PULMONARY PATHOLOGY JOURNAL CLUB
(April 2024 articles)
May 25, 2024

I. Articles for Discussion

Fraune C et al. Usefulness and limitations of current diagnostic strategies for pulmonary mucosa-associated lymphoid tissue lymphoma: lessons learned from a large cohort. Arch Pathol Lab Med 2024;148:419-429 (prepared by Y. Butt)

Purpose: To evaluate the diagnostic usefulness and limitations of current diagnostic strategies for pulmonary MALT lymphoma as the diagnosis can be challenging.

Methods: A retrospective review of 120 cases of pulmonary MALT lymphoma from 2014 through 2021 was performed.

Results: Clinicoradiologic presentations overlapped with previous observations in patients with MALT lymphoma, such as a wide age range, female predominance, frequent association with autoimmune disease or immunodeficiency, and broad imaging findings. The histopathologic diagnosis was based on a combination of morphology, immunohistochemistry, and demonstration of B-cell lineage clonality. Two-thirds (76 of 113) of MALT lymphomas had lymphoplasmacytoid cytomorphology. Occasionally, MALT lymphomas were associated with granulomas/giant cells (29%, 35 of 120) or immunoglobulin deposition disease (21%, 25 of 120), including light chain/heavy chain deposition disease, amyloidosis, and/or crystal storing histiocytosis. While CD5, CD10, Bcl-2, and Bcl-6 rarely revealed aberrancies, aberrant CD43 expression either on B-cells or on plasma cells was detected in 42% (27 of 64) of cases, including cases for which proof of clonality could not be obtained. κ/λ in situ hybridization was particularly useful for tumors with lymphoplasmacytoid morphology but performed poorly in lymphomas having no plasmacytic differentiation. κ/λ immunohistochemistry showed no additional usefulness when applied together with κ/λ in situ hybridization. Immunoglobulin gene rearrangement studies by polymerase chain reaction achieved high detection rates of clonality in all cytomorphologic subgroups.

Take Home Messages: (1) A thorough morphologic review of H&E-stained diagnostic material remains essential to evaluate architectural and cytomorphologic features. (2) An IHC workup should minimally include CD3, CD20, and CD138 to evaluate T-cell, B-cell, and plasma cell components, respectively, and should include markers to evaluate B-cell immunophenotype (CD5, CD10, Bcl-6, Bcl-2, CD43, and cyclin-D1) and B-cell follicular dendritic cell meshworks (CD21 or CD23). (3) While CD5 and CD10 rarely reveal B-cell immunophenotypic aberrancies in pulmonary MALT lymphoma, CD43 has a robust diagnostic usefulness for aberrantly staining B cells or plasma cells (about 40%), and its usefulness is retained in difficult cases with unsuccessful demonstration of clonality. (4) The performance of various strategies to demonstrate clonality depends on the cytologic composition. Both κ and λ light-chain ISH have a good success rate in cases with plasmacytic differentiation, but low performance with pure lymphoid or monocytoid cytomorphology. κ/λ IHC contributes minimal additional usefulness in cases with unrevealing κ/λ ISH and is not recommended. PCR testing for immunoglobulin gene

rearrangements has a high success rate in all cytomorphologic subtypes and should be preferred in cases with minimal plasmacytic differentiation. (5) Flow cytometry is underused in the diagnosis of pulmonary MALT lymphoma. Awareness of surgical pathology personnel should be increased to secure a fresh tissue sample from lung biopsies of unknown mass lesions or infiltrates of the lung, particularly when prompted by suggestive findings during frozen section evaluation. (6) Identification of LCDD/HCDD, amyloidosis, or CSH in the biopsy should prompt pathology workup for a pulmonary MALT lymphoma. (7) In cases with no proof of clonality, the diagnosis of MALT lymphoma can be reached from prominent morphologic findings such as B-cell mass lesions, the presence of documented immunophenotypic aberrancy, or associated LCDD/HCDD, amyloidosis, or CSH. In the absence of these findings, a descriptive diagnosis and clinical follow-up may represent a clinically meaningful alternative.

