

Chapter 18

Approach to the Diagnosis and Management of Diffuse Cystic Lung Diseases



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Introduction

Diffuse cystic lung diseases (DCLDs) are a heterogeneous group of diseases that differ significantly with respect to pathogenesis, clinical course, treatment, and prognosis. Underlying DCLD is usually discovered in one of the following scenarios:

1. Patients presenting with chronic respiratory symptoms such as cough and/or dyspnea on exertion.
2. Patients presenting with acute onset symptoms due to complications such as spontaneous pneumothorax.
3. Screening in at-risk populations such as adult women with tuberous sclerosis complex (TSC) or those with personal or family history of other genetic conditions such as Birt-Hogg-Dubé (BHD) syndrome.
4. Incidentally discovered abnormalities on chest or abdomen imaging done for other reasons.

Patients with DCLDs can have respiratory symptoms such as cough and dyspnea, and it is not uncommon to misdiagnose patients as having one of the more prevalent diseases such as chronic obstructive pulmonary disease or asthma. Pneumothorax is another common complication and can be the presenting

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manifestation of underlying DCLDs, thereby confusing the picture with primary spontaneous pneumothorax [1]. A detailed knowledge about these diseases is thus necessary for proper management of these patients. Chest high-resolution computed tomography (HRCT) remains the single most useful noninvasive diagnostic test for the evaluation of suspected DCLDs. DCLDs often have characteristic imaging findings, which can help narrow the differential diagnoses. Frequently, a confident diagnosis can be made based on CT findings and integration with clinical information. However, confirmatory tests, by either laboratory testing, tissue biopsy, or genetic analysis may be required in some cases, where clinico-radiological information is not sufficient to establish a confident diagnosis.

In this chapter, we summarize the approach toward the proper diagnosis and management of patients presenting with DCLD. In particular, we focus on the major causes of DCLDs that are most likely to be encountered in clinical practice: lymphangioleiomyomatosis (LAM), BHD, pulmonary Langerhans cell histiocytosis (PLCH), lymphocytic interstitial pneumonia (LIP)/follicular bronchiolitis (FB), amyloidosis/light chain deposition disease (LCDD), and malignancy.

Clinical Evaluation

History

A thorough and comprehensive history may provide invaluable information that can help identify the underlying etiology of DCLDs. The development of acute, rapidly progressive cystic change is usually suggestive of an infectious, inflammatory, or traumatic origin, whereas chronic processes are more likely to be secondary to neoplastic, congenital, lymphoproliferative, or other slowly progressive disorders [2].

Patient demographics may make certain diseases more likely than others. Diseases such as congenital pulmonary airway malformation (CPAM), bronchopulmonary dysplasia, and other congenital malformations are seen primarily in childhood but can uncommonly present *de novo* in the adult [3, 4]. Sporadic LAM is almost exclusively seen in women. While approximately 10–15% of men with TSC can have pulmonary cysts characteristic of LAM, symptomatic LAM in TSC is almost exclusively restricted to women. There is a strong association between cigarette smoking and diseases that can present with cystic changes in the lungs such as PLCH, desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis, such that the presence of these diseases is unlikely in a never-smoker.

Detailed family history is an important component of history taking when evaluating patients with DCLDs. Family history of pulmonary cysts on chest imaging, pneumothoraces, skin lesions, or renal tumors can be suggestive of BHD or TSC-LAM. A history of pneumothorax within the second-degree relatives is much more suggestive of BHD than LAM [5].

Common respiratory symptoms attributable to DCLDs include cough and dyspnea on exertion. Cough is usually nonproductive; however, hemoptysis and chyloptysis can occur in a small proportion of patients with LAM [6]. Dyspnea is rare in patients where cysts or other parenchymal abnormalities are limited such as in BHD. Dyspnea can however develop or worsen acutely due to a spontaneous pneumothorax. Spontaneous pneumothorax is more common in patients with LAM, BHD and PLCH, as opposed to the other DCLDs, and usually presents in the third or fourth decade of life similar to the overall demographic of patients with a primary spontaneous pneumothorax. However, in contrast to primary spontaneous pneumothorax, DCLD patients presenting with a spontaneous pneumothorax have a much higher risk of recurrence if treated conservatively [7]. Pneumothorax can also occur in patients with *Pneumocystis jiroveci* pneumonia (PJP), connective tissue disorders such as Marfan and Ehlers-Danlos syndrome, and patients with cystic pulmonary metastases especially from underlying sarcomas such as osteogenic sarcoma, angiosarcoma, and synovial cell sarcoma with higher reported rates in patients on chemotherapy [8].

A complete review of systems is essential and often provides helpful diagnostic clues. The presence of sicca symptoms, dental caries, increased thirst, arthritis/synovitis, skin rash, and/or Raynaud's can suggest autoimmune LIP/FB as the cause of the DCLD. Frequent infections might suggest underlying immune deficiency states such as HIV and common variable immune deficiency (CVID), which are associated with LIP/FB. History of bone pain, skeletal lesions, and/or polydipsia may be a feature of extrapulmonary involvement due to histiocytic disorders such as PLCH and Erdheim-Chester disease. A subset of LAM patients may experience chylous discharge through urine, stool, or vagina. Cyclical variation of symptoms in conjunction with their menstrual cycles and post-coital hemoptysis may also be present in a subset of LAM patients.

Presence of certain diseases or manifestations can help narrow down the differential diagnosis (Table 18.1). Skin lesions and/or renal tumors can be seen in patients with BHD and in patients with TSC-LAM. Presence of DCLD in patients with TSC is highly suggestive of LAM. Similarly, the presence of renal angiomyolipomas or co-existing chylous effusions in women with characteristic cystic change on chest CT is considered diagnostic for LAM. FB/LIP is associated with a wide variety of underlying systemic autoimmune diseases, lymphoproliferative diseases, and immunodeficiency states (e.g., common variable immunodeficiency, HIV). Pulmonary amyloidosis and LCDD are commonly associated with underlying plasma cell dyscrasias or connective-tissue disorders, particularly Sjögren's, where MALT lymphoma may also be seen [9–11]. Common clinical features of systemic amyloidosis include nephrotic syndrome with or without renal insufficiency, congestive cardiomyopathy, sensorimotor and/or autonomic peripheral neuropathy, hepatomegaly, macroglossia, and hemostatic abnormalities [12]. Patients with LCDD often have co-existing renal involvement, usually in conjunction with hematological malignancies such as multiple myeloma or lymphoma [13, 14].

Table 18.1 Clinical features of diffuse cystic lung diseases

Organ system involved	Typical manifestations	DCLD associations
Dermatologic	Hypomelanotic macules, ash-leaf spots, shagreen patch, subungual fibromas, skin tags, and café au lait spots	TSC-LAM
	Fibrofolliculomas	BHD
	Papulonodular rash	PLCH
	Petechiae, purpura, nail dystrophy	Amyloidosis
Nervous system/ocular	Cognitive impairment, seizures, subependymal giant cell astrocytomas, cortical glioneuronal hamartomas, subependymal nodules, retinal phakomas	TSC-LAM
	Diabetes insipidus	PLCH
	Neuropathy	Amyloidosis
Cardiac	Cardiomyopathy	Amyloidosis
Thoracic	Pneumothorax	LAM, BHD, PLCH
	Chylous pleural effusions	LAM
Abdominal/GI/GU	Angiomyolipomas	LAM
	Chylous ascites	LAM
	Renal neoplasms: hybrid oncocyctic tumors, chromophobe renal cell carcinomas, clear cell renal cell carcinomas, and renal oncocytomas	BHD
	Splenomegaly	CVID/LIP
	Hepatomegaly	Amyloidosis
	Proteinuria, renal failure	LCDD, amyloidosis
Musculoskeletal	Lytic bone lesions	PLCH
	Sclerotic bone lesions	TSC-LAM, ECD
	Raynaud's phenomenon	LIP/FB secondary to CTD
Others	Fatigue	LAM, PLCH, autoimmune and immune dysregulatory disorders such as Sjögren's, lupus, and CVID
	Sicca symptoms	Sjögren's, amyloidosis
	Lymphadenopathy	PLCH, LAM, amyloidosis, other lymphoproliferative disorders
	Lymphangioliomyomas	LAM
	Macroglossia	Amyloidosis

BHD Birt-Hogg-Dubé syndrome, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *DCLD* diffuse cystic lung diseases, *ECD* Erdheim-Chester disease, *FB* follicular bronchiolitis, *GI* gastrointestinal, *GU* genito-urinary, *LAM* lymphangioliomyomatosis, *LCDD*, light chain deposition disease, *LIP* lymphocytic interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *TSC* tuberous sclerosis complex

Physical Examination

Pulmonary exam is usually not specific enough to help ascertain a diagnosis in patients with DCLDs. Wheezing is rare in DCLDs and if present usually suggests underlying COPD or asthma. Bibasilar rales can be heard in patients with LIP or other ILDs with interstitial infiltrates or fibrosis. A high-pitched blowing sound termed “amphoric breathing” can sometimes be heard in cases of large cysts communicating with the bronchus due to turbulent airflow [15]. Diminished breath sounds on one side compared to the contralateral side might suggest the presence of a pneumothorax.

