Pulmonary Pathology Journal Club

October 31, 2015 (September articles)

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Articles for Discussion

1. Valente K, Blackham AU, Levine E, et al. A Histomorphologic Grading System That Predicts Overall Survival in Diffuse Malignant Peritoneal Mesothelioma With Epithelioid Subtype. Am J Surg Pathol. 2016 Sep;40(9):1243-8.

Background/ Purpose:

Build on work by Kadota et al (*Mod Path* 2012), who proposed grading scheme for pleural epithelioid mesothelioma utilizing nuclear grade and mitotic count;

Say that malignant peritoneal mesothelioma (MPeM) has different etiology, clinical course, and therapy

Materials and Methods

Retrospective review of 51 cases of MPeM from Wake Forest from 1984-2013

Study group: 46 epithelioid MPeM

Patients had been treated with similar therapy:

Cytoreductive surgery AND

Hyperthermic intraperitoneal chemo (mitomycin-C vs cisplatin based)

Microscopy review (biopsy and surgical specimens):

Nuclear atypia: nuclear size, uniformity, shape, membrane outlines and irregularity, N/C ratio, chromatin pattern, prominence of nucleoli

Assigned an atypia grade of 1, 2, or 3

Mild (gr 1): uniform nuclei in size and shape, low N/C ratio, homogenous chromatin w/ fine granular pattern, indistinct nucleoli or very small nucleoli

Severe (gr 3): marked membrane irregularity, bizarre contours, nuclear enlargement, marked variability in size and shape, high N/C ratio, coarsely granular chromatin, and/ or prominent large nucleoli

Claimed tumors “exhibited little to no heterogeneity”

Mitotic count: Evaluated in 50 HPFs w/ highest mitotic activity and counted as avg. MF/ 10 HPFs

Mitotic score 1: 0 to 1 per 10 HPF; Score 2: 2 to 4 per 10 HPF; Score 3: > 5 per 10 HPF

Two-tier grading scheme:

Low grade: 3 or less

High grade: 4-6

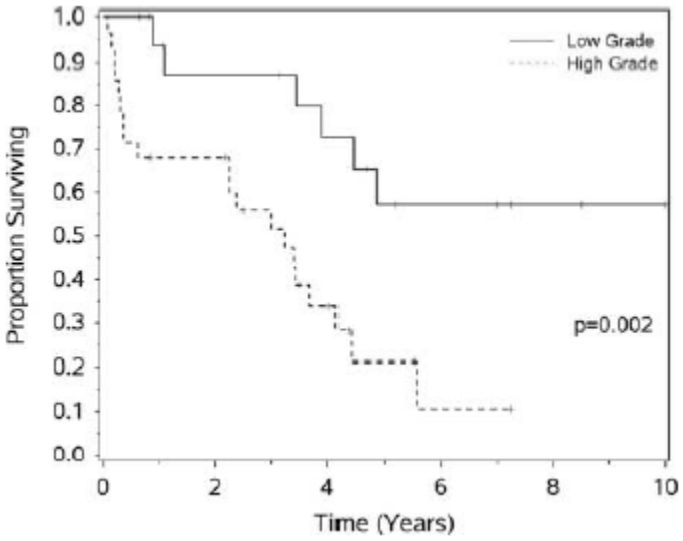
Evaluated overall survival (OS) and progression-free survival (PFS)

R0, R1, R2a: deemed complete resections (“disease free” after surgery)

R2b, R2c (6 mm or greater in gross residual disease): not disease free after surgery

Results

18 cases in Low-grade tier; 28 cases in High-grade tier



Overall Survival (p= 0.002)

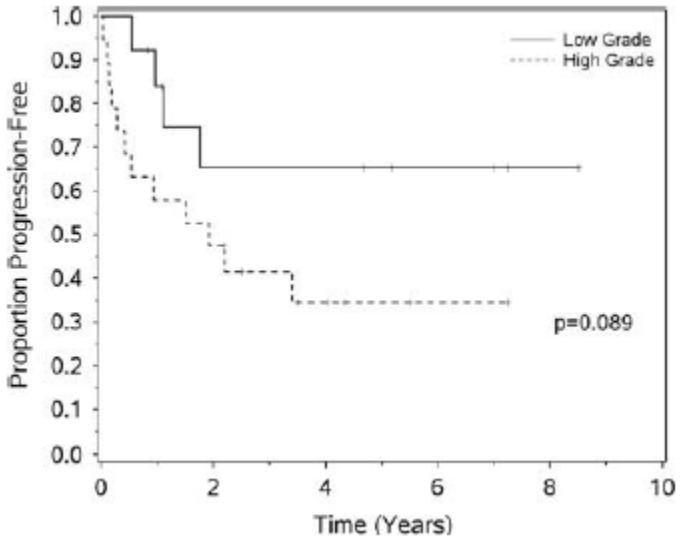
Low grade: median 11.9 y (51% at 5 y)

