Clinical History:
The patient is a 32-year-old woman, who presents with left-sided chest pain and is found to have a large left pneumothorax.
Pulmonary Pathology

Case 8

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No relevant financial relationships or conflicts of interest to disclose.
Diagnosis

• Reactive eosinophilic pleuritis
  • Commonly seen in the setting of pneumothorax

What is the etiology?
Considerations for Spontaneous Pneumothorax

• Primary
  • Pleural blebs

• Secondary
  • COPD/Emphysema
  • Other cystic lung disease
    • Langerhans cell histiocytosis (LCH)
    • Lymphangioleiomyomatosis (LAM)
    • Birt-Hogg-Dubé
  • Necrotizing lung infections
  • Malignancy (e.g. cystic metastases)
  • Thoracic endometriosis (catamenial pneumothorax)
Lymphangioleiomyomatosis
Patient History

• 32-year-old woman, who presents with right-sided chest pain

• Reports that her symptoms began while eating breakfast and she “knew it was a pneumothorax”

• Two weeks prior she had undergone left-sided pleurodesis for a pneumothorax
“Multiple small thin-walled cystic abnormalities distributed in both the upper and lower lobes.”
Thin-Walled Lung Cysts

Radiographic Differential to Pathologic Diagnosis
Learning Objectives

At the conclusion of this activity, participants should be able to...

• Describe the radiographic qualities of parenchymal cystic lung disease and the radiologic differential diagnosis.

• Recognize the spectrum of lesions seen in Langerhans cell histiocytosis.

• Identify “LAM” cells and understand the limitations of immunohistochemistry in the diagnosis of lymphangioleiomyomatosis.
## Cystic Lung Disease

The Radiologist’s Perspective

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<th>Common</th>
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<td>Emphysema</td>
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<td>Cystic Bronchiectasis</td>
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<td>Honeycombing</td>
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Fleischner Society Glossary of Terms for Thoracic Imaging: “A cyst appears as a round parenchymal lucency or low-attenuating area with a well-defined interface with normal lung.” (RSNA, 2008)

Quality and distribution of the lung cysts, as well as the context help narrow the differential diagnosis for the radiologist.
Honeycombing in usual interstitial pneumonia

- Subpleural cysts with multilayering
- Confirmatory findings (context): reticulation & traction bronchiectasis
Cystic Lung Disease
The Radiologist’s Perspective

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Webb et al. (2015) High-resolution CT of the lung 5th ed
Modified from Table 19-1
Thin-Walled Cysts
The Radiologist’s Perspective

“Cystic Lung Disease”
- Intraparenchymal cysts with visible walls
- Numerous and symmetrical with normal-appearing intervening lung parenchyma

Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Lymphocytic interstitial pneumonia
Birt-Hogg-Dubé syndrome
Thin-Walled Cysts
Pathologic Diagnosis

- Langerhans cell histiocytosis
- Lymphangioleiomyomatosis
- Lymphocytic interstitial pneumonia
- Birt-Hogg-Dubé syndrome

Cysts affiliated with focal proliferations of diagnostic cells within the interstitium
Thin-Walled Cysts

Pathologic Diagnosis

- Langerhans cell histiocytosis
- Lymphangioleiomyomatosis
- Lymphocytic interstitial pneumonia
- Birt-Hogg-Dubé syndrome

A cellular chronic interstitial pneumonia, characterized by diffuse expansion of the alveolar septa by non-clonal lymphocytes and plasma cells that is most commonly seen in the setting of underlying immunodeficiency or systemic connective tissue disease (Sjögren’s syndrome).
Cystic amyloidosis associated with MALT lymphoma
Thin-Walled Cysts
Pathologic Diagnosis

- Autosomal dominant inherited disorder caused by germline mutations in the tumor suppressor gene, *folliculin*

- No specific radiographic or histologic features in the lung to diagnose Birt-Hogg-Dubé syndrome, but characteristics include:
  - Fibrofolliculomas
  - Renal neoplasms
  - Pneumothorax (~40%)
Lower lobe predominant blebs and intraparenchymal cysts lined by pneumocytes

May be worthwhile to suggest the possibility of Birt-Hogg-Dubé syndrome in patients with bilateral, lower lobe cysts who present with pneumothorax