In contrast to the limited utility of pulmonary examination in patients with suspected DCLDs, extrapulmonary findings can often provide clinically useful diagnostic clues. Clubbing is rare and, if present, can be suggestive of underlying malignancy. Particular attention must be paid to the signs of underlying connective tissue disease or skin findings suggestive of BHD or TSC. Patients with BHD often have characteristic skin fibrofolliculomas, which are white to flesh-colored papules, 2–4 mm in size, on the face, neck, ear lobes, and upper trunk, and are not painful or pruritic. These lesions can be difficult to differentiate from perifollicular fibroma and angiofibromas, which are more commonly seen in TSC [16, 17]. Uncommonly, skin lesions presenting as brown to purplish papules and eczematoid or seborrhealike lesions can be seen in patients with PLCH [18]. Petechiae, purpura, and nail dystrophy can be seen in patients with systemic amyloidosis [19]. Presence of connective tissue disorders such as skeletal anomalies, hyperextensibility, and distinct facial features could suggest a genetic syndrome such as Marfan or Ehlers-Danlos syndrome.

Diagnostic Evaluation

Laboratory testing can be a useful adjunct to aid in establishing the diagnosis of DCLDs (Table 18.2). Serum vascular endothelial growth factor-D (VEGF-D) levels are elevated in women with sporadic LAM compared to healthy controls and patients with other DCLDs, and serum VEGF-D levels ≥ 800 pg/mL are considered diagnostic in patients with typical CT features [20, 21]. A probable diagnosis of LAM based on serum VEGF-D levels ≥ 600 pg/mL may be sufficient in some situations, such as for patients who have a low burden of disease that would not justify treatment, or those who are not interested in therapies or interventions [21]. It is critical to not confuse VEGF-D quantification with the more commonly commercially available VEGF quantification. In the United States, serum VEGF-D testing performed in a manner meeting College of American Pathologists (CAP)/Clinical Laboratory Improvements Amendments (CLIA) standards is only available at the

Table 18.2 Useful laboratory tests for patients with diffuse cystic lung diseases

Laboratory test	Indication	Interpretation
ANA, anti-Ro/SSA and anti-La/SSB antibodies, RF, anti-CCP	Suspected CTD	High titers suggest underlying CTD. CTD can be associated with LIP
Serum immunoglobulins	Suspected LIP, immunodeficiencies	Hypergammaglobulinemia in LIP associated with autoimmune conditions such as Sjögren's; Hypogammaglobulinemia can occur in the setting of CVID; High serum IgE in hyper IgE syndrome
Serum protein electrophoresis, serum immunofixation, and serum-free light chain quantification	Suspected amyloidosis, LCDD	Combined testing increases sensitivity; Addition of urine immunofixation and urine protein electrophoresis can further increase sensitivity; Altered free light chain ratio can be present in patients with LCDD; Can be positive in a variety of plasma cell dyscrasias and lymphoproliferative disorders
HIV	Suspected HIV	HIV can be associated with LIP or infections such as PJP
Serum VEGF-D	Suspected LAM	Serum VEGF-D ≥ 800 pg/mL is highly specific for the diagnosis of sporadic LAM in women with compatible radiologic features

BHD Birt-Hogg-Dubé syndrome, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *DCLD* diffuse cystic lung diseases, *ECD* Erdheim-Chester disease, *FB* follicular bronchiolitis, *GI* gastrointestinal, *GU* genito-urinary, *LAM* lymphangioliomyomatosis, *LCDD* light chain deposition disease, *LIP* lymphocytic interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *TSC* tuberous sclerosis complex, *ANA* anti-nuclear antibody, *CCP* cyclic citrullinated peptide, *HIV* human immunodeficiency virus, *PJP* *Pneumocystis jiroveci* pneumonia, *VEGF-D* vascular endothelial growth factor-D

Translational Trial Development and Support Laboratory based at Cincinnati Children's Hospital Medical Center. Directions for test requisition, sample processing, and shipment are available here: <https://www.testmenu.com/cincinnatichildrens/Tests/665748>.

Autoimmune panel can suggest underlying rheumatological disease, particularly Sjögren's, which can be associated with FB/LIP. Approximately 80% of patients with FB/LIP also have serum dysproteinemias; most commonly hypergammaglobulinemia, but hypogammaglobulinemia can occur in the setting of CVID [22]. Screening for monoclonal proteins should be pursued in patients suspected to have amyloidosis or LCDD. A comprehensive panel that includes serum immunofixation (IFE), serum protein electrophoresis (SPEP), and serum free light chain (FLC) should be ordered to ensure adequate sensitivity [23, 24]. Addition of urine IFE and UPEP can further increase sensitivity particularly in LCDD [24]. Attention should

be paid to the free light chain ratio as this may be the only abnormality present on screening in some patients [25].

Besides the abovementioned labs, genetic analyses can be useful in certain patients. For instance, *FLCN* mutation analysis is available as a diagnostic test and detects mutations in ~90% of patients with BHD and should be considered in patients with family history of pneumothorax, renal tumors, skin lesions, or patients with feature, suggestive of BHD in the absence of a positive family history [26]. Similarly, detection of *TSC1/TSC2* mutations can help confirm the presence of underlying TSC in cases where the clinical criteria for TSC have not been met and there is high clinical suspicion [27].

Pulmonary Function Testing

Pulmonary function testing (PFT) in patients with DCLDs can be normal, or demonstrate obstructive, restrictive, or mixed abnormalities depending on cause and extent of disease. Patients with LAM, PLCH and FB most often have obstructive defects. PFTs are often normal in patients with BHD. While PFTs do not have diagnostic value, they have been shown to correlate with extent of disease on CT and serve as the primary modality used to monitor disease course and response to therapy in patients with DCLDs [28, 29]. In addition, the rate of change in PFTs is a commonly utilized end point in clinical trials aiming to develop novel therapeutic options for DCLD patients.

Radiological Assessment

Chest X-rays are usually not helpful in detailed evaluation of pulmonary cysts but can reveal the presence of pneumothorax or pleural effusions, which can sometimes be seen in patients with DCLDs and may warrant intervention. HRCT scanning is crucial in the evaluation of patients with DCLD. Critical review of the HRCT for cyst characteristics such as shape, size, wall thickness, and distribution, as well as other co-existing findings can reveal patterns that can help accurately diagnose the underlying condition in greater than two-thirds of patients [30–32], and substantially narrow the differential in the rest. The CT features of various DCLDs have been discussed in detail in Chap. 3, and key features are summarized in Tables 18.3 and 18.4, and Fig. 18.1.

Evaluation of cystic lung disease begins with ascertaining that the lesions on HRCT scan are true cysts and not mimics such as cavities, emphysema, and cystic bronchiectasis as discussed in Chap. 14. However, occasionally true cysts and cyst mimics may co-exist in the same patient. Solitary cysts are usually congenital,

Table 18.3 Diagnostic consideration based on CT chest findings

CT findings		DCLD associations
Cyst distribution	Diffuse	LAM
	Upper lobe predominance	PLCH
	Lower lobe predominance	BHD, LIP, amyloidosis/LCDD ^a
Cyst morphology	Smooth, round	LAM
	Lentiform	BHD
	Irregular, dumbbell, bizarre	PLCH
	Internal structures/ septations	BHD, FB/LIP, amyloidosis, malignancy
Associated findings	Nodules	PLCH, cystic metastases, amyloidosis, LCDD, LIP
	Ground-glass opacities	PJP, DIP, LIP
	Lymphadenopathy	LIP, LAM, amyloidosis, LCDD, cystic metastases
	Pleural effusions	LAM, lymphomas, cystic metastases

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^aCan also be diffuse

age-related phenomenon or may be a remnant of prior trauma or infection. Age-related cysts are mostly 1–5 in number, in the peripheral area of the lower lobes and remain unchanged or slightly increase in size over time [33]. These can be seen in people above 40 years old, and the prevalence increases with age. However, all solitary cysts should not be ignored, as malignancy can also present as a solitary cyst. One helpful clue to distinguish between age-related benign solitary/few cysts from malignancy associated-cysts can be the wall thickness; increased wall thickness has been associated with increasing chances of malignancy. However, the reliance on wall thickness is not 100% sensitive or specific as early cancers can present with cystic airspaces that are initially thin but became thicker overtime. Lesions can also develop nodules (endophytic or exophytic) or increase in nodule size or density over time with a consequent decrease in airspace size; however, this is not a consistent feature [34]. Other features suggestive of malignancy are nonuniform cystic walls, cyst septations, ground-glass opacity around the cyst and irregular margins, lymphadenopathy, and presence of solid or nonsolid tissue intermixed with cysts [35–37].

