Chapter 1
Definition and Classification of Diffuse Cystic Lung Diseases

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Definition and Terminologies

The diffuse cystic lung diseases (DCLDs) are a diverse group of lung disorders characterized by the presence of multiple parenchymal lucencies of regular or irregular spherical shape, bordered by thin walls that form a well-defined interface with normal lung [1, 2]. At a conceptual level and for the purposes of this book, it is useful to distinguish the primary DCLDs from other diffuse lung diseases that can produce cystic change (or change that appears cystic) as part of secondary pathophysiologic process, such as emphysema or pulmonary fibrosis. In addition, we propose to define "multicystic lung diseases" that typify the DCLDs as those that produce more than ten identifiable cystic lesions on high-resolution computed tomography (HRCT), and "paucicystic lung diseases" as those that typically present with fewer than ten cysts, such as primary lung cancers and echinococcus. Five examples of prototypical DCLDs that present in a multicystic fashion are lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), connective tissue-related follicular bronchiolitis (FB), Birt-Hogg-Dube syndrome (BHD), and light chain deposition disease (LCDD). Although often grouped with the interstitial lung diseases (ILDs), the differential diagnosis, pathophysiology, and presentation of the family of DCLDs are fundamentally distinct from the fibrotic lung disorders. The most common DCLDs more often affect younger rather than older adults, produce radiographic lucencies more often than densities, more often present with obstructive rather than restrictive physiology, are more commonly associated with pneumothorax, and as a group tend to be associated with slower progression and a better prognosis than the scarring lung diseases. Current thinking regarding the molecular pathophysiology of the ILDs also diverges from that of the

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DCLDs, in that the former are commonly attributed to repeated lung micro-injury to the epithelium with impaired healing, while the latter are thought to result from destructive inflammatory processes that "dissolve" lung structures, check-valve driven overdistension, or dysregulated cell-cell adhesion. Unlike the ILDs, disease progression in the DCLDs tends to follow a slow and generally linear course, rather than one marked by acute exacerbations or a relapsing, remitting pattern, as is typical of nonspecific interstitial pneumonia (NSIP) and idiopathic pulmonary fibrosis (IPF). As with the ILDs, it is possible in some cases to be confident about the diagnosis based on clinical and imaging features without the need for tissue confirmation, and it is not always necessary to establish a certain diagnosis for disease that is mild, early, or very slowly progressive. It is important to be aware, however, that there are interventions that change disease course for at least two of the most common disorders, sirolimus for LAM and smoking cessation for PLCH, and that in some cases aggressive measures including bronchoscopic or surgical biopsy are indicated to reach a definitive diagnosis.

This introductory chapter focuses on the classification and differential of the diffuse cystic lung diseases.

Defining Cysts and Differentiating Them from Other Pulmonary Parenchymal Lucencies

Cysts should be differentiated from a variety of other air-filled intra-parenchymal lesions such as airspace dilation in emphysema, bullae, pneumatoceles, honeycombing, bronchiectasis, and cavities (Table 1.1). Cysts usually contain air and

Table 1.1 Cyst and mimics [1]

Cyst	Thin-walled (<2 mm), spherical parenchymal lucency interfaced with normal lung
Cavity	Gas-filled space within pulmonary consolidation, mass, or nodule, typically thick walled (>2 mm) and more irregularly shaped than cysts
Bulla	Spherical focal lucency, ≥1 cm in diameter, bounded by a thin wall (usually <1 mm). It is usually accompanied by emphysematous changes in the adjacent lung
Bleb	Cystic air space bounded by a thin wall adjacent to the visceral pleura, typically <1 cm in size
Emphysema	Permanently enlarged airspaces distal to the terminal bronchiole with destruction of alveolar walls. Usually without visible walls on CT
Pneumatocele	Approximately round, thin-walled, air-filled space in the lung. Most frequently caused by infections, trauma, or aspiration of hydrocarbon fluid and usually transient
Honeycombing	Clustered cystic air spaces, typically 3–10 mm in diameter but occasionally as large as 2.5 cm. Usually subpleural
Bronchiectasis	Localized or diffuse bronchial dilatation, usually resulting from chronic infection, proximal airway obstruction, or congenital bronchial abnormality