High grade: median 3.3 y (21% at 5 y)

Progression Free Survival (p=0.089)

Low grade: median 4.7 y

High grade: median 1.9 y



- No statistically significant differences in resection groups between tiers “when evaluating the proportion of each defined group within each tier”.

- No statistically significant differences between tiers in subset of complete resections (R0 and R1)

5/18 (28%) – low grade

5/28 (18%) – high grade

- No statistically significant differences between grades w/ regard to received chemotherapy regimen

Take-home message (authors)

Recommend grading epithelioid mesotheliomas into low and high grades.

2. Attanoos RL, Alchami FS, Pooley FD, et al. Histopathology. 2016 Sep;69(3):492-8. Usual interstitial pneumonia in asbestos-exposed cohorts - concurrent idiopathic pulmonary fibrosis or atypical asbestosis? Histopathology. 2016 Sep;69(3):492-8.

Background/ Purpose:

CAP-PPS guideline on pathologic diagnosis of asbestosis:

- Diffuse interstitial fibrosis
- Identification of asbestos bodies (difficult/ problematic/ inconsistent)

'Appropriate' fibrosis (allegedly) –

- Always paucicellular; Lacks any significant inflammation; Collagenous rather than fibroblastic
- Lower lobe, peripheral zone like UIP
- Temporal and spatial homogeneity of fibrotic NSIP

Does UIP pattern fibrosis occur in asbestosis, or is it IPF in an exposed subject?

Materials and Methods

Cases pulled from archives of the UK Medical Research Council (MRC) Pneumoconiosis Unit at University Hospital Llandough

- Slides from 258 heavily exposed patients (4 cohorts: dockyard, insulation, gas mask factory, textile factory), out of approx. 25,000 workers
  - Study group of 233 cases
  - 25 cases excluded: 13 from "concurrent" pathology, 9 from no lung fibrosis
- Lung biopsy and autopsy material
- Formal ferruginous/ asbestos-body counts NOT performed

Results

3/ 233 – UIP pattern fibrosis

Fibrotic NSIP pattern observed (no specifics)

Table 1. Correlation of the usual interstitial pneumonia cases with mineral fibre analysis

Case no.	Exposure duration/ course/ latency (years)	Total retained amphibole asbestos fibres ($\times 10^6$)/g dry lung	Median amphibole fibres – all grades of fibrosis (grades 1–4) for asbestos cohort	Fibre count – percentile of all cases for the complete asbestos cohort
Case 1 Dockyard	NK	23.2	123.3	<5th
Case 2 Dockyard	NK	36.7	123.3	<10th
Case 3 Cape Uxbridge	2.1/3.6/38	48	582	<5th

NK, Not known.

Conclusion: UIP pattern reflected UIP/ IPF, not asbestosis, based on:

- Low fiber counts in tissue
- Known dose-response curve between fiber counts and lung fibrosis
- Overly long latency period (10-15 year expected latency based on heavy asbestos exposure)
- Asbestosis has a 'slow clinical tempo', whereas Case 3 was quickly (<4 years) progressive
- Expected rate of UIP/ IPF in study population

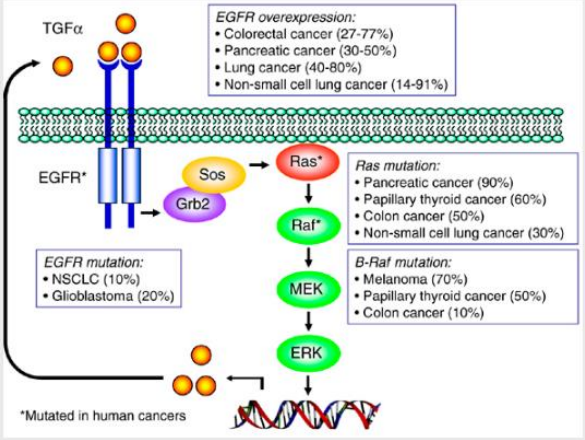
Take-home message (authors)

Asbestosis should NOT include cases with UIP pattern fibrosis, irrespective of status of asbestos biomarkers.