Tomasicchio M, et al. SARS-CoV-2 viral replication persists in the human lung for several weeks after symptom onset. Am J Respir Crit Care Med 2024;209:840-851 (prepared by M.C. Aubry)

Background

- Case fatality due to Beta and Delta variants of COVID-19 particularly high in ventilated patients. Even with the Omicron variant fatality significantly high in elderly and immunocompromised
- SARS-CoV-2 can persist in tissue several weeks after onset of symptoms as detected by PCR and IHC, probably non-replication-competent (need cultures). And replication-competent in URT only 2-8 days.

Aim

- Assess presence of replicating virus in the LRT and study correlation with altered pulmonary immunity.

Methods

- 42 decedents (18 Beta, 24 Delta) and 18 ambulatory controls
- Tissue samples of lung and nasopharyngeal swabs in all decedents. Other organs in the Delta group.
- Viral cultures, PCR for secondary bacterial infections, IHC for CD3 and CD8, EM, WGS of SARS-CoV-2, RNA seq of Delta lung, Confocal of ACE2 cells infected with SARS

Results

- Median age 53 yo, 48% M; time of onset of symptoms to death was median of 17 days (9-22).
- Persistent viral replication in ventilated patients both nasopharyngeal (38% at median Day 13 vs 5.5% in ambulatory patients at Day 12) and within the lung (38% at median Day 15). In the Delta group, only patients with lung +viral cultures that PCR detectable virus in other organs and adipose tissue.
- Lung viral+ culture patients Delta vs Beta: no difference in age, co-morbidities, in viral load but in the Delta group, more accelerated deaths and bacterial infections.
- Lung viral+ culture patients vs culture negative:
    - No difference in steroid use, viral load by PCR on admission nasopharyngeal swab.
    - Less CD3 and CD8+ T-cells
    - No difference in histology except more hemophagocytosis

  - Transcriptomic analysis shows 11 upregulated and 4 down regulated genes, involving pro-inflammatory pathways and viral entry/defense - Elevated CA12, CD177, SDCBP2
  - Up-regulation of several of the viral genes
  - *GREM1* and *FGFBP1* may predict for lung culture positive patients with specificity and sensitivity of 90%

Conclusion

- A large portion (38%) of patients with severe COVID have persistent ongoing viral replication, many at 2 and more weeks, in nasopharynx and lungs for Delta and Beta variants versus ambulatory patients (nasopharynx).
- However, not clear how have persistent viral replication affects outcome for the most part since all these patients eventually died. The only difference and only for the Delta group was more patients with accelerated deaths bacterial infections in a cohort who already had a poor outcome of median 17 days survival.

Naso J, et al. Pulmonary gangliocytic paraganglioma: An under-recognized mimic of carcinoid tumor. Hum Pathol 2024;146:23-27 (prepared by A. Khoor)

Background:

- Gangliocytic paragangliomas are rare neoplasms occurring almost exclusively in the ampullary region of the gastrointestinal tract
- Five cases of primary pulmonary gangliocytic paragangliomas had been previously reported

Methods:

- The authors reported their experience with 3 additional examples

Results:

- Patients
  - A 32-year-old man, a 69-year-old woman, and a 55-year-old man
- Presentation
  - Endobronchial (2 cases) or upper lobe lung mass, ranging from 1.5 to 2.5 cm in maximum dimension
- Biopsy and endobronchial debulking specimens
  - Classic triphasic morphology of gangliocytic paraganglioma, with epithelial, spindled and ganglion-like cells
- Immunohistochemistry
  - Epithelial component
    - Keratin, synaptophysin and chromogranin A
    - TTF-1 in 2 cases
  - Schwannian spindled cells
    - S-100 protein and glial fibrillary acidic protein (GFAP)
  - Ganglion cells
    - Synaptophysin
- Ki-67 labelling index
  - Low (<2%)

Conclusion:

- Primary pulmonary gangliocytic paragangliomas should be distinguished from carcinoid tumors, given the different natural histories and risk stratification approaches for these morphologically similar tumors
- Awareness that gangliocytic paraganglioma may occur in the lung and appropriate immunohistochemical studies are key to correct diagnosis

Wu YL, et al. Alectinib in resected ALK-positive non-small cell lung cancer. N Engl J Med 2024;390:1265-1276 (prepared by M. Kelly)

Background:

- Approximately 5% of patients with NSCLC have ALK-positive disease and are more likely to be younger and have more advanced disease
- In resectable ALK-positive NSCLC, the primary treatment is surgery, with adjuvant/neoadjuvant treatment (platinum-based chemotherapy)
- However adjuvant therapy provides only modest improvement in outcomes
- Immunotherapy is not an option in NSCLC with oncogenic driver alterations
- In the phase 3 ADAURA trial adjuvant osimertinib showed a significant benefit with respect to disease-free survival in EGFR mutation–positive NSCLC of stage IB, II, or IIIA and this large disease-free survival benefit has an overall survival benefit
- Alectinib is a potent oral ALK TKI inhibitor with high levels of efficacy in patients with advanced ALK-positive NSCLC and there is a need to assess the efficacy and safety of adjuvant alectinib as compared with chemotherapy in patients with resected ALK-positive NSCLC
- This paper reports results from the primary analysis of the randomized, open-label, phase 3 ALINA trial, which is investigating the efficacy and safety of adjuvant alectinib as compared with standard chemotherapy in patients with resected ALK-positive NSCLC

Methods:

- A global, phase 3, open-label, randomized trial in which patients with completely resected, ALK-positive NSCLC stage IB, II, or IIIA randomly assigned in a 1:1 ratio to receive oral alectinib for 24 months or IV platinum-based chemotherapy in four 21-day cycles.
- The primary end point was disease-free survival (DFS)
- Other end points included CNS DFS, overall survival, and safety.

Results:

- 130 patients randomized to alectinib - 127 chemotherapy
- DFS at 2 years: 93.8% - alectinib group, 63.0% - chemotherapy group (hazard ratio (HR) 0.24; 95% CI, 0.13 to 0.45; P<0.001)

- Clinically meaningful benefit with alectinib with respect to CNS DFS as compared with chemotherapy (HR 0.22; 95% CI, 0.08 to 0.58).
- Data for overall survival not available yet
- No unexpected safety findings were observed

Conclusions:

- Adjuvant alectinib significantly improved DFS as compared with platinum based chemotherapy and is a promising new strategy for relevant patients
- Need remains for prospective trials to identify the most effective treatment duration of adjuvant targeted therapies and to investigate a combination of chemotherapy and alectinib
- Currently, biomarker testing for ALK alterations in resectable NSCLC is mainly performed to exclude patients from receiving immunotherapy, but the data reinforce the need for rapid biomarker testing for ALK alterations across **all** stages of NSCLC

Saito-Koyama R, et al. Morphometric analysis of nuclear shape irregularity as a novel predictor of programmed death-ligand 1 expression in lung squamous cell carcinoma. Virchows Arch 2024;484:609-620 (prepared by K. Butnor)

Purpose: To explore nuclear atypia evaluated using morphometry as a potential predictor of PD-L1 status in squamous cell lung carcinoma.

Methods: Whole-slide images of 95 cases from the Cancer Genome Atlas database and 30 cases from a Japanese cancer center were subject to morphometric analysis using the ImageJ software. A total of 20 cells with the 10 largest nuclei in 2 images from representative areas were selected. The border of each nucleus was traced and a variety of parameters were measured, including area, perimeter, maximum diameter, and aspect ratio

Results: Nuclear atypia, particularly nuclear shape irregularity, correlated with PD-L1 status.

Take Home Message: Nuclear shape irregularity correlates with PD-L1 expression in squamous cell lung carcinoma. Whether it can be used as a surrogate for PD-L1 immunohistochemistry remains to be determined.

II. Articles for Notation

Original Articles

Neoplastic

Melchior L, et al. Multicenter evaluation of an automated multiplex, RNA-based molecular assay for detection of *ALK*, *ROS1*, *RET* fusions and *MET* exon 14 skipping in NSCLC. Virchows Arch 2024;484:677-686 (prepared by K. Butnor)

Purpose: To assess the performance of the fully automated RT-PCF-based Idylla™ GeneFusion Assay to detect actional rearrangements in advanced NSCLC.

Methods: Results of this assay were compared with earlier results of routine reference technologies including FISH, IHDC, rt-PCR and NSG in 326 archival advanced NSCLC FFPE samples.

Results: There was high sensitivity/specificity for all tested rearrangements (*ALK* 96.1/99.6%, *ROS1* 96.7%/99.0%, *RET* fusion 100%/99.3%, *MET* exon 14 skipping 92.5%/99.6%) and a low failure rate (0.9%) with this assay.

Take Home Message: Given its short turnaround time (~ 3 hrs), this could be an efficient upfront screening tool for detecting actionable alterations in FFPE NSCLC samples.

