Diffuse Cystic Lung Disease Part I

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Abstract

The diffuse cystic lung diseases (DCLDs) are a group of pathophysiologically heterogeneous processes that are characterized by the presence of multiple spherical or irregularly shaped, thin-walled, air-filled spaces within the pulmonary parenchyma. Although the mechanisms of cyst formation remain incompletely defined for all DCLDs, in most cases lung remodeling associated with inflammatory or infiltrative processes results in displacement, destruction, or replacement of alveolar septa, distal airways, and small vessels within the secondary lobules of the lung. The DCLDs can be broadly classified according to underlying etiology as those

caused by low-grade or high-grade metastasizing neoplasms, polyclonal or monoclonal lymphoproliferative disorders, infections, interstitial lung diseases, smoking, and congenital or developmental defects. In the first of a two-part series, we present an overview of the cystic lung diseases caused by neoplasms, infections, smoking-related diseases, and interstitial lung diseases, with a focus on lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis.

Keywords: lymphangioleiomyomatosis; pulmonary Langerhans cell histiocytosis; high-resolution computed tomography; tuberous sclerosis; lung cysts

The diffuse cystic lung diseases (DCLDs) are a diverse group of lung disorders characterized by the presence of multiple regular or irregular spherical parenchymal lucencies bordered by a thin wall and having a well defined interface with normal lung (1). The advent of high-resolution computed tomography (HRCT) scanning has transformed our approach to the DCLDs, revealing patterns that substantially narrow the differential, and, in some cases, providing a definitive diagnosis. The differential diagnosis of DCLDs encompasses a broad set of diseases that can be classified based on underlying pathophysiologic mechanisms, including neoplastic, congenital, genetic, developmental, lymphoproliferative,

infectious, inflammatory, or smoking related (Table 1).

In part I of this review, we provide an overview of the neoplastic etiologies of DCLDs with a focus on lymphangioleiomyomatosis (LAM) and pulmonary Langerhans cell histiocytosis (PLCH). In addition, we discuss DCLDs secondary to infectious etiologies, smoking-related diseases, and interstitial lung diseases (ILDs). In part II, we will describe the DCLDs arising from lymphoproliferative, congenital, developmental, and genetic etiologies. We will conclude by discussing the mechanisms of pulmonary cyst formation, the radiological and pathological evaluation of cystic lung disease, and an approach

to the diagnosis and management of the DCLDs.

LAM

LAM is an uncommon cystic lung disease caused by infiltration of the lung with smooth muscle cells that arise from an unknown source, spread via blood and lymphatics, and contain growth-activating mutations in tuberous sclerosis genes (2, 3). LAM occurs in patients with tuberous sclerosis complex (TSC-LAM) and in a "sporadic" form in patients who do not have tuberous sclerosis (S-LAM) (4). In TSC-LAM, tuberous sclerosis mutations are found in all cells, whereas, in S-LAM, tuberous sclerosis mutations are found

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Table 1. Classification of Diffuse Cystic Lung Diseases

Classification	Description
1. Neoplastic	Lymphangioleiomyomatosis—sporadic as well as associated with tuberous sclerosis Pulmonary Langerhans cell histiocytosis, and non-Langerhans cell histiocytoses, including Erdheim Chester disease Other primary and metastatic neoplasms, such as sarcomas, adenocarcinomas, pleuropulmonary blastoma, etc.
2. Genetic/developmental/congenital	Birt-Hogg-Dubé syndrome Proteus syndrome, neurofibromatosis, Ehlers-Danlos syndrome Congenital pulmonary airway malformation, bronchopulmonary dysplasia, etc.
3. Associated with lymphoproliferative disorders	Lymphocytic interstitial pneumonia Follicular bronchiolitis Sjögren syndrome Amyloidosis Light-chain deposition disease
4. Infectious	<i>Pneumocystis jiroveci</i> Staphylococcal pneumonia Recurrent respiratory papillomatosis Endemic fungal diseases, especially coccidioidomycosis Paragonimiasis
5. Associated with interstitial lung diseases	Hypersensitivity pneumonitis Desquamative interstitial pneumonia
6. Smoking related	Pulmonary Langerhans cell histiocytosis Desquamative interstitial pneumonia Respiratory bronchiolitis
7. Other/miscellaneous	Post-traumatic pseudocysts Fire-eater's lung Hyper-IgE syndrome
8. DCLD mimics	Emphysema α_1 -antitrypsin deficiency Bronchiectasis Honeycombing seen in late-stage scarring interstitial lung diseases

Definition of abbreviation: DCLD = diffuse cystic lung disease.