Cysts in LAM are numerous and are uniformly round or oval and diffusely distributed throughout the pulmonary parenchyma. BHD cysts have a lower lung zone predominance, and frequently abut the pleural surface and proximal segments of the lower lobe pulmonary artery or veins. The larger cysts are often irregular or lentiform in shape and can be multiseptated. Another key feature of BHD is the elliptical

Table 18.4 Summary of clinical, radiological, and pathologic features of major DCLEDs

	LAM	PLCH	BHD	LIP/FB	Amyloidosis/LCDD
Clinical features					
Clinical features	Dyspnea, Pneumothorax, Chylothorax	Dyspnea, Cough, Pneumothorax, Constitutional symptoms such as fatigue, weight loss, and fever	Pneumothorax, Family history of pneumothorax	Dyspnea, Symptoms suggestive of underlying etiologies such as sicca symptoms associated with Sjögren's	Dyspnea
Typical age at diagnosis (years)	20–40	20–40	30–40	Variable	Variable
Gender	F >> M	F = M	F = M	F > M	Unknown
Smoking	–	+++	–	–	–
Family history	+/- Absent in sporadic LAM. Autosomal dominant in TSC	–	++ (autosomal dominant)	–	–
Pneumothorax	+++	++	+++	Unknown, almost certainly less than LAM, BHD, and PLCH	Unknown, almost certainly less than LAM, BHD, and PLCH
Extrapulmonary manifestations	AMLs, lymphadenopathy, lymphangioliomyomas, chyloous effusions; TSC and its associated systemic manifestations such as seizures, cognitive impairment, and skin lesions	Diabetes insipidus, Lytic bone lesions, Skin rash	Skin fibrofolliculomas, Renal tumors	Sicca symptoms, Other varying manifestations according to underlying disease such as arthralgia, synovitis, skin rash, Raynaud's, and frequent infections	Lymphoproliferative disorders, renal failure, systemic amyloidosis, hematologic malignancies

(continued)

Table 18.4 (continued)

	LAM	PLCH	BHD	LIP/FB	Amyloidosis/LCDD
HRCT features					
Cysts					
Distribution	Diffuse, random	Upper and middle lung zones; spares costophrenic angles	Basilar, subpleural especially the paramediastinal regions, also tend to abut vessels	Diffuse, random, often with eccentric vessels	Diffuse, random
Shape	Round, uniform	Bizarre, irregular, variable wall thickness	Elliptical, lentiform	Round, variable; may contain internal structure/septations	Round, variable
Size	2 mm to 2 cm	Variable, 2 mm to >2 cm	Mostly <1 cm	Variable, 3 mm to >3 cm	Mostly <2 cm
Nodules	+/- Absent in sporadic LAM. Common in patients with TSC-LAM where they represent a benign condition known as multifocal micronodular pneumocyte hyperplasia (MMPH)	++ Micro and macro nodules with or without cavitation	-	+/- Centrilobular, usually micronodules. Larger nodules may be suggestive of underlying MALT lymphoma	+++ Nodules – can be large
Ground-glass opacities	- Except in rare circumstances where they may represent chylous congestion of the pulmonary parenchyma	- Except in patients with concomitant smoking-related pathologies such as DIP	-	+++	-
Other HRCT findings	Pleural effusions in ≤20% of patients. More common in sporadic LAM than TSC-LAM	Reticulations	-	Interlobular septal thickening Air-trapping	Lymphadenopathy

Diagnostic testing					
Laboratory	Serum VEGF-D	Serum and urine studies for diabetes insipidus	–	Polyclonal dysproteinemia ANA, anti-SSA, anti SSB (Sjögren's) HIV, quantitative immunoglobulins	Monoclonal dysproteinemia Light chain immunoglobulins
Genetic testing	Typically not needed for the diagnosis of sporadic LAM. Germline <i>TSC</i> mutations in <i>TSC-LAM</i>	<i>BRAF</i> and other <i>MAPK</i> pathway mutations such as <i>NRAS</i> and <i>MAP2K1</i>	Germline <i>FLCN</i> gene mutations	–	–
Diagnostic yield of TBBx	>50%	30–50%	0	Unknown, likely <30%	Unknown, likely not helpful
Typical histopathological findings on lung biopsy	Infiltration by HMB-45 + ve LAM cells with smooth muscle phenotype	S100- and CD11a-positive Langerhans cells with intracellular Birbeck granules by electron microscopy; stellate fibrotic scars in late stages	Intra-parenchymal and subpleural cysts abutting interlobular septae and lacking abnormal cell proliferations or significant fibro-inflammatory component	LIP: diffuse interstitial polyclonal lymphocytic infiltrate FB: Peribronchiolar polyclonal follicular lymphoid hyperplasia with germinal centers	Amyloid: amorphous protein deposits with fibrillar ultrastructure and apple-green birefringence by Congo red stain viewed under polarized light LCDD: typically monotypic kappa light chain deposition with finely granular ultrastructure lacking apple-green birefringence by Congo red stain and polarized light

(continued)

Table 18.4 (continued)

LAM	PLCH	BHD	LIP/FB	Amyloidosis/LCDD
Other histopathological features		Skin biopsy showing fibrofolliculomas	Lip biopsy showing focal lymphocytic sialadenitis in Sjögren's	Abdominal fat pad or bone marrow biopsy showing amyloid or light chain deposition

Modified from Gupta et al. [2]

BH Birt-Hogg-Dubé syndrome, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *DCLD* diffuse cystic lung diseases, *ECD* Erdheim-Chester disease, *FB* follicular bronchiolitis, *GI* gastrointestinal, *GU* genito-urinary, *LAM* lymphangioleiomyomatosis, *LCDD* light chain deposition disease, *LIP* lymphocytic interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *TSC* tuberous sclerosis complex, *ANA* anti-nuclear antibody, *CCP* cyclic citrullinated peptide, *HIV* human immunodeficiency virus, *PJP Pneumocystis jirovecii* pneumonia, *VEGF-D* vascular endothelial growth factor-D, *CT* computed tomography, *DIP* desquamative interstitial pneumonia, *AML* angiosarcoma, *BRAF* v-Raf murine sarcoma viral oncogene homolog B, *F* female, *HMB* human melanoma black, *M* male, *MALT* mucosa-associated lymphoid tissue, *MAPK* mitogen-activated protein kinase

