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Review Article

Diffuse Cystic Lung Disease: A Literature Review

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Abstract

Diffuse cystic lung diseases (DCLD) are a heterogeneous group of pulmonary disorders that are characterized by multiple air-filled spaces or cysts within the lung parenchyma. Several other lung diseases can radiologically present the same as DCLD. High-resolution computed tomography (HRCT) provides an accurate description of the morphological characteristics of these cystic lesions. This knowledge of cystic CT patterns is important for narrowing the differential diagnosis, although a multidisciplinary approach is necessary to make the correct diagnosis. The clinical features and radiological findings are quite similar in many patients; therefore, an exploration of the appropriate diagnosis is a great clinical challenge. This literature review focuses on the major DCLDs: lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome (BHD), and lymphocytic interstitial pneumonia (LIP).

Keywords: BHD, Diffuse Cystic Lung Diseases, LAM, LIP, Follicular Bronchiolitis, PLCH

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Introduction

Diffuse cystic lung disease (DCLD) is a heterogeneous group of pathophysiological lung processes characterized by cyst formation. Cysts in DCLD are characterized by thin walls less than two millimeters thick, a round shape, lucency on radiographs, location within normal lung tissue, and occurrence in more than one lobe and bilaterally.[1–3] It is important to differentiate primary DCLD from other lung diseases in which cysts are present as part of a secondary pathophysiological process. Cysts may be unwalled, have very thin or thick walls, be unconnected to normal lung parenchyma, and be found in unusual locations. Therefore, a single or multiple cysts in a localized lung area should be distinguished from cavities, pneumatoceles, or bullae, and multiple cysts scattered throughout both lungs should be distinguished from emphysema, honeycombing, and cystic bronchiectasis. Multicystic lung disease, defined by more than ten identifiable cystic lesions on HRCT, is characteristic of DCLD, while paucicystic lung disease is defined by fewer than ten cystic lesions.[4,5]

The differential diagnosis of DCLD is classified based on the underlying pathophysiology, which may be neoplastic, congenital, genetic, acquired, lymphoproliferative, infectious, inflammatory, or smoking-related. The diagnosis of DCLD is based on the number, shape, size, morphology, and distribution of cysts within the lung, as well as possible parenchymal abnormalities and the patient's clinical history. The clinical presentation of DCLD differs from that of fibrotic interstitial lung disease (ILD) in general.[4,6] The clinical presentation and radiological findings in the differential diagnosis of DCLD are very similar in most patients. Therefore, establishing a correct diagnosis remains a significant challenge. In this literature review, we will describe the DCLDs most frequently encountered in clinical practice, namely lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), Birt-Hogg-Dubé syndrome (BHD), and lymphocytic interstitial pneumonia (LIP).[3,7]

Parenchymal Abnormalities Resembling Cystic Lesions

Cysts in DCLD must be differentiated from other air-filled intraparenchymal lesions that mimic cystic lesions, such as cavities, bullae, pneumatoceles, emphysema, honeycombing, and cystic bronchiectasis (Figure 1). A cavity is a gas-filled space that appears lucent or low-attenuation within a pulmonary consolidation, mass, or nodule. Relatively thick walls (>2 mm) and a more irregular shape distinguish cavities

from cysts. Bullae, on the other hand, are air spaces larger than one centimeter in size with thin walls. Radiologically, they appear as rounded focal lucencies delimited by barely visible walls, no larger than one millimeter, and are usually located subpleurally. Multiple bullae are usually accompanied by adjacent paraseptal and centrilobular emphysema. Bullae can be distinguished from cysts by their barely visible thin walls, subpleural location, and adjacent emphysema.[5]

Pneumatoceles are true cysts, but they are usually transient and most often caused by infection, trauma, or aspiration of hydrocarbon fluids. Radiologically, a pneumatocele appears as a nearly spherical, thin-walled air space. Pneumatoceles in pneumonia may be accompanied by consolidation and ground-glass opacities (GGO). Centrilobular emphysema is the most common type of pulmonary emphysema, typically presenting as decreased lung attenuation, with no visible walls, and a predilection for the upper lung. Centrilobular emphysema may appear similar to thin-walled cysts, but differs in that the cysts are larger, fewer in number, non-centrilobular in location, and have more visible walls than centrilobular emphysema.[4,5]