have a wall thickness of less than 2 mm, but they can occasionally contain fluid or solid material and wall thickness may vary. Pneumatoceles are true cysts, but these are usually transient and are most frequently caused by infection, trauma, or aspiration of liquid hydrocarbons. The term "honeycombing" refers to clusters of round 3- to 10-mm diameter lucencies, with 1- to 3-mm wall thickness that are often stacked on top of each other in layers [1]. It is usually subpleural, and associated with other features of pulmonary fibrosis such as traction bronchiectasis and reticulations, and as such, it is usually easily distinguished from the cystic change of the DCLDs. Bronchiectasis results in dilated, thick-walled bronchi, which can also appear cystic, and may be clustered in a manner that mimics DCLDs. It can be readily differentiated from cysts based on continuity of the dilated airspace with the airways on contiguous CT sections. Cavities are thick-walled (>2 mm) and are more irregularly-shaped than cysts. These can be found within a mass, nodule, or area of consolidation.

Differentiating DCLDs from Emphysema

Emphysema describes a group of disorders that produce airspace dilation and pulmonary parenchymal lucencies that are easily confused with the cysts that occur in DCLDs, and it is therefore prudent to enlist the help of an expert radiologist to exclude the diagnosis before embarking on a comprehensive DCLD evaluation. The most common form of pulmonary emphysema is centrilobular emphysema due to tobacco or biomass fuel exposure. The dilated airspaces in centrilobular emphysema are typically spherical or polygonal in shape, surrounded by compressed lung tissue and peri-lobular vessels rather than a well-defined wall [3] and often have internal structure such as interlobular septa or a "central dot," which represents a centrilobular artery coursing through the secondary pulmonary lobule [4]. Paraseptal emphysema involves the more distal part of the secondary pulmonary lobule, and usually presents as subpleural rows of elongated, thin-walled, air-filled structures. Alpha 1 antitrypsin deficiency is a heritable form of emphysema that is often associated with panlobular emphysema, which involves the destruction of the entire secondary pulmonary lobule, and loss of the distinction between affected and normal areas [5]. Over time, the radiographic appearance becomes one of diffuse hyperlucency, rather than of focal parenchymal lucencies. Bullae are considered to be focal emphysematous areas, and frequently abut areas of centrilobular or panlobular emphysema [1, 5]. Bullae are usually >1 cm in diameter but can vary in size, sometimes filling a large fraction of the hemithorax. Blebs are smaller in size (<1 cm) and often describe lesions that abut or are visible on the pleural surface, but use of this term is discouraged because the distinction based solely on an arbitrary size cut off is not particularly meaningful or useful [1].

Distinguishing Paucicystic Lung Disease from Multicystic Lung Disease Consistent with DCLD

A common clinical dilemma is determining the relevance of a few cysts discovered as an incidental finding on chest CT. The first consideration is whether they represent pathological versus non-pathological cysts. Pulmonary cysts apparent on chest CT can occur as part of aging-related changes of the lungs in nonsmoking individuals. Aging-related cysts are typically first seen in individuals after the age of 40 years [6], and increase in prevalence with age to 5% at 40–49 years and 13% at an age over 80 years [6]. The number of cysts that can be found on the CT of aging individuals rarely (<1%) exceed 4 [6]. Ryu et al. therefore proposed that the presence of four or more cysts is a reasonable threshold for the number of cysts that can be considered abnormal [7]. The Tuberous Sclerosis Alliance Consensus Guidelines suggest using >4 as the number of cysts that establish the diagnosis of LAM in a nonsmoking individual with tuberous sclerosis complex (TSC) [8], although this metric is entirely empiric, and European Respiratory Society guidelines suggest using >10 cysts as a cut off for diagnosing LAM in a patient with TSC [9].