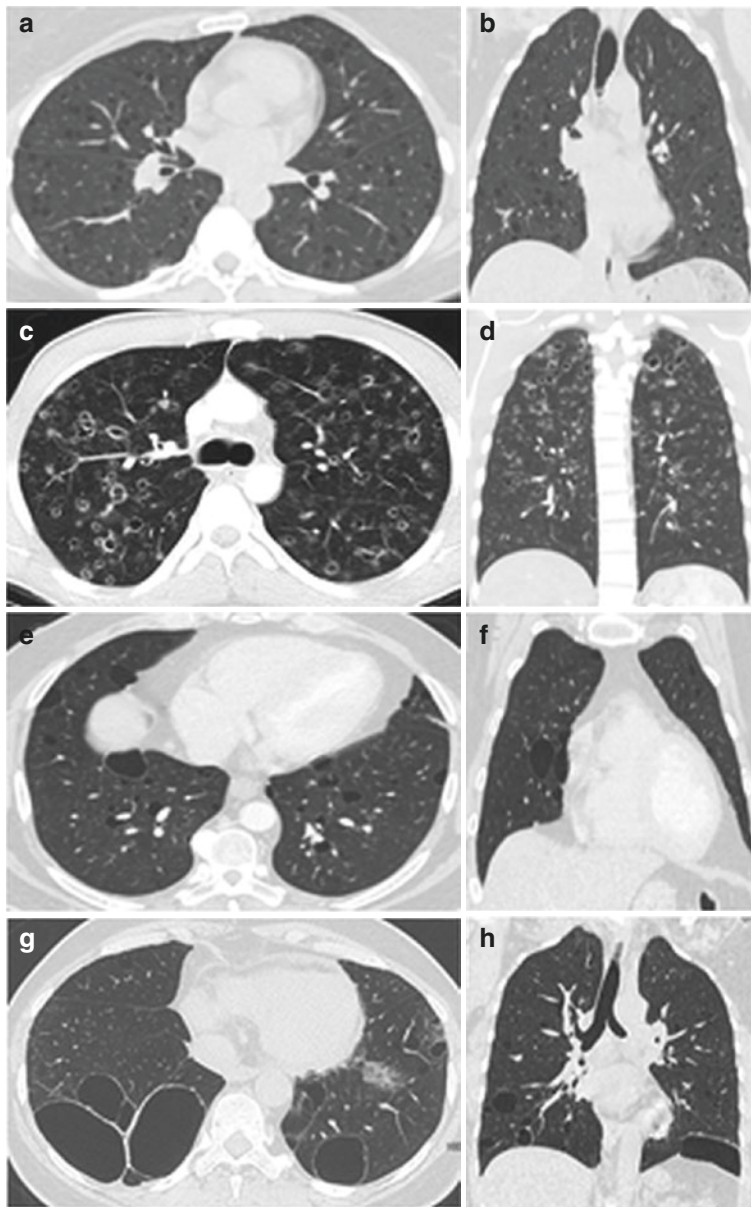


Fig. 18.1 Chest computed tomography images of common diffuse cystic lung diseases. (a) Axial and (b) coronal cuts on high-resolution chest computed tomography (HRCT) of a patient with lymphangioliomyomatosis showing multiple smooth, round, thin-walled parenchymal cysts. (c) Axial and (d) coronal cuts on HRCT chest of a patient with pulmonary Langerhans cell histiocytosis showing multiple nodules and cysts. (e) Axial and (f) coronal cuts on HRCT chest of a patient with Birt-Hogg-Dubé syndrome showing lentiform cysts in a basilar distribution. (g) Axial and (h) coronal cuts on HRCT chest of a patient with lymphocytic interstitial pneumonia in a patient with showing multiple cysts of varying sizes and ground-glass opacities

(floppy) paramediastinal cysts; the presence of three or more elliptical paramediastinal cysts or disproportionate paramediastinal cysts is considered to be pathognomonic of BHD [38]. Recently, a quantitative analysis using paired inspiratory and expiratory CTs for estimating the extent of cyst-airway communication has been found to be useful in distinguishing BHD from other DCLDs [39].

The cysts in PLCH have varying sizes and shapes, with a predominance in the mid and upper lung fields and relative sparing of the lung bases and costophrenic angles. FB/LIP cysts vary in size and can be >50–70 mm in diameter and often have eccentric vessels at the periphery. The cysts in LIP are randomly distributed with a slight basal predominance. Lymphoma can complicate cystic lung disease in LIP and should be considered if there is associated nodularity especially large nodules, consolidation, and/or effusions [40]. Cysts in amyloidosis and LCDD are thin-walled, multiple, bilateral, small to medium in size, and often in a peribronchovascular distribution with lower lobe predominance [9, 10, 41].

Besides detailed evaluation of cysts, attention should also be paid to ancillary findings such as nodules, ground-glass opacities, lymphadenopathy, and pleural effusions. Nodules can be seen in PLCH, cystic metastases, LIP, amyloidosis, and LCDD. The presence of calcified nodules is a fairly characteristic finding seen in amyloidosis but not in LCDD and can be used to differentiate between the two conditions [9, 10]. Nodules in LIP are generally small and centrilobular. Ground-glass opacities are often seen in patients with PJP, DIP, and LIP. Due to the presence of smoking exposure in the vast majority of patients with PLCH, co-existing RB/DIP-like changes are commonly seen in PLCH and can cause the appearance of ground-glass attenuation on HRCT [42]. Mediastinal and hilar lymphadenopathy can be seen in LIP, amyloidosis, and cystic metastases. Lymphadenopathy can be bulky and associated with calcification in amyloidosis [43]. Lymphadenopathy can also be seen in patients with LAM; however, the lymphadenopathy in LAM generally tends to follow a reverse cranio-caudal gradient such that the biggest lymph nodes are in the pelvic region and tend to get progressively less bulky along the thoracic duct. Intervening lung parenchyma between cysts appears grossly normal in LAM and BHD. This is especially true for patients with sporadic LAM. Patients with TSC-LAM, however, can have multiple bland appearing nodules in addition to the cystic change. These micronodular changes most commonly represent a benign condition known as multifocal micronodular pneumocyte hyperplasia (MMPH). MMPH does not tend to progress or cause physiological impairment in these subjects [44]. It must be noted that cystic metastasis particularly from endometrial stromal sarcomas can also present exclusively as pulmonary cysts without any other radiographic abnormality [45].

Other radiological imaging may also help in clinching the diagnosis in DCLDs. Abdominal imaging can show renal tumors, which can be suggestive of LAM or BHD. AMLs are pathognomonic of LAM [46], and majority can be easily identified on CT scan and MRI due to their high fat content [47]. Identification of extrapulmonary neoplasms can be suggestive of cystic metastasis. The renal tumors in BHD can be bilateral and multifocal and provide a clue to the underlying diagnosis [48].

18-Fluoro deoxy (FDG) positron emission tomography (PET) scan can sometimes be useful in evaluation of cystic lung lesions. FDG-PET is often positive in lung cancers and metastases but given that lesions smaller than 1 cm may fall below the sensitivity threshold for FDG-PET, it can yield false-negative results when solid components, such as wall thickness or nodule size, are below this threshold [49, 50]. Moreover, FDG-PET is often negative in tumors with low metabolic activity such as low-grade adenocarcinomas and in situ pulmonary adenocarcinomas. FDG-PET may be helpful in assessing extrapulmonary disease activity in patients with PLCH and amyloidosis [51–53]. Within the lungs, a positive FDG-PET scan in PLCH is more likely in patients with early disease associated with predominantly nodular chest CT scan findings and can at times be difficult to differentiate from malignancy [51, 52]. Results for PET-CT in amyloidosis are also variable but a standardized uptake value (SUV) uptake greater than 3.0 should raise suspicion for malignancies or associated lymphoma or plasmacytoma [53]. PET-CT can also be helpful in evaluation for malignancy in patients with Sjögren's where a SUV max in the parotid gland of ≥ 4.7 and/or the presence of focal pulmonary lesions can be highly suggestive of lymphoma [54].

Pathological Evaluation

Pathologic evaluation may be required in patients where diagnosis remains uncertain after a thorough review of the clinical and radiological data. Bronchoalveolar lavage (BAL) has limited diagnostic utility and is primarily useful to rule out infectious etiologies such as PJP. The presence of more than 5% CD1a cells on BAL has been proposed as a confirmatory diagnostic finding in patients with suspected PLCH but is limited by its lack of sensitivity and is not clinically useful in most patients [55]. Bronchoscopy with transbronchial lung biopsy can be helpful in establishing the diagnosis in cases of LAM and PLCH with the diagnostic yield being more than 50% in patients with LAM and 30–50% in patients with PLCH [2]. Transbronchial lung cryobiopsy is a relatively new technique that involves freezing the lung tissue with compressed cold gas and allows the extraction of larger pieces of tissue than the traditional forceps-guided transbronchial lung biopsy. The safety and diagnostic yield of transbronchial lung cryobiopsy in patients with DCLD has not been systematically evaluated. As such, its use is perhaps best reserved in centers with expertise in the technique. Anecdotal evidence suggests that transbronchial lung cryobiopsy may be a potentially useful modality to obtain tissue in DCLD patients and is likely to have better diagnostic yield than conventional transbronchial lung biopsy [56, 57]. Video-assisted thoracoscopic surgery (VATS)-guided surgical lung biopsy remains the gold standard modality to obtain tissue for histopathological confirmation.