Honeycombing, which forms due to damaged and fibrotic lung tissue, contains numerous cystic air spaces with thick, fibrous walls and is an advanced stage of various lung diseases. On HRCT, honeycombing appears as clustered lucent areas, three to ten millimeters in diameter, with well-defined borders and thick walls, located subpleurally, especially in the lower lung. They usually appear as multiple layers but can appear as a single layer and are associated with signs of pulmonary fibrosis such as traction bronchiectasis and reticulation, making them easily differentiated from cystic changes in DCLD.[4,5]

Bronchiectasis is irreversible bronchial dilation, either localized or diffuse, usually resulting from chronic infection, proximal airway obstruction, or congenital bronchial abnormalities. Bronchiectasis can be cylindrical, varicose, or cystic, depending on the affected bronchus. Cystic bronchiectasis can be mistaken for cysts on cross-section and is differentiated from cysts by careful examination of adjacent CT images based on the continuity of the dilated airspaces with the airways.[5]

Lymphangioleiomyomatosis (LAM)

Lymphangioleiomyomatosis (LAM) is a neoplasm with a low metastatic rate, primarily occurring in young women of childbearing age. It can occur sporadically (sporadic lymphangioleiomyomatosis, S-LAM) or in association with tuberous sclerosis complex (TSC-LAM). LAM is characterized by the abnormal proliferation of smooth muscle-like cells (LAM cells), with benign histological characteristics, and spread through the lymphatic system, targeting the lung parenchyma. These LAM cells eventually form thin-walled cysts within the lung parenchyma.[8]

Shortness of breath that worsens with activity and spontaneous pneumothorax are the most common symptoms of LAM. The most common pulmonary function abnormalities in LAM are airflow obstruction and decreased pulmonary diffusion capacity.[9,10] Cysts in LAM are regular, round, thin-walled, multiple, well-circumscribed, measuring two to ten millimeters, and distributed throughout both lungs. Cyst formation in LAM is caused by obstruction of terminal bronchioles by LAM cells with dilation of distal air spaces and/or degradation of lung parenchyma due to an imbalance between proteases and protease inhibitors. Computed tomography (CT) imaging can reveal pneumothorax, renal angiomyolipoma (AML), chylothorax, chylous ascites, and abdominal and pelvic lymphangioleiomyoma (Figure 2). Regular centrilobular nodules caused by multifocal micronodular pneumocyte hyperplasia and areas of GGO secondary to alveolar hemorrhage or lymphatic congestion can also be found.[3,11]

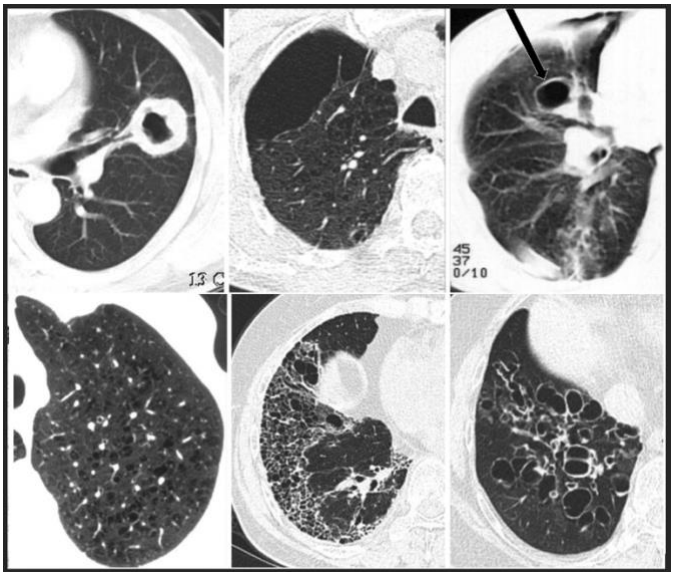

Figure 1. Parenchymal lesions resembling cystic lesions: (A) cavities, (B) bullae, (C) pneumatoceles, (D) emphysema, (E) honeycombing, and (F) cystic bronchiectasis; Adapted from Lee et al.[5], licensed under the CC BY-NC 4.0 License.

