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Diffuse Cystic Lung Disease

An APCCMPD Ambulatory-Care Curriculum Teaching Script

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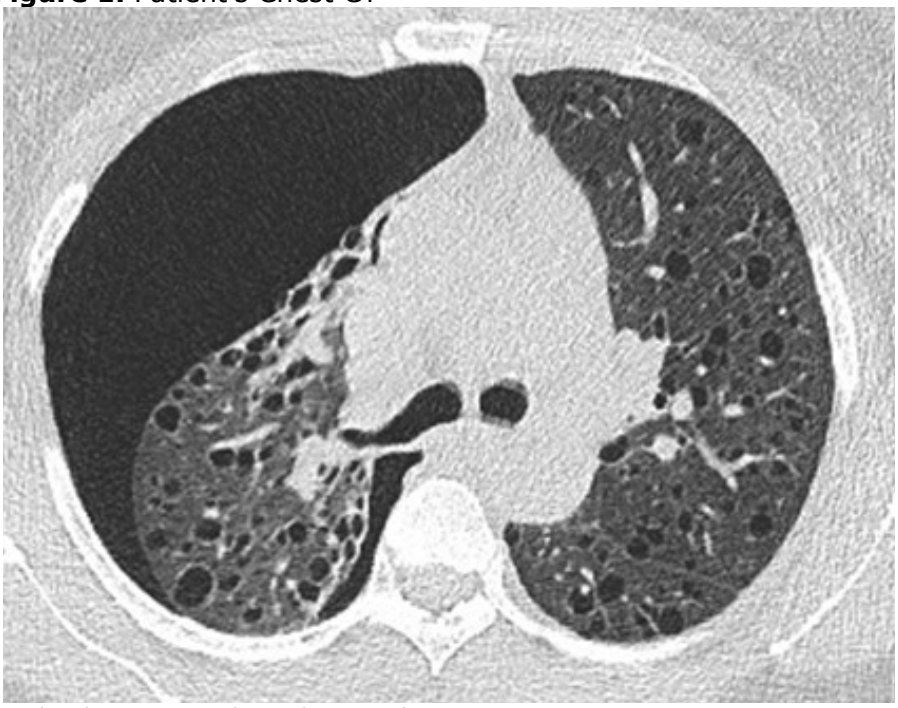
Diffuse Cystic Lung Disease

Scenario 1:

Ms. Jones is a 20 year-old woman, 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 right-sided pneumothorax on chest CT (Figure 1). She was successfully treated with chest tube thoracostomy and sent home. She follows up in your pulmonary clinic today. She feels well with no significant respiratory complaints.

Figure 1. Patient's Chest CT



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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?

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?

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

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Scenario 1 (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 FEV1/FVC 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?

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

Question 6: Ms. Jones asks you about prognosis of her disease and how it compares to other diffuse cystic lung diseases. What do you tell her?

Diffuse Cystic Lung Disease

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

Scenario 1:

Ms. Jones is a 20 year-old woman, 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 right-sided pneumothorax on chest CT (Figure 1). She was successfully treated with chest tube thoracostomy and sent home. She follows up in your pulmonary clinic today. She feels well with no significant respiratory complaints.