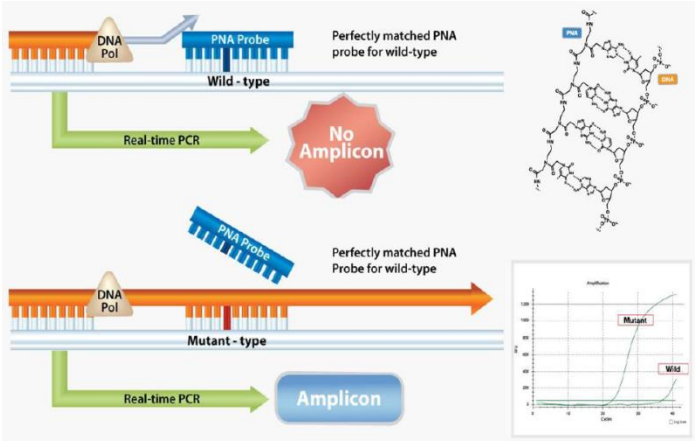
Appropriate fibrosis in asbestosis is fibrotic NSIP-like.

3. Kamionek et al. Mutually exclusive extracellular signal-regulated kinase pathway mutations are present in different stages of multifocal pulmonary Langerhans cell histiocytosis supporting clonal nature of the disease. Histopathology 2016 Sept;69: 499-509

Purpose: To study the prevalence of mutations in the MAPK signaling pathway (RAS-BRAF-MEK-ERK) in cellular and fibrotic stages of PLCH



Oncogene (2007) 26, 3291-3310



Panagene PNAClamp KRAS Mutation Detection Kit (Ver.2)

Methods:

PLCH (28 pts)			Other smoking related diseases		
Cellular (n=10)	Mixed cellular/fibrotic (n=4)	Fibrotic (n=14)	RB-ILD (n=2)	DIP (n=4)	RB-ILD/DIP (n=2)

Real-time PCR was performed with and without a peptide nucleic acid (PNA) clamp designed to block amplification of wild-type sequences. Mutation status was confirmed by Sanger sequencing.
Next-generation sequencing covers the known hot-spot mutations in KRAS, NRAS, HRAS, BRAF and the entire coding sequence of the MAP2K1 gene.
BRAF IHC analysis: reviewed and scored by at least 2 pathologists who were blinded to the molecular results.

Results:

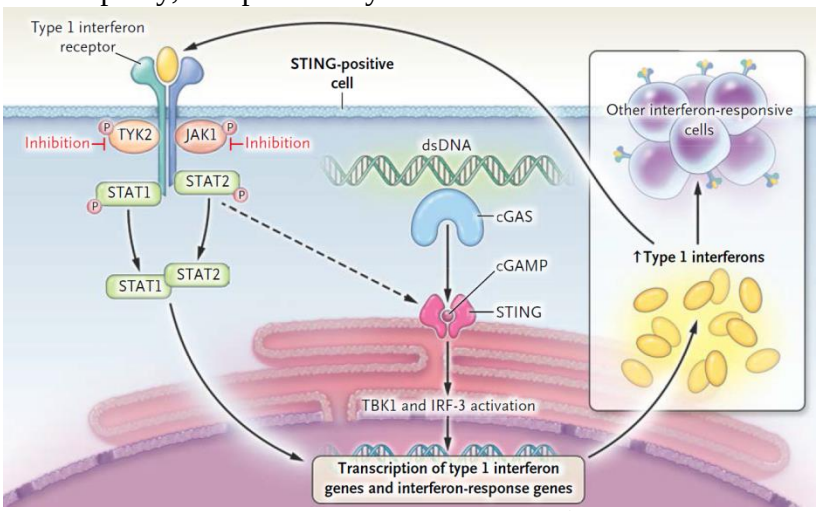
PLCH (28 pts: 15 F, 13 M; 18-68 y/o; 5-72 pack-years smoking hx; b/l lung diz in all CT)			
	Cellular (n=10)	Mixed cellular/fibrotic (n=4)	Fibrotic (n=14)
BRAF ^{V600E}	**8/12** (67%; failed assay in 2 cellular cases)		**1/14** (7%)
MAP2K1	**3/12**		**2/14**
KRAS	None		**2/14** (both have concurrent lung cancer)
Total	**11/12 (92%)**		**5/14**
Total	**16/24 (67%)**		