Classification and Epidemiology

The DCLDs can be broadly classified according to underlying etiology as those associated with low-grade or high-grade metastasizing neoplasms, polyclonal or monoclonal lymphoproliferative disorders or plasma cell dyscrasias, infections, autoimmune or connective tissue disease, smoking, and congenital or developmental defects [2] (Table 1.2). However, as shown in Fig. 1.1**,** significant overlap exists among these etiologies. For instance, LCDD could be classified as a lymphoproliferative disorder, a plasma cell dyscrasia, or a low-grade neoplasm. The true prevalence of the DCLDs is poorly understood. Rough estimates for prevalence of LAM, BHD, and PLCH in the United States are in the neighborhood of a few persons per million, while for LCDD and FB the range is likely to be lower and higher, respectively. Although individually rare, collectively the DCLDs have a significant impact upon the population at large [10]. Lack of prospective natural history profiling or consensus guidelines for diagnosis and classification for most DCLDs further compound difficulties in ascertaining accurate, population-based epidemiological data for many of these rare disease [11]. For example, there is no widely accepted definition for how to classify lung disease in Sjögren's syndrome, a disorder that is associated with both interstitial and cystic changes. The prevalence and incidence data of some of the common causes of DCLDs are listed in Table 1.3.

Table 1.2 Classification of diffuse cystic lung diseases

- Neoplastic
  - *Low-grade malignancies*
    - Lymphangioleiomyomatosis – sporadic as well as associated with tuberous sclerosis complex
    - Histiocytosis
      - Pulmonary Langerhans cell histiocytosis
      - Non–Langerhans cell histiocytoses, such as Erdheim-Chester disease, Rosai-Dorfman disease
  - *High-grade malignancies*
    - Primary pulmonary neoplasms
      - Nonsmall cell carcinomas
      - Mesenchymal cystic hamartoma
      - Pleuropulmonary blastoma
      - Lymphoma
    - Sarcomas
      - Angiosarcomas
      - Osteosarcomas
      - Synovial cell sarcoma
      - Ewing sarcoma
      - Leiomyosarcoma
      - Rhabdomyosarcoma
      - Endometrial stromal sarcoma
      - Wilms tumor
      - Pineal teratoma
      - Other sarcomas
    - Metastatic epithelial tumors
      - Adenocarcinomas of the gastrointestinal and genitourinary tract
    - Systemic malignancies
      - Lymphoma
- Genetic/developmental/congenital
  - Birt-Hogg-Dubé syndrome
  - Phakomatoses – Cowden syndrome, neurofibromatosis, Proteus syndrome
  - Connective tissues diseases – Marfan syndrome, Ehlers-Danlos syndrome (type IV)
  - COPA syndrome
  - Down syndrome
  - Congenital pulmonary airway malformation, bronchopulmonary dysplasia, etc.
- Associated with lymphocytic infiltration, lymphoproliferative disorders, plasma cell dyscrasias
  - Lymphoid interstitial pneumonia
  - Follicular bronchiolitis
  - Castleman disease
  - Lymphomatoid granulomatosis
  - Amyloidosis
  - Light chain deposition disease
  - Hypersensitivity pneumonitis
- Infectious
  - *Pneumocystis jiroveci pneumonia*
  - Staphylococcal pneumonia
  - Recurrent respiratory papillomatosis
  - Endemic fungal diseases especially coccidioidomycosis
  - Paragonimiasis
  - Hydatid cysts (*Echinococcus*)
  - COVID-19 pneumonia

(continued)

Table 1.2 (continued)

Associated with interstitial lung diseases
Hypersensitivity pneumonitis
Desquamative interstitial pneumonia
Smoking-related
Pulmonary Langerhans cell histiocytosis
Desquamative interstitial pneumonia
Respiratory bronchiolitis/smoking-related cystic lung disease
Other/miscellaneous
Posttraumatic pseudocysts
Fire-eaters lung
Hyper IgE syndrome
Acute respiratory distress syndrome
Pulmonary alveolar microlithiasis
Cyst mimics
Emphysema/bullae
Alpha-1 antitrypsin deficiency
Bronchiectasis
Honeycombing seen in late stage scarring interstitial lung diseases

Modified from [2]