Xiang C, et al. Unraveling the significance of MET focal amplification in lung cancer: integrative NGS, FISH, and IHC investigation. Mod Pathol 2024;37:100451 (prepared by M. Kelly)

Background:

- The MET proto-oncogene encodes a tyrosine kinase receptor (TKI) whose increased activity promotes tumour growth by providing anti-apoptotic and pro-migratory signals
- MET amplification (METamp) occurs as a *de novo* driver in 1- 5% of treatment-naïve NSCLC and is one of the commonest mechanisms of acquired resistance (AR) after progression on therapies targeted against other genes such as ROS, EGFR etc
- METamp can occur through focal copy number gains of the MET gene alone (focal amplification), or duplication of chromosome 7 (polysomy)
- There is a lack of consensus on a standardized definition for MET amplification or overexpression and variable cutoffs between studies and diagnostic assays
- There is a need to identify patients who are oncogenically addicted to METamp and most likely to benefit from MET inhibitors which was the aim of this study

Methods:

- MET amplification/overexpression status was performed in a cohort of 231 patients with NSCLC using FISH and NGS (for METamp) and IHC (for overexpression) and the clinical relevance of these approaches in predicting the efficacy of MET inhibitors was evaluated
- In addition, the biological characteristics, clinicopathological features, and clinical efficacy of MET inhibitors among METamp-stratified patients was analyzed using NGS data from another 22,010 lung cancer cases

Results:

- Of the 231 cases, 145 showed METamp/overexpression using at least 1 method, only half could be identified by all 3 methods
- Inconsistency between NGS and FISH primarily occurred with polysomy.
- Patients with focal amplification had a better response to MET inhibitors compared to those with polysomy
- There was a strong correlation between focal amplification and PDL-1 expression

Limitations: Patients in the first cohort were preselected using FISH which might have introduced a bias into the analysis of the performance of the 3 methods. Only 28 patients in this cohort received MET inhibitors, and some of were treated with combination therapies.

Conclusions:

- Overall nothing new is presented here and the results are similar to those found in other studies e.g. focal amplification rather than polysomy is widely recognized as a better predictor of response to targeted therapy against MET
- This paper does not provide any new data to help identify patients who are oncogenically addicted to METamp
- The authors loosely use the term 'amplification' for results with IHC which strictly should be referred to as 'overexpression' since only a portion of such cases are due to amplification alone, with some cases being related to mutations for example.

Kops S, et al. Rapid on-site evaluation of touch imprint cytology in navigation bronchoscopy for small peripheral pulmonary nodules. Cancer Cytopathol 2024;132:233-241 (reviewed by Y. Butt)

Background: Rapid on-site evaluation (ROSE) of cytopathology plays an important role in determining whether representative samples have been taken during navigation bronchoscopy. With touch imprint cytology (TIC), histologic samples can be assessed using ROSE. Although advised by guidelines, there have been almost no studies on the performance of TIC during navigation bronchoscopy. The objective of this study was to evaluate the value of TIC-ROSE (forceps/cryobiopsy) in combination with conventional ROSE (cytology needle/brush).

Methods: In this single-center, prospective cohort study, patients who had pulmonary nodules with an indication for navigation bronchoscopy were consecutively included. The primary outcome of the study was the concordance of ROSE and the procedural outcome. The concordance rates of TIC-ROSE and the combination of TIC-ROSE plus conventional ROSE were compared.

Results: Fifty-eight patients with 66 nodules were included. Conventional ROSE and TIC-ROSE were assessable in 61 nodules (90.9%) each. By combining both ROSE techniques, all sampled lesions were assessable. Combining conventional ROSE with TIC-ROSE showed concordant results in 51 of 66 cases (77.3%) versus 44 of 66 (66.7%) and 48 of 66 (72.8%) concordant results for conventional ROSE and TICROSE alone, respectively, compared with the procedural outcome. There was no indication of tissue depletion as a result of TIC. The combined ROSE

approach had a statistically significant higher concordance rate compared with conventional ROSE alone.

Conclusions: TIC-ROSE is a cheap, easily implementable technique that can result in higher concordant ROSE outcomes. This could lead to more efficient procedures and possibly higher diagnostic results. In a monomodality sampling setting with only histologic samples, TIC can provide ROSE.