- Somatic mutations in BRAF, MAP2K1 and KRAS found in PLCH are mutually exclusive.
-The mean age of patients with cellular stage was **41.6** years v.s. **55.1** years for patients with fibrotic stage.
- 7 of the 28 subjects had concurrent primary lung malignancy (6-adenocarcinoma; 1-NSCLC).
- With two exceptions, all lesions with multiple foci showed the same BRAF or MAP2K1 mutations.
- Other smoking-related lung disorders showed wild-type status at all gene loci examined.

Take-home message:
- This study is compatible with previous studies with an overall frequency of 35% for BRAF^{V600E} (table 3).
- The overall mutation frequency of 67% (16 of 24) supports that most PLCH lesions are neoplastic in origin.
- Rare MAP2K1 mutations in multiple foci provides stronger evidence for the clonal origin of PLCH.
- BRAF^{V600E} mutations were dominant in cellular lesions, whereas non-BRAF mutations were distributed evenly in cellular and fibrotic lesions.
- BRAF inhibitors could be a potential adjuvant for treatment in cases refractory to smoking cessation.
- Unsolved question- is disease progression mutation-driven? How to explain the biology of multifocal clonal proliferation?

4. Picard et al. Severe Pulmonary Fibrosis as the First Manifestation of Interferonopathy (TMEM173 Mutation) Chest 2016 Sept;150 (3): e65-e71

Purpose: To report 3 additional cases (2 familial, 1 sporadic) of the recently described autoinflammatory syndrome linked to a gain-of-function mutation of *TMEM173*, a gene encoding the stimulator of interferon genes (STING), which is associated with a clinical syndrome called STING-associated vasculopathy with onset in infancy (SAVI). The main clinical features include early-onset systemic inflammation, cutaneous vasculopathy, and pulmonary inflammation/fibrosis.



Liu Y. et al. N Eng J of Med. 2014; 371(6):507-518

Results:

	Case #1 (son)	Case #2 (mother)	Case #3
Age/sex	12 y/o M	34 y/o F	14 y/o M
Onset	Failure to thrive since 1 y/o; 5 y/o-chronic cough and digital clubbing	Had been followed for ILD since 20 y/o	Failure to thrive since 5 months old; age 3-dyspnea on exertion mild hypoxia; age 10-cor pulmonale
Other symptoms	Telangiectasia and chilblains since age 11	Acral telangiectasia, atrophic plaques on the hands, and nail dystrophy, as well as erythematous rash over the fingertips; chronic polyarthralgia	mild skin lesions of telangiectasia and chilblains since age 12
Blood	Decreased CD4+ T and NK cells; normal B cells a/w oligoclonal hypergammaglobulinemia; IFN signature		
PE	Positive b/l basal crackles	Positive b/l basal crackles	
PFT	Severe restrictive PFT with a decreased DLco	Predominant obstructive (FEV1/FVC-50%), hyperinflation (RV/TLC-170%) and decreased DLco	restrictive PFT with a decreased DLco
HRCT	Subpleural and central cystic lesions (paraseptal emphysema) and reticulations/fibrosis, no traction bronchiectasis (Fig. 1A)	Honeycombing/cysts and traction bronchiectasis with upper lobe predominance (Fig. 1B)	Diffuse b/l ground glass areas and honeycombing, no traction bronchiectasis (Fig. 1C)
Histology	Multiple peribonchiolar lymphoid aggregates a/w fibrosis (Fig. 3A-3C, 3E)	Bronchiectasis/microscopic honeycombing with lymphoid aggregates (Fig. 3D)	Pulmonary inflammatory infiltrates with lymphoid nodules and emphyesema
Outcome	Planning for b/l lung transplantation due to progression of lung dysfunction	Died of multiple organ failure 3 months after b/l lung transplantation	On lung transplantation list

- For all 3 cases, no mutations were identified among common disease causing genes associated with pulmonary fibrosis (*SFTPC, SFTPB, ABCA3, TERT, TERC*).
- 2 familial cases were screened by whole-exome sequencing (WES). A mutation in the TMEM173 gene encoding for the DNA sensor STING (stimulator of interferon genes) was identified.

