CYSTIC LUNG DISEASE

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Case Presentation: 24 year old woman with Pleuritic Pain

- 24 year old woman
- Right sided pleuritic pain of sudden onset
- 3 months of mild exertional dyspnea
- No cough, sputum nor wheezing
- Mild fatigue
- No infectious symptoms
- ROS negative
Case Presentation: 24 year old woman with Pleuritic Pain

- Normal Vital Signs
- Decreased breath sounds bilaterally
- Chest hyperinflated
- Right sided chest tube with significant air leak
- No other abnormal finding
Case Presentation: 24 year old woman with Pleuritic Pain

- WBC 5000/mm³
- Hgb 13 gm/dl
- Electrolytes normal
- Creatinine 0.7 mg/dl
- PaO2 70, PaCO2 37 on RA
24 year old woman with Pleuritic Pain
Hospital Day 3

- 4-5 large cups of water were at the bedside
- A diagnostic Test was performed
Diagnosis:
Pulmonary Langerhans cell Histiocytosis
Cystic Lung Diseases
Fleischner Society Definition

- **Cyst**: Thin walled (<2mm) spherical parenchymal lucency, interfaced with normal lung
- **Cavity**: Gas filled space within pulmonary consolidation, mass or nodule; typically thick walled (>2mm) and more irregularly shaped than cysts
- **Bulla**: Spherical focal lucency, ≥ 1 cm, bounded by a thin wall (<1mm). Usually emphysematous change in adjacent lung
- **Bleb**: Cystic Airspace bounded by a thin wall adjacent to the visceral pleura, typically <1 cm in size
- **Pneumatocoele**: Approximately round, thin walled, air-filled space. Generally caused by infection, trauma, aspiration of hydrocarbon, usually transient
Cystic Lung Diseases

• Broad differential diagnosis
• HRCT narrows the differential, often providing a definitive diagnosis
  – Neoplastic
  – Congenital,
  – Genetic,
  – Developmental,
  – Lymphoproliferative,
  – Inflammatory or Infectious
  – Smoking Related
Mechanisms of Cyst Formation

- Check Valve Obstruction
- Destruction of the bronchiolar wall
- Ischemia
- Remodeling by MMP and other matrix degrading enzymes
Cystic Lung Diseases

- Langerhans Cell Histiocytosis
- Lymphangioleiomyomatosis
- Birt-Hogg Dube
- Others
Langerhans Cell Histiocytosis
Langerhans Cell Histiocytosis

- 3-4% of Lung Biopsies
- Age 20-40
- 90% are smokers
- Can be multisystem especially in the pediatric population
Langerhans Cell Histiocytosis: A Cigarette Smoke Promoted Dendritic Neoplasm?

- Langerhans cells are dendritic cells that regulate mucosal immunity
- S100 staining
- Cd1a surface antigen
- Birbeck rod shaped inclusions
Langerhans Cell Histiocytosis: A Cigarette Smoke Promoted Dendritic Neoplasm?

- Cigarette smoking activates Langerhans Cells via GM-CSF and TGF-B
- Clonal pattern with extrapulmonary LCH
- Clonal or polyclonal in PLCH
- BRAF, ARAF and MAP2K1 mutations in LCH and PLCH (50%)
- C/W a myeloid neoplasm
Langerhans Cell Histiocytosis

- Langerhans cells and other immune cells produce bronchiolocentric nodules that precede airway remodeling and cyst formation
- Eosinophilic infiltration with other inflammatory cells
- Metallomatrix proteins lead to cyst formation
- Late: predominantly advanced bullous and cystic disease
Langerhans Cell Histiocytosis
Pulmonary Langerhans Cell Histiocytosis: Presentation

- 1/3 asymptomatic at diagnosis
- 2/3 cough, dyspnea, fatigue
- 1/5 constitutional symptoms such as weight loss or fever
- 10-20% present with pneumothorax
- 10-15% extrapulmonary including skin, bone, hypothalamus, lymph nodes
- 90% are smokers
Pulmonary Langerhans Cell Histiocytosis: PFT

- 1/5 normal at diagnosis
- 2/3 reduced DICO
- Often obstructed
- Lung volumes reduced, normal or increased
Pulmonary Langerhans Cell Histiocytosis: Imaging

- Thin walled Cysts
- Nodules several mm to 2 cm
- Cysts with Bizarre shape
- Apical and midlung predominant
Langerhans Cell Histiocytosis
Langerhans Cell Histiocytosis
Langerhans Cell Histiocytosis
Langerhans Cell Histiocytosis
Suspect Pulmonary Langerhans Cell Histiocytosis:

- Cystic or Nodular infiltrates
- Pneumothorax
- Smokers
- Skin Rash
- Diabetes Insipidus
Pulmonary Langerhans Cell Histiocytosis: Diagnosis