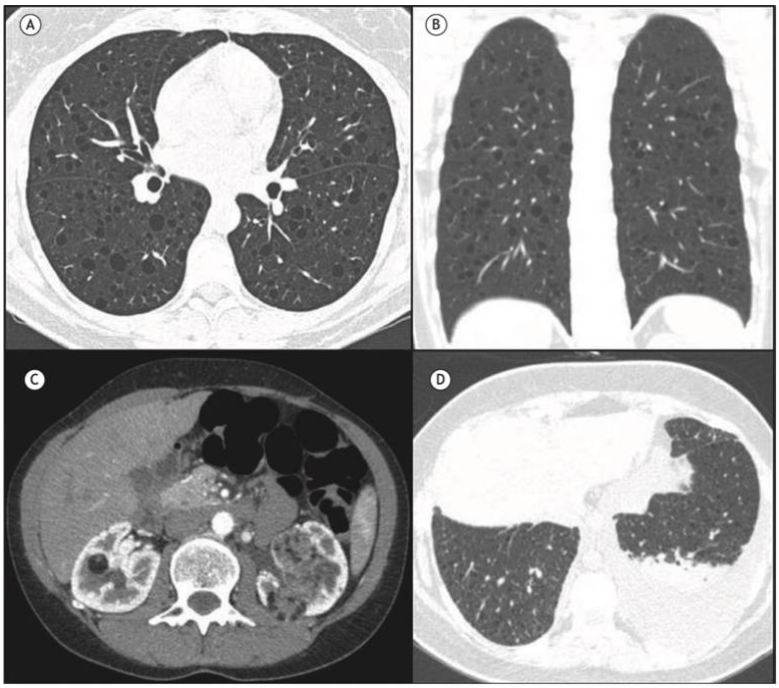

Figure 2. CT scan of a patient with LAM. (A) axial view and (B) coronal view. CT scan of the chest shows diffuse pulmonary cysts with regular walls. (C) axial view. CT scan of the abdomen shows bilateral heterogeneous renal masses consistent with angiomyolipoma. (D) axial view. CT scan of the chest shows diffuse pulmonary cysts and a left chylothorax; Adapted from Baldi et al.[11], under the Creative Commons Attribution license.

The diagnosis of LAM can be confirmed by HRCT findings of cysts characteristic of LAM with the presence of one of the previously mentioned clinical manifestations, namely tuberous sclerosis complex, renal AML, lymphangioleiomyoma, chylothorax, or chylous ascites. If one of the characteristics described above is absent, the diagnosis can be confirmed by an increase in serum vascular endothelial growth factor D (VEGF-D) levels above 800 pg/mL. If serum VEGF-D levels are not available or if serum VEGF-D levels are not elevated, a lung biopsy is recommended. Transbronchial lung biopsy has a positive yield of more than 60%, has a high safety rate, and should be the first choice before surgical lung biopsy.[3,11]

Pulmonary Langerhans Cell Histiocytosis (PLCH)

Another common form of DCLD is pulmonary Langerhans cell histiocytosis (PLCH), a rare neoplastic lung disease characterized by peribronchiolar lesions containing activated dendritic cells known as Langerhans cells (LC). The lungs are most commonly affected, with other organs rarely affected. More than 90% of cases are associated with a history of smoking. Cigarette smoke can induce abnormal proliferation and migration of dendritic cells with mitogen-activated protein (MAP) kinase mutations to the lungs. Secondary activation of the immune system causes damage to the bronchiolar walls and leads to the formation of peribronchiolar nodules, cavities, and cystic damage.[3,11,12] Respiratory symptoms of PLCH are nonspecific and include cough, shortness of breath, pleuritic chest pain, sometimes hemoptysis, and spontaneous pneumothorax. Pneumothorax occurs in 30–45% of patients with PLCH.[3,12]