On pathology, true cysts have an epithelial cell lining compared to discontinuous epithelial lining resulting from parenchymal loss as seen in emphysema or

post-traumatic pseudocysts. Histological features of BHD cysts are generally not distinctive and may be indistinguishable from those of emphysema, but can include hyperplastic type II pneumocyte-like cells and positive staining for PCNA and p-S6 [58]. LAM, PLCH, amyloidosis, LCDD, and metastatic disease may show diagnostic cellular proliferations or material deposition. Proliferation of spindle cells that stain positive for HMB-45, smooth muscle actin, and estrogen and progesterone receptors is characteristic of LAM, while infiltration with Langerhans cells positive for CD1a, Langerin, and S100 is seen in PLCH [59]. Amorphous eosinophilic material is seen in amyloidosis and LCDD, and distinction can be made based on Congo red staining or material deposition seen on electron microscopy [59]. Cellular interstitial infiltrates are seen in patients with FB/LIP. Immunohistochemical studies and flow cytometry should be performed in order to distinguish between the polyclonal populations of lymphocytes seen in LIP and a monotypic cell population seen in malignant lymphoproliferative disorders.

Occasionally, the diagnosis may be established by biopsy of an involved site outside the thorax. Biopsy of skin fibrofolliculomas can establish the diagnosis of BHD and is particularly important as lung biopsy in patients with BHD is not pathognomonic. Bone biopsy can be pursued for suspected lesions in PLCH. Lip biopsy is usually the procedure of choice in the diagnosis of suspected Sjögren's. Subcutaneous abdominal fat aspirate and bone marrow biopsy may be examined for suspected amyloid, but a negative result does not necessarily exclude pulmonary amyloidosis [12].

Diagnostic Approach

While a large proportion of patients may present with symptoms secondary to DCLDs, it is not uncommon for patients to present with mild or no symptoms. A considerable subgroup of patients with DCLDs, especially those without underlying high-grade malignancies, may remain stable and not warrant any therapy. Moreover, pulmonary cysts can develop normally in some individuals, as an age-related phenomenon, and do not always represent a true pathology. Thus, the diagnostic algorithm and management must be tailored according to the individual patient's presentation, risks and preferences. For instance, it may be reasonable to pursue serial longitudinal monitoring of the clinical course in a patient with mild DCLD due to uncertain cause as long as there are minimal or no symptoms, and pursue invasive diagnostic testing if and when patient is at risk of morbidity or mortality due to disease. On the other hand, if there is a suspicion for high-grade malignancy – further evaluation with biopsy, FGD-PET, and/or serial CT scans should be pursued regardless of symptoms. We usually tend to follow the clinical course in asymptomatic or minimally symptomatic patients who do not have substantial physiological (normal PFTs) or radiological disease burden (≤ 10 cysts on CT).

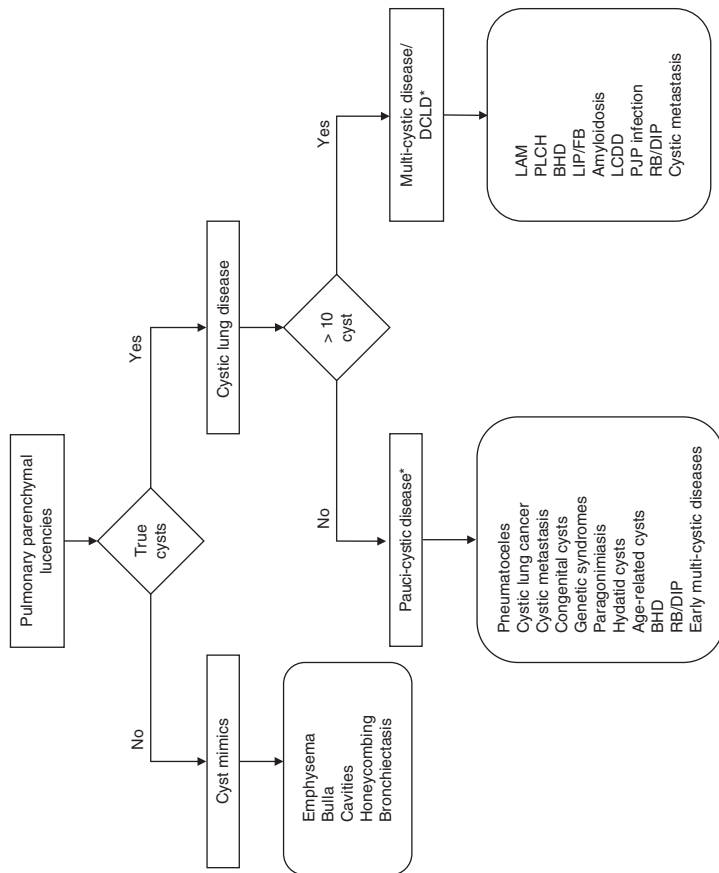
We tend to approach evaluation of DCLDs in a stepwise manner where the first step is to decipher whether the parenchymal lucencies represent true cysts or other noncystic parenchymal opacities. Once we identify true cysts, we categorize the patients on the basis of underlying cyst profusion into pauci-cystic (≤ 10 cysts) or multi-cystic (> 10 cysts) (Fig. 18.2). Age-related cysts and a variety of diseases such as parasitic infections, traumatic pneumatoceles, primary lung cancers, and congenital cysts generally present with pauci-cystic disease. It is worth mentioning, however, that occasionally the diseases typically associated with multi-cystic chest radiology may be detected very early in the disease course at a pauci-cystic stage, highlighting the importance of continued longitudinal monitoring of patients with cystic lung disease. A proposed algorithm for work-up of patients with pauci-cystic and multi-cystic DCLDs is shown in Figs. 18.3 and 18.4.

Diagnosis of DCLD involves a detailed clinical and radiological assessment as discussed previously, with the need for invasive biopsies considered on a case-by-case basis depending upon the disease and symptom burden and the patient/physician's desire to establish a certain diagnosis. Key clinical, radiological, and pathological features of common causes of DCLDs are summarized in Table 18.4. Disease-specific diagnostic guidelines are available for a few diseases such as LAM and BHD and also for diseases associated with DCLDs such as TSC (associated with LAM) and Sjögren's (associated with LIP, amyloidosis, and/or LCDD), and are summarized in Table 18.5.

Management

Screening for DCLDs

Screening for DCLDs with CT scan of chest should be pursued in certain situations. While all cases of recurrent spontaneous pneumothorax should undergo evaluation by CT scan, preferably after re-expansion of the lung, the role of CT scan after the first episode of spontaneous pneumothorax remains unclear. It is advisable to consider chest CT imaging in first-time spontaneous pneumothorax if there is a positive family history or if the patient is female, because the discovery of either BHD or LAM, respectively, has important management implications [26]. We follow the approach of performing CT scan after first episode of an apparent primary spontaneous pneumothorax in all patients as this approach can lead to timely diagnosis of underlying conditions and allow the pursuit of appropriately aggressive interventions to reduce the pneumothorax recurrence risk. The strategy to pursue screening chest CT scan to evaluate for DCLDs in patients presenting with an apparent primary spontaneous pneumothorax has been demonstrated to be cost-effective in a recent analysis [1, 60].



* There can be some overlap between the etiologies of pauci-cystic and multi-cystic diseases. For instances, some disorders such as BHD, RB/DIP, and cystic metastasis can have pauci as well as multi-cystic presentation. In addition, if diagnosed relatively early in their course, multi-cystic diseases may be identified at a pauci-cystic stage.