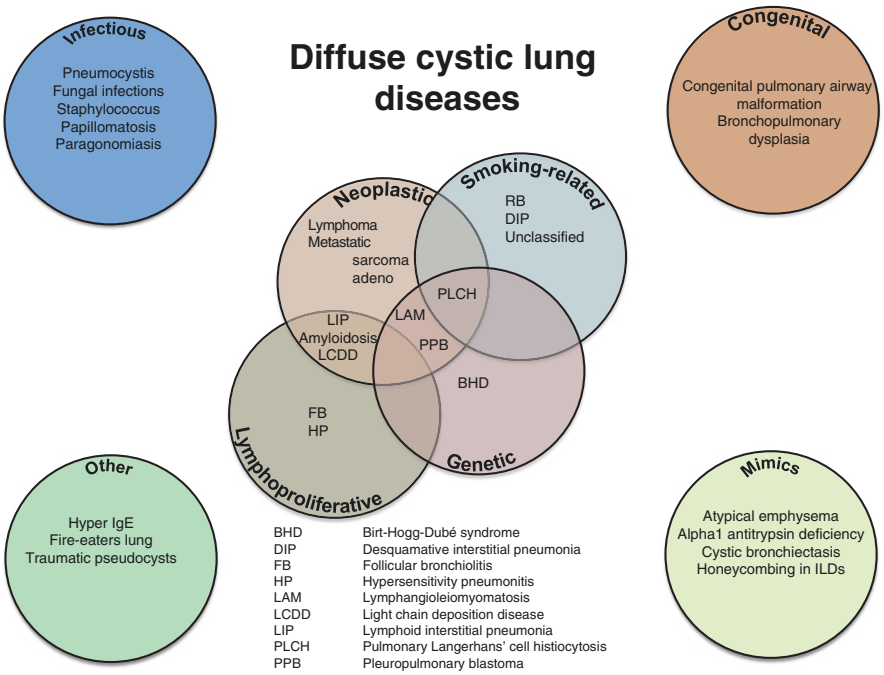

Fig. 1.1 Venn diagram of the diverse and overlapping etiologies of the DCLDs.

Table 1.3 Epidemiology of cystic lung disease

Diseases	Estimated prevalence (per million)	Estimated incidence (per million/ year)	Percentage with cysts
Lymphangioleiomyomatosis [15]	5 (3.4–7.8)[a]	0.2–0.3[a]	100%
Pulmonary Langerhans cell histiocytosis [18, 74, 75]	2.7[b]	NA	40–90%
Birt-Hogg-Dubé syndrome [27, 28, 76]	5[c]	NA	77–89%
Primary Sjögren syndrome [77–83]	608	69	10–46%
AL amyloidosis [37, 44, 84, 85]	40	10–15	<5%
Light chain deposition disease	NA	NA	<5%

AL amyloid light chain, *NA* not available
[a]in women
[b]Japanese data only in males
[c]European Data Only

Neoplastic Causes of DCLDs

Two forms of DCLD that are considered low-grade neoplasms are LAM and PLCH. LAM was historically considered to be an interstitial lung disease but has more recently been categorized as a perivascular epithelial cell (PEC) omatous mesenchymal tumor in the 2015 World Health Organization Classification of Lung Tumors [12]. LAM cells are clonal in origin, have growth-promoting biallelic mutations in the tuberous sclerosis genes, and exhibit metastatic and invasive behaviors [12, 13]. LAM can occur in sporadic form or can be inherited in up to 80% of women with TSC [14]. The estimated prevalence of sporadic LAM is reported to be approximately 5 (3.4–7.8) cases/million women with an incidence of 0.2–0.3/million women/year [15], but the true prevalence is likely greater. LAM has been recently reported to constitute 1% of the ILD population in Germany [16].

Pulmonary Langerhans cell histiocytosis is classified by the WHO as a lymphohistiocytic neoplasm. Recently, activating mutations of specific mitogen-activated protein kinases ($BRAF^{V600E}$ and others) have been found to be present in >50% of patients with PLCH [12]. PLCH most often occurs as a single organ disorder involving the lung but can also be associated with skin, bone, or pituitary involvement. Pulmonary involvement can also be seen in up to 15% of patients with systemic Langerhans cell histiocytosis, a disease that occurs more commonly in early childhood [17]. A national survey of hospital discharges conducted in Japan estimated the prevalence of PLCH to be 0.27 per 100,000 males and 0.07 per 100,000 females [18]. This is likely an underestimation as PLCH has been reported in up to 7% of patients with ILD [19, 20]. Pulmonary cysts can also occur in up to 12% of patients with non–Langerhans cell histiocytosis such as Erdheim-Chester disease [21, 22] and Rosai-Dorfman disease [23, 24].