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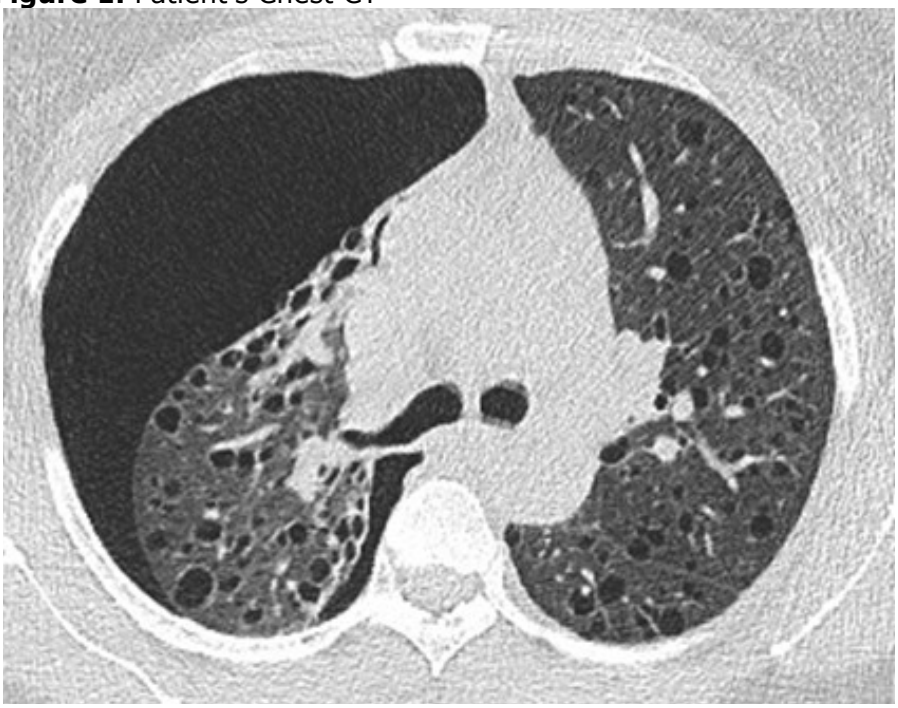

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Question 1: In addition to the pneumothorax, the radiologist notes some cystic changes on her scan. The cysts are small, round and uniform with a lower lobe predominance. How are the different types of cystic changes on CT characterized?

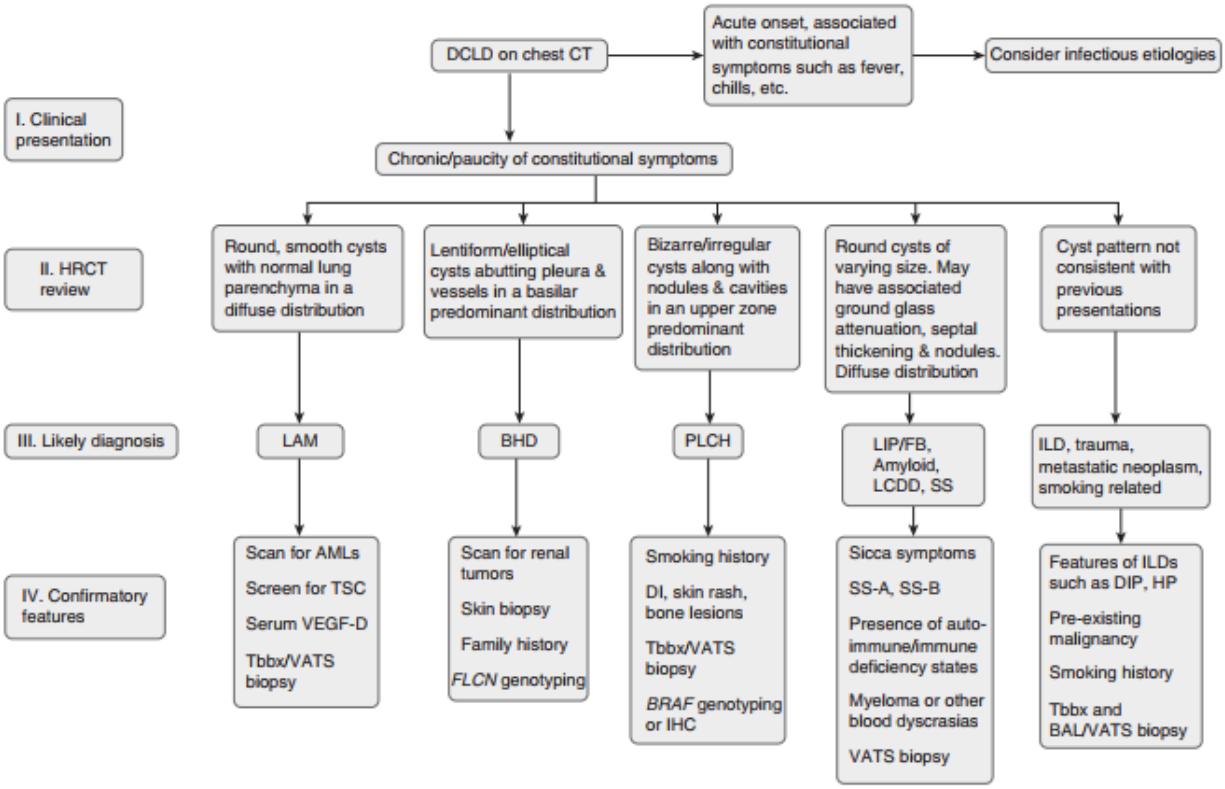
Cystic changes constitute:

- **Cysts**: thin walled (<2 mm), spherical parenchymal lucency or low attenuation area with a well-defined interface with normal lung, occur without associated emphysema
- **Bulla**: spherical focal lucency, > 1 cm in diameter, bounded by thin wall, often accompanied by emphysema in adjacent lung
- **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?

The differential diagnosis for cystic lung disease is broad, though 4 of the common considerations are: LAM (Lymphangioleiomyomatosis), PLCH (Pulmonary Langerhans Cell Histiocytosis), BHD (Birt-Hogg-Dube syndrome), and LIP (Lymphocytic interstitial pneumonia). There are several algorithmic approaches to the diagnosis of diffuse cystic lung disease primarily based on radiographic appearance, patient characteristics, and extrapulmonary findings (Figures 2, 3, and 4).

Figure 2. Diffuse Cystic Lung Disease Diagnostic Algorithm



LCDD = light-chain deposition disease; SS = Sjogren syndrome

Figure taken from Gupta, N., et al. (2015). Diffuse cystic lung disease. Part II. American Journal of Respiratory and Critical Care Medicine, 192(1), 17–29.

Figure 3. Diffuse Cystic Lung Disease Diagnostic Algorithm (Alternate)

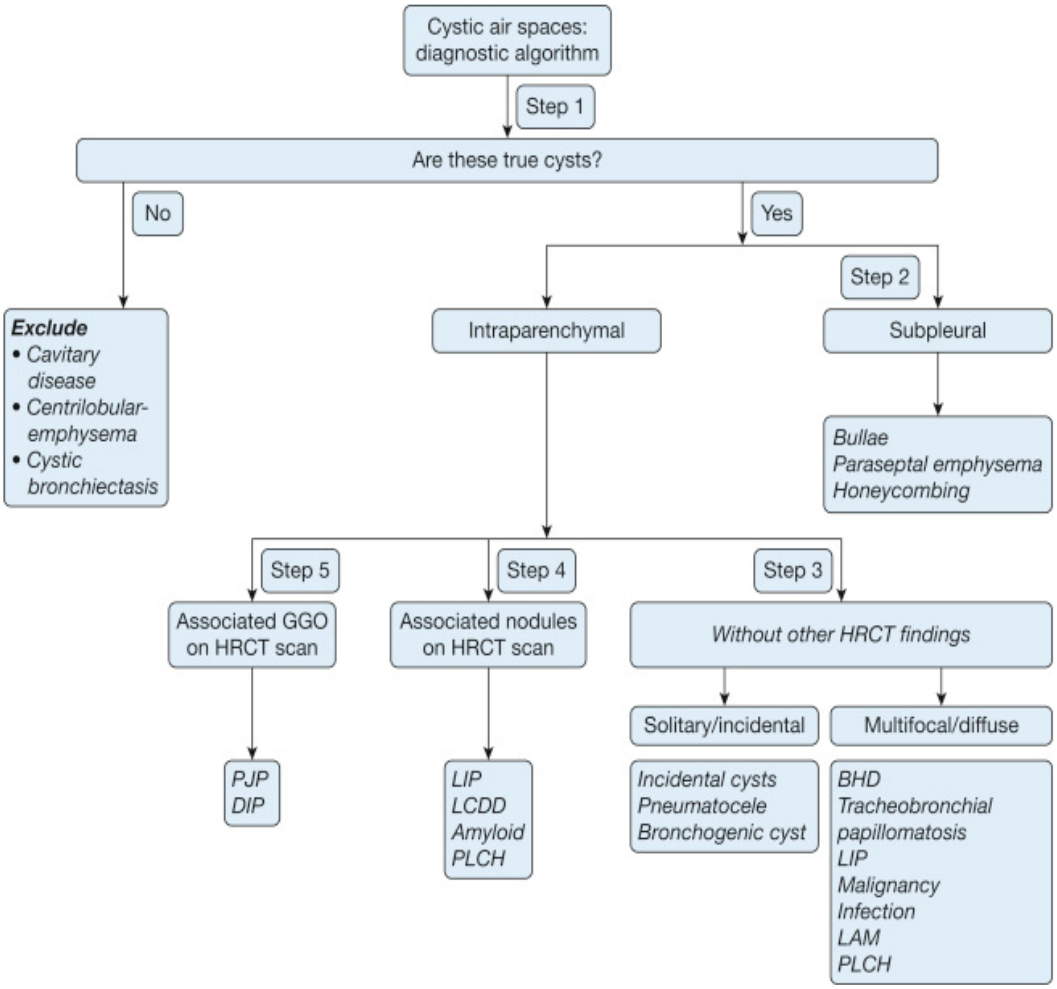


Figure taken from Raoof, S., et al. (2016). Cystic lung disease: Algorithmic approach. *Chest, 150*(4), 945–965.

