

Pulmonary Pathology Journal Club

(March 2020 Articles)

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Articles for Discussion

1. Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis.

Allen RJ et al. Am J Respir Crit Care Med. 2020 Mar 1;201(5):564-574

Purpose: To improve our understanding of factors that increase IPF susceptibility by identifying previously unreported genetic associations.

Methods: The group performed genome-wide analyses across three independent studies and meta-analyzed these results to generate the largest genome-wide association study of IPF to date (2,668 IPF cases and 8,591 controls). They performed replication in two independent studies (1,456 IPF cases and 11,874 controls) and functional analyses (including statistical fine-mapping, investigations into gene expression, and testing for enrichment of IPF susceptibility signals in regulatory regions) to determine putatively causal genes. Polygenic risk scores were used to assess the collective effect of variants not reported as associated with IPF.

Results: We identified and replicated three new genome-wide significant ($P, 5.31 \times 10^{-28}$) signals of association with IPF susceptibility (associated with altered gene expression of KIF15, MAD1L1, and DEPTOR) which support recent research showing mTOR signaling promotes lung fibrogenesis and also implicates spindle-assembly genes in the development of IPF. They also confirmed associations at 11 previously reported loci. Polygenic risk score analyses showed that the combined effect of many thousands of as yet unreported IPF susceptibility variants contribute to IPF susceptibility.

Take Home Messages: This is a nice study looking at genome-wide associated studies; however, more work is needed to determine the biological significance of the associated identified in the disease pathogenesis.

Decreased DEPTOR expression associated with increased susceptibility to IPF supports recent studies demonstrating the importance of mTOR signaling in lung fibrosis.

New signals of association implicating KIF15 and MAD1L1 suggest a possible role of mitotic spindle-assembly genes in IPF susceptibility.

2. Malignant Diffuse Mesothelioma in Women: A Study of 354 Cases.

Pavliko EN, Liu B et al. Am J Surg Pathol. 2020 Mar;44(3):293-304.

Purpose: To evaluate diffuse mesothelioma cases in women including a detailed pathologic examination, and detailed information regarding tumor location, survival, and exposures.

Methods: The database of a single institution was searched for cases in which the gross distribution of tumor, histomorphology, and Immunohistochemical profile was diagnostic of MM. There were 2858 cases of histologically confirmed MM, pleural, and peritoneal, and 354 of those (12%) occurred in women. Cases of well differentiated papillary mesothelioma and localized mesothelioma were excluded. Data collected included diagnosis, information regarding tumor location and morphologic variant, tumor immunohistochemical profile, exposure history, presence of asbestosis and/or pleural plaques, smoking history, and survival from date of diagnosis. Fiber analysis was performed on 67 of 374 cases.

Result Highlights

Demographics

- Statistically different difference in age at time of diagnosis for pleural tumors (median age 67) and peritoneal tumors (median age 52); MM in younger women is more often seen in the peritoneum.

Histology and Immunohistochemistry

- % of epithelioid pleural mesotheliomas in women is higher (72%) than for the entire series (56%)
- % of epithelioid peritoneal mesotheliomas in women (82%) is similar to the entire series (82%)

Survival

- Patients with epithelioid mesothelioma lived significantly longer than those with biphasic or sarcomatoid mesothelioma
- No significant survival difference between biphasic and sarcomatoid mesothelioma
- No difference for epithelioid tumors if exposure was due to household exposure or occupational.
- For non-epithelioid tumors occupational exposures had a worse survival probability as compared to household exposures only.

Occupation/Exposure History

- 70% of cases with household exposures only

Objective markers of asbestos exposure (Asbestosis, parietal pleural plaques, fiber analysis)

- 50% of cases with data (96 cases) had parietal pleural plaques; consistent with prior data in women, but much lower than seen in men

- Tremolite/actinolite/anthophyllite (TAA) were the most common fiber type detected (82%) with tremolite predominating, and amosite and crocidolite (AC) were present in slightly less than half of all cases (48%), with amosite predominating. Chrysotile was detected in 9% of cases and was never the lone fiber type
- Asbestosis present in small number of cases (5%)

Take Home Messages

- Malignant mesothelioma is much less common in women than men and over half of cases are attributable to household exposures.
- Epithelioid mesotheliomas in women have a better survival rate as compared to sarcomatoid and biphasic mesotheliomas.