Take-home message: STING-associated lung fibrosis should be considered; be aware of potential fatal outcome of b/l lung transplantation; blocking IFN signaling with JAK inhibitors could be a promising therapeutic strategy.

Articles for notation

Martinez-Balzano et al. Cystic Lung Disease Among Patients With Sjögren Syndrome Frequency, Natural History, and Associated Risk Factors. Chest 2016 Sept.;150 (3):631-639

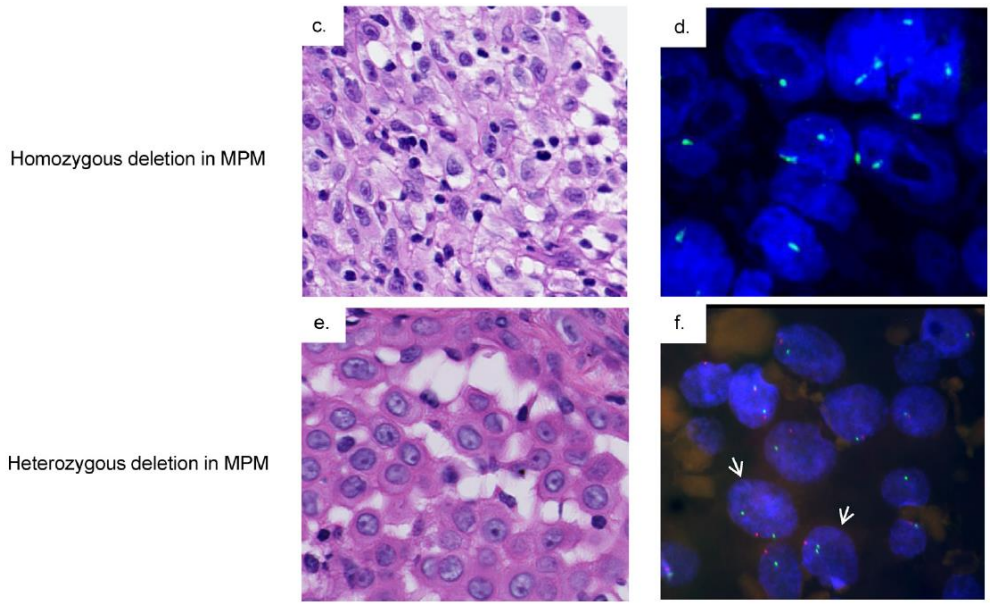
Purpose: Retrospective study of primary and secondary Sjögren syndrome (SS), focusing on the evaluation of cystic lung disease (CLD) on chest imaging to determine its frequency, progression over time, and associated risk factors and complications.

Results:
- This is a study primarily focusing on the radiologic and clinical follow up of CLD in SS, most of which have no pathologic correlations.
- CLD, without other radiographic findings, may represent a direct manifestation of SS, since cases of CLD in SS associated with pulmonary amyloidosis, LIP, and hematologic malignancies often show other radiographic abnormalities, such as nodules and GGO.
- CLD in SS is associated with older age, anti-SSA/Ro autoantibodies, and a diagnosis of secondary SS.
- No progression in terms of size, number of cysts, or lung function decline in most individuals in this cohort after a median 4-year follow-up, irrespective of smoking history.
- SS-associated CLD with mild respiratory symptoms, and no other radiographic findings, could be managed with close clinical observation including PFTs. SLB and repeat CT imaging may not be needed.

Hamasaki et al. Low homozygous/high heterozygous deletion status by p16 FISH correlates with a better prognostic group than high homozygous deletion status in malignant pleural mesothelioma. Lung Cancer 2016 Sept.; 99:155-161

Purpose: To study the significance of heterozygous deletion of p16 in malignant pleural mesothelioma (MPM) in terms MPM diagnosis and prognosis.