Standard chest radiographs are of limited value because some small lesions are not visible. HRCT imaging plays a crucial role in the diagnosis of PLCH. The initial and characteristic appearance of PLCH is centrilobular or peribronchiolar nodules, 10–20 millimeters in diameter, with irregular borders. In the early stages, the cysts are thick-walled and vary in shape (separate or coalescing, creating a "cloverleaf" appearance). As they progress, the cysts become larger and thinner-walled. The lesions have a characteristic distribution, with a predominance in the upper and middle lung regions (Figure 3). Pneumothorax occurs in 15% of cases, with varying degrees of severity. Other radiological features associated with smoking are also frequently seen, such as emphysematous bullae or GGO. Enlargement of the pulmonary trunk, pulmonary arteries, and cardiomegaly may be seen in advanced disease, reflecting pulmonary hypertension.[11,12]

Confirmation of the diagnosis of PLCH can be made in young smokers with HRCT findings showing a combination of nodules and cysts in the upper or middle lung fields and the absence of nodules and cysts in the costophrenic sinuses. In cases of cysts without nodules, the diagnosis can be confirmed by bronchoscopy. In 30% of cases of PLCH, the diagnosis is made by transbronchial lung biopsy with bronchoscopy, making it important to rule out other similar diagnoses. In some cases, surgical lung biopsy is necessary for a definitive diagnosis, providing better results and serving as the gold standard.[2,3,11]

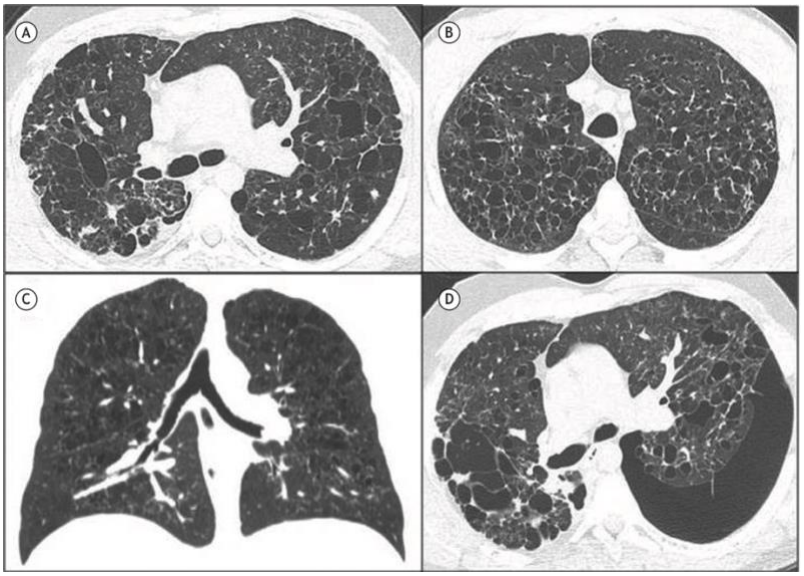

Figure 3. CT scan images of a patient with PLCH. In A, irregular cysts, irregularly circumscribed centrilobular nodules in the upper lobe (axial section). In B, irregular thin-walled cysts (axial section). In C, irregular cysts predominate in the upper lobe and spare the costophrenic sinus area (coronal section). In D, irregular cysts, multiple centrilobular nodules, and a left pneumothorax (axial section); Adapted from Baldi et al.[11], under the Creative Commons Attribution license.

Birt-Hogg-Dubé (BHD) Syndrome

Birt-Hogg-Dubé syndrome (BHD), a rare autosomal dominant disorder that presents as DCLD, is characterized by lung cysts, hair follicle tumors, and kidney tumors. BHD is caused by mutations in the folliculin (FLCN) gene. The mechanism of cyst formation is likely through activation of the mammalian target of rapamycin (mTOR) pathway, leading to cell damage or adhesion protein deficiency, resulting in increased vulnerability of the alveolar-septal junction, which can lead to tearing due to mechanical forces during respiration.[3,13]