A proposed classification for the DCLDs discussed in parts I and II of this review is presented. Many DCLDs have overlapping features and can be classified in more than one category. Pulmonary Langerhans cell histiocytosis is classified as both a neoplasm and a smoking-related cystic lung disease. Similarly, desquamative interstitial pneumonia is an interstitial lung disease as well as a smoking-related cystic lung disease. Although classified as a lymphoproliferative disorder, light-chain deposition disease could also be considered under the neoplastic category. Similarly, hyper-IgE syndrome, although classified as other/miscellaneous, could also be classified under the category of infections causing cystic lung disease.

only in neoplastic lesions (5, 6). TSC-LAM occurs in over 30% of women with TSC (7–9), and as many as 10–15% of men with TSC (10, 11), but S-LAM appears to be almost entirely restricted to women, with only one published exception to date (12).

The average age at diagnosis of LAM is about 35 years, but rare cases have been reported in prepubertal females (13) and octogenarians (14). The diagnosis of LAM is recorded in about 3.4–7.8 per million women in the United States and Europe (15), which, if extrapolated across the globe, would predict a prevalence of 35,000 patients with LAM on earth. This is certainly an underestimate, however. Given the global prevalence of TSC of about 1 million persons (16) and a conservative

estimate of 30–40% penetrance of LAM in female patients with TSC (7–9, 17), the predicted worldwide prevalence of patients with TSC-LAM alone is 150,000–200,000. Yet most patients who seek medical attention for LAM have S-LAM rather than TSC-LAM. Partial explanations for this paradox may include that TSC-LAM and S-LAM appear to have different natural histories, that only a fraction (5–10%) of patients with TSC-LAM become symptomatic, and that other health priorities may impede patients with TSC from seeking medical attention for pulmonary issues.

Pathogenesis

TSC and TSC-LAM are caused by mutations in either of the two known TSC genes, *TSC1*

or *TSC2*, whereas only *TSC2* mutations have been reported in S-LAM. In patients with TSC or TSC-LAM, mutations in TSC genes are present in all cells, including the germ line (“first hit”), and neoplasms and dysplasias arise in various organs when somatic “second hit” TSC mutations occur. In patients with S-LAM, both first- and second-hit TSC mutations appear to occur after conception in somatic tissues, and to be confined to lesions in the lung, kidney, and lymph nodes (5, 18). These genetic patterns are consistent with the occasional occurrence of vertical transmission of TSC-LAM, but never S-LAM (19).

Genetic analysis of blood (19), lymphatic fluid, and recurrent LAM

lesions in the donor allografts of patients with LAM who have undergone lung transplantation (3–5) have revealed that LAM cells circulate and metastasize (20). *TSC1* and *TSC2* encode large proteins, called hamartin and tuberlin, respectively, that form a heterodimer that regulates cell growth, survival, and motility downstream of protein kinase B in the phosphoinositide 3-kinase signaling pathway (21, 22). Hamartin or tuberlin deficiency or dysfunction results in up-regulated activity of mechanistic target of rapamycin (mTOR), which leads to increased protein translation and ultimately inappropriate cellular proliferation, migration, and invasion. Additional “cancer-like” programs that are activated by mTOR in LAM cells include suppression of autophagy, shift from oxidative phosphorylation to glycolytic (Warburg) metabolism (23), and expression of the metastasis-promoting lymphangiogenic vascular endothelial growth factors (VEGFs), VEGF-C and VEGF-D (2). Serum levels of VEGF-D are elevated in about 50–70% of patients with LAM, and are useful both diagnostically and prognostically (24–26). At autopsy, the conducting lymphatics are often extensively infiltrated with LAM cells and contain luminal clusters of LAM cells enveloped by a single layer of lymphatic endothelial cells (27, 28). These “tumor emboli” presumably reach the pulmonary microvasculature via the anastomosis between the thoracic duct and left subclavian vein in the neck (29), and once wedged in the lung capillary bed, likely promote a program of “frustrated lymphangiogenesis” driving chaotic lymphatic channel development and cystic remodeling (2). Matrix metalloproteinase (MMP) imbalances involving MMP-2, MMP-9, and tissue inhibitor of metalloproteinase-3 have been described in LAM lesions and may play a role in matrix degradation (30–32). The role of estrogen in disease initiation and/or progression is incompletely understood, but recent evidence suggests that estrogen can activate protein kinase B, facilitate metastasis (33, 34), and promote dysregulated protein translation through up-regulation of Fra1 (Fos-related antigen 1) (35). LAM cells have perivascular epithelioid cell morphology and staining characteristics, but the cell and organ of origin are unclear (36). Candidate primary organ sources for LAM cells include the uterus (37), kidney, genitourinary tract, and the lymphatic system.