Figure 4. 2025 CHEST Clinical Algorithm for Cystic Lung Disease Diagnosis

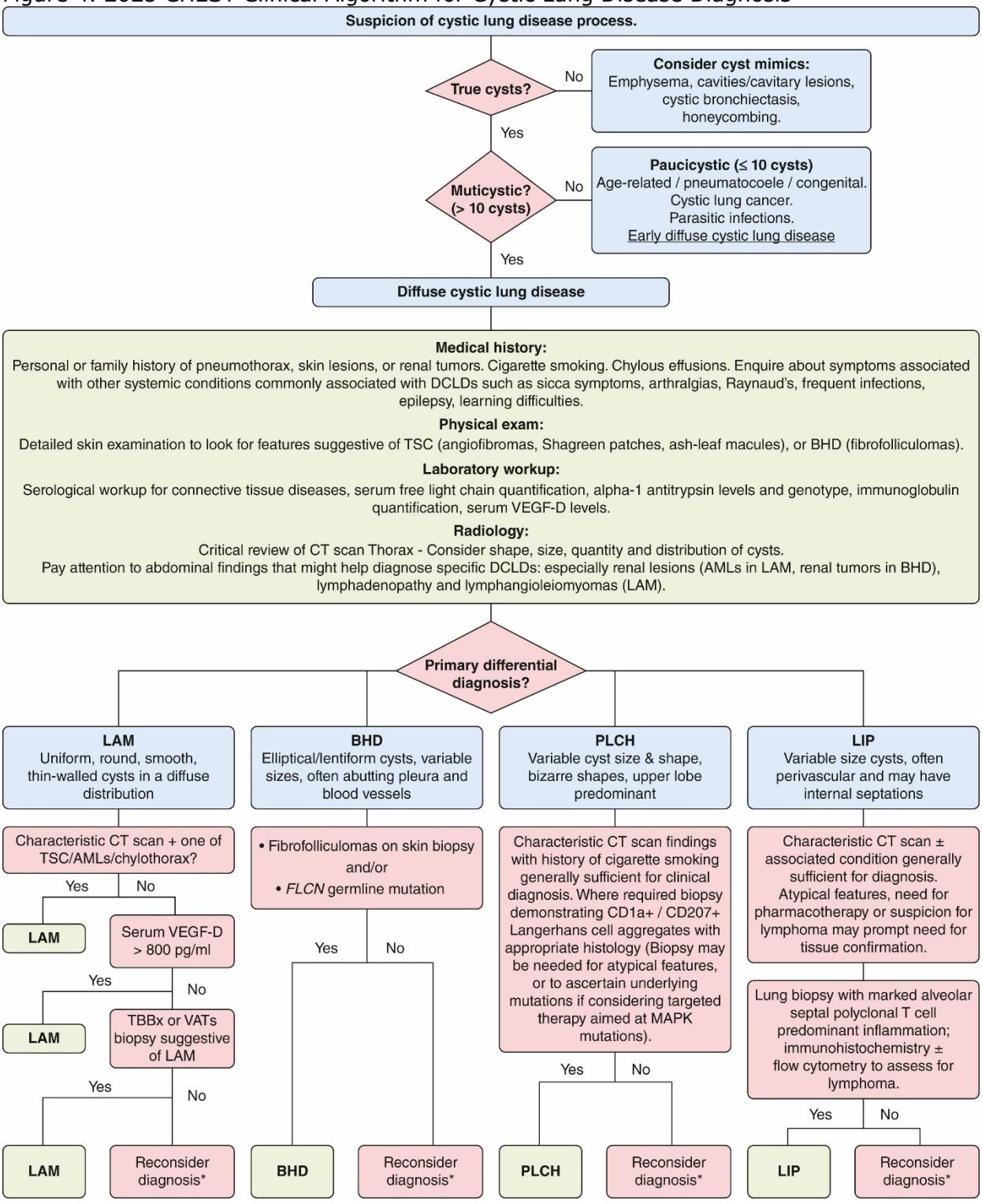


Figure taken from Franciosi, AN et al. Diffuse Cystic Lung Disease: A Clinical Guide to Recognition and Management Chest 2025

1. **Lymphangioleiomyomatosis (LAM)**
    a. **Characteristics**:
        i. Sporadic LAM or in association with tuberous sclerosis complex (TSC)-LAM
        ii. Sporadic LAM is a disease almost exclusive to women of childbearing age
    b. **Symptoms/Exam**:
        i. 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)
        ii. Renal angiomyolipomas (seen up to 30% of patients with LAM)
        iii. Cutaneous or neurologic manifestations of TSC or known TSC diagnosis
    c. **CT Findings**:
        i. Round, uniform cysts measuring 3-5 mm, diffusely distributed including juxtaphrenic recesses
    d. **Diagnostics**:
        i. Serum VEGF-D level >800 pg/mL (send-out lab to Cincinnati Children's Hospital)
        ii. HMB-45+ LAM cells on pathology or histology

2. **Pulmonary Langerhans Cell Histiocytosis (PLCH)**
    a. **Characteristics**:
        i. Current or prior smoking history, young adults (20-40 years)
    b. **Symptoms**:
        i. Nonproductive cough and dyspnea, spontaneous pneumothorax, weight loss, fatigue, chest pain, fever, bone pain or fracture
    c. **CT**:
        i. Early disease: Bronchiolocentric nodules
        ii. Later disease: irregular, bizarre shaped cysts & stellate-shaped fibrotic scars; upper lung zone predominance
    d. **Diagnostics**:
        i. Pathology with Langerhans cells stain S-100 positive, CD1a-positive
        ii. BAL with >5% of cells with CD1a immunostaining