3. Morphomolecular motifs of pulmonary neoangiogenesis in interstitial lung diseases.

Ackermann M, Stark H et al. Eur Respir J. 2020 Mar 12;55(3).

Purpose: Examine histopathology, microvascular anatomy and gene expression in three main histopathological subtypes of interstitial lung disease (UIP/IPF; NSIP/iNSIP; and AFE/RAS, iPPFE). This is a comprehensive analysis with state-of-the-art technology focusing on remodeling-associated angiogenesis.

Methods: The group performed comprehensive and compartment-specific analysis of 24 human lung explants with usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP) and alveolar fibroelastosis (AFE) using histopathology, microvascular corrosion casting, micro-computed tomography based volumetry and gene expression analysis using Nanostring as well as immunohistochemistry to assess remodelling associated angiogenesis.

Results:

- UIP pattern lungs showed a higher density of upstream vascularity and lower density in perifocal blood vessels
- NSIP and AFE lungs revealed densely packed alveolar septal blood vessels
- Vascular remodeling in NSIP and AFE is characterized by a prominent intussusceptive neoangiogenesis
- Vascular remodeling in UIP showed an increase in sprouting of new vessels into the fibrotic areas.
- Insight into angiogenesis-related gene expression:
 - 16 genes are significantly upregulated in AFE lungs, four genes are differentially expressed in UIP lungs, and one gene in NSIP lungs
 - IGF1 is significantly upregulated as a common denominator of AFE and UIP
 - MEG3 is significantly expressed in UIP and NSIP.
 - THY1 is highly expressed in NSIP and AFE

Take Home Messages: Excellent paper contributing to the understanding of the pathogenesis of fibrosing pulmonary disease. There are marked differences in the vascular alterations in UIP pattern as compared with NSIP and AFE lungs. UIP pattern cases showed a higher density of upstream vascularity and lower density in perifocal blood vessels and sprouting angiogenesis as compared with NSIP and AFE lungs show showed densely packed alveolar septal blood vessels and prominent intussusceptive neoangiogenesis. The higher frequency of intussusceptive angiogenesis and THY1 upregulation are observed in NSIP and AFE lungs suggests that THY1 might be one of the crucial factors to attract circulating endothelial progenitor cells.

4. Factors associated with nodal metastasis in 2-centimeter or less non-small cell lung cancer.

Pani E, Kennedy G et al. J Thorac Cardiovasc Surg. 2020 Mar;159(3):1088-1096.

Purpose: To evaluate if patients with NSCLC \leq to 2.0 cm can be safely spared lymphadenectomy and the associated morbidity.

Methods: Retrospective study of patients treated for NSCLC \leq 2.0 cm at a single institution from 2005 to 2017 (555 patients, 12.3% with positive lymph nodes). The group examined patient demographics and tumor variables for associations with LN metastases via univariable and multivariable analyses.

Results:

- Tumors \leq 1 cm were less likely to have LN metastases than 1.1- to 2-cm tumors (6.8% vs 13.3%); however no statistically significant difference.
- Histologic type was not associated with LN status.
 - In an adenocarcinoma subgroup analysis, micropapillary predominant tumors were more likely to have LN metastases as compared to lepidic.
- All invasive mucinous adenocarcinomas and minimally invasive adenocarcinomas were N0.
- History of previous malignancy associated with lower chance of positive lymph nodes.
- Increased BMI associated with higher chance of positive lymph nodes.

Take Home Messages: Largest study to date examining variables associated with LN status in patients with small \leq 2.0 NSCLC tumors. While some subtypes of small adenocarcinomas may not need a LN evaluation, but this information is rarely available pre- or intraoperatively. Thus, LN evaluation is recommended for all patients with NSCLC.