Pathology

Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of the lung parenchyma, airways, lymphatics, and blood vessels, associated with areas of thin-walled cystic change (Figure 1A) (38). There are two major cell morphologies in the LAM lesions: small, spindle-shaped cells and cuboidal epithelioid cells (39). LAM cells stain positively for smooth muscle actin, vimentin, desmin, and estrogen and progesterone receptors (40). The cuboidal cells within LAM lesions also react with a monoclonal antibody called HMB-45 (human melanoma black-45) developed against the premelanosomal protein, glycoprotein-100, an enzyme in the melanogenesis pathway (Figure 1C) (39). LAM lesions express VEGF-C and VEGF-D, and often contain an abundance of lymphatic channels lined by VEGFR-3-expressing endothelial cells (28, 29). LAM cells generally expand the interstitium without violating tissue planes, but have occasionally been observed to invade the airways, pulmonary

artery, diaphragm, aorta, and retroperitoneal fat, as well as to destroy bronchial cartilage and arteriolar walls and occlude pulmonary arteriolar lumens (27, 41).

Diagnostic Approach

The following presentations warrant consideration of HRCT screening for LAM: (1) young-to-middle-aged nonsmoking women with pneumothorax (42); (2) asymptomatic females with TSC after age 18 years and every 5–10 years thereafter, per Tuberous Sclerosis Association guidelines (43, 44); (3) incidental discovery of an angiomyolipoma (45), lymphangiomyoma, cysts in the lung bases on abdominal CT, and unexplained chylous ascites or chylous effusions; and (4) unexplained progressive dyspnea on exertion in women with presentations that are atypical for chronic obstructive pulmonary disease or asthma.

The European Respiratory Society Guidelines indicate that the diagnosis of LAM can be made with reasonable certainty on the basis of characteristic cystic change

Figure 1. Lymphangioleiomyomatosis (LAM). Multiple smooth, round, thin-walled parenchymal cysts apparent on computed tomography imaging (A) correspond to histopathologic findings of parenchymal cystic spaces separated by normal intervening lung parenchyma (B) with focal aggregates of spindle and epithelioid LAM cells (B and C, arrows) with characteristic human melanoma black-45 (HMB-45) staining by immunohistochemistry (C, arrow, brown stain). Original magnifications: 10× (B); 40× (C).

on CT in a patient with tuberous sclerosis, angiomyolipoma, lymphadenopathy, or chylothorax (46). A serum VEGF-D level greater than 800 pg/ml in a patient with typical HRCT findings is also diagnostic for LAM (25).

Efforts should be made to establish the diagnosis with certainty before considering chronic treatment with agents that have potential toxic adverse effects. We recommend the following “least-invasive” stepwise approach to diagnosis when a patient with thin-walled cysts on HRCT is evaluated for LAM: (1) thorough personal history and family history for TSC, LAM, or pneumothorax; (2) serum VEGF-D testing; (3) CT or magnetic resonance imaging of the abdomen to screen for the presence of lymphangiomyomas and angiomyolipomas; (4) transbronchial biopsy (which has a yield of >60% and appears to be safe based upon small series) (47, 48) or cytological examination of pleural fluid, lymph nodes, or masses (49); and, if necessary, (5) video-assisted thoracoscopic surgery lung biopsy. When tissues are obtained, consultation with an expert pathologist who is familiar with LAM is essential. LAM is typically negative on fluorodeoxyglucose–positron emission tomography (PET), which can be useful in distinguishing LAM from other neoplastic mimics, such as lymphoma, malignant perivascular epithelioid cell tumor, or ovarian cancer (50).

Management

Angiomyolipomas that exceed 4 cm in size are more likely to bleed (51) and should be evaluated for embolization or treatment with mTOR inhibitors (52). Air travel is safe in most patients with LAM (53, 54). Bronchodilators are warranted in patients with reversible airflow obstruction on pulmonary function testing and in patients who report symptomatic benefit from a bronchodilator trial (55). Pleurodesis should be performed with the initial pneumothorax in each hemithorax, because the rate of ipsilateral recurrence is greater than 70% (56). Lung transplantation is an important option for patients with LAM, and can be safely performed by experienced surgeons in most patients, despite prior unilateral or bilateral pleurodesis (57–59).