Thin-Walled Cysts
Pathologic Diagnosis

Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Lymphocytic interstitial pneumonia
Birt-Hogg-Dubé syndrome
Langerhans Cell Histiocytosis (LCH)

Eosinophilic granuloma; Langerhans cell granulomatosis

Pulmonary LCH is an interstitial lesion seen in current or former smokers, characterized by the presence of modified histiocytes (Langerhans cells).
Pulmonary LCH now considered by many to be a myeloid neoplasm

*BRADF V600E mutation detected in ~30% of patients
  • Mutations are more common in extrapulmonary/systemic LCH

*MAP2K1/MEK1* mutations have been reported in some BRAF V600E-negative cases
“Scar emphysema”
Paracatricial airspace enlargement
“Brochiolocentric stellate fibrosis, consistent with fibrotic Langerhans cell histiocytosis”
Langerhans Cell Histiocytosis
Clinical and Radiographic Features

- Peak incidence 40 years (range 18-70)
- No sex predilection, but male predominance earlier in life and female predominance later in life
- Symptoms:
  - Most commonly cough and dyspnea
  - Pneumothorax (25%)
  - ~10% asymptomatic
- HRCT: Upper lobe predominant nodules (1-5 mm) and cysts
Lymphangioleiomyomatosis (LAM)

Rare disorder affecting almost exclusively women and characterized by proliferation of smooth muscle-like (“LAM”) cells throughout the interstitium of the lung.
PEComatous tumors
- LAM
- PEComa (clear cell tumor)
- Diffuse PEComatosis

LAM is “a low-grade destructive metastasizing neoplasm, as the lesional cells usually have growth-promoting biallelic mutations in the tuberous sclerosis gene TSC2.”

“[LAM] cells also show evidence of clonal origin, as well as invasive and metastatic potential”

Travis et al. J Thorac Oncol 2015
“Epitheloid” LAM cells

“Spindle” LAM cells
# Immunohistochemistry

HMB-45 expression is highly variable (17 to 67%)

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<tr>
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<tr>
<td>SMA</td>
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<td>HMB-45</td>
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<td>Negative</td>
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<tr>
<td>ER/PR</td>
<td>Positive</td>
<td>Negative</td>
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Chu SC et al. CHEST 1999  
Lymphangioleiomyomatosis

- Almost always women
- Mean age of diagnosis 41 years
- Caused by mutations in TSC genes; sporadic (85%)
  - Cystic lung disease
  - Renal angiomyolipomas
  - Most common presenting event pneumothorax (~35%)
- HRCT: Numerous, diffuse cysts
- Serum VEDF-D diagnostic biomarker (LAM > 692.5 pg/mL; sensitivity 97.9% and specificity 100%)

Mou Y et al. Lymphology 2016
Follow-up on our patient...

- 1.5 years prior to current hospitalization presents with abdominal pain, discovered to have a left-sided renal angiomyolipoma
- During a subsequent hospitalization for pancreatitis, imagining studies showed cystic lung disease
  - Normal VEGF-D levels
- Four hospitalizations for pneumothorax
- Given history of angiomyolipoma and cystic lung disease with radiographic and histologic findings compatible with LAM, clinically considered to have LAM
Take Home Points

• The radiographic differential diagnosis for parenchymal cystic lung disease includes LCH, LAM, LIP, and Birt-Hogg-Dubé syndrome.

• LCH comprises a spectrum of lesions from cellular nodules to bronchiolocentric fibrosis.

• HMB-45 expression in LAM cells is highly variable, so histolomorphologic features and correlation with any available imaging studies might be helpful in establish a diagnosis of LAM with confidence.
Questions?
Thank You!
Case 8 (Thoracic Pathology) Summary

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DIAGNOSIS: Lymphangioleiomyomatosis

CLINICAL HISTORY:
The patient is a 32-year-old woman, who presents complaining of right-sided chest pain that occurred while eating breakfast. Chest imaging confirmed the presence of a large right-sided pneumothorax with “multiple small thin-walled cystic abnormalities distributed in both the upper and lower lobes.” Her past medical history is most significant for renal angiomyolipoma and multiple hospitalizations for pneumothorax. She was clinically labeled as having lymphangioleiomyomatosis, a diagnosis supported by the findings in her lung wedge resection.