Lung cysts in BHD develop in adults between the ages of 40 and 50. The prevalence of spontaneous pneumothorax in patients with BHD is reported to range between 25% and 75%. A family history of pneumothorax is found in 35% of cases. The main radiological feature that distinguishes cysts in BHD is the predominant and characteristic location of round to lentiform, thin-walled lung cysts of varying sizes, distributed in the basal and subpleural regions of the lungs (Figure 4). The histological appearance of BHD cysts is sometimes indistinguishable from emphysema, surrounded by normal lung parenchyma and lacking evidence of neoplastic cell proliferation or significant inflammation.[11,13]

Pulmonary function tests show normal values for forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC, with a mild decrease in the diffusing capacity of the lung for carbon monoxide (DLCO) in advanced cases. Skin lesions, including fibrofolliculomas and trichodiscomas, are the most common manifestation of BHD, occurring in 90% of patients. The characteristic skin lesions of BHD are whitish, dome-shaped papules, measuring one to five millimeters, located on the face and upper trunk. Biopsy of multiple skin lesions is required to confirm the diagnosis. Kidney cancer is the most life-threatening manifestation of BHD, occurring in 25% of patients with a mean age of 50.4 years.[3,11,13]

Spontaneous pneumothorax in young patients, especially those with a previous or family history of pneumothorax, skin lesions, or renal tumors, should prompt evaluation for the diagnosis of BHD. Thoracic HRCT imaging is the most useful modality for the initial evaluation of patients with suspected pulmonary BHD but is insufficient to establish a definitive diagnosis. Pulmonary cysts occur in 80–100% of BHD patients and are commonly confused with blebs, bullae, or emphysema, but the location of BHD-associated cysts is predominantly basal and paraseptal, unlike the apical distribution of airspace enlargement in emphysema.[13] Genetic testing for FLCN mutations should be offered to patients suspected of having BHD to confirm the diagnosis and to facilitate family screening.[13]

Lymphocytic Interstitial Pneumonia (LIP)

Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative disorder characterized by interstitial infiltration by lymphocytes, plasma cells, and other elements of the lymphoreticular system in the alveolar septum. LIP is most prevalent in female patients aged 40–50 years without known risk factors. It is usually associated with other systemic diseases, particularly connective tissue diseases, such as Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), human immunodeficiency virus (HIV) infection, Epstein-Barr virus infection, and acquired immunodeficiency.[6,11]

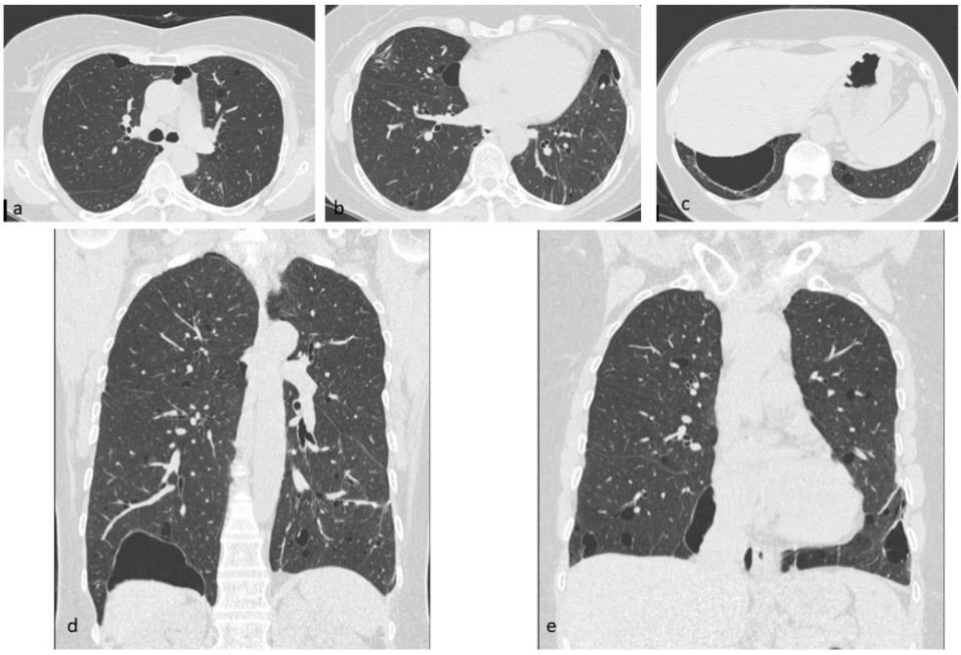

Figure 4. BHD cysts with a basal lung distribution (d) and a paramediastinal distribution (a–c, e). The cysts vary in shape: irregular, septate, and round. Multiplanar reconstruction on coronal sections; Reproduced from Aquilina et al.[6], under the CC BY 4.0 License.

