Pulmonary Journal Club Oct 2023 (Articles from September 2023)

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Articles for Discussion

Page

Articles for Notation – Neoplastic

12 Rudin C. Clinical Benefit From Immunotherapy in Patients With SCLC Is Associated With Tumor Capacity for Antigen Presentation. J Thorac Oncol. 2023 Sep;18(9):1222-1232.

Articles for Notation - Non-Neoplastic

13 Lu L. Clinical and Histopathologic Characteristics of Recurrent Sarcoidosis in Posttransplant Lungs: 25 Years of Experience. Am J Surg Pathol. 2023 Sep 1;47(9):1034-1038.

Letters, Brief Communications, Case Reports

14 Wilkinson Z. All that glitters isn't gold: an unusual case of Pneumocystis jirovecii pneumonia. Histopathology. 2023 Sep;83(3):487-489.

15 Kumagai E. A case of lung carcinoma with a unique biphasic feature: Implications for histogenesis of “fake mucoepidermoid carcinoma” developing in the peripheral lung. Pathol Int. 2023 Sep;73(9):463-468.

15 Richier Q. Pulmonary Aspergilloma. N Engl J Med. 2023 Sep 21;389(12):1132.

16 Ali B. Photographic Negative of Pulmonary Edema” in Chronic Eosinophilic Pneumonia. N Engl J Med. 2023 Sep 28;389(13):1220.

Reviews

17 Johnson S. Pulmonary Hypertension: A Contemporary Review. Am J Respir Crit Care Med. 2023 Sep 1;208(5):528-548.

17 Conroy M. Neoadjuvant immune checkpoint inhibitor therapy in resectable non-small cell lung cancer. Lung Cancer. 2023 Sep:183:107314.

Articles for Discussion

Ohtani-Kim SJ. Efficacy of Preoperative Biopsy in Predicting the Newly Proposed Histologic Grade of Resected Lung Adenocarcinoma. Mod Pathol. 2023 Sep;36(9):100209.

Introduction:

A novel histologic grading system for invasive lung adenocarcinomas (LUAD) has been newly proposed and adopted by the World Health Organization (WHO) classification. The authors aimed to evaluate the concordance of newly established grades between preoperative biopsy and surgically resected LUAD samples. Additionally, factors affecting the concordance rate and its prognostic impact were also analyzed.

Methods:

In this study, surgically resected specimens of 222 patients with invasive LUAD and their preoperative biopsies collected between January 2013 and December 2020 were used. The authors determined the histologic subtypes of preoperative biopsy and surgically resected specimens and classified them separately according to the novel WHO grading system.

Results:

The overall concordance rate of the novel WHO grades between preoperative biopsy and surgically resected samples was 81.5%, which was higher than that of the predominant subtype. When stratified by grades, the concordance rate of grades 1 (well-differentiated, 84.2%) and 3 (poorly differentiated, 89.1%) was found to be superior compared to grade 2 (moderately differentiated, 66.2%).

Discussion:

Overall, the concordance rate was not significantly different from biopsy characteristics, including the number of biopsy samples, biopsy sample size, and tumor area size. On the other hand, the concordance rate of grades 1 and 2 was significantly higher in tumors with smaller invasive diameters, and that of grade 3 was significantly higher in tumors with larger invasive diameters.

Conclusions / Take home point:

Preoperative biopsy specimens can predict the novel WHO grades, especially grades 1 and 3 of surgically resected specimens, more accurately than the former grading system, regardless of preoperative biopsy or clinicopathologic characteristics.

Churg A. Pathologic Criteria for the Diagnosis of Usual Interstitial Pneumonia vs Fibrotic Hypersensitivity Pneumonitis in Transbronchial Cryobiopsies. Mod Pathol. 2023 Sep;36(9):100221.

Introduction:

Transbronchial cryobiopsy (TBCB) is increasingly used for the diagnosis of fibrosing interstitial pneumonias, but there are few detailed descriptions of the pathologic findings in such cases. It has been proposed that a combination of patchy fibrosis and fibroblast foci with an absence of alternative features is diagnostic of usual interstitial pneumonia (UIP; ie, idiopathic pulmonary fibrosis [IPF]) in TBCB.

