M, Aurora P, Calder A, Wetzke M, Kappler M, Cunningham S, Schwerk N, Bush A, and the other child-EU collaborators. International management platform for children's interstitial lung disease (child-EU). Thorax. 2018;73:231-9.**

Comment: Here for those who do pediatric pathology.

Pleura and Mediastinum

1. **Scott RM, Henske EP, Raby B, Boone PM, Rusk RA, Marciniak SJ. Familial pneumothorax: towards precision medicine. Thorax. 2018;73:270-6.**

Background: One in ten patients with primary spontaneous pneumothoraces have a family history that can occur in isolation but also be the sign of a more serious genetic disorder.

Methods: Review of clinical manifestations and underlying biology of genetic causes of familial pneumothorax.

Results: Sections on defects of tumor suppressors.

BHD.

TSC and LAM.

Marfan syndrome.

Loeys-Dietz syndrome.

Ehlers-Danlos syndrome.

Alpha-1 antitrypsin deficiency.

Homocystinuria.

Discussion: Nice review.

Comment: You got to love any article that starts with a story about elephants (they have a fused visceral and parietal pleura which fixes the lung to the chest wall)! This developmental pleurodesis likely prevents pneumothoraces caused by high transmural pressures experienced during trunk-snorkeling. I love it.

2. **Padda SK, Yao X, Antonicelli A, Riess JW, Shang Y, Shrager JB, Korst R, Detterbeck F, Huang J, Burt BM, Wakelee HA, Badve SS. Paraneoplastic syndromes and thymic malignancies: an examination of the international thymic malignancy interest group retrospective database. J Thorac Oncol. 2018;13(3)436-46.**

Background: Thymic epithelial tumors may be associated with a variety of paraneoplastic/autoimmune (PN/AI) syndromes.

Methods: ITMIG database review to determine treatment characteristics associated with PN/AI and prognostic role of PN/AI syndromes for patients with thymic epithelial tumors (TET).

Results: 6670 patients identified from 1951 to 2012.

PN/AI syndromes associated with younger age, female gender, thymoma histologic type, early stage tumor and increased rate of total thymectomy and complete resection status. In multivariate analysis, recurrence-free survival and OS, PN/AI syndromes were not an independent prognostic factor.

Discussion: This study confirms prior data that PN/AI syndrome status is not an independent factor associated with overall survival.