The clinical course of LAM is characterized by progressive dyspnea on exertion, recurrent pneumothorax, and chylous fluid accumulations in the chest

and abdomen (60). By 10 years after diagnosis, approximately 55% of patients with LAM experience shortness of breath with daily activities, 20% require supplemental oxygen, and 10% have died (61, 62). Airflow obstruction and hyperinflation are the most common physiologic manifestations, and FEV₁ declines at rates that vary from 50 to 250 ml/yr (63–67). Lung function decline is more rapid in patients with S-LAM, premenopausal patients, and patients with an elevated serum VEGF-D (24), and is likely accelerated by pregnancy and use of estrogen-containing medications.

The Multicenter International LAM Efficacy of Sirolimus (MILES) Trial was a double-blind, randomized, parallel-group trial of 1 year of treatment with sirolimus versus placebo, followed by 1 year of observation (68). Inclusion criteria included a definite diagnosis of LAM and an FEV₁ less than 70% predicted. Patients who were treated with placebo lost approximately 10% of their lung function over the course of the treatment year. In contrast, patients who received sirolimus had stable lung function, improved quality of life, and improved functional performance. Side effects typical of mTOR inhibitors were common, but serious adverse events were balanced in the two groups. Patients with elevated VEGF-D tended to decline faster without treatment and to respond better to sirolimus (24). During the observation year, lung function decline resumed in the sirolimus group and paralleled that of the placebo group. Based on the MILES trial, we recommend sirolimus treatment for patients with LAM who have FEV₁ less than or equal to 70% predicted. The optimal duration of treatment is unclear, but because the effect of the drug is suppressive rather than remission inducing, most patients have been maintained on treatment indefinitely. Recent studies from Japan suggest that low-dose sirolimus (trough serum level < 5 ng/ml compared with the trough level of 5–15 ng/ml in the MILES trial) is effective, which, if borne out by other studies, may enhance the safety of long-term treatment (69). Sirolimus treatment of patients with other presentations of LAM has also been shown to be effective in small series, including chylous effusions, lymphangiomyomas, and patients with rapidly declining lung function while awaiting transplant (63, 70). Trials are needed to

determine the risks and benefits of treating patients with early disease, and to define optimal dose and duration of therapy. Lung transplantation remains an important option for patients with end-stage LAM, despite reports of recurrence in the graft (57, 58, 71–73), because survival rates are comparable to those of other diseases, and graft failure due to recurrence has not been reported.

PLCH

PLCH is a DCLD most commonly encountered in young adult smokers (74). Approximately 90% of adult patients with PLCH smoke cigarettes or have a history of exposure to substantial second-hand smoke (74, 75). About two-thirds of patients with PLCH present with nonspecific symptoms of shortness of breath or cough, but many are asymptomatic or minimally symptomatic (smoker’s cough) and identified incidentally by chest radiography (74). Constitutional symptoms, such as weight loss and fever, may occur in approximately 20% of patients (74). Sudden-onset chest pain and dyspnea often herald the occurrence of pneumothorax, which develops in approximately 15% of patients (76). A small proportion of patients with PLCH may have symptoms due to disease outside of the thorax.

Pathogenesis

The earliest lesion in PLCH is the peribronchiolar accumulation of Langerhans and other immune cells (77–79) (Figures 2A–2C). Langerhans cells are specialized epithelial-associated dendritic cells that regulate mucosal airway immunity. Cigarette smoke may be a key factor mediating the accumulation and activation of Langerhans cells (80) through induction of cytokines, such as granulocyte/macrophage colony-stimulating factor and transforming growth factor- β (77, 81). Osteopontin, a glycoprotein with chemotactic activity for monocytes, Langerhans cells, and dendritic cells, has recently been shown to be spontaneously released by bronchioalveolar macrophages obtained by lavage from patients with PLCH (82). This finding is especially intriguing, since osteopontin overexpression in murine lungs is associated with interstitial accumulation of Langerhans cells (82).

Figure 2. Pulmonary Langerhans cell histiocytosis. Multiple nodules and cysts seen on computed tomography (CT) imaging (A) with histology showing cellular nodules (B), some with central cavities (B, *) containing diagnostic Langerhans cell aggregates highlighted by positive immunohistochemical staining for CD1a (C, brown stain) typical of the early cellular stage of the disease. Coronal CT image from another patient showing multiple bizarre-shaped cysts in an upper-zone–predominant distribution, with sparing of the costophrenic angles representative of later-stage disease (D). Histologic features typical of later disease stages include cystic spaces (E) associated with paucicellular stellate fibrosis (E, arrow). Accumulations of smoking-related pigmented macrophages (F, arrowhead) are frequently seen in the surrounding parenchyma. Original magnifications: 2× (E); 4× (B); 40× (C); 100× (F).