A variety of high-grade primary and metastatic neoplasms can present with pulmonary cysts. These typically present as solid or subsolid nodules or masses that cavitate and evolve to become thin-walled cysts. Cystic changes can be seen in 1% to 4% of patients with nonsmall cell lung cancer (NSCLC) [25], with adenocarcinomas being the most common, followed by squamous cell carcinomas, and poorly differentiated carcinomas. The cystic lesions caused by primary epithelial lung tumors tend to be few in number and associated with irregular or thicker-walled cysts, consistent with a paucicystic pattern, and it is rare for this mode of neoplastic cystic remodeling in the lung to produce a multicystic pattern that closely mimics a prototypical DCLD such as LAM or BHD. In contrast, metastatic epithelial tumors from abdominal viscera (see Table 1.2) or the genitourinary tract can produce multiple cystic lesions, and pulmonary metastases from sarcomas can be associated with cystic or cavitary lesions in up to 25% of patients [26]. Indeed, metastatic endometrial stromal sarcomas and synovial sarcomas can be quite difficult to distinguish from the DCLDs. Pulmonary lymphomas are neoplasms that can also be associated with cystic lesions, but they are categorized under pulmonary lymphoproliferative disorders below.

DCLDs Caused by Genetic or Developmental Defects

Several DCLDs have a known genetic basis (Table 1.4). Those with mutations that drive cellular metastasis and invasion, such as LAM and PLCH, are listed with the neoplastic diseases above but obviously overlap with genetic causes. An example in which the cyst-causing mutations are thought to be present in resident lung cells, Birt-Hogg-Dubé syndrome, is a disorder that is associated with renal and hair follicle tumors, and cystic lung disease in approximately 77% to 89% of patients [27, 28]. BHD is caused by mutations in the folliculin (FLCN) gene encoding the tumor suppressor protein, folliculin, which plays a key role in intercellular adhesion. A variety of genetic disorders such as Marfan syndrome, Ehlers-Danlos syndrome (type IV), neurofibromatosis, Cowden syndrome, Proteus syndrome, COPA syndrome, and Down syndrome can be associated with pulmonary cysts. Cystic fibrosis was named for manifestations of fibrosis and cyst formation in the pancreas rather than the lung, where it manifests primarily as bronchiectasis [29]. Similarly, other genetic syndromes such as alpha-1 antitrypsin deficiency, cutis laxa [30], Williams-Beuren syndrome [31], and FLNA mutation [32] can also disrupt lung architecture but predominantly cause emphysema and/or bronchiectasis.

Cystic lung diseases that occur in children are commonly due to genetic mutations. Pleuropulmonary blastoma (PPB) is the most common primary pediatric lung tumor, which can manifest as a cystic neoplasm associated with mutations in the *DICER1* gene [33]. Congenital pulmonary airway malformation (CPAM) (formerly known as congenital cystic adenomatoid malformation), bronchogenic cysts, bronchopulmonary dysplasia, congenital lobar emphysema, congenital bulla, congenital bronchiectasis, and bronchial atresia can present as a DCLD in childhood. Many of these produce paucicystic rather than multicystic disease.