Methods:

The authors reviewed 121 TBCB in which a diagnosis of fibrotic hypersensitivity pneumonitis (FHP; n = 83) or IPF (n = 38) was made by multidisciplinary discussion and evaluated a range of pathologic features.

Results:

Patchy fibrosis was found in 65 of 83 (78%) biopsies from FHP and 32of 38 (84%) biopsies from UIP/IPF cases. Fibroblast foci were present in 47 of 83 (57%) FHP and 27 of 38 (71%) UIP/IPF cases. Fibroblast foci/patchy fibrosis combined did not favor either diagnosis. Architectural distortion was seen in 54 of 83 (65%) FHP and 32 of 38 (84%) UIP/IPF cases (odds ratio [OR] for FHP, 0.35; P = .036) and honeycombing in 18 of 83 (22%) and 17 of 38 (45%), respectively (OR, 0.37; P = .014). Airspace giant cells/granulomas were present in 13 of 83 (20%) FHP and 1 of 38 (2.6%) UIP/IPF cases (OR for FHP, 6.87; P = .068), and interstitial giant cells/granulomas in 20 of 83 (24%) FHP and 0 of 38 (0%) UIP/IPF (OR, 6.7 x 106; P = .000).

Conclusions:

The authors conclude that patchy fibrosis plus fibroblast foci can be found in TBCB from both FHP and UIP/IPF. The complete absence of architectural distortion/honeycombing favors a diagnosis of FHP, as does the presence of airspace or interstitial giant cells/granulomas, but these measures are insensitive, and many cases of FHP cannot be separated from UIP/IPF on TBCB.

Argyropoulos K. Correlation of Programmed Death-Ligand 1 Expression With Lung Adenocarcinoma Histologic and Molecular Subgroups in Primary and Metastatic Sites. Mod Pathol. 2023 Sep;36(9):100245.

Introduction:

Programmed death-ligand 1 (PD-L1) expression in terms of the tumor proportion score (TPS) is the main predictive biomarker approved for immunotherapy against lung nonsmall cell carcinoma.

Aim:

Although some studies have explored the associations between histology and PD-L1 expression in pulmonary adenocarcinoma, they have been limited in sample size and/or extent of examined histologic variables, which may have resulted in conflicting information.

Methods:

In this observational retrospective study, the authors identified primary and metastatic lung adenocarcinoma cases in the span of 5 years and tabulated the detailed histopathologic features, including pathological stage, tumor growth pattern, tumor grade, lymphovascular and pleural invasion, molecular alterations, and the associated PD-L1 expression for each case. Statistical analyses were performed to detect associations between PD-L1 and these features.

Results:

Among 1658 cases, 643 were primary tumor resections, 751 were primary tumor biopsies, and 264 were metastatic site biopsies or resections. Higher TPS significantly correlated with high-grade growth patterns, grade 3 tumors, higher T and N stage, presence of lymphovascular invasion, and presence of MET and TP53 alterations, whereas lower TPS correlated with lower-grade tumors and presence of EGFR alterations.

Conclusions / Take home point:

There was no difference in PD-L1 expression in matched primary and metastases, although higher TPS was observed in metastatic tumors due to the presence of high-grade patterns in these specimens. TPS showed a strong association with a histologic pattern. Higher-grade tumors had higher TPS, which is also associated with more aggressive histologic features. Tumor grade should be kept in mind when selecting cases and blocks for PD-L1 testing.

Lo Y-C. Subtype of SCLC Is an Intrinsic and Persistent Feature Through Systemic Treatment. JTO Clin Res Rep. 2023 Aug 16;4(9):100561.

Introduction:

SCLC is an aggressive malignancy with poor outcome. Most patients have disease recurrence despite treatments with multiple modalities. Subtyping of SCLC has been proposed recently, and novel agents targeting specific subtypes are actively being investigated. In this study, we evaluated the plasticity of subtypes in paired pre- and post-treatment samples. The aim was to understand possible subtype evolution after chemotherapy resistance that could lead to alternate targeted therapy strategies.

