

## Diffuse Cystic Lung Disease

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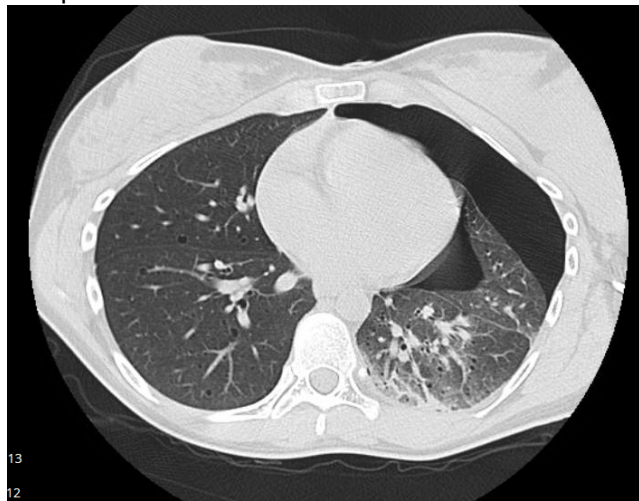
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### Educational Objectives:

1. Review the diagnostic approach for diffuse cystic lesions on CT
2. Understand the differential diagnosis for diffuse cystic lung disease (DCLD)
3. Review the current therapies and management for the most common DCLDs

Ms. Jones is a 20 year-old female non-smoker with no significant past medical history who developed sudden onset of cough and pleuritic chest pain while on vacation. She had no history of trauma. She presented to an emergency department in the community and was found to have a left-sided pneumothorax. She was treated with chest tube thoracostomy and sent home. She follows up in your pulmonary clinic today. She feels well with no significant respiratory complaints.



**Question 1: In addition to the pneumothorax, the radiologist notes some cystic changes on her scan. The cysts are small, round and uniform with a lower lobe predominance. How are the different types of cystic changes on CT characterized?**

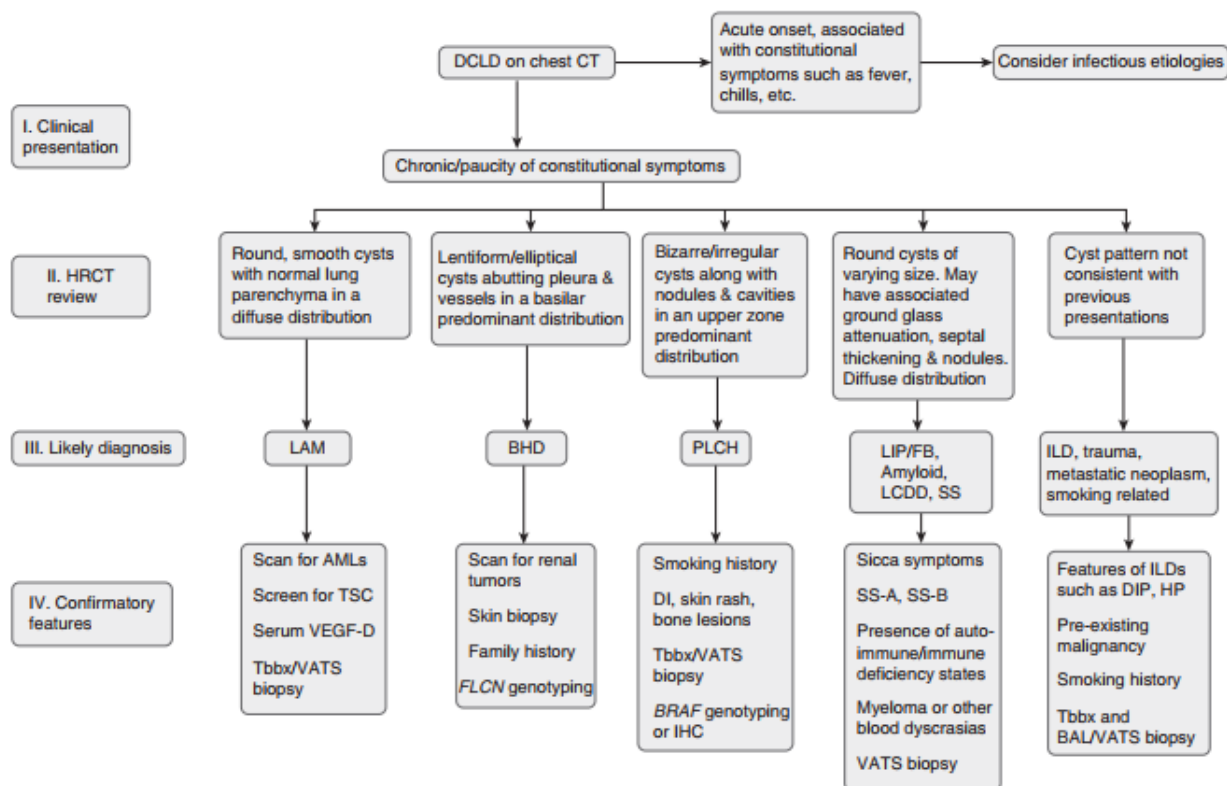
Cystic changes constitute:

- **Cysts:** thin walled (2 mm), spherical parenchymal lucency or low attenuation area with a well-defined interface with normal lung
- **Bulla:** spherical focal lucency, > 1 cm in diameter, bounded by thin wall
- **Bleb:** cystic air space bounded by thin wall adjacent to visceral pleura, <1 cm
- **Mimickers:** Emphysema, bronchiectasis, honeycombing, cavities

**Question 2: Ms. Jones has been healthy prior to this hospitalization and was given the diagnosis of “spontaneous pneumothorax” in the hospital. You inform her that she has a diffuse cystic lung disease. What is the differential diagnosis for her disease?**

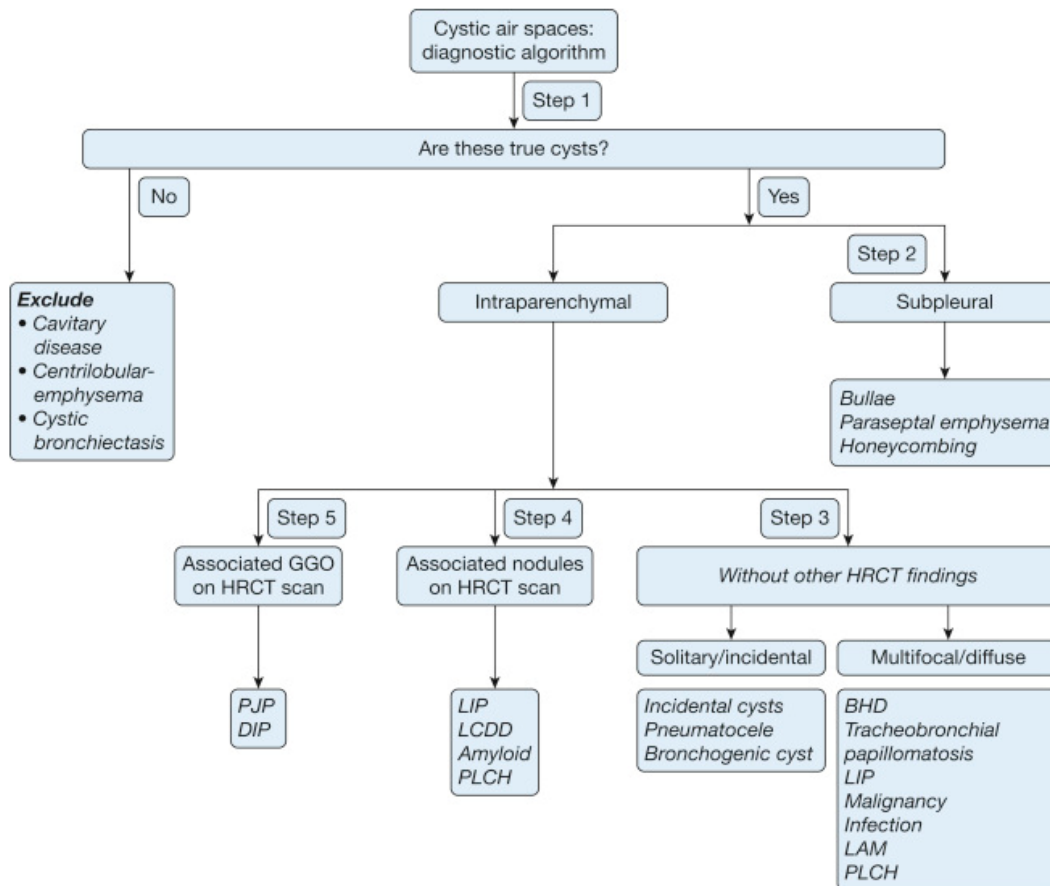
Differential for cystic lung disease is usually one of four: LAM (Lymphangioleiomyomatosis), PLCH (Pulmonary Langerhans Cell Histiocytosis), BHD (Birt-Hogg-Dube syndrome), or LIP (lymphoid interstitial pneumonia)

**Diffuse cystic lung disease algorithm**



Gupta N et al, AJRCCM June 2015

## Cystic Lung Disease Algorithm



Raoff S et al. Chest Oct 2016

- **Lymphangiomyomatosis (LAM)**

- **Characteristics:**

- Sporadic LAM or tuberous sclerosis complex (TSC)-LAM
- LAM is a disease almost exclusive to women of childbearing age