Table 1.4 Genetic syndromes associated with diffuse cystic lung diseases

Diseases	Associated genes	Category	Pulmonary features	Other clinical features
Syndromes associated with tumors				
Tuberous sclerosis complex [86]	*TSC1, TSC2*	AD	Pulmonary cysts (LAM) in 30–40% in females and 10–15% in men, MMPH, pleural effusions	Skin lesions, seizures, developmental delays, tumors in various organs
Birt-Hogg-Dubé syndrome [27, 28]	*FLCN*	AD	Pulmonary cysts in 77–89%	Cutaneous hamartomas, renal cysts, and renal cancers
Neurofibromatosis [87]	*NF-1, NF-2*	AD	Emphysema (25%), cysts (25%), ground-glass abnormality (37%), bullae (50%), and reticular abnormalities (50%)	Skin lesions, hamartomas, optic gliomas, and neurofibromas
Cowden syndrome [88, 89]	*PTEN*	AD	Cysts in 80%, nodules	Mucocutaneous and visceral hamartomas and an increased lifetime risk of thyroid, breast, endometrial, renal, and colon cancers
DICER1 syndrome [90]	*DICER1*	AD	Pleuropulmonary blastoma (PPB), pulmonary cysts	Thyroid gland neoplasia, ovarian tumors, and cystic nephroma
Syndromes of disordered connective tissue				
Marfan syndrome [91]	*FBN1*	AD	10% have apical blebs and bullae	Tall stature, joint laxity, aortic dilation, arachnodactyly, pectus excavatum, and ocular findings
Vascular Ehlers-Danlos syndrome [type IV] [92–94]	*COL3A1*	AD	Pulmonary blebs, cystic lesions, and hemorrhagic or fibrous nodules	Easy bruising, thin and translucent skin, and tissue fragility
Loeys-Dietz syndrome [95]	*TGFBR1, TGFBR2*	AD	Pneumothorax	Aortic dilation, skeletal deformities, bifid uvula, velvety, translucent skin

(continued)

Table 1.4 (continued)

Diseases	Associated genes	Category	Pulmonary features	Other clinical features
Cutis laxa [30]	*FBLN5, FBLN4, EFEMP2, LTBP4, ELN*	AD/AR	Emphysema; bronchiectasis	Loose, saggy, inelastic skin, hernias, visceral diverticula, joint hypermobility
FLNA mutation [32]	*FLNA*	XL	Cysts, emphysema	Intellectual disability, seizures, and cardiac valvular anomalies
Others				
Down syndrome [96, 97]	-	Chromosomal, trisomy 21	Cysts in 20–36%; usually subpleural, Sleep apnea	Dysmorphic features, developmental delay, congenital malformations
Proteus syndrome [98]	*AKT1*	Somatic mosaic mutation	Cysts in 9%	Asymmetric growth, nevi, vascular malformations
COPA Syndrome [99]	*COPA*	AD	Pulmonary cysts (80%), diffuse alveolar hemorrhage, and follicular bronchiolitis	Arthritis, proteinuria, nephropathy, autoantibodies
"Brain-thyroid-lung" syndrome [100]	*NKX2-1*	AD	Cysts, alveolar proteinosis, interstitial pneumonitis	Chorea, other neurological symptoms, hypothyroidism

AD autosomal dominant, *AR* autosomal recessive, *LAM* lymphangioleiomyomatosis, *MMPH* multifocal micronodular pneumocyte, *XL* X-linked

DCLDs Associated with Lymphoproliferative Disorders or Plasma Cell Dyscrasias

Benign lymphoproliferative disorders such as lymphoid interstitial pneumonia (LIP) and follicular bronchiolitis (FB) can be associated with cystic lung disease. Indeed, pulmonary cysts have been reported in up to 60% to 80% of patients with LIP and FB [34], but the presentation with diffuse pulmonary lucencies without significant interstitial change that is characteristic of the DCLDs is much less common. LIP is characterized by diffuse involvement of lung parenchyma with reactive pulmonary lymphoid tissue, whereas FB refers to a pattern of lymphoid follicular hyperplasia centered on airways, vessels, and interlobular septa consistent with a

lymphatic distribution, though most patients have elements of both pathologies. FB and LIP are typically associated with an underlying condition, most commonly autoimmune disorders such as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, or immunodeficiency states such as human immunodeficiency virus (HIV) and common variable immune deficiency; but they can also (rarely) be idiopathic. Malignant lymphoproliferative disorders including lymphomas can also cause cystic change in the lung [35, 36]. Moreover, marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma can develop within pulmonary cysts and nodules in LIP, Sjögren's disease, amyloidosis, and LCDD [36–39]. Cysts have also been reported in other lymphoproliferative disorders such as Castleman disease [40, 41] and lymphomatoid granulomatosis [42], and about 13% of patients with chronic hypersensitivity pneumonitis (HP) [43].