Methods:

A total of 68 samples from 32 patients with sufficient paired specimens were identified from 1998 to 2022. ASCL1, NEUROD1, and POU2F3 immunohistochemistry studies were performed

on all cases, and subtyping by predominant expression was determined. Subtype comparison in each patient was performed, and expression analysis was performed on the basis of subtypes.

Results:

Of 32 cases, 28 (88%) had the same subtype in pre- and first post-treatment specimens. Protein expression level of subtype-specific transcription factor remained stable after chemotherapy. Two of five (40%) NEUROD1-predominant SCLC switched to ASCL1-predominant phenotype after treatment. One case had a pitfall of scoring ASCL1 on specimen with marked crushing artifacts. One case revealed the challenge of proper subtyping for samples with borderline POU2F3 expression.

Conclusions:

Subtype of SCLC generally remains the same after acquiring chemotherapy resistance. Plasticity was observed with rare cases switching from NEUROD1-predominant to ASC1-predominant SCLC. Resubtyping is unnecessary for the consideration of novel subtype-specific targeted agents, except cases with NEUROD1-predominant subtype.

Articles for Notation

Schaefer I. Recurrent Tumor Suppressor Alterations in Primary Pericardial Mesothelioma. Mod Pathol. 2023 Sep;36(9):100237.

Background:

- Primary pericardial mesotheliomas are extremely rare, accounting for <1% of all mesotheliomas, and their molecular genetic features and predisposing factors remain to be determined.

Methods:

- Here, the authors report the clinicopathologic, immunohistochemical, and molecular genetic findings of 3 pericardial mesotheliomas without pleural involvement.
- Three cases diagnosed between 2004 and 2022 were included in the study and analyzed by immunohistochemistry and targeted next-generation sequencing (NGS); corresponding nonneoplastic tissue was sequenced in all cases.

Results:

- Two patients were female and 1 was male, aged between 66 and 75 years. Two patients each had prior asbestos exposure and were smokers.
- Histologic subtypes were epithelioid in 2 cases and biphasic in 1 case.
- Immunohistochemical staining identified expression of cytokeratin AE1/AE3 and calretinin in all cases, D2-40 in 2 cases, and WT1 in 1 case.
- Staining for tumor suppressors revealed loss of p16, MTAP, and Merlin (NF2) expression in 2 cases and loss of BAP1 and p53 in 1 case. Abnormal cytoplasmic BAP1 expression was observed in an additional case.
- Protein expression abnormalities correlated with NGS results, which showed concurrent complete genomic inactivation of CDKN2A/p16, CDKN2B, MTAP, and NF2 in 2 mesotheliomas and of BAP1 and TP53 in 1 mesothelioma each, respectively.
- In addition, 1 patient harbored a pathogenic BRCA1 germline mutation, which resulted in biallelic inactivation in the mesothelioma.
- All mesotheliomas were mismatch repair proficient and showed several chromosomal gains and losses. All patients died from disease.

Conclusions:

- The study demonstrates that pericardial mesotheliomas share common morphologic, immunohistochemical, and molecular genetic features with pleural mesothelioma, including recurrent genomic inactivation of canonical tumor suppressors.
- The study adds new insights into the genetic landscape of primary pericardial mesothelioma and highlights BRCA1 loss as a potential contributing factor in a subset of cases, thereby contributing to refined precision diagnostics for this rare cancer.

Lawson N. Impact of Decalcification, Cold Ischemia, and Deglycosylation on Performance of Programmed Cell Death Ligand-1 Antibodies With Different Binding Epitopes: Comparison of 7 Clones. Mod Pathol. 2023 Sep;36(9):100220.

Background:

- Programmed cell death ligand-1 (PD-L1) expression levels in patients' tumors have demonstrated clinical utility across many cancer types and are used to determine treatment eligibility.
- Several independently developed PD-L1 immunohistochemical (IHC) predictive assays are commercially available and have demonstrated different levels of staining between assays, generating interest in understanding the similarities and differences between assays.
- Previously, the same group identified epitopes in the internal and external domains of PD-L1, bound by antibodies in routine clinical use (SP263, SP142, 22C3, and 28-8).

Aim:

- Variance in performance of assays utilizing these antibodies, observed following exposure to preanalytical factors such as decalcification, cold ischemia, and duration of fixation, encouraged additional investigation of antibody-binding sites, to understand whether binding site structures/conformations contribute to differential PD-L1 IHC assay staining.