3. **Lymphocytic interstitial pneumonia (LIP)**
    a. **Characteristics**:
        i. More common in women; often seen in 4^{th}-6^{th} decade
        ii. Associated with variety of autoimmune syndromes or immunodeficiency (Sjogren's syndrome, RA, SLE, HIV, CVID, hSCT)
    b. **Symptoms**:
        i. Cough and dyspnea; fever, night sweats, weight loss
    c. **CT**:
        i. Diffuse, ground-glass opacity, poorly defined centrilobular nodules, interlobular septal thickening, and diffuse scattered cysts
        ii. Cysts may have basilar and peribronchovascular predominance; often affect <10% of lung
    d. **Diagnostics**:
        i. Lung biopsy with diffuse interstitial polyclonal lymphocytic infiltrate

4. **Birt-Hogg-Dube Syndrome (BHD)**
    a. **Characteristics**:
        i. Autosomal dominant, strong family history
        ii. Occurs in 30-40-year olds
    b. **Symptoms**:
        i. Spontaneous pneumothorax
        ii. Skin lesions (fibrofolliculomas), renal tumors
    c. **CT**:
        i. Variable cyst size and morphology (round, oval, lentiform), subpleural, lower lung zone predominance
        ii. Unaffected lung is normal in appearance
    d. **Diagnostics**:
        i. *FLCN* genetic evaluation
        ii. Skin biopsy if fibrofolliculomas are present

5. **Amyloid/Light Chain Deposition Disease**
    a. **Cystic amyloidosis**:
        i. Can be associated with Sjogren's syndrome and other CTDs, systemic AL amyloidosis, or MALT lymphoma
    b. **LCDD**:
        i. Multisystem disease (renal, heart, liver, lung); Associated with underlying plasma cell dyscrasia (multiple myeloma, Waldenstrom)
    c. **CT**:
        i. round, variable cysts in diffuse random distribution; nodules abutting cyst walls
    d. **Diagnostics (pathology)**:
        i. Amyloid – amorphous protein deposits with apple-green birefringence by Congo red stain under polarized light
        ii. LCDD – monotypic kappa light chain deposition without apple-green birefringence by Congo red stain under polarized light
6. **Other**
    a. Infections: PJP, echinococcosis, coccidioidomycosis, recurrent respiratory papillomatosis (HPV)
    b. Desquamative interstitial pneumonia
    c. Hypersensitivity pneumonitis, sarcoidosis
    d. 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?

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 a combination of clinical, radiologic, and lab data.

- Expert radiologists and expert pulmonologists can diagnose LAM via HRCT with accuracy of >80% (Gupta N et al. 2015).

After HRCT, possible next steps depending on diagnostic suspicion:

1. Serum biomarkers
    a. LAM: VEGF-D level (Diagnostic >=800 pg/mL)
2. Genetic testing
    a. PLCH: BRAF, MAP2K1
    b. BHD: FLCN
3. Further imaging
    a. LAM: CT or MRI of abdomen to screen for lymphangiomyomas or renal angiomyolipomas; consider MRI brain
    b. PLCH: PET scan can detect extrapulmonary lesions
    c. BHD: CT or MRI of abdomen to screen for renal tumors
4. Skin biopsy
    a. BHD: punch biopsy of skin fibrofolliculomas
5. Pulmonary function testing
    a. LAM: obstruction, air trapping, reduced diffusion; may be normal
    b. PLCH: variable, early (restrictive), late (obstruction)
    c. LIP: restriction, reduced DLCO
    d. BHD: Often normal
6. Bronchoscopy for EBUS/transbronchial biopsy (Xu et al. 2021; Vassallo et al. 2004)
    a. LAM: yield 60%
    b. PLCH: yield 30%
    c. LIP: yield is low
7. VATS
    a. May be required if unable to make a diagnosis with less invasive means

Scenario 1 (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 (3.20L, 92% predicted) and FVC in the setting of normal TLC and FEV1/FVC ratio, normal DLCO (94% predicted). A 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?