Protein deposition diseases such as amyloid and light chain diseases can also present as DCLDs and are often associated with lymphoproliferative disorders or plasma cell dyscrasias. Amyloidosis is a group of diseases characterized by extracellular deposition of amyloid protein in an abnormal fibrillary fashion, which can occur in any organ including the lungs. The most common amyloid found in the lung is AL type in which deposition of protein derived from immunoglobulin light chains is associated with lung involvement in up to 28% of patients [44]. Pulmonary involvement in AL amyloid most commonly manifests as septal and parenchymal ground glass or nodular infiltrates, tracheobronchial disease, pleural disease, and mediastinal or hilar lymphadenopathy. Cysts in pulmonary amyloidosis occur less commonly; present in about 11% of patients, and are commonly associated with underlying connective tissue disorders, particularly Sjögren's syndrome [37]. Light chain deposition disease (LCDD) is similar to amyloidosis in that it presents with multisystem disease, but the light chain fragments do not form amyloid fibrils [45]. LCDD most commonly affects the kidneys but pulmonary predominant presentation as a DCLD has been reported, usually in association with Sjögren's syndrome, hematological malignancy (especially multiple myeloma), or lymphoma [38, 46, 47].

Smoking-Related DCLDs

There are two causes of smoking-related cystic lung disease, desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis (RB). Cystic pulmonary change occurs in approximately one-third of DIP cases, usually on a background of diffuse ground-glass opacification [48]. Smoking can also lead to small airway destruction, producing a diffuse cystic pattern on chest imaging, often but not always in the setting of respiratory bronchiolitis [49–51].

ILDs Associated with Cystic Change

Cystic change in the lung has also been reported in ILDs that present with a component of fibrocystic parenchymal remodeling [52], such as sarcoidosis [53, 54] and pulmonary alveolar proteinosis (PAP) [55], IPF [56], and in late stages of pulmonary alveolar microlithiasis [57–59].

DCLDs Caused by Infections

Pneumocystis jiroveci pneumonia (PJP) is probably the most common infectious cause of DCLD and can occur in up to a third of patients [60, 61]. Cysts are much more common in PJP patients with co-existing HIV than in non-HIV PJP patients [62]. Diffuse pulmonary pneumatoceles can be seen with necrotizing bacterial infections, particularly those due to *Staphylococcus* and *Streptococcus*, and is primarily seen in children [63]. Certain parasites such as Echinococcus (hydatid cysts) and paragonimiasis are notorious for causing pulmonary cysts [64], usually in a paucicystic fashion. Respiratory papillomatosis primarily affects children and can cause cysts associated with nodules [65]. Cystic changes have recently been reported in up to 10% of patients with COVID-19 pneumonia [66]. A variety of infections such as lung abscesses, necrotizing pneumonias, septic pulmonary nodules, *Nocardia*, mycobacterial infections, and fungal pneumonias can produce radiolucencies that are usually more appropriately classified as cavities than cysts [67].

Other Causes of DCLDs

Posttraumatic pulmonary pseudocysts can occur after blunt chest trauma in up to 10% of patients, and these usually resolve over 1–6 months [68]. Accidental aspiration of petroleum derivatives during fire-eating demonstrations can also lead to development of cystic pattern on chest CT due to multiple pneumatoceles that may last for a few weeks to months [69]. Hyper-IgE syndrome (AD-HIES), formerly known as Job syndrome, is a autosomal dominant primary immunodeficiency condition characterized by markedly elevated serum IgE levels and multiple cutaneous and sinopulmonary infections that can result in pneumatoceles [70]. Subpleural cysts can also occur in patients with acute respiratory distress syndrome (ARDS), usually in late phase disease after prolonged ventilation [71]. Pulmonary vasculitidies such as granulomatosis with polyangiitis can result in cystic change, and rheumatoid nodules may cavitate and evolve to become cystic lung lesions.