- **Symptoms:**

- Dyspnea on exertion, spontaneous pneumothoraces (can be the presenting symptom in up to a third of patients), pleural effusion seen in 10-30% of patients (chylothorax)

- **CT Findings:**

- Round, uniform cysts measuring 3-5 mm, lower lung zone predominance

- **Diagnostics:**

- VEGF-D >800 pg/mL
- LAM cells on pathology or histology

- **Extrapulmonary manifestations:**

- Renal angiomyolipomas (seen up to 30% of patients with LAM)
- Cutaneous or neurologic manifestations of TSC

- **Pulmonary Langerhans Cell Histiocytosis (PLCH)**
  - **Characteristics:**
    - Current or prior smoking history, young adults (20-40 years)
  - **Symptoms:**
    - Nonproductive cough and dyspnea, spontaneous pneumothorax, weight loss, fatigue, chest pain, fever
  - **CT:**
    - Bronchiolocentric nodules, cavitory nodules, cysts, irregularly, bizarre, shaped cysts & stellate-shaped fibrotic scars; upper lung zone predominance
  - **Diagnostics:**
    - S-100 positive
    - BAL with >5% of cells with CD1a immunostaining
  
- **Lymphocytic interstitial pneumonia (LIP)**
  - **Characteristics:**
    - Associated with variety of autoimmune syndromes or immunodeficiency (Sjogren syndrome, RA, SLE, HIV, CVID, hSCT)
  - **Symptoms:**
    - Cough and dyspnea; fever, night sweats, weight loss
  - **CT:**
    - Diffuse, ground-glass opacity, poorly defined centrilobular nodules, interlobular septal thickening, and diffuse scattered cysts.
  - **Diagnostics:** Lung biopsy
  
- **Birt-Hogg-Dube Syndrome (BHD)**
  - **Characteristics:**
    - Autosomal dominant
    - Occurs in 30-40-year old
  - **Symptoms:**
    - Spontaneous pneumothorax
    - Skin lesions (fibrofolliculomas), renal tumors
  - **CT:**
    - Variable cyst size and morphology (round, oval, lentiform), subpleural, lower lung zone predominance
  - **Diagnostics:**
    - FLCN genetic evaluation
    - Skin biopsy if fibrofolliculomas are present
  
- **Amyloid/Light Chain Deposition Disease**
  - **Amyloidosis:** Associated with SS
  - **LCDD:** Multisystem disease (renal, heart, liver, lung); Associated with underlying plasma cell dyscrasia (multiple myeloma, Waldenstrom)
  - **CT:** round, variable cysts in diffuse random distribution; nodules abutting cyst walls
  
- **Other**
  - Infections: PJP, echinococcosis, coccidioidomycosis, recurrent respiratory papillomatosis (HPV)
  - Desquamative interstitial pneumonia
  - Hypersensitivity pneumonitis, sarcoidosis
  - Lung adenocarcinoma, metastatic lesions (sarcoma)

**Question 3:** You suspect your patient has LAM. Ms. Jones wants to know how definitive her diagnosis is based on the data that you have. Would you recommend additional diagnostic testing?

### Accuracy of HRCT for LAM

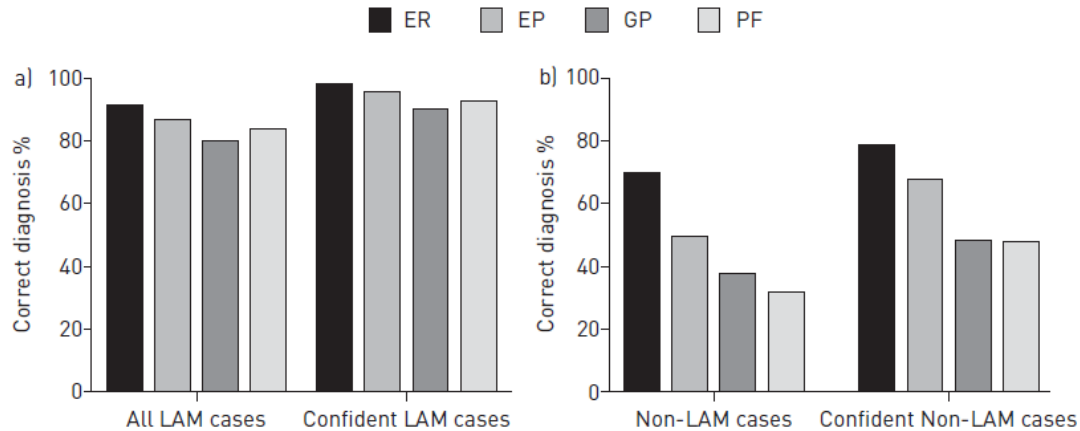


FIGURE 1 Accuracy rates of diagnosing diffuse cystic lung diseases based on high-resolution computed tomography (HRCT) characteristics. a) Accuracy rates of diagnosing lymphangiomyomatosis (LAM) based on HRCT images. b) Accuracy rates of diagnosing non-LAM cystic lung diseases based on HRCT images. ER: expert radiologists; EP: expert pulmonologists; GP: general pulmonologists; PF: pulmonary fellows.