Articles for Notation

Neoplastic

1. Heterogeneity of PD-L1 Expression in Lung Mixed Adenocarcinomas and Adenosquamous Carcinomas

Zito Marino F, Rossi G et al. Am J Surg Pathol. 2020 Mar;44(3):378-386

Summary: The group analyzed the expression of PD-L1 in different intratumor subtypes and/or growth patterns in a series of mixed adenocarcinomas (73 cases, varying histologic subtypes) and adenosquamous lung carcinomas (6 cases).

Take home message: PDL1 expression is quite heterogeneous in mixed adenocarcinomas (more frequently heterogeneous in micropapillary and solid patterns) and adenosquamous carcinomas (expression more frequent in the squamous cell component), partly contributing to explaining the discrepant results between biopsy and surgical resections and discordant clinical effectiveness in regard to PD-L1-positive or negative ADC diagnosed on cytology/small biopsy. The series is limited by the relatively small number of adenosquamous carcinomas (only 6).

Small biopsies may not be representative of PD-L1 expression in a particular tumor.

2. Adequacy of Cytologic Samples by Ultrasound-Guided Percutaneous Transthoracic Fine-Needle Aspiration Cytology of Peripheral Pulmonary Nodules for Morphologic Diagnosis and Molecular Evaluations: Comparison With Computed Tomography-Guided Percutaneous Transthoracic Fine-Needle Aspiration Cytology.

Cozzolino I, Ronchi A et al. Arch Pathol Lab Med. 2020 Mar;144(3):361-369.

Summary: The authors compared ultrasounds guided fine needle aspiration procedures to computed tomography guided procedures in select patients (peripheral, subpleura, and paravertebral pulmonary nodules) and found that the ultrasound guided procedures had similar adequacy results without significant differences in terms of diagnostic rate, number of passes, and cellularity. The time of the procedure was shorter for ultrasound guided procedures (13.1 minutes on average compared to 23.6 minutes) as well as less expensive and safer.

Take home message: For selected pulmonary nodules (peripheral, subpleural, and paravertebral) ultrasound guided procedures are potentially quicker, safer, and less expensive as compared with computed tomography guided procedures.

3. Real-world use and survival outcomes of immune checkpoint inhibitors in older adults with non-small cell lung cancer.

Youn B, Trikalinos NA et al. *Cancer*. 2020 Mar 1;126(5):978-985.

Summary: The group used the Surveillance, Epidemiology, and End Results (SEER)–Medicare linked database to determine the characteristics and prognosis of older adults with NSCLC who were treated with immune checkpoint inhibitors in routine oncology practice as this cohort was excluded from the original trials looking of immune checkpoint inhibitors.

Take home message: Many older adults with NSCLC who initiated immune checkpoint inhibitors had multiple comorbidities, a history of autoimmune disease, or poor performance status. Factors associated with poor prognosis among patients with advanced NSCLC were also associated with worse survival in older adults treated with immune checkpoint inhibitors.

4. The IASLC Lung Cancer Staging Project: Analysis of Resection Margin Status and Proposals for Residual Tumor Descriptors for Non-Small Cell Lung Cancer.

Edwards JG, Chansky K et al. *J Thorac Oncol*. 2020 Mar;15(3):344-359

Summary: The group analyzed data collected by the IASLC and used to inform the current eighth edition of the TNM to seek to establish the validity of the proposed definition of resection margin status (R0, R1, R2 and R (un) – uncertain). R(un), with a resection defined as uncertain when the resection margins have been proved to be free of disease microscopically but one of the following circumstances exists: (1) the intraoperative lymph node evaluation has been less rigorous than SND or LSND, (2) the highest mediastinal node removed is positive, (3) the bronchial resection margin (BRM) shows carcinoma in situ (CIS), and (4) the pleural lavage cytologic (PLC) examination result is positive (R1(cyb)).

Take home message: R descriptors have prognostic relevance, with R(un) survival stratifying between R0 and R1. Therefore, a detailed evaluation of R factor is of particular importance in the design and analyses of clinical trials of adjuvant therapies.

5. Beyond Margin Status: Population-Based Validation of the Proposed International Association for the Study of Lung Cancer Residual Tumor Classification Recategorization.

Osarogiagbon RU, Faris NR et al. *J Thorac Oncol*. 2020 Mar;15(3):371-382.