In rarer cases, LIP is associated with Hashimoto's thyroiditis, pernicious anemia, primary biliary cirrhosis, myasthenia gravis, dysproteinemia, chronic active hepatitis, and Castleman's disease. Patients with LIP may be asymptomatic, and common clinical manifestations are cough, worsening shortness of breath, decreased exercise tolerance accompanied by fever, chest pain, weight loss, and joint pain typical of autoimmune disease involvement. On pulmonary function tests, the most common pattern is restrictive.[6,11] Cysts vary in size, ranging from a few millimeters to 30 mm, and are thin-walled, of variable shape, and diffusely distributed with a predominance in the lower lobes and in the peribronchovascular area with involvement of the central lung. The number of cysts is usually fewer than in LAM or PLCH. On chest radiography, a linear or fine reticular pattern can be found.[6,11,14,15]

Table 1. HRCT features and characteristics of DCLD (LIP/FB, lymphocytic interstitial pneumonia and follicular bronchiolitis)

	LAM	**PLCH**	**BHD**	**LIP/FB**
Distribution	Scattered, irregular	Upper and middle parts of the lungs, excluding the costophrenic angles	Basal/peripheral/subpleural, paramediastinal	Scattered, irregular, peribronchovascular
Shape and size	Round, even, thin walls, size 2 mm – 2 cm	Uneven shape, irregular, thin walls, size 2 mm – >2 cm	Uneven, irregular, segmented or round shape, thin walls, size <1 cm	Round and variable, thin walls, size 3 mm – 1 cm
Other findings from HRCT	Pleural effusion	Centrilobular nodules, cavities and reticulations	Cysts often abut the pleura and proximal blood vessels.	GGO, septal thickening, centrilobular nodules
Genetic patterns	Autosomal dominant or sporadic	Not inherited	Autosomal dominant	Not inherited
Prevalence of pneumothorax	70%	10–20%	24%	Unknown
Incidence of recurrent pneumothorax	73%	63%	75%	Unknown, likely rare
Risks associated with smoking	No	Yes	No	No
Sex	Female >> Male	Female = Male	Female = Male	Female > Male

In the acute phase, pulmonary cysts are present, accompanied by additional findings such as GGO with a reticular pattern or small, low-density centrilobular nodules, and subpleural and perilobular nodules with higher density or consolidation on CT scan.[16] Less common findings include thickening of the interlobular septa, pleural thickening due to subpleural nodules, and enlarged mediastinal or hilar lymph nodes. LIP responds to steroid or immunosuppressive therapy, allowing the opacities to diminish in chronic disease, leaving only perivascular cysts. If no systemic disease is clearly diagnosed, the diagnosis of LIP can be confirmed histologically. In some severe cases, LIP can be accompanied by pulmonary fibrosis or progress to lymphoma.[6,11]

Conclusion

Diffuse cystic lung diseases (DCLD) are a heterogeneous group of pathophysiological lung diseases characterized by the formation of multiple cysts. Cavities, bullae, pneumatoceles, emphysema, honeycombing, and cystic bronchiectasis can all present similarly to DCLD. Therefore, it is important to differentiate primary DCLD from other lung parenchymal disorders that mimic cystic lesions. The clinical and radiological features of DCLD are very similar, making a definitive diagnosis difficult and challenging. The most common forms of DCLD encountered in clinical practice are LAM, PLCH, BHD, LIP, and follicular bronchiolitis (FB), each of which has clinical and radiological features that can characterize it (Table 1).

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