- Transbronchial biopsy positive in 30%
  - 5% CD1a positive cells on BAL suggestive, not sensitive
- Surgical lung or extrapulmonary biopsy often required
- FDG positive, helpful for extrapulmonary lesions
- In the correct context HRCT may be sufficient
Langerhans Cell Histiocytosis: Management Components

• Smoking Cessation
• Pharmacotherapy
  – Corticosteroids controversial
  – Chemotherapy
    • Cladribine
      – Greater response with nodular, thick walled lesions
    • Therapies with BRAF inhibitors if mutation present
• Pulmonary hypertension evaluation
• Lung transplant
• Manage Complications
Langerhans Cell Histiocytosis: Prognosis

• ½ stabilize clinically and radiologically with smoking cessation
• ¼ disease improves regardless of smoking cessation
• ¼ disease progresses despite smoking cessation
Langerhans Cell Histiocytosis: Prognosis

- Prognosis better with early diagnosis
- Impact of immune suppression on mortality not clear
- Decline in PFT associated with worse prognosis
- ? Higher risk of neoplasms
Lymphangioleiomyomatosis
Lymphangioleiomyomatosis: A Disorder of TSC Genes

- Infiltration of lung by smooth muscle (LAM) cells arising from unknown source
- LAM cells circulate and metastasize
- Conducting lymphatics extensively infiltrated by LAM cells
Lymphangioleiomyomatosis

LAM nodule

Lymphatic channel formation

Tissue Remodeling

LAM cell clusters

Circulating LAM cells

Lymphatic circulation

Venous circulation

Potential Sources of LAM cells

Lung

Kidney

Uterus

Lymphatics

Unknown

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MedStar Health
Lymphangioleiomyomatosis: A Disorder of TSC Genes

- Growth activating mutations in tuberous sclerosis genes
- TSC-LAM: Tuberous sclerosis complex
  - 30% of women with tuberous sclerosis, 10-15% of men with TSC
- S-LAM: Sporadic without tuberous sclerosis
  - Entirely in women
Lymphangioleiomyomatosis: A Disorder of TSC Genes

• TSC and TSC-LAM caused by mutations in TSC1 (hamartin) or TSC2 (tuberin) genes
• S-LAM caused by TSC2 mutations
• Tuberin or hamartin deficiency result in upregulated mTOR
Lymphangioleiomyomatosis: A Disorder of TSC Genes

- M-TOR activation
  - Expression of VEGFs
  - Inappropriate cell proliferation, migration and invasion
- VEGF-D elevated in 50-70% of LAM Patients
- Estrogen may promote metastasis and dysregulated protein translation
Molecular target of RAPAMYCIN
Pathology: Smooth Muscle Infiltration of Parenchyma, Airways, Lymphatics with Areas of Thin Walled Cystic Change
Lymphangioleiomyomatosis: Presentation

- Average age at diagnosis = 35 years
- Global prevalence 1 million
- Underdiagnosed
  - Only 5-10% of patients with TSC-LAM become symptomatic
- Angiomyolipomas
# Lymphangioleiomyomatosis: Presentation

Table 1
Demographic and clinical features of lymphangioleiomyomatosis patients followed at the National Heart, Lung, and Blood Institute

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Patients</th>
<th>Sporadic LAM</th>
<th>TSC-LAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>554</td>
<td>460</td>
<td>94</td>
</tr>
<tr>
<td>Age of LAM diagnosis</td>
<td>40.4 ± 9.8</td>
<td>41.1 ± 9.4</td>
<td>36.4 ± 10.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age, first symptom</td>
<td>36.4 ± 10</td>
<td>37.0 ± 9.9</td>
<td>33.2 ± 9.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Presenting Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>353 (64%)</td>
<td>318 (69%)</td>
<td>35 (37%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>188 (34%)</td>
<td>150 (33%)</td>
<td>38 (40%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>47 (9%)</td>
<td>44 (10%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Chylous effusions</td>
<td>43 (10%)</td>
<td>33 (7%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Abdominal, pelvic or back pain</td>
<td>67 (12%)</td>
<td>59 (13%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>No respiratory symptoms</td>
<td>27 (5%)</td>
<td>8 (2%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Extrapulmonary Findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphangioleiomyomas</td>
<td>189 (34%)</td>
<td>177 (38%)</td>
<td>12 (12.8%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Angiomyolipomas</td>
<td>280 (51%)</td>
<td>190 (41.3%)</td>
<td>90 (95.7%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bilateral angiomyolipomas</td>
<td>141 (13.2%)</td>
<td>61 (13.2%)</td>
<td>80 (85.1%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chylous effusions</td>
<td>106 (19%)</td>
<td>93 (20%)</td>
<td>13 (13.8%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> P<.05. Significantly different from sporadic LAM.