Non-neoplastic

Agarwal R, et al. Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses. Eur Respir J 2024;63:2400061 (prepared by A. Khoor)

Background:
- The International Society for Human and Animal Mycology (ISHAM) working group proposed recommendations for managing allergic bronchopulmonary aspergillosis (ABPA) a decade ago
- There was a need to update these recommendations due to advances in diagnostics and therapeutics

Methods:
- An international expert group was convened to develop guidelines for managing ABPA (caused by Aspergillus spp.) and allergic bronchopulmonary mycosis (ABPM; caused by fungi other than Aspergillus spp.) in adults and children using a modified Delphi method (two online rounds and one in-person meeting)

Results (Expert Recommendations):
- Diagnosis of ABPA
    - Screen for A. fumigatus sensitization using fungus-specific IgE in all newly diagnosed asthmatic adults and difficult-to-treat asthmatic children
    - Diagnose ABPA in those with predisposing conditions or compatible clinico-radiological presentation, with a mandatory demonstration of fungal sensitization and serum total IgE $\geqslant$500 IU·mL−1 and two of the following
        - Fungal-specific IgG, peripheral blood eosinophilia or
        - Suggestive imaging
- Diagnosis of ABPM
    - Consider ABPM in those with an ABPA-like presentation but normal A. fumigatus-IgE
    - Diagnosing ABPM requires repeated growth of the causative fungus from sputum
- Treatment
    - Do not routinely treat asymptomatic ABPA patients
    - Oral prednisolone or itraconazole monotherapy for treating acute ABPA (newly diagnosed or exacerbation), with prednisolone and itraconazole combination only for treating recurrent ABPA exacerbations

Conclusion:
- The experts have framed consensus guidelines for diagnosing, classifying and treating ABPA/M for patient care and research

Noguera-Castells A et al. Epigenetic Fingerprint of the SARS-CoV-2 infection in the lung of lethal COVID-19. Chest 2024;165:820-824 (reviewed by Y. Butt)

Background: A common trait amongst severely affected patients with COVID-19 is lung damage and respiratory failure, the most common cause of death. In addition, the persistence of lung lesions in survivors of COVID-19 could be related to prolonged symptoms. The objective of the analysis was to identify genomic loci with distinct DNA methylation status in the lungs of patients with COVID-19 vs the control cohort.

Methods: Clinical data and autopsy samples of lung tissues were retrospectively collected from 36 patients with polymerase chain reaction test confirmed SARS-CoV-2 infection and lung involvement (COVID-19 group) from April 18, 2020, to April 23, 2021, and 18 individuals without SARS-CoV-2 infection from July 7, 2018, to December 14, 2020 (control group). DNA methylation profiles were established using the Infinium Methylation EPIC Microarray.

Results: The authors unveiled 2,205 CpG sites with a differential methylation status between the COVID-19 and control groups. to unfold the biological functions of the identified 160 genes associated with the COVID-19 lung DNA methylation profile, we data mined gene sets by Gene Ontology, MSigDB Hallmarks, KEGG, and Panther databases using Gene Set Enrichment Analysis. The results showed an enrichment for “chemokine,”, “interferon gamma,” “inflammation,” “transforming growth factor-beta,” and “Wnt” signaling pathways, also an enrichment in genes whose translated proteins were in the endosomal-lysosomal system (false discovery rate< 0.05) (Mendeley data9). Thus, the characterized genes and pathways support that lung tissues of patients with COVID-19 undergo a DNA methylation shift associated with disrupted endosomal-lysosomal system homeostasis within a microenvironment of enhanced fibrosis and marked immune response and hyperinflammatory state.

Conclusions: The data, in addition to shedding light on the role of epigenetically regulated genes in COVID-19 lung damage, pinpoints specific DNA methylation events that might result in long-term complications. The genes that are differentially methylated mainly are involved in chronic inflammation, vascular imbalance, and fibrosis, which are the primary events leading to the long-term clinical presentation of COVID-19. Therefore, remodeling this DNA methylation landscape by epigenetic agents could potentially be a strategy to mitigate the fibrotic environment seen in long-term COVID-19 cases. Because DNA methylation inhibitors are used in hematologic malignancies, these agents could be considered to treat the severe disorder, as currently assessed on the first clinical trial of this type (http://clinicaltrials.gov/ct2/show/NCT04482621).