Summary: The IASLC proposal to recategorize the residual tumor (R) classification for resected NSCLC requires validation. The study used a 2009-2019 population-based multi institutional NSCLC resection cohort from the United States to classify resections using the proposed criteria (see previous summary).

Take home message: The proposed R classification recategorization variables were mostly prognostic, except the highest mediastinal nodal station involvement. Further categorization of R-uncertainty by severity of nodal quality deficit should be considered.

6. Cytology for PD-L1 testing: A systematic review.

Gosney JR, Boothman AM et al. Lung Cancer. 2020 Mar;141:101-106.

Summary: This systematic review evaluated the success rate, concordance, and clinical utility of using cytology specimens to assess tumor PD-L1 expression levels compared with histology specimens from patients with advanced NSCLC. In 709 specimens, across seven publications, the proportion of cytology specimens evaluable for PD-L1 testing was 92.0 %. The analyses suggest that using cytology specimens to assess PD-L1 expression is feasible, with good levels of concordance between cytology and histology specimens using PD-L1 tumor cell expression cutoffs of ≥ 1 % and ≥ 50 %.

Take home message: Cytology samples can be used to assess PD-L1 expression in patients with NSCLC. This is an interesting read taken together with article #1 which addresses heterogeneity in PD-L1 expression.

7. Micropapillary pattern is associated with the development of brain metastases and the reduction of survival time in EGFR-mutation lung adenocarcinoma patients with surgery.

Li C, Shen Y et al. Lung Cancer. 2020 Mar;141:72-77

Summary: This is a retrospective study to evaluate the role of micropapillary pattern in patients with EGFR-mutated NSCLC patients with brain metastases. The study looked at 332 EGFR-mutant lung adenocarcinoma cases with complete resection and patients were classified based on the presence/absence of micropapillary pattern and presence/absence of brain metastases. Intracranial disease-free survival, systemic disease-free survival and overall survival were evaluated.

Take home message: Micropapillary pattern was related to the earlier recurrence and shortened survival time. In addition, micropapillary pattern was an independent poor prognostic factor for the increase of brain metastases rate and the shortened time of brain metastases development after surgery.

8. Comparison of continuous measures across diagnostic PD-L1 assays in non-small cell lung cancer using automated image analysis.

Widmaier M, Wiestler T et al. *Mod Pathol*. 2020 Mar;33(3):380-390.

Summary: The group developed a computer-aided automated image analysis with customized PD-L1 scoring algorithm that was evaluated via correlation with manual pathologist scores and used to determine comparability across PD-L1 immunohistochemistry assays. 471 samples for scored. Image analysis and pathologist scores were highly concordant, with F1 scores (a statistical measure of precision and recall) ranging from 0.8 to 0.9 across varying matched PD-L1 cutoffs.

Take home message: A novel automated image analysis scoring algorithm was developed that was highly correlated with pathologist scores. The algorithm permitted quantitative comparison of existing PD-L1 diagnostic assays, confirming previous findings that indicate a high concordance between the Ventana SP263 and Dako 22C3 and 28-8 PD-L1 immunohistochemistry assays.

9. Genomic Underpinnings of Tumor Behavior in In Situ and Early Lung Adenocarcinoma.

Qian J, Zhao S et al. *Am J Respir Crit Care Med*. 2020 Mar 15;201(6):697-706

Summary: In an effort to understand the molecular basis of early adenocarcinoma progression this group extracted DNA from 21 ADCs in situ (AISs), 27 minimally invasive ADCs (MIAs), and 54 fully invasive ADCs and subjected it to deep next-generation sequencing and tested against a custom panel of 347 cancer genes. We found that deleterious mutation burden was significantly greater in invasive ADC, whereas more copy number loss was observed in AIS and MIA. Intratumor heterogeneity establishes early, as in AIS. Twenty-one significantly mutated genes were shared among the groups. Mutation signature profiling did not vary significantly, although the APOBEC signature was associated with ADC and poor survival. Subclonal KRAS mutations and a gene signature consisting of PIK3CG, ATM, EPPK1, EP300, or KMT2C mutations were also associated with poor survival. Mutations of KRAS, TP53, and NF1 were found to increase in frequency from AIS and MIA to ADC. A cancer progression model revealed selective early and late drivers.