<sup>b</sup> P<.01. Significantly different from sporadic LAM.
Lymphangioleiomyomatosis
Lymphangioleiomyomatosis
Lymphangioleiomyomatosis
LAM Associated Angiomyolipoma
Intraabdominal Lymphangioleiomyoma
Suspect Lymphangioleiomyomatosis

- Cystic Change on CT
- Tuberous Sclerosis
- Angiomyolipoma
- Chylothorax
- VEGF-D >800 pg/ml
LAM: Diagnostic Algorithm

1. **Chest CT consistent with LAM**
   - **Abdominal CT**
     - Angiomyolipoma or lymphatic disease present
     - **TSC present** (clinical exam ± genotyping)
   - **Serum VEGF-D >800 pg/mL**
   - Lung biopsy required or contraindicated
2. **Definite LAM**
3. **Other diagnosis**
4. **Probable LAM**

Knowledge and Compassion Focused on You

MedStar Health
Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

National Institutes of Health Rare Lung Diseases Consortium and the MILES Trial Group

NEJM April 2011

NEJM 2011;364:1595

November 21, 2017

Knowledge and Compassion Focused on You

MedStar Health
Lymphangioleiomyomatosis: Management

• Sirolimus if FEV1 < 70%
• Accelerated decline in pregnancy
• Accelerated decline with estrogen use
• Lung transplant

NEJM
2011;364:1595
Lymphangioleiomyomatosis: Management

• Screen for angiomyolipomas
  – >4cm likely to bleed
  – Treat with MTOR inhibitors and or embolization
• 70 % recurrence of PTX
  – Pleurodese first episode
Birt-Hogg-Dube
Birt-Hogg-Dube: Folliculin Gene Mutation

- Autosomal Dominant
- Genetic testing available
- Mutations in folliculin (FLCN) gene (a tumor suppressor protein)
- Dysregulation in M-TOR signaling
- Hair Follicle tumors
- Renal Neoplasms
Birt-Hogg-Dube; Pulmonary Cysts

- Basal subpleural thin walled Cysts
- Typically seen in 4\textsuperscript{th} - 5\textsuperscript{th} decade
- By age 50 there is an 80% penetrance
- 24% of those with cysts develop pneumothorax
- Pneumothorax 32 times that of general population
- **Prevalence in young patients presenting with PTX 5-10%**
- Pneumothorax recurrence 75%
Birt-Hogg-Dube: Renal Neoplasms

• Renal Cancer in 25%
  – Mean age 50.4
  – Chromophobe adenomas and oncocytomas
  – Bilateral and multifocal in >50%

• Screen for renal neoplasms age 20
Fibrofolliculoma: Birt Hogg Dube
Birt-Hogg-Dube: Imaging
Other ILDs with Cystic Change

- IPF
- Chronic Hypersensitivity pneumonitis
- Sarcoidosis
RBILD and DIP (32-75%) associated with lung cysts
Infections Associated with Lung Cysts

Pneumocystis

Infection Causing Lung Cysts
• Pneumocystis
• Staph aureus
• Coccidiomycosis
• Other fungal
• Human papillomavirus
• Paragonimioasis
CYSTIC LUNG DISEASE AND LYMPHOPROLIFERATIVE DISORDERS

• Follicular Bronchiolitis or LIP
  – Autoimmune
    • Sjogrens syndrome
    • SLE
    • RA
  – Immunodeficiency
    • HIV
    • Common variable immunodeficiency

• Lymphoid infiltrates with B and T cells
  – Germinal Centers in FB and LIP associated with SS
LIP/FB

- Ground Glass
- Centrilobular nodules
- Cysts in 68%
- May be associated with MALT lymphoma
- Malignant transformation to lymphoma is rare
- Median survival LIP 5-10 years
Sjogren's Syndrome

- HRCT abnormal in 60-90%
- Cysts in 10-50%
  - Random
  - Internal structure
  - Can be associated with amyloidosis
Follicular Bronchiolitis
Other Disease In the Lymphoproliferative Spectrum

- Amyloidosis
  - Cavitary nodules
  - Diffuse cystic lung disease
  - Associated with MALT lymphoma
Amyloidosis
Other Diseases In the Lymphoproliferative Spectrum

- **Light Chain Deposition Disease**
  - Lymphoproliferative diseases with renal involvement
  - Diffuse cystic lung disease
    - Multiple small diffuse
    - Large cystic spaces with nodules mimic PLCH
    - Has been associated with B cell clone in lung suggestive of lymphoproliferative disorder
    - Often progressive leading to respiratory failure
Cystic Lung Diseases

- Wide spectrum of disease
- Considerable progress in the last decade
- Many with neoplastic characteristics
- Prognosis and course highly variable
- Diagnosis often made based on imaging characteristics and ancillary findings
Questions