Methods:

- The authors proceeded to further investigate the epitopes on PD-L1 bound by these antibodies, alongside the major clones utilized in laboratory-developed tests (E1L3N, QR1, and 73-10).
- Characterization of QR1 and 73-10 clones demonstrated that both bind the PD-L1 C-terminal internal domain, similar to SP263/SP142.

Results:

- The results demonstrate that under suboptimal decalcification or fixation conditions, the performance of internal domain antibodies is less detrimentally affected than that of external domain antibodies 22C3/28-8.
- Furthermore, the authors show that the binding sites of external domain antibodies are susceptible to deglycosylation and conformational structural changes, which directly result in IHC staining reduction or loss.
- The binding sites of internal domain antibodies were unaffected by deglycosylation or conformational structural change.

Take Home Points:

- This study demonstrates that the location and conformation of binding sites, recognized by antibodies employed in PD-L1 diagnostic assays, differ significantly and exhibit differing degrees of robustness.
- These findings should reinforce the need for vigilance when performing clinical testing with different PD-L1 IHC assays, particularly in the control of cold ischemia and the selection of fixation and decalcification conditions.

Chen-Yost H. Characterizing the distribution of alterations in mesothelioma and their correlation to morphology. Am J Clin Pathol. 2023 Sep 1;160(3):238-246.

Background:

- Mesothelioma is a lethal disease that arises from the serosal lining of organ cavities.
- Several recurrent alterations have been observed in pleural and peritoneal -mesotheliomas, including in BAP1, NF2, and CDKN2A.
- Although specific histopathologic parameters have been correlated with prognosis, it is not as well known whether genetic alterations correlate with histologic findings.

Methods:

- The authors reviewed 131 mesotheliomas that had undergone next-generation sequencing (NGS) at our institutions after pathologic diagnosis.
- There were 109 epithelioid mesotheliomas, 18 biphasic mesotheliomas, and 4 sarcomatoid mesotheliomas. All our biphasic and sarcomatoid cases arose in the pleura.
- Of the epithelioid mesotheliomas, 73 were from the pleura and 36 were from the peritoneum. On average, patients were 66 years of age (range, 26-90 years) and predominantly male (92 men, 39 women).

Results:

- The most common alterations identified were in BAP1, CDKN2A, NF2, and TP53.
- Twelve mesotheliomas did not show a pathogenic alteration on NGS.
- For epithelioid mesotheliomas in the pleura, the presence of an alteration in BAP1 correlated with low nuclear grade (P = .04), but no correlation was found in the peritoneum (P = .62).
- Similarly, there was no correlation between the amount of solid architecture in epithelioid mesotheliomas and any alterations in the pleura (P = .55) or peritoneum (P = .13).
- For biphasic mesotheliomas, cases with either no alteration detected or with an alteration in BAP1 were more likely to be epithelioid predominant (>50% of the tumor, P = .0001), and biphasic mesotheliomas with other alterations detected and no alteration in BAP1 were more likely to be sarcomatoid predominant (>50% of the tumor, P = .0001).

Take Home Points:

- This study demonstrates a significant association between morphologic features associated with a better prognosis and an alteration in BAP1.

Elliott D. Clinically Occult Diffuse Pleural Mesothelioma in Patients Presenting With Spontaneous Pneumothorax. Am J Clin Pathol. 2023 Sep 1;160(3):322-330.

Background:

- To report histologic features of unsuspected diffuse pleural mesothelioma (DPM) in surgical specimens for pneumothorax and demonstrate how ancillary markers support a diagnosis of malignancy in this context.

Aim:

- The authors explored whether pneumothorax may be a clinical manifestation of mesothelioma in situ (MIS).

Methods:

- A single-institution database search identified patients who underwent surgical resection for spontaneous pneumothorax (n = 229) and/or were diagnosed with DPM (n = 88) from 2000 to 2020.