Gupta N et al. Eur Respir J. 2015

The definitive diagnosis of LAM is made via identification of LAM cells pathologically or cytologically in lung, lymph node, or body fluid. However, a clinical diagnosis of LAM can also be made using combination of clinical, radiologic, and lab data.

### After HRCT, next steps

- Serum biomarkers
  - LAM: VEGF-D- (Diagnostic  $\geq 800$  pg/mL)
- Genetic testing
  - PLCH: BRAF, MAP2K1
  - BHD: FLCN
- Further imaging
  - LAM: CT or MRI of abdomen to screen for lymphangiomyomas or AMLs; consider MRI brain
  - PLCH: PET scan can detect extrapulmonary lesions.
  - BHD: CT or MRI of abdomen to screen for renal tumors
- Skin biopsy
  - BHD: punch biopsy of skin fibrofolliculomas
- Pulmonary function testing
  - LAM: obstruction, air trapping, reduced diffusion
  - PLCH: variable, early (restrictive), late (obstruction)
- Bronchoscopy for EBUS/transbronchial biopsy
  - LAM: yield 60%
  - PLCH: yield 30%
  - LIP: yield is low
- VATS (last resort)
  - LIP: often indicated for diagnosis

Scenario continued:

CT abdomen/pelvis with contrast was performed demonstrating large right renal angiomyolipoma (12.4 cm). Serum VEGF-D was 854 pg/mL (reference <600). Pulmonary function testing demonstrated normal pulmonary function with normal FEV1 (FEV1 3.20L, 92% predicted) and FVC in the setting of normal TLC and ratio, normal DLCO (94%). Diagnosis of LAM is made.

**Question 4: Four weeks after her hospitalization, she feels well. What is the next step for management of this patient?**

- After initial pneumothorax, pleurodesis should be performed.
- Thereafter, continue general supportive care:
  - Avoid tobacco
  - Annual and age-based vaccinations
  - Supplemental oxygen if needed
  - Avoidance of estrogen containing medications
  - Pulmonary rehabilitation
  - Psychosocial support
  - Refer patient to LAM center
- Obtain abdominal-pelvic imaging to assess for renal and extrarenal angiomyolipomas
- PFTs to assess for airflow obstruction, can use bronchodilators if reversibility is present
- For patients with FEV1 <70% predicted:
  - mTOR inhibitors
    1. **Sirolimus** (1mg PO QD targeting a trough level of 5-15 ng/ml)
      - a. 2011 NEJM study showed Sirolimus stabilized lung function, improved functional status, quality of life, and reduced serum VEGF-D levels
    2. **Everolimus** (second-line)

**Question 5: Ms. Jones has a trip to Miami for spring break planned in 1 week. She asks, "can travel by airplane?"**

- Many factors should be considered (degree of lung function impairment, cyst burden, history of pneumothoraces, etc)
- In general, air travel is considered safe for most patients with LAM. However, in patients with reduced reserve, other modes of transportation should be explored
- Risk of pneumothorax in LAM patients <3% based on retrospective series

**Question 6: Ms. Jones asks you about prognosis of her disease and how it compares to other DCLD?**

- **LAM:**
  - Lung function decline rate of ~50-250 ml/year
  - More rapid in S-LAM, premenopausal patients, elevated serum VEGF-D
  - Earlier studies reported median survival of 8-10 years. Newer data show much longer survival with 10-year survival >85%.

- **PLCH:**
  - Variable lung function decline after smoking cessation (and avoidance of second-hand smoke exposure) ranging from resolution to continued progression
  - Monitor lung function via serial PFTs
  - Treatment in progressive decline: corticosteroids (No great data to support use), chemotherapy (vinblastine, cladribine)
- **BHD:**
  - Unclear
  - Renal cancer seen in >25%; screening starts at age 20, Q3 years
- **LIP:**
  - Unclear
  - May progress to MALT

**Question 7: Ms. Jones wants to know if there are any other medications that are an option to treat her disease.**

- Unfortunately, options are limited. Therapies with unclear benefits based on very small studies include statins, doxycycline, hydroxychloroquine, celecoxib
- Patient can consider clinical trials and lung transplantation if disease is severe enough (selection criteria similar to those for other chronic lung diseases)

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