The Langerhans cells in PLCH lesions have an activated phenotype with abundant expression of costimulatory molecules (79). Whether infection or other activating signals play a role in the abnormal activation and persistence of Langerhans cells is not known. The persistence of activated Langerhans cells and secondary recruitment of other immune cells results in the formation of cellular nodules that precede the development of airway remodeling and cystic change (Figures 2A–2C). MMPs produced by immune cells in the PLCH nodules likely play an important role in the airway remodeling and bronchiolar destruction and eventual formation of lung cysts (83). Whether PLCH represents a clonal proliferative process (akin to a neoplasm) or a polyclonal reactive process induced by cigarette smoke has been debated for a long time. Recent studies revealed the presence of mutations in *BRAF* (v-Raf murine sarcoma viral oncogene homolog B), *ARAF* (v-Raf murine sarcoma 3611 viral oncogene homolog), and *MAP2K1* (mitogen-activated protein kinase kinase 1) (cell cycle–regulating pathways

that are mutated in a number of malignancies and other disease states) in lesional Langerhans cells of both PLCH and systemic forms of LCH (84–86). The most commonly identified *BRAF* mutation in PLCH is V600E, which is also a prevalent mutation in melanoma. The identification of *BRAF* and *MAP2K1* mutations in up to 50% of PLCH cases suggests that at least a proportion of PLCH is a cigarette smoke–induced or –promoted dendritic cell neoplasm that is associated with a prominent immune-inflammatory component.

Pathology

Accumulation of Langerhans and other immune cells around terminal and respiratory bronchioles is one of the earliest histopathologic findings in PLCH (Figures 2A–2C) (78). Morphologically, these bronchiolocentric lesions evolve from highly cellular micro- and macronodules to a paucicellular, and often stellate-shaped, fibrotic scars later in the disease process (Figures 2D and 2E) (78, 87). Langerhans cells in tissue specimens can be identified

by their unique morphological features (pale, eosinophilic cytoplasm with indistinct cell borders, and grooved nuclei with small or inconspicuous nucleoli) and immunohistochemical staining for S-100 and CD1a (Figure 2C). In later stages, pericatricial airspace enlargement and cavitation of nodules can occur (Figure 2) (78, 87). Smoking-induced changes, such as respiratory bronchiolitis (RB) and distal airspace macrophage accumulation resembling desquamative interstitial pneumonia (DIP), are commonly seen on lung biopsy (Figure 2F) (100). Venous and arterial structures are frequently abnormal. In some patients, a prominent vasculopathy that mimics idiopathic pulmonary arterial hypertension may occur (87).

Diagnostic Approach

The diagnosis of PLCH should be considered not only in individuals with cystic or nodular infiltrates on chest imaging, but also in cigarette smokers or former smokers with indeterminate upper lobe infiltrates, patients with a history of spontaneous or recurrent pneumothorax, and any patient with lung infiltrates and a history of skin rash or diabetes insipidus. Pulmonary function testing may be normal, or demonstrate obstructive, restrictive, or mixed abnormalities (74). Normal lung function or mild restrictive impairment is more common in earlier phases of disease, whereas obstructive defects predominate in more advanced disease (74, 88). A proportion of patients with PLCH have abnormal pulmonary vascular function measurements, such as reduced diffusing capacity for carbon monoxide and oxygen desaturation during exercise. In patients with advanced PLCH, which is usually accompanied by extensive cystic lung disease, lung function testing often reveals obstruction and air trapping together with reduction in diffusing capacity and hypoxemia.

Whenever PLCH is suspected, a chest HRCT should be performed. Characteristic imaging findings include nodular and cystic abnormalities that occur predominantly in upper and middle lung zones (Figures 2A and 2D) (89). PLCH cysts are often bizarrely shaped, in contrast to the more uniform and bland-appearing cysts typical of other DCLDs. When clinical and radiographic features suggest PLCH, further evaluation may be indicated to establish a definitive diagnosis.

Figure 3. Cystic pleuropulmonary blastoma. Irregular, unilateral cysts apparent on computed tomography imaging (A) are characterized histologically as cysts (B) lined by a benign epithelium (B and C, arrows) with an underlying cambium layer of condensed immature mesenchymal cells (B and C, *). Original magnifications: 4× (B); 40× (C).