Results:

- Spontaneous pneumothorax without clinical, radiologic, or intraoperative suspicion of mesothelioma was the initial presentation in 2 (2.3%) of 88 patients diagnosed with DPM.
- This represented 0.9% (2/229) of all patients undergoing surgical management of pneumothorax but accounted for a larger proportion of older patients (12.5% older than 70 years).
- Immunohistochemistry for BAP-1 and/or MTAP confirmed the diagnosis of DPM in 2 cases.
- Mesothelioma in situ was identified retrospectively by immunohistochemistry in 1 case of spontaneous pneumothorax from a 77-year-old man who developed invasive DPM 25 months later.
- No additional cases of MIS were identified in 19 surgical lung resections for spontaneous pneumothorax.

Take Home Points:

- Histologic examination of bleb resections with ancillary testing for cases with ambiguous features is essential for detection of early DPM.
- It is uncertain whether spontaneous pneumothorax may represent a clinical manifestation of MIS.

Weissferdt A. Basaloid Squamous Cell Carcinomas of the Thymus With Prominent B-Cell Lymphoid Hyperplasia: A Clinicopathologic and Immunohistochemical Study of 10 Cases. Am J Surg Pathol. 2023 Sep 1;47(9):1039-1044.

Methods:

- Ten cases of basaloid squamous cell carcinomas of the thymus are presented.
- The patients are 6 women and 4 men ranging in ages between 51 and 72 years (average: 61.5 y), who presented with nonspecific symptoms of cough, dyspnea, and chest pain with no history of malignancy, myasthenia gravis, or other autoimmune disease.
- Surgical resection of the mediastinal masses via thoracotomy or sternotomy was performed in all patients.

Results:

- Grossly, the tumors varied in size from 2 to 8 cm, were light tan in color, solid and slightly hemorrhagic, and had infiltrative borders.
- Histologically, scanning magnification showed elongated interanastomosing ribbons of tumors cells embedded in a lymphoid stroma containing germinal centers.
- At higher magnification, the tumors cells were round to oval with moderate amounts of lightly eosinophilic cytoplasm, oval nuclei, moderate cellular atypia, and mitotic activity ranging from 3 to 5 mitotic figures per 10 HPFs.
- In 8 cases, the tumor invaded perithymic adipose tissue, in 1 case the tumor infiltrated pericardium, and in 1 case, the tumor involved the pleura.
- Immunohistochemical stains showed positive staining in the epithelial component for pancytokeratin, p63, keratin 5/6, and p40, while CD20 and CD79a characterized the lymphoid component.
- Clinical follow-up was obtained in 7 patients. Two patients died within 24 months and 5 patients remained alive between 12 and 60 months.

Take Home Points:

- The current cases highlight the unusual feature of B-cell lymphoid hyperplasia in these tumors and their potential aggressive behavior.

Wang Y. POU2F3: A Sensitive and Specific Diagnostic Marker for Neuroendocrine-low/negative Small Cell Lung Cancer. Am J Surg Pathol. 2023 Sep 1;47(9):1059-1066.

Background:

- POU2F3 (POU class 2 homeobox 3) is a novel transcription factor used to define the special molecular subtype of small cell lung cancer (SCLC) known as SCLC-P.
- Nevertheless, the sensitivity and specificity of POU2F3 immunohistochemical (IHC) staining have not been fully investigated.

Methods:

- In this study, the authors explored the expression of POU2F3 by IHC in a large cohort of SCLC clinical samples (n=246), other common lung cancer types (n=2207), and various other cancer types (n=194).

Results:

- The results showed that POU2F3 was strongly nuclear stained in 13.41% (33/246) of SCLC cases, with negative or minimal labeling for thyroid transcription factor-1 and neuroendocrine (NE) markers.
- Compared with POU2F3-negative SCLC, SCLC-P harbored fewer TP53 and RB1 mutations. POU2F3 was also expressed in 3.13% (8/256) of squamous cell carcinomas (SCCs) and 20% (2/10) of large cell NE carcinomas (LCNECs), whereas other lung cancer types were negative.
- In addition to lung cancer, POU2F3 was positive in 22.2% (4/18) of thymic tumors.
- All other tumors were POU2F3-negative except for thymic carcinoma, although sparsely distributed weak nuclear staining was observed in lung adenocarcinoma, cervical SCC, and colorectal carcinoma.
- The sensitivity and specificity of POU2F3 in NE-low/negative SCLC were 82.1% and 99.4%, respectively.
- Notably, some rare unique patterns of POU2F3 expression were observed. One case of thymic SCC was characterized by diffuse and uniform cytomembrane staining. One case of esophageal NE tumor was nuclear-positive, while the normal proliferating squamous epithelium was strongly membrane-stained.