Fig. 18.2 Algorithm to classify cystic lung diseases based on chest computed tomography. BHD Birt-Hogg-Dubé syndrome, DIP desquamative interstitial pneumonia, FB follicular bronchiolitis, LAM lymphangioleiomyomatosis, LCDD light chain deposition disease, LIP lymphocytic interstitial pneumonia, PLCH pulmonary Langerhans cell histiocytosis, PJP pneumocystis jiroveci pneumonia, RB respiratory bronchiolitis

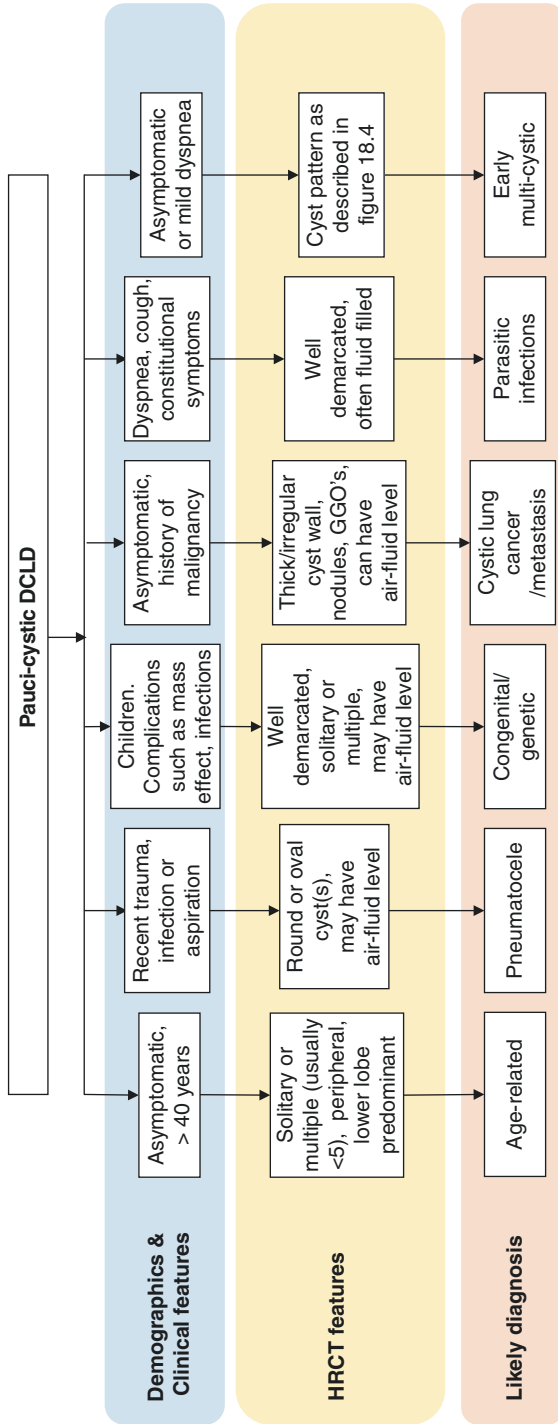


Fig. 18.3 Algorithm to guide approach to the diagnosis of pauci-cystic lung diseases. GGOs ground-glass opacities

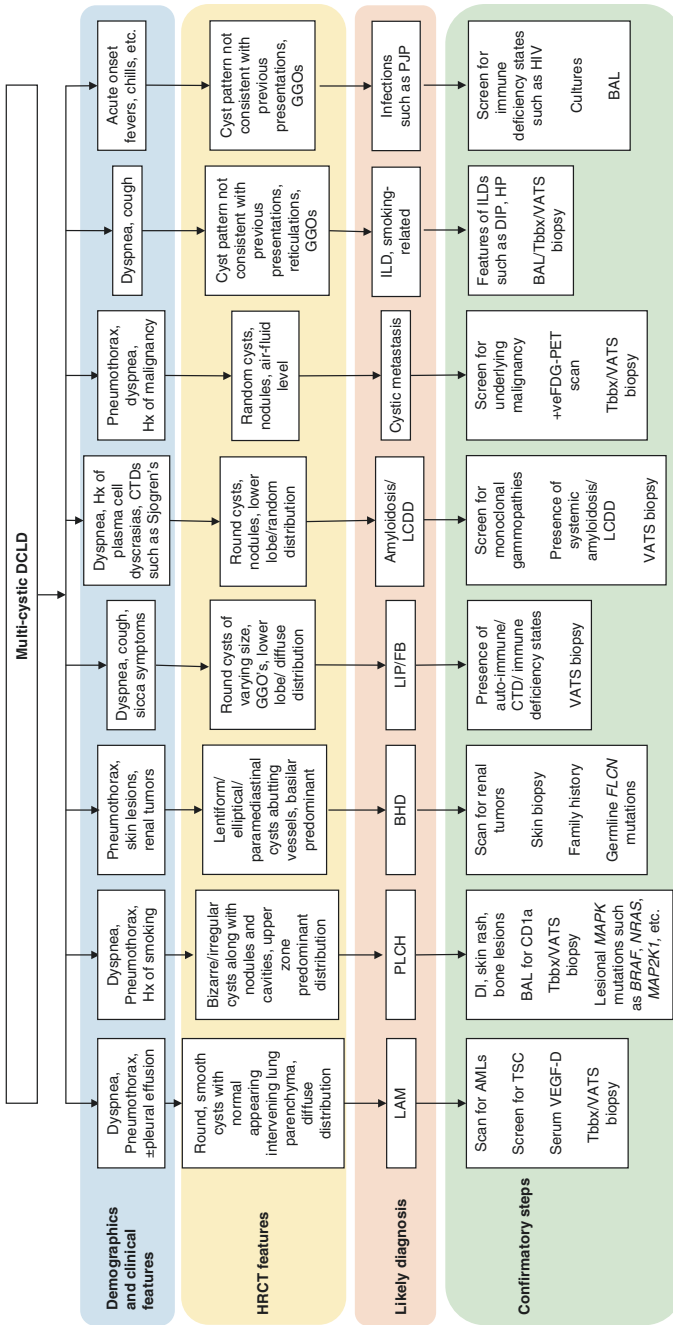


Fig. 18.4 Algorithm to guide approach to the diagnosis of diffuse multi-cystic lung diseases. AML, angiomylipoma, BAL, bronchoalveolar lavage, BHD Birt-Hogg-Dubé syndrome, BRAF v-Raf murine sarcoma viral oncogene homolog B, CT computed tomography, CTD connective tissue diseases, DCLD diffuse cystic lung disease, DI diabetes insipidus, DIP desquamate interstitial pneumonia, FB follicular bronchiolitis, FDG-PET 18-Fluoro deoxy positron emission tomography, FLCN folliculin, GGOs ground-glass opacities, HRCT high-resolution computed tomography, HP hypersensitivity pneumonitis, ILD interstitial lung disease, LAM lymphangioleiomyomatosis, LCDD light chain deposition disease, LIP lymphoid interstitial pneumonia, MAPK mitogen-activated protein kinase, PLCH pulmonary Langerhans cell histiocytosis, SS Sjogren syndrome, Tbtx transbronchial biopsy, TSC tuberous sclerosis complex, VATS video-assisted thoracoscopic surgery, VEGF-D vascular endothelial growth factor-D. (Modified from Gupta et al. [2])

Certain high-risk patient groups warrant screening CT scans to evaluate for underlying DCLDs. Given the high prevalence of LAM in women with TSC, all women with TSC should undergo a baseline chest HRCT starting at the age of 18 years, regardless of pulmonary symptoms. In cases where the screening CT is negative, repeat imaging can be performed every 5 years, or sooner as dictated by pulmonary symptoms [61]. For TSC women with documented evidence of LAM on chest CT, the repeat HRCT interval can be reduced to every 2–3 years in order to gauge the trajectory of disease progression. These follow-up CT scans can be done using low-dose radiation protocols. In addition, these patients should undergo periodic (at least annual) pulmonary function testing. Sporadic renal AMLs (without TSC) can be associated with LAM in approximately 10% of the patients and discovery of renal AMLs should prompt consideration of screening for LAM with chest CT [62].

Table 18.5 Diagnostic criteria for key DCLDs and their underlying disease associations

Disease	Diagnostic criteria
LAM [20]	<p>Compatible clinical history and characteristic HRCT of the chest + one or more of the following features:</p> <ol style="list-style-type: none"> 1. Presence of TSC 2. Renal angiomyolipoma(s) 3. Elevated serum VEGF-D ≥ 800 pg/ml 4. Chylous effusion (pleural or ascites) confirmed by tap and biochemical analysis of the fluid. 5. Lymphangioliomyomas (lymphangiomyomas) 6. Demonstration of LAM cells or LAM cell clusters on cytological examination of effusions or lymph nodes 7. Histopathological confirmation of LAM by lung biopsy or biopsy of retroperitoneal or pelvic masses
BHD [91, 92]	<p>Diagnosis requires one major or two minor criteria:</p> <p>Major criteria</p> <ol style="list-style-type: none"> 1. At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset 2. Pathogenic <i>FLCN</i> germline mutation <p>Minor criteria</p> <ol style="list-style-type: none"> 1. Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous pneumothorax 2. Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology 3. A first-degree relative with BHD <p>Alternative diagnostic criteria in patients with lung cysts</p> <p>Characteristic or compatible lung HRCT with one of the following:</p> <ol style="list-style-type: none"> 1. Skin biopsy positive for fibrofolliculoma 2. Confirmed family history of BHD in first- or second-degree family member 3. Histologic confirmation of chromophobe renal carcinoma or hybrid oncocytic tumor 4. Genetic testing positive for <i>FLCN</i> mutation