Take home message: This study revealed differences in deleterious tumor mutation burden, copy number alterations, gene signatures, and driver gene clonality that include association with clinical outcome. Once validated in new cohorts, these results may have an impact on clinical practice. Interestingly, most genomic alterations found in ADC are already present in AIS.

Non-neoplastic

1. Etiology, Risk Factors, and Biomarkers in Systemic Sclerosis with Interstitial Lung Disease.

Khanna D, Tashkin DP et al. Am J Respir Crit Care Med. 2020 Mar 15;201(6):650-660.

Summary: The article reviews systemic sclerosis associated ILD with a focus on pathogenesis, risk factors, and patient characteristics associated with the condition, with a view to identifying patients most at risk for the disease and its progression. They also highlight similarities and differences between SSc-ILD and idiopathic pulmonary fibrosis.

Take home message: Risk factors for progressive SSc-ILD include older age, male sex, degree of lung involvement on baseline high-resolution computed tomography imaging, reduced DLCO, and reduced FVC. It does not share the same genetic risk factors as IPF. The presence of anti-Scl-70 antibodies and absence of anti-centromere antibodies indicate increased likelihood of progressive ILD. Elevated levels of serum Krebs von den Lungen-6 and C-reactive protein are both associated with SSc-ILD severity and predict progression.

2. An Organ System-Based Approach to Differential Diagnosis of Amyloid Type in Surgical Pathology.

Giannini G, Nast CC. Arch Pathol Lab Med. 2020 Mar;144(3):379-387

Summary: The goal was to provide a guide to likely amyloid type based on the organ involved. The lung is one of the more common sites of amyloid deposition.

Take home message: AL, ATTR, AA are common amyloid types in the lung with ALECT2, Ab2M representing rare types.

3. From pests to tests: training rats to diagnose tuberculosis.

Fiebig L, Beyene N et al. Eur Respir J. 2020 Mar 20;55(3).

Summary: Chromatographic techniques allow characterization of the organic compounds causing odors. Analytical chemistry resulted in the discovery of TB-specific volatile organic compound (VOC) patterns. For a rat to reliably recognize an odor, it takes behavioral training involving positive reinforcement and discrimination learning. It also requires roughly 3000 samples for the rat to form a concept of the TB odor across its various expressions (i.e. samples that differ in bacterial load and that have been collected

from patients of all ages and sexes) while preventing the cunning rat from using extraneous cues that might otherwise covary with positive samples (such as comorbid disease or how the samples are handled at the clinic) and circumvent detection of new TB cases.

Take home message: An interesting article adding to the growing body of knowledge surrounding the ability of animals to detect disease- rats can smell tuberculosis!

4. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Final Report.

Layden JE, Ghinai I et al. N Engl J Med. 2020 Mar 5;382(10):903-916

Summary: This is the final report based on the preliminary report released 9/6/2019. The group collected data on 98 patients who reported use of e-cigarette devices and related products in the 90 days before symptom onset and had pulmonary infiltrates on imaging and whose illnesses were not attributed to other causes. A total of 95% of the patients were hospitalized, 26% underwent intubation and mechanical ventilation, and two deaths were reported. A total of 89% of the patients reported having used tetrahydrocannabinol products in e-cigarette devices, although a wide variety of products and devices was reported.

Take home message: Although the definitive substance or substances contributing to injury have not been definitively determined, this initial cluster of illnesses represents an emerging clinical syndrome or syndromes. This data supports CDC recommendations that person no use THC-containing e-cigarette, or vaping, products, particularly from informal sources. Although vitamin E acetate appears to e associated with EVALI there are many different substances/product sources that are still being investigated. The best recommendation is to refrain from all e-cigarette/vaping products.

5. An Animal Model of Inhaled Vitamin E Acetate and EVALI-like Lung Injury.

Bhat TA, Kalathil SG et al. N Engl J Med. 2020 Mar 19;382(12):1175-1177.