Take Home Points:

- This is the largest cohort of clinical samples to confirm that POU2F3 is a highly sensitive and specific diagnostic marker for NE-low/negative SCLC.

Rudin C. Clinical Benefit From Immunotherapy in Patients With SCLC Is Associated With Tumor Capacity for Antigen Presentation. J Thorac Oncol. 2023 Sep;18(9):1222-1232.

Background:

- A small percentage of patients with SCLC experience durable responses to immune checkpoint blockade (ICB).
- Defining determinants of immune response may nominate strategies to broaden the efficacy of immunotherapy in patients with SCLC.
- Prior studies have been limited by small numbers or concomitant chemotherapy administration.

Methods:

- CheckMate 032, a multicenter, open-label, phase 1/2 trial evaluating nivolumab alone or with ipilimumab was the largest study of ICB alone in patients with SCLC.
- The authors performed comprehensive RNA sequencing of 286 pretreatment SCLC tumor samples, assessing outcome on the basis of defined SCLC subtypes (SCLC-A, -N, -P, and -Y), and expression signatures associated with durable benefit, defined as progression-free survival more than or equal to 6 months.
- Potential biomarkers were further explored by immunohistochemistry.

Results:

- None of the subtypes were associated with survival.
- Antigen presentation machinery signature ($p = 0.000032$) and presence of more than or equal to 1% infiltrating CD8+ T cells by immunohistochemistry (hazard ratio = 0.51, 95% confidence interval: 0.27-0.95) both correlated with survival in patients treated with nivolumab.
- Pathway enrichment analysis revealed the association between durable benefit from immunotherapy and antigen processing and presentation.
- Analysis of epigenetic determinants of antigen presentation identified LSD1 gene expression as a correlate of worse survival outcomes for patients treated with either nivolumab or the combination of nivolumab and ipilimumab.

Take Home Points:

- Tumor antigen processing and presentation is a key correlate of ICB efficacy in patients with SCLC.
- As antigen presentation machinery is frequently epigenetically suppressed in SCLC, this study defines a targetable mechanism by which we might improve clinical benefit of ICB for patients with SCLC.

Lu L. Clinical and Histopathologic Characteristics of Recurrent Sarcoidosis in Posttransplant Lungs: 25 Years of Experience. Am J Surg Pathol. 2023 Sep 1;47(9):1034-1038.

Background:

- Lung transplantation is the definitive therapy for end-stage pulmonary sarcoidosis.
- While recurrent sarcoidosis in allografts has been described in several case reports, the incidence and clinicopathologic characteristics remain unclear.

Aim:

- In this study, the authors characterize the clinical and histopathologic features of recurrent sarcoidosis diagnosed in posttransplant lung surveillance transbronchial biopsies (TBBx).

Methods:

- The authors identified 35 patients who underwent lung transplant for pulmonary sarcoidosis during the study period.

Results:

- Among them, 18 patients (51%) experienced recurrent sarcoidosis posttransplant.
- These included 7 females and 11 males with mean age at recurrence of 51.6 years.
- The average time interval from transplant to recurrence was 252 days (22 to 984 d).
- All TBBx contained >4 pieces of alveolated lung tissue with no evidence of International Society for Heart and Lung Transplantation (ISHLT) grade A2, A3, or A4 acute cellular rejection; chronic rejection; or antibody-mediated rejection.
- There were 33 surveillance TBBx that contained granulomatous inflammation with a mean of 3.6 well-formed granulomas per TBBx (range: 1 to >20).
- Multinucleated giant cells were identified in 11 TBBx (33.3%), with 1 case containing asteroid bodies.
- While most of the granulomas were "naked granulomas," 5 cases (15.2%) showed prominent lymphoid cuffing.
- Two cases showed evidence of fibrosis. One of the granulomas had focal necrosis; however, no infectious organisms were identified by special stains and clinical correlation suggested this case represented recurrent sarcoidosis.
- Biopsies of recurrent sarcoidosis usually show multiple well-formed granulomas with giant cells in more than half of the cases, while lymphoid cuffing, fibrosis, asteroid bodies, and necrotizing granulomas are uncommon findings.