Results:



- MPMs **without** homozygous deletions of p16 (5 patients) showed significant better prognosis than those **with** positive homozygous deletion of p16 (24 patients).
- Within p16 homozygous-deletion positive MPMs (with poorer prognosis), the low homozygous-deletion/high heterozygous-deletion pattern may belong to a better prognostic subgroup than other MPMs with high homozygous-deletion. However, large cohort study is needed to confirm this conclusion.

Nakamura et al. Epidermal growth factor receptor mutations in adenocarcinoma in situ and minimally invasive adenocarcinoma detected using mutation-specific monoclonal antibodies. Lung Cancer 2016 Sept.;99:143-147

Purpose: To study EGFR mutation rates in adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) using both DNA analysis and mutation-specific immunohistochemistry.

Results:
- DNA assay and mutation-specific immunohistochemistry provided similar EGFR mutation rates in AIS (27% vs 23%) and MIA (43% each).
- Mutation-specific monoclonal antibodies are useful to confirm and support DNA assay results in detecting EGFR mutations.
- Not sure about the significance of this study, since EGFR mutation rates in early adenocarcinoma have already been reported by various groups with a broad range of mutation rate (17% to 86% in AIS; 17% to 83% in MIA). Any need to know the EGFR mutation status for early-stage adenocarcinoma (AIS and MIA), which is curable by complete resection?

Katsuya et al. Expression of programmed death 1 (PD-1) and its ligand (PD-L1) in thymic epithelial tumors: Impact on treatment efficacy and alteration in expression after chemotherapy. Lung Cancer 2016 Sept.;99:4-10

Purpose: To study the frequency of PD-1/PD-L1 expression in thymoma and thymic carcinoma before and after chemotherapy.

Results:
- In this cohort study (12 thymoma and 18 thymic carcinoma), 67% thymoma and 41% thymic carcinoma were positive for PD-L1 expression for specimen obtained before chemotherapy, which is substantially higher than PD-L1 expression in other tumors (15%-22% in non-small cell lung cancer, 0% in small cell lung cancer, and 20% in malignant pleural mesothelioma)
- In this cohort study, there are 6 cases that had specimens obtained before and after chemotherapy and showed that tumor expression of PD-L1 and the tumor infiltrating immune cell expression of PD-1 were all increased after chemotherapy. However, the caveat for this conclusion is that the specimen type was different before and after chemotherapy (before chemo: biopsy specimen; after chemo: resection specimen) and the PD-L1 positivity in resection specimens was higher than that for the biopsy specimen regardless of the status of chemotherapy.

Song et al. Altered expression of programmed death-ligand 1 after neo-adjuvant chemotherapy in patients with lung squamous cell carcinoma. Lung Cancer 2016 Sept.;99:166-171

Purpose: To study the impact of neoadjuvant chemotherapy on PD-L1 expression and its prognostic significance in lung squamous cell carcinoma (SCC).

Background:
- Among EGFR-mutant patients with paired, pre- and post-TKI biopsies, the expression level of PD-L1 rose after EGFR-TKI dosing. However, it declined after ALK-inhibitor treatment. Despite reports of altered

expression of PD-L1 in targeted therapy patients, no study has ever discussed the results of PD-L1 expression before and after chemotherapy in SCC patients.

Results:
- 11 out of 76 SCC patients showed inconsistent PD-L1 expression before and after chemotherapy, in which 9 patients switched from negative to positive for PD-L1 expression while 2 patients showed the reverse. Therefore, combination of PD-1/PD-L1 blockade after chemotherapy may be a promising therapeutic strategy if this finding could be further confirmed. The specimen nature (biopsy vs resection) before and after chemotherapy is not specified in the article.
- The inconstancy of PD-L1 expression before and after chemotherapy indicated that PD-L1 expression should be monitored dynamically.
- Postoperative positive status of PD-L1 was a better predicator for survival than PD-L1 status pre-neoadjuvant chemotherapy. However, for a limited sample size, this conclusion must be interpreted with caution.
- Limitations of this study: small sample size; the duration and regimens of neoadjuvant chemotherapy were variable among patients.

Kadota K, et al. Nuclear grade based on transbronchial cytology is an independent prognostic factor in patients with advanced, unresectable non-small cell lung cancer. Cancer Cytopathol. 2016 Sep;124(9):630-40.