Pulmonary Differential Diagnosis of Rare or Unusual Conditions

Establishing the diagnosis of a rare pulmonary disease or condition requires the formulation of a comprehensive differential diagnosis. None of us are familiar with all of the thousands of rare disorders that can present to our practices, and the correct diagnosis cannot be made if it is not considered. The history and physical exam are the cornerstones that provide the initial clues to nature of the underlying process. The CT scan of the chest has become the most useful imaging tool to develop the pulmonary differential diagnosis and pulmonary function testing can help to narrow the field by characterizing the nature of the pulmonary physiologic defect. Corroborative studies such as abdominal imaging for renal disease, serologies, sputum or pleural fluid analyses, transbronchial or surgical lung biopsy, and, most recently, genetic studies can help to establish a definitive diagnosis.

There are several resources available to obtain more information about the DCLDs. All the DCLDs meet the definition of rare or orphan diseases, whether based on the National Center for Accelerating Translational Research (NCATS) definition as a disorder with a prevalence of fewer than 200,000 affected individuals within the United States or the European ORPHANET definition of fewer than 1 in 2,000 people (www.orphanet.net) [72]. Based on the NCATs definition, there are approximately 25 million people in the United States afflicted with over 6,500 rare diseases [73]. The NCATs Genetic and Rare Disease Information Center maintains a web-based, searchable list of over 6,000 rare diseases with links to various information sources. The National Organization for Rare Diseases (www.raredisease.org) is a nongovernmental federation of organizations that seeks to expand recognition and treatment of individuals with these rare illnesses. There are several additional databases devoted to rare lung disorders, including the British Orphan Lung Disease (BOLD) register that was established in 2000 (www.britthoracic.org.uk/ClinicalInformation/RareLungDiseasesBOLD/tabid/110/Default.aspx); the British Pediatric Orphan Lung Disease (BPOLD) registry of 9 rare pediatric lung disorders in the United Kingdom (www.bpold.co.uk); and the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM"O"P") in France (http://germop.univ-lyon1.fr/). In the United States, the NIH Rare Lung Disease Consortium (RLDC) was founded in 2003 with collaborating centers throughout the United States, Canada, and Japan. The RLDC has ongoing clinical trials and studies in several rare lung diseases including LAM, PAP, and PLCH. Several patient advocacy groups and registries provide education, support, and research funding missions for the DCLDs including the LAM Foundation (www.thelamfoundation.org), the Birt-Hogg-Dubé Foundation (www.bhdsyndrome.org), the Myrovlitis Trust (www.myrovlytistrust.org), the Pleuropulmonary Blastoma/DICER1 Registry

(https://www.ppbregistry.org), the Sjögren's Foundation (www.Sjogrens.org), and the Histiocytosis Association (www.histio.org).

The chapters that follow present the fascinating spectrum of DCLDs, many of which have provided extraordinary insight into the molecular pathogenesis of lung disease. The final chapter suggests an approach to the diagnosis and management of the DCLDs, using algorithms that favor the least invasive and most context appropriate options.

Key Learning Points

- Diffuse cystic lung diseases (DCLDs) represent a unique set of disorders characterized by thin-walled parenchymal lucencies that are fundamentally distinct from the typical interstitial lung diseases.
- While individually rare, DCLDs can be caused by a variety of neoplasms, polyclonal or monoclonal lymphoproliferative disorders or plasma cell dyscrasias, infections, autoimmune or connective tissue diseases, smoking, and genetic or developmental defects; and collectively the DCLDs occur in a substantial number of patients.
- Prototypical DCLDs that present in a multicystic fashion include lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis (PLCH), connective tissue-related follicular bronchiolitis (FB), Birt-Hogg-Dubé syndrome (BHD), and light chain deposition disease (LCDD).
- A thorough knowledge of the presentation and key manifestations and radiographic patterns of the DCLDs is needed to arrive at an accurate diagnosis and differentiate these disorders from more common causes of parenchymal lucencies that can mimic the DCLDs such as emphysema, bronchiectasis, fibrotic lung disease, and cavitary lung diseases.

Conflicts of Interest The authors declare no conflicts of interest.

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