Take Home Points:

- Pathologists should be aware of these features, as recurrence of sarcoidosis following lung transplant occurs in more than half of patients.

Wilkinson Z. All that glitters isn't gold: an unusual case of Pneumocystis jirovecii pneumonia. Histopathology. 2023 Sep;83(3):487-489.

- A 45-year-old, essentially healthy woman, healthcare worker, current tobacco smoker, and infrequent cannabis user, who presented to an outside hospital with acute shortness of breath and severe right chest pain.
- Chest computed tomography (CT) imaging revealed pneumothorax and bilateral cavitary and noncavitary lesions, as well as air space consolidation predominantly in the upper lobes.
- After initial stabilization of the patient, a video-assisted thorascopic surgery (VATS) lung biopsy was performed in an outside institution to further characterize the lesions.

- The pathology report indicated the presence of PAS/PAS-Diastase-positive intra-alveolar, eosinophilic acellular material along with rare foci of granulomatous inflammation and emphysema, with a final diagnosis of PAP.
- AFB and GMS stains were reported negative. Blood and serological testing, including aspergillus, as well as cultures from the VATS procedure, were negative for growth.
- It was concluded that the patient's diagnosis was PAP, likely of autoimmune cause, given her lack of exposure risks (i.e. high-level dust or silicate contact) or other risk factors.
- Three weeks later, the patient presented to our institution due to worsening right-sided pain and dyspnea.
- Repeat CT imaging showed innumerable bilateral cavitary opacities throughout both lungs, with a masslike noncavitary opacity in the right lower lobe.
- The outside lung biopsy was reviewed at our institution. Numerous foci of “frothy” material were seen in the airspaces in association with extensive necrosis, foci of granulomatous inflammation, and some interstitial inflammatory infiltrates.
- Patchy, weak PAS-positive material was seen, without the usual morphology of PAP.
- GMS stains were repeated, which revealed numerous GMS-positive cystic organisms with intracystic bodies, consistent with Pneumocystis jirovecii.

Kumagai E. A case of lung carcinoma with a unique biphasic feature: Implications for histogenesis of “fake mucoepidermoid carcinoma” developing in the peripheral lung. Pathol Int. 2023 Sep;73(9):463-468.

- A 67-year-old male smoker with idiopathic pulmonary fibrosis (IPF).
- A subpleural tumor in the left lower lobe, embedded in fibrotic tissue, was resected.
- Histologically, the tumor consisted of major and minor components of mucoepidermoid carcinoma (MEC) and surrounding conventional lepidic adenocarcinoma, respectively.
- Both components had the same TP53 somatic mutation (p.V157F) but not Mastermind-like 2 (MAML2) gene rearrangement.
- The two components may have developed from an identical origin.
- The tumor could be trans-differentiating from lepidic adenocarcinoma to MEC, possibly promoted by IPF-induced tissue damage.
- The final diagnosis was "adenosquamous carcinoma with mucoepidermoid-like features (that may originate from lepidic adenocarcinoma)."
- This case has implications for the potential histogenesis of peripheral lung MEC.
- Over time, the MEC would expand and outgrow the lepidic adenocarcinoma, making it impossible to distinguish between fake and true MEC.
- The present case suggests that peripheral MEC could differ from proximal MEC in its histogenesis and molecular genetics.

- Thus, careful examination is necessary to diagnose peripheral lung MEC, particularly in patients with interstitial lung diseases.

Richier Q. Pulmonary Aspergilloma. N Engl J Med. 2023 Sep 21;389(12):1132.