(continued)

Table 18.5 (continued)

Disease	Diagnostic criteria
TSC [27]	<p>Major features</p> <ol style="list-style-type: none"> 1. Hypomelanotic macules (≥ 3, at least 5-mm diameter) 2. Angiofibromas (≥ 3) or fibrous cephalic plaque 3. Ungual fibromas (≥ 2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias 7. Subependymal nodules 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM) 11. Angiomyolipomas (≥ 2) <p>Minor features</p> <ol style="list-style-type: none"> 1. "Confetti" skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (≥ 2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas <p>Definite diagnosis: Two major features (except for a combination of LAM and angiomyolipomas without other features) or one major feature with ≥ 2 minor features or identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue</p> <p>Possible diagnosis: Either one major feature or ≥ 2 minor features.</p>
Sjögren's ^a [93]	<ol style="list-style-type: none"> 1. Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm² (weight /score = 3) 2. Anti-SSA/Ro-positive (weight /score = 3) 3. Ocular staining score ≥ 5 (or van Bijsterveldscore ≥ 4) in at least one eye (weight /score = 1) 4. Schirmer's test ≤ 5 mm/5 min in at least one eye (weight /score = 1). 5. Unstimulated whole saliva flow rate ≤ 0.1 mL/min (weight /score = 1) <p>Diagnosis of Sjögren's requires a score of ≥ 4 and exclusion of history of head and neck radiation treatment, active hepatitis C infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, and IgG4-related disease</p>

BHD Birt-Hogg-Dubé syndrome, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *DCLD* diffuse cystic lung diseases, *ECD* Erdheim-Chester disease, *FB* follicular bronchiolitis, *GI* gastrointestinal, *GU* genito-urinary, *LAM* lymphangioleiomyomatosis, *LCDD* light chain deposition disease, *LIP* lymphocytic interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *TSC* tuberous sclerosis complex, *ANA* anti-nuclear antibody, *CCP* cyclic citrullinated peptide, *HIV* human immunodeficiency virus, *PJP* *Pneumocystis jiroveci* pneumonia, *VEGF-D* vascular endothelial growth factor-D, *CT* computed tomography, *DIP* desquamative interstitial pneumonia, *AML* angiomyolipoma, *BRAF* v-Raf murine sarcoma viral oncogene homolog B, *F* female; *HMB* human melanoma black, *M* male, *MALT* mucosa-associated lymphoid tissue, *MAPK* mitogen-activated protein kinase, *AIDS* acquired immunodeficiency syndrome, *HRCT* high-resolution computed tomography, *Ig* immunoglobulin

^aAssociated with LIP, amyloidosis, and/or LCDD

General Management

As with any other chronic lung disease, it is advisable to quit smoking and inhalation of any potentially harmful agents such as vaping and marijuana. Smoking (and marijuana) cessation is the cornerstone of treatment in patients with PLCH and can lead to disease regression or stabilization in a substantial proportion of patients. Patients should be advised to stay up to date with influenza and pneumococcal vaccines. Pulmonary rehabilitation could be an effective intervention to improve symptoms, health-related quality of life, and functional status in patients with impaired exercise tolerance [63, 64]. General recommendations applicable to all DCLD patients are highlighted in Table 18.6.

Spontaneous pneumothorax is common in DCLD patients, particularly in patients with LAM, BHD and PLCH, and carries a very high risk of recurrence [7]. Patients should be made aware of symptoms suggestive of pneumothorax, and an action plan should be formulated in case of emergency. In contrast to patients with primary spontaneous pneumothorax, given the high risk of recurrence, patients with DCLDs (especially LAM, BHD, and PLCH) presenting with a spontaneous pneumothorax should undergo pleurodesis to reduce the recurrence risk following the first episode of spontaneous pneumothorax rather than waiting for a recurrent event [20, 65, 66]. We prefer VATS-guided mechanical pleurodesis as the initial modality. It is worth mentioning that prior pleurodesis is not a contraindication for future lung transplantation [67] and that when making the decision whether to pursue pleurodesis or not, generally more weight should be assigned to the reduction in morbidity arising from recurrent spontaneous pneumothoraces as opposed to the possibility of future technical difficulties in case there is need for lung transplantation.

Situations leading to increase in cyst size or pressure can predispose patients to develop pneumothorax. In accordance with the Boyle's law of inverse relationship between pressure and volume, lung cysts have the potential to expand in size when exposed to atmospheric pressure changes such as during air travel or deep-sea diving. It is usually advised to avoid deep-sea diving as development of pneumothorax

Table 18.6 General recommendations applicable to all patients with DCLDs

Smoking cessation
Stay up to date on vaccination including annual influenza vaccination and both pneumococcal (PPSV23 and PCV13) vaccines
Air travel is safe for most patients with DCLDs. The risk of inflight pneumothorax is approximately 1 per 100 flights. Patients should be educated about the typical symptoms of pneumothorax and instructed to seek medical attention if they have new-onset symptoms suggestive of a pneumothorax
Advise against scuba diving due to the potential risk of spontaneous pneumothorax
Patients should be aware of symptoms of pneumothorax and have an action plan. Pleurodesis should be considered following the first episode of pneumothorax. Prior pleurodesis is not a contraindication for lung transplantation [94].

Modified from Obaidat et al. [95]

PCV pneumococcal conjugate vaccine, PPSV pneumococcal polysaccharide vaccine

in these situations can potentially become life-threatening [68]. Air travel has been shown to have a low risk (~1 episode of spontaneous pneumothorax per 100 flights) particularly in patients with LAM, BHD, and PLCH. This risk of pneumothorax with air travel is usually not considered prohibitive unless the patient has severely reduced cardiopulmonary reserve and cannot tolerate a pneumothorax. Patients should be counselled about this risk and educated about concerning symptoms that might prompt appropriate medical evaluation prior to undertaking air travel. In addition to the risk of pneumothorax associated with air travel, DCLD patients should also undergo evaluation for the need of supplemental oxygen during air travel. These issues have been covered in detail in Chap. 17 of this textbook.

Specific Treatment

Inhaled bronchodilators can be tried, especially in patients with reversible airflow obstruction on pulmonary function testing and in patients who report symptomatic benefit from a bronchodilator trial [55, 69, 70]. Concomitant asthma may be present in some patients, and inhaled corticosteroids may be beneficial in this subset.

Disease-modifying therapies for LAM, PLCH, FB/LIP, and amyloidosis are available and should be considered if patients develop significant symptoms or exhibit a progressive decline in pulmonary function (Table 18.7). Use of the mechanistic target of rapamycin (mTOR) inhibitor, sirolimus, has been shown to stabilize lung function decline and improve the quality of life in patients with LAM, and is recommended for patients with abnormal lung function as defined by forced expiratory volume in one-second (FEV1) less than or equal to 70% predicted [46]. Sirolimus has also been shown to be effective in LAM patients with chylous complications such as chylous effusions, lymphangioliomyomas, and in patients with rapidly declining lung function. mTOR inhibitors are efficacious and safe in controlling AML burden in patients with TSC, while preserving the renal parenchyma [71, 72]. Cladribine (2-chlorodeoxyadenosine) has been shown to be helpful in refractory systemic LCH and has also been used in isolated PLCH with reported improvement [73–75]. Multiple other chemotherapeutic regimens have been tried in patients with PLCH with limited success. Targeted treatment of PLCH with BRAF or MEK inhibition may be a promising therapeutic approach in the near future [76]. Treatment of FB/LIP relies on managing the underlying cause. Immunosuppression can be helpful in idiopathic LIP and LIP associated with autoimmune disease [77]. Clinical and radiological resolution of LIP has been reported with the use of antiretroviral drugs in cases of LIP secondary to HIV [78]. Treatment of amyloidosis and LCDD depends on the extent of organ involvement and options include autologous stem cell transplantation and a variety of chemotherapeutic drugs [79]. Solitary malignancy and some congenital lesions such as CPAM and bronchogenic cysts may be amenable to surgical resection because of their propensity to enlarge and to