Review Articles

Johnson S, et al. Diagnosis of cystic lung diseases: a position statement from the UK Cystic Lung Disease Rare Disease Collaborative Network. Thorax 2024;79:366-377 (prepared by K. Butnor)

A nice review of the clinicoradiologic and pathophysiologic features of cystic lung diseases, including LCH, BHD, LIP, LAM, light chain deposition disease, cystic pulmonary amyloidosis, low-grade metastatic neoplasms, various etiologies of small airway disease-related cystic lung disease, and lung cysts in NF-1. There is a flow chart for the work-up of cystic lung disease in Figure 6.

Miller JL et al. An updated contextual approach to mesothelial proliferations in pleural effusion cytology leveraging morphology, ancillary studies, and novel biomarkers. Arch Pathol Lab Med 2024;148:409-418 (reviewed by Y. Butt)

Pleural effusions are common cytologic specimens that can be leveraged to make diagnoses of malignancy that drive appropriate patient management. However, the overlap in morphologic features of reactive mesothelial proliferations, mesotheliomas, and adenocarcinomas can create diagnostic pitfalls in the cytologic evaluation of pleural fluids. This is a nice article looking at the morphologic spectrum of benign and malignant mesothelial proliferations in pleural effusions, as well as relevant clinicoradiologic contexts and ancillary tests looking at existing scientific and clinical literature.

Case Reports

Fagundes M, et al. Twenty-year-old patient with polyarthritis since childhood showing cysts and ground glass attenuation on HRCT. Thorax 2024;79:384-385 (prepared by K. Butnor)

Case Summary: A 20-year-old women with polyarthritis, muscle weakness, dyspnea, and multiple ICU stays for respiratory failure since 4 months of age. HRCT showed cysts and ground glass with reticular infiltrates and lung biopsy demonstrated follicular bronchiolitis. Genetic testing found a pathogenic mutation in the coatomer protein complex, subunit alpha (COP-α).

Take Home Message: COPA syndrome is an autosomal dominant disease that primarily affects the joints, lungs, and kidneys. Manifestations include early onset arthralgia/arthritis, cough, dyspnea, and hemoptysis. Most patients have positive ANA and ANCA. Lung biopsy often shows numerous peribronchovascular and subpleural reactive lymphoid follicles. The treatment of choice is JAK inhibitors.

George G, et al. ALK-rearranged CD30-positive poorly differentiated lung adenocarcinoma, mimicking anaplastic large-cell lymphoma. Histopathol 2024;84:900-902 (reviewed by A. Khoor)

Huynh A et al. A 52-year-old woman with dysarthria, ataxia, xanthelasmas, and miliary pulmonary nodules. Chest 2024;165:e95-e100 (reviewed by Y. Butt)

Case Summary: A 52-year-old woman with no significant medical history was referred for expedited workup of progressive dysarthria and ataxia over the past year. Prior CT angiography

of the head and neck showed no relevant neurologic findings but did reveal miliary lesions in the lung apices. Review of systems was negative for any respiratory, constitutional, or rheumatologic symptoms, except for new xanthelasma-like lesions over her forehead. She previously had smoked with 20 pack-years and had no TB risk factors. MRI of the face showed a 21-mm mass within the left external temporal fascia. MRI of the head showed diffuse leptomeningeal enhancement, right frontal lobe enhancement, and cerebellar and brainstem T2/fluid-attenuated inversion recovery hyperintensity, which prompted her admission. Repeat CT chest scan 2 months after the initial CT scan showed new patchy ground-glass opacities, confluent nodularity scattered throughout the lower lobes, and subpleural consolidation in the right upper lobe. Biopsy specimens of the temporal fascia mass showed diffuse dermal proliferation of foamy histiocytes with equivocal BRAF V600E mutation immunohistochemical stain. Subsequent mutation-specific polymerase chain reaction confirmed the presence of a BRAF mutation at codon 600.

Take Home Message: Erdheim-Chester disease (ECD) is a rare and clinically heterogenous disease that is characterized by the presence of CD68-positive, CD1a-/S100-negative foamy histiocytes on biopsy of affected tissues. The distribution of pulmonary nodules in ECD is often described as centrilobular, subpleural, or both, with an upper lobe predominance in most cases. This case highlights a rare example with a miliary-like pattern of nodules in the lung.