- A 51-year-old man from the Democratic Republic of Congo presented to the emergency department with a 1-week history of small-volume hemoptysis. Sixteen months before presentation, computed tomography (CT) of the chest had shown a right upper lung cavitation that was a sequela of treated pulmonary tuberculosis.
- At the current presentation, physical examination was notable for reduced breath sounds at the apex of the right lung. A repeat CT of the chest showed thickening of the wall of the right upper lung cavitation and a new intracavitary mass.
- A serum sample was positive for aspergillus-specific IgG antibodies and negative for human immunodeficiency virus antibodies.
- A diagnosis of pulmonary aspergilloma was made.
- Sputum samples had been collected to identify the fungus species, test for antifungal susceptibility, and assess for concurrent tuberculosis, which was ruled out. Septate hyphae branching at acute angles were seen on microscopy. A sputum culture grew a smoky-gray fungal colony containing uniseriate conidiophores.
- Aspergillus fumigatus was identified by means of mass spectrometry.
- Treatment with voriconazole was initiated.
- The patient was lost to follow-up before plans for a lobectomy could be made.
- Fourteen months later, he presented with massive hemoptysis and underwent pulmonary-artery embolization.

Ali B. Photographic Negative of Pulmonary Edema" in Chronic Eosinophilic Pneumonia. N Engl J Med. 2023 Sep 28;389(13):1220.

- A 54-year-old woman with asthma and allergic rhinitis presented to the emergency department with a 3-month history of productive cough and dyspnea. She also reported fevers, chills, night sweats, and an unintentional 9-kg (20-lb) weight loss.
- Her medications were montelukast, cetirizine,and an albuterol inhaler. She was a lifelong nonsmoker and had not traveled recently.
- On lung examination, there was expiratory wheezing and diffuse crackles.
- Laboratory testing showed an absolute eosinophil count of 5240 per cubic millimeter (reference range, 40 to 360).
- A chest radiograph showed peripheral airspace opacities on both sides. Subsequent computed tomography of the chest showed upper lobe–predominant peripheral and subpleural consolidations that spared the perihilar region. The radiographic pattern was described as a

"photographic negative of pulmonary edema" — a finding suggestive of chronic eosinophilic pneumonia.
- Serum testing for IgE against Aspergillus fumigatus, antibodies against coccidioides, and antineutrophil cytoplasmic antibodies was negative.
- Bronchoscopy with bronchoalveolar lavage was notable for 74% eosinophils in the cell count (reference value, <2) and negative tests for infectious diseases.
- A diagnosis of chronic eosinophilic pneumonia was made.

Johnson S. Pulmonary Hypertension: A Contemporary Review. Am J Respir Crit Care Med. 2023 Sep 1;208(5):528-548.

- Major advances in pulmonary arterial hypertension, pulmonary hypertension (PH) associated with lung disease, and chronic thromboembolic PH cast new light on the pathogenetic mechanisms, epidemiology, diagnostic approach, and therapeutic armamentarium for pulmonary vascular disease.
- Here, the authors summarize key basic, translational, and clinical PH reports, emphasizing findings that build on current state-of-the-art research.
- The review includes cutting-edge progress in translational pulmonary vascular biology, with a guide to the diagnosis of patients in clinical practice, incorporating recent PH definition revisions that continue emphasis on early detection of disease.
- PH management is reviewed including an overview of the evolving considerations for the approach to treatment of PH in patients with cardiopulmonary comorbidities, as well as a discussion of the groundbreaking sotatercept data for the treatment of pulmonary arterial hypertension.

Conroy M. Neoadjuvant immune checkpoint inhibitor therapy in resectable non-small cell lung cancer. Lung Cancer. 2023 Sep:183:107314.

- Only a minority of lung cancers are resectable at diagnosis, and many of these will eventually relapse.
- Adjuvant chemotherapy in this setting has a modest survival advantage, and there is significant need for new approaches to improve cure rates.
- Checkpoint inhibitor immunotherapy has transformed the prognosis for advanced lung cancer, and is increasingly being used in the neoadjuvant setting alone, or in combination with cytotoxic chemotherapy.
- While this has demonstrated convincing improvements in event-free survival and pathologic response, questions remain over optimal duration of therapy, predictive and prognostic biomarkers, response assessment and combination with other modalities.

- In addition, these results must be considered in the context of recent positive studies of adjuvant immunotherapy.
- The authors summarise preclinical context and clinical trials in this space, discuss areas of controversy and pitfalls, and consider future challenges.