Summary: The group exposed 30 mice to aerosols generated from vitamin E acetate, a mixture of propylene glycol and vegetable glycerin(PG-VG), or air (controls). The levels of vitamin E acetate measured in mouse BAL fluid suggest that this chemical was effectively delivered to the lungs of the exposed mice and match the findings of vitamin E acetate in BAL fluid from patients with EVALI. Cells isolated from the BAL fluid of vitamin E acetate-exposed mice contained numerous lipid-laden macrophages

Take home message: This is a mouse model showing accumulation of foamy macrophages after exposure to vitamin E acetate. Interestingly, they did not appear to induce significant acute lung injury implying that it not vitamin E acetate alone that is inducing the lung injury seen in humans.

6. Radiologic, Pathologic, Clinical, and Physiologic Findings of Electronic Cigarette or Vaping Product Use-associated Lung Injury (EVALI): Evolving Knowledge and Remaining Questions.

Kligerman S , Raptis C et al. Radiology. 2020 Mar;294(3):491-505.

Summary: Chest CT findings in EVALI most commonly show a pattern of acute lung injury on the spectrum of organizing pneumonia and diffuse alveolar damage. In this review, the authors summarize the current state of the art for the imaging and pathologic findings of this disorder and outline a few of the major questions that remain to be answered. EVALI, characterized primarily by acute lung injury consisting of histopathologic and imaging patterns of organizing pneumonia, diffuse alveolar damage, or both, has emerged as a serious and sometimes fatal complication of vaping. Both nicotine and tetrahydrocannabinol products have been associated with EVALI, and although vitamin E acetate has been found in bronchoalveolar lavage fluid in many patients with EVALI, it is unclear whether this represents the cause of injury or merely a marker of exposure.

Take home message: Given the almost infinite combinations of devices, unknown or loosely regulated compounds in vaping liquids, and alterations to delivery systems, pinpointing the exact cause(s) of EVALI has been challenging, although vitamin E acetate has been strongly implicated. Vaping has potential long term effects including nicotine and THC addition, cardiovascular disease, and chronic pulmonary injury. While the radiologic and pathologic findings are not specific, in the appropriate clinical context, EVALI can be suggested.

Case Reports and Letters

1. Early Aspergillosis in Cystic Fibrosis and Air Trapping: Guilt by Association?

Nichols DP, Moss RB. Am J Respir Crit Care Med. 2020 Mar 15;201(6):644-645

Take home message: The group provides substantial further evidence for relatively high prevalence and potential pathogenicity of early lower airways *Aspergillus* infection without allergic sensitization.

2. On the Origin of Lung Cancers.

Pennycuik A, Janes SM. Am J Respir Crit Care Med. 2020 Mar 15;201(6):646-647

Take home message: A nice editorial on the previously reviewed article (Qian et al).

3. Microbial Toxins in Nicotine Vaping Liquids.

Lee MS, Christiani DC. Am J Respir Crit Care Med. 2020 Mar 15;201(6):741-743

Take home message: JUUL pod products were contaminated with microbial toxins, and the tobacco and menthol flavors were substantially much more contaminated than other flavors.

4. Vaping, lung damage, and cytopathology: A new twist in the medical mystery: Accumulating evidence has clarified the role of cytopathology in the diagnosis of vaping-associated lung injuries and implicated vitamin E acetate as a likely culprit.

Nelson B. Cancer Cytopathol. 2020 Mar;128(3):153-154

Take home message: A nice article reviewing the confusion surrounding oil red O, lipid pneumonia, vitamin E acetate and the role of cytology in the diagnosis of EVALI. The author incorrectly uses the term 'cryptogenic' organizing pneumonia however.

5. Fighting the teen vaping epidemic: With rates of adolescent vaping on the rise, experts caution that new federal rules targeting e-cigarettes may not be strong enough.

Printz C. Cancer. 2020 Mar 15;126(6):1147-1148.

Take home message: Teen e-cigarette use more than doubled between 2017 and 2019, with 25% of 12th graders, 20% of 10th graders, and 9% of 8th graders reporting nicotine vaping within the past month. This is an important public health concern and banning certain flavored vaping products is not sufficient. It is a complex issue to allow vaping devices to be used by adults trying to quit smoking traditional cigarettes but not allow teens to use them.