MICROSCOPIC DESCRIPTION:
Perhaps, the most striking change at low magnification is eosinophilic pleuritis, characterized by a fibrinous exudate on the visceral pleural surface with abundant eosinophils. The eosinophils are focally present within alveolar spaces in the peripheral lung zones, but without an associated eosinophilic pneumonia. This is accompanied by subtle intraparenchymal cysts. Within the cyst walls, there are focal nodular aggregates of plump spindle cells that resemble modified smooth muscle with abundant pale-staining granular to clear cytoplasm. Immunohistochemical stains show these cells as positive for SMA with variable staining for ER and focal immunoreactivity for HMB-45. Together with the histomorphology, these findings support the diagnosis of lymphangioleiomyomatosis.

DISCUSSION:
Radiographically, the identification of multiple, bilateral thin-walled parenchymal lung cysts has a differential diagnosis of lymphocytic interstitial pneumonia (LIP), Birt-Hogg-Dubé syndrome (BHD), Langerhans cell histiocytosis (LCH), and lymphangioleiomyomatosis (LAM). While the distribution of the cysts may lead the radiologist to favor one entity over another, at times, particularly in the setting of advanced disease, all of these entities may still be offered as possibilities in an interpretive comment. Fortunately, as pathologists, these clinical and radiographic considerations rarely live together on a differential diagnosis.

LIP is a cellular chronic interstitial pneumonia, characterized by diffuse expansion of the alveolar septa by non-clonal lymphocytes and plasma cells. LIP is most commonly seen in the setting of underlying immunodeficiency or systemic connective tissue disease (Sjögren’s syndrome). Although LIP is commonly thought be the most common cause of cystic lung disease in patients with Sjögren’s syndrome, MALT
lymphoma, which may be affiliated with cystic amyloid, seems to be more commonly encountered on lung wedge biopsies in this patient population.

BHD is an autosomal dominant inherited disorder caused by germline mutations in the tumor suppressor gene, *folliculin*. While there are no specific radiographic or histologic features in the lung to diagnose BHD, the finding of bilateral, lower lobe predominant blebs and intraparenchymal cysts may be sufficient to propose the possibility of BHD. Pneumothorax is often the initial presenting complaint, preceding the development of other characteristic clinical findings. Since these patients often develop renal neoplasms, they may benefit from increased screening.

Pulmonary LCH is an interstitial lesion, seen almost exclusively in current or former smokers, characterized by the presence of modified histiocytes (Langerhans cells). LCH has a peak incidence of 40 years, but has been described in a broad age range of 18 to 70 years. There is no sex predilection, but there is male predominance earlier in life and female predominance later, due to men smoking at an earlier age and women starting later in life. Patients most commonly present with cough and dyspnea, and pneumothorax occurs in about 25 percent of individuals. HRCT is classically described as upper lobe predominant nodules and cysts, the latter predominating the later stages of disease. Histologically, early lesions are seen as cellular peribronchiolar nodules that expand the interstitium by a mixed inflammatory infiltrate that includes lymphocytes, plasma cells, eosinophils, and diagnostic Langerhans cells, which as positive by CD1a by immunohistochemistry. As lesions age, they become less cellular and more fibrotic with a characteristic stellate configuration associated with paracaticritional airspace enlargement (“scar emphysema”). Although LCH is now regarded by many as a myeloid neoplasm, *BRAFV600E* mutations are present in only about 30 percent of patients and are observed more commonly in the systemic rather than pulmonary form.

LAM occurs almost exclusively in women with mean age of diagnosis at 41 years. The majority of cases are sporadic and caused by mutations in the tuberous sclerosis complex genes, *TSC1* and *TSC2*. Disease manifestations include cystic lung disease and renal angiomyolipomas. Pneumothorax is the most common presenting event. As described in our case, HRCT shows numerous, bilateral diffuse lung cysts. Morphologically, the cysts contain variably prominent interstitial proliferations of spindled or epithelioid “smooth muscle-like” cells. Immunoreactivity for HMB-45 can be helpful in supporting a diagnosis of LAM, but may be negative or very focal, particularly in spindled LAM cells.

**ADDITIONAL READING:**