Table 18.7 Disease-specific management considerations for common DCLDs

Disease	Disease-modifying therapy	Other management considerations
LAM	mTOR inhibitors (sirolimus, everolimus). Typically prescribed to patients with abnormal lung function (FEV1 <70% predicted), substantial disease burden (need for supplemental oxygen, DLCO <60%), evidence of accelerated disease progression (FEV1 decline >100 ml/year), or patients with problematic chylous complications such as chylous pleural effusions	Screen for renal angiomyolipomas; Obtain detailed history and perform physical examination to look for underlying TSC; Evaluate for PH in advanced disease, patients with hypoxemic respiratory failure, clinical signs suggestive of right ventricular strain, or out of proportion reduction in DLCO
PLCH	Smoking cessation. Typically, the first and only management option for a substantial proportion of patients with PLCH Cladribine/Cytarabine MEK/BRAF inhibitors	Enquire about symptoms suggestive of extrapulmonary involvement such as lytic bone lesions and diabetes insipidus; Evaluate for PH in patients with hypoxemic respiratory failure, clinical signs suggestive of right ventricular strain, or out of proportion reduction in DLCO
BHD	None	Periodic longitudinal screening for renal tumors; Screen family members for the presence of BHD
LIP/FB	Immunosuppression, especially in patients with other noncystic parenchymal abnormalities such as ground-glass opacities	Evaluate for underlying autoimmune disease and immunodeficiencies; Consider biopsy for suspicious lesions suggestive of lymphoma such as pulmonary nodules with increasing size
Systemic amyloidosis/ LCDD	Chemotherapy Bone marrow transplantation	Evaluate for underlying lymphoproliferative diseases and plasma cell dyscrasias as well as other extrapulmonary organ involvement

BHD Birt-Hogg-Dubé syndrome, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *DCLD* diffuse cystic lung diseases, *ECD* Erdheim-Chester disease, *FB* follicular bronchiolitis, *GI* gastrointestinal, *GU* genito-urinary, *LAM* lymphangioleiomyomatosis, *LCDD* light chain deposition disease, *LIP* lymphocytic interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *TSC* tuberous sclerosis complex, *ANA* anti-nuclear antibody, *CCP* cyclic citrullinated peptide, *HIV* human immunodeficiency virus, *PJP* *Pneumocystis jiroveci* pneumonia, *VEGF-D* vascular endothelial growth factor-D, *CT* computed tomography, *DIP* desquamative interstitial pneumonia, *AML* angiomyolipoma; *BRAF* v-Raf murine sarcoma viral oncogene homolog B, *F* female, *HMB* human melanoma black, *M* male, *MALT* mucosa-associated lymphoid tissue, *MAPK* mitogen-activated protein kinase, *DLCO* diffusing capacity of the lung for carbon monoxide, *FEV1* forced expiratory volume in 1 second, *MEK* mitogen-activated protein kinase kinase, *mTOR* mechanistic target of rapamycin, *PH* pulmonary hypertension

become infected as well as the potential risk for transformation into malignancy [80]. Lung transplantation remains a viable management option for patients with advanced DCLDs with patients having post-transplant survival either similar to (in case of PLCH) or better than (in case of LAM) the patients undergoing lung transplantation for other pulmonary disorders [81–85]; however, recurrence of disease in allograft can occur in some patients with LAM and PLCH [86].

Active surveillance and management for co-existing conditions or complications is warranted for certain DCLDs. Patients with LAM should be evaluated for presence of TSC and AMLs [61]. Serial screening of renal tumors in BHD is recommended [48]. Development of lymphoma is the most dreaded complications of Sjögren's and can occur in ~5% of patients [77]. Although guidance on appropriate screening of lymphoma in these patients is lacking, development of three or more risk factors such as salivary gland enlargement, lymphadenopathy, Raynaud phenomenon, anti-Ro/SSA or/and anti-La/SSB autoantibodies, rheumatoid factor positivity, monoclonal gammopathy, and C4 hypocomplementemia have been associated with development of lymphoma [87]. Pulmonary hypertension is known to occur in patients with DCLDs, particularly LAM and PLCH [88–90], which may need further evaluation.

Conclusion

The combined synergy between scientists, clinicians, and patient advocacy organizations (Table 18.8) has enabled transformative progress in our understanding of the molecular pathogenesis and the development of novel therapeutic options in patients with DCLDs. The recent progress in LAM is perhaps the best exemplar of the abovementioned synergy driving meaningful progress. In a relatively short time span of approximately two decades, the collaborative effort between patients and scientists has led to major scientific breakthroughs in LAM, including identification of the causative gene, clear understanding of the disease pathogenesis, discovery of a blood-based biomarker that aids noninvasive diagnosis, and the development of FDA-approved treatment. Active efforts are underway to emulate the example of LAM and apply similar approaches to drive progress in other DCLDs. In conclusion, we submit that the DCLDs represent a unique set of disorders that are fundamentally distinct from the typical interstitial lung diseases in almost every aspect including the pathophysiology, radiological features, clinical phenotypes, natural history, and management strategies. Although rare individually, collectively DCLDs represent a substantial minority of the pulmonary practice and are being increasingly identified due to widespread use of CT scans and increased awareness. Knowledge regarding the nuances of appropriately diagnosing and treating DCLDs for clinicians is critical in order to provide optimal care to these patients. Finally, the discoveries made in this field are not only impacting the lives of patients with DCLDs but are also providing crucial insights into the pathobiology of more common conditions.

Table 18.8 Key organizations focused on advancing healthcare and research for patients with DCLDs and related rare diseases

Lymphangiomyomatosis/ tuberous sclerosis	The Lymphangiomyomatosis (LAM) Foundation (https://www.thelamfoundation.org) Tuberous Sclerosis Alliance (http://www.tsalliance.org)
Birt-Hogg-Dubé syndrome	BHD Foundation (https://www.bhdysndrome.org) Myrovlytis Trust (www.myrovlytistrust.org)
Pulmonary Langerhans cell histiocytosis	Histiocytosis Association (https://www.histio.org)
Amyloidosis/LCDD	Amyloidosis Foundation (https://amyloidosis.org)
Sjögren's	Sjögren's Foundation (https://www.sjogrens.org)
Other organizations focused on rare diseases	Rare Lung Diseases Consortium (https://www.rarediseasesnetwork.org/cms/rld) National Organization for Rare Disorders (NORD) (http://www.rarediseases.org) International Rare Disease Research Consortium (IRDIRC) (http://www.irdirc.org) Orphanet (http://www.orpha.net) The European Organisation for Rare Diseases (http://www.eurordis.org)

BHD Birt-Hogg-Dubé syndrome, *CTD* connective tissue disease, *CVID* common variable immune deficiency, *DCLD* diffuse cystic lung diseases, *ECD* Erdheim-Chester disease, *FB* follicular bronchiolitis, *GI* gastrointestinal, *GU* genito-urinary, *LAM* lymphangiomyomatosis, *LCDD* light chain deposition disease, *LIP* lymphocytic interstitial pneumonia, *PLCH* pulmonary Langerhans cell histiocytosis, *TSC* tuberous sclerosis complex, *ANA* anti-nuclear antibody, *CCP* cyclic citrullinated peptide, *HIV* human immunodeficiency virus, *PJP* *Pneumocystis jiroveci* pneumonia, *VEGF-D* vascular endothelial growth factor-D

Key Learning Points

- When evaluating a patient with cystic change on chest imaging, a detailed history with particular attention to demographics, inhaled exposures such as smoking, family history, and search for extrapulmonary features, including cutaneous, pleural, and intra-abdominal manifestations, can provide crucial insight into the underlying diagnosis.
- High-resolution computed tomography is an essential component of the evaluation process, and careful evaluation of the cyst characteristics, such as profusion, distribution, and morphology, combined with ancillary pulmonary and extrapulmonary findings, can help differentiate between the various causes of cystic lung diseases in a large proportion of patients.
- Laboratory analysis can provide valuable information in patients with suspected DCLDs, and can sometimes be diagnostic such as elevated VEGF-D in LAM or establishment of diagnosis of Sjögren's in a patient suspected to have FB/LIP.
- Invasive procedures such as lung biopsy may be needed in some patients after exhausting the noninvasive diagnostic work-up. The decision to pursue invasive diagnostic procedures should be taken with careful consideration of future management implications and the knowledge that the diagnosis of DCLDs can generally be established by noninvasive means in over two-thirds of the patients.

- Management of patients with DCLDs includes attention to the prevention and management of complications such as spontaneous pneumothorax. There is a high risk of recurrence of pneumothorax in these patients, and pleurodesis should be considered following the initial episode of spontaneous pneumothorax rather than waiting for a recurrent episode.
- Disease-modifying therapies are available for certain DCLDs, such as mTOR inhibitors for LAM, with lung transplantation reserved for patients with advanced disease.

Conflicts of Interest The authors declare no conflicts of interest.

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