6. Acute Respiratory Failure Associated With Vaping.

Fryman C, Lou B et al. Chest. 2020 Mar;157(3):e63-e68

Take home message: This case series highlights common clinical findings as well as the varied radiographic and histopathologic features of acute respiratory failure associated with vaping predominantly marijuana-based products. This does not add anything significantly new to the literature on the topic, despite its claim.

7. A 46-Year-Old Woman With a Mediastinal Mass.

Majumdar U, Farver CF, Mehta AC. Chest. 2020 Mar;157(3):e69-e73.

Take home message: A case report of a paraganglioma in the mediastinum with a good overview of mediastinal masses.

8. A 78-Year-Old Man With Recurrent Hemoptysis and Persistent Pulmonary Nodule.

Chew SY, Tan CS et al. Chest. 2020 Mar;157(3):e79-e84.

Take home message: A case of Pulmonary actinomycosis, which can often be mistaken for malignancy on imaging. Risk factors for developing pulmonary actinomycosis include poor dental hygiene, alcohol abuse, diabetes mellitus, immunocompromised host status, and underlying chronic lung diseases such as COPD and bronchiectasis.

9. An 80-Year-Old Woman With a Solitary Pulmonary Nodule.

Gibier JB, Colombat M et al. Chest. 2020 Mar;157(3):e85-e89.

Take home message: The authors present a rare case of a crystal-storing histiocytosis (CSH) in the lung, a rare lesion characterized by intra-lysosomal accumulation of immunoglobulin, forming crystals within the cytoplasm of histiocytes and plasma cells. The characteristic histology consists of sheets of epithelioid CD68+ histiocytes containing eosinophilic cytoplasmic inclusions.

10. Small airways and early origins of COPD: pathobiological and epidemiological considerations.

Polverino F, Soriano JB. Eur Respir J. 2020 Mar 5;55(3).

Take home message: Small airway remodeling may also be a primary event in asthma pathogenesis if it is the result of disturbed lung development. The small airway wall structure can be altered very early in life, and can indeed precede airway wall inflammation and thus may present as a primary event in asthmatic lungs.

11. Parietal Pleura-Based Malignant Perivascular Epithelioid Cell Neoplasm Protruding Into Serous Cavity: A Hitherto Unrecognized Occurrence.

Pelosi G, Sabella G et al. J Thorac Oncol. 2020 Mar;15(3):462-466.

Take home message: A challenging case of a malignant perivascular epithelioid cell neoplasm (PEComa) of the thoracic parietal pleura.

12. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients.

Zou L, Ruan F et al. *N Engl J Med.* 2020 Mar 19;382(12):1177-1179.

Take home message: Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat. The analysis suggests that the viral nucleic acid shedding pattern of patients infected with SARS-CoV-2 resembles that of patients with influenza and appears different from that seen in patients infected with SARS-CoV. The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients.

13. Malignant mesothelioma in situ diagnosed by methylthioadenosine phosphorylase loss and homozygous deletion of CDKN2A: a case report.

Minami K, Jimbo N et al. *Virchows Arch.* 2020 Mar;476(3):469-473

Take home message: A 73 year old man with a history of asbestos exposure and massive unilateral pleural effusion was found on biopsy to have a single layer of atypical mesothelial cells without invasive lesions . These mesothelial cells exhibited a loss of methylthioadenosine phosphorylase (MTAP) by immunohistochemistry and homozygous deletion of CDKN2A (p16) by FISH, leading to the diagnosis of MIS. This is an important lesion not to miss.

14. Distal-type bronchiolar adenoma of the lung expressing p16INK4a - morphologic, immunohistochemical, ultrastructural and genomic analysis - report of a case and review of the literature.

Tachibana M, Saito M et al. *Pathol Int.* 2020 Mar;70(3):179-185

Take home message: The authors report a case of a bronchiolar adenoma (ciliated muconodular papillary tumor) that expressed p16 along with a review of this rare entity.