1. After initial pneumothorax, ipsilateral pleurodesis should be performed.
2. Thereafter, continue general supportive care:
    a. Avoidance of estrogen containing medications
    b. Avoid tobacco
    c. Annual and age-based vaccinations
    d. Supplemental oxygen if needed
    e. Pulmonary rehabilitation
    f. Psychosocial support
    g. Refer patient to LAM center
    h. Lung transplantation consideration as needed
3. Obtain abdominal-pelvic imaging to assess for renal and extrarenal angiomyolipomas
4. PFTs to assess for airflow obstruction, can use bronchodilators if reversibility is present
5. For patients with FEV1 <70% predicted, air trapping, rapid decline in lung function, low DLCO or exertional desaturation, symptomatic chylous effusions, or high burden of cystic disease:

a. mTOR inhibitors (continued indefinitely, as tolerated)
    i. **Sirolimus** (1-2 mg PO QD targeting a trough level of 5-15 ng/ml, typically around 10)
        1. 2011 *NEJM* study (MILES trial) showed sirolimus stabilized lung function, improved functional status, quality of life, and reduced serum VEGF-D levels
    ii. **Everolimus** (second-line)

Disease-specific management considerations for other etiologies of cystic lung disease:

1. **PLCH**
    a. Mainstay of therapy is smoking cessation, including marijuana smoking cessation
    b. Systemic therapy: considered in refractory cases
        i. **Cladribine** has been shown to have high response rate, though disease progression in 5-year follow up period is ~30%
            1. Phase II: Cladribine improved lung function in half of the patients at 1 year (Benattia et al. ERJ 2026; 67(5): 2501464)
        ii. Systemic corticosteroids are not recommended
    c. ICS may be used in those with evidence of reversible obstruction
2. **BHD**
    a. Primary goal is prevention of pneumothoraces
        i. Consider pleurodesis after first episode of spontaneous pneumothorax
        ii. Tobacco avoidance
    b. mTOR inhibitors (ie rapamycin) are considered, though efficacy in preventing cyst formation has not been demonstrated
3. **LIP**
    a. Treatment of underlying condition; often corticosteroid responsive
    b. IVIG used in case of CVID-associated LIP

Question 5: Ms. Jones has a trip to Miami for spring break planned in 1 week. She asks, "Can I 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 per flight 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?

1. **LAM:**
    a. Lung function decline rate of ~50-250 ml/year
    b. More rapid in S-LAM, premenopausal patients, elevated serum VEGF-D
    c. Earlier studies reported median survival of 8-10 years. Newer data show much longer survival with 10-year survival >85%; estimated median transplant-free survival 23 years from diagnosis

2. **PLCH**:
    a. Variable lung function decline after smoking cessation (and avoidance of second-hand smoke exposure) ranging from resolution to continued progression
    b. Monitor lung function via serial PFTs
    c. Treatment in progressive decline: corticosteroids (no great data to support use), chemotherapy (vinblastine, cladribine)
3. **BHD**:
    a. Unclear / variable clinical course
4. Renal cancer seen in >25%; Screening starts at age 21 or at the time of diagnosis and should be performed at least every 36 months until a renal mass is detected. Once a lesion is detected, the imaging frequency should be individualized based on tumor size and growth rate. Ultrasonography may miss small isoechoic tumors. CT or MRI is preferred, with MRI favored when possible to limit radiation exposure. **LIP**:
    a. Unclear / variable clinical course
    b. Approximately 5% of patients with LIP acquire malignant, low-grade, B-cell lymphoma

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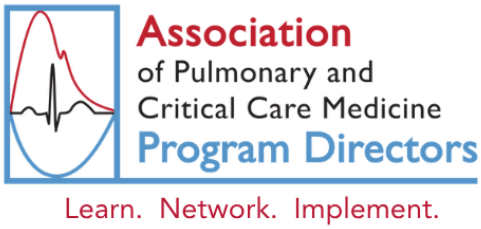

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