Study correlating nuclear grade (as assessed by nuclear diameter using image analysis software) on cytology samples in unresectable NSCLC with prognosis. A "nuclear major diameter" of > 15 micrometers, or > 5 lymphocytes, was found to be an independent prognostic factor of worse overall survival.

Mancuso G, et al. Prognostic impact of a 3-MicroRNA signature in cytological samples of small cell lung cancer. Cancer Cytopathol. 2016 Sep;124(9):621-9

Cytology-based study correlating expression levels of 3 specific micro-RNAs with overall survival in small cell lung carcinoma. Patients with a low expression level of the 3-MicroRNA panel had a better OS in univariate and multivariate analyses.

Wick, MR. Mediastinal pathology and the contributions of Dr. Juan Rosai. Seminars In Diagnostic Pathology 2016 Sept.;33:319-332

Review article of Dr. Rosai's contribution on mediastinal pathology, including thymic epithelial lesions, mediastinal neuroendocrine tumors, mediastinal lymphoma and other hematopoietic lesions, thymolipoma, thymoliposarcoma, mediastinalsolitary fibrous tumor, intrathymic Langerhans cell histiocytosis, mediastinal germ cell neoplasms, and multi-locular thymic cyst.

Shien et al. Predictive biomarkers of response to PD-1/PD-L1 immune checkpoint inhibitors in non–small cell lung cancer. Lung Cancer 2016 Sept.;99:79-87

Review article of response to PD-1 pathway immune checkpoint inhibitors in patients with non-small cell lung cancer, mainly focusing on results of clinical trials.

Spira A, Halmos B, Powell CA. Update in Lung Cancer 2015. Am J Respir Crit Care Med. 2016 Sep 15;194(6):661-71.

Review, mainly targeted for a clinician audience with updates and recommendations on lung cancer epidemiology, screening, pulmonary nodule evaluation, lung cancer genomics and molecular biomarkers, and management guidelines of both early and advanced stage NSCLC.

Kim J, Jang SJ, Choi CM, et al. Correlation of Histologic Subtypes and Molecular Alterations in Pulmonary Adenocarcinoma: Therapeutic and Prognostic Implications. Adv Anat Pathol. 2016 Sep;23(5):330-8

An overview of what is known in the literature regarding correlation between histologic subtypes of adenocarcinoma with certain molecular alterations (for mutations: EGFR, KRAS, P53, HER2, BRAF) (for gene rearrangements: ALK, ROS1, RET, NRG1)

Piña-Oviedo S1, Moran CA. Primary Mediastinal Classical Hodgkin Lymphoma. Adv Anat Pathol. 2016 Sep;23(5):285-309.

Excellent and exhaustive review with great discussion on differential diagnosis.

Escudero et al. Expression of developing neural transcription factors in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Virchow Archiv 2016 Sept.;469:357-363

Case Report of 3 cases of DIPNECH and investigation of the expression of three developing neural transcription factors (DNTFs: TTF1, ASCL1, and POU3F2).

Warren et al. Ten Years of Chronic Cough in a 64-Year-Old Man With Multiple Pulmonary Nodules. Chest 2016 Sept.;150:e81-e85

Case Report: A 64-year-old man with a history of prostate cancer; CT chest showed a dominant lung nodule (1.8 cm) and multiple bilateral 2- to 7- mm pulmonary nodules; Diagnosis: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) associated with typical carcinoid tumor

Cherian et al. A 34-Year-Old Pregnant Woman With Cough, Chest Pain, and a Left Upper Lobe Mass. Chest 2016 Sept.;150:e81-e85

Case Report: A 34-year-old woman with a large LUL mass (8.2 cm), which was diagnosis as pulmonary blastoma.

Mason et al. 'Inflammatory myofibroblastic tumour'-like dedifferentiation of anaplastic lymphoma kinase-rearranged lung adenocarcinoma. Histopathology 2016 Sept.;69:510-515

Case Report of a 30-year-old woman with an ALK-rearranged poorly differentiated lung adenocarcinoma with a predominant sarcomatoid component that was morphologically indistinguishable from IMT.

Owen et al. A rare intravascular tumour diagnosed by endobronchial ultrasound. Thorax 2016 Sept.;71:869-870

Case Report of a 24-year-old woman with a large mass in left main pulmonary artery, which was diagnosed as inflammatory myofibroblastic tumor.