Bronchoscopy with transbronchial lung biopsy is diagnostic in about 30% of cases, and is valuable in excluding other diagnoses that mimic PLCH (47, 90). In some instances, surgical lung biopsy is required for definitive diagnosis. Occasionally, the diagnosis may be established by biopsy of an involved site outside the thorax (skin or bone lesions, for example). PLCH lesions are often fluorodeoxyglucose avid, and PET scanning may be helpful to assess the extent of disease activity outside the thorax or detect occult extrapulmonary disease (91).

Management

The three key components of PLCH management include: (1) smoking cessation and avoidance of second-hand smoke exposure when applicable; (2) consideration for pharmacotherapy (including chemotherapy); and (3) assessment and treatment of any disease-specific

complications, including pneumothorax, hypoxemic respiratory failure, diabetes insipidus, and secondary pulmonary hypertension. Although the natural history of disease after smoking cessation has not been fully characterized, smoking cessation may promote disease stabilization/regression, and sometimes complete resolution, of PLCH (75, 92). Some patients have an excellent prognosis and experience very little decline in lung function, whereas others develop progressive lung disease, even after smoking cessation (88). Serial pulmonary function measurements at 3–6 monthly intervals is a reasonable approach for longitudinal disease follow up, especially for patients with impaired lung function at presentation (88). Pharmacotherapy should be considered for patients with impaired lung function, and especially when serial lung function testing demonstrates a progressive decline in FEV₁ (88) despite successful smoking

cessation. Anecdotal experience suggests that oral corticosteroids have limited efficacy, and, although combinations of corticosteroids with vinblastine (standard therapy in childhood LCH) appear to have been effective in some patients, this combined therapy is often poorly tolerated by adult patients with PLCH. Case reports and small series suggest that chlorodeoxyadenosine (also known as cladribine or 2-CDA) may induce remission or improvement of nodular and possibly even cystic lesions (93–95). In a recent report, cladribine as a single agent led to improvement in lung function, CT findings, and pulmonary hemodynamics in cases of PLCH that were progressive despite smoking cessation. Greater response was seen in patients with nodular/thick-walled lesions with increased uptake on PET scan (95). Azathioprine, methotrexate, and other drugs may show efficacy in selected cases (96). With identification of causative mutations, targeted therapies, such as *BRAF* inhibitors, may become promising future therapeutic options for a subset of patients with PLCH (97). Caution must be exercised, however, as these agents have been linked to development of resistance and other neoplasms (98). Patients should be screened for pulmonary hypertension

Table 2. List of Malignancies Reported to Be Associated with Cystic Pulmonary Lesions

Malignancies
Primary pulmonary neoplasms
Bronchioalveolar cell carcinoma
Mesenchymal cystic hamartoma
Pleuropulmonary blastoma
Lymphoma
Sarcomas of various cell types
Angiosarcomas
Osteosarcomas
Synovial cell sarcoma
Ewing’s sarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Endometrial stromal sarcoma
Wilm’s tumor
Pineal teratoma
Other sarcomas
Metastatic epithelial tumors
Adenocarcinomas of the gastrointestinal and genitourinary tract
Systemic malignancies
Lymphoma

Data from References 105–109.

by echocardiography, and, when appropriate, serial echocardiographic assessment may be necessary to identify patient subgroups that develop significant pulmonary hypertension. The identification of pulmonary hypertension should prompt consideration of a vasodilator therapy trial, as some patients may respond symptomatically and physiologically (99). Pneumothoraces should be managed in a standard fashion, and early pleurodesis considered, as the rate of recurrence is high (76). Lung transplantation is an option for patients with severe lung function impairment and/or moderate to severe pulmonary hypertension.

Non-LCH

Other non-Langerhans cell forms of histiocytosis, especially Erdheim-Chester disease (ECD), can rarely produce pulmonary cysts (100). ECD is characterized by xanthomatous infiltration of involved tissues by foamy histiocytes (101), which stain positively for CD68 and are negative for CD1a staining (100). Almost all patients with ECD have involvement of the osseous structures, most commonly in the form of osteosclerosis of the long bones (101). Pulmonary involvement can be detected in 50% of cases by HRCT (100). Although the predominant HRCT findings include interlobular septal thickening and centrilobular micronodules, small microcysts associated with bronchial distortion are present in 12% of patients (100). Similar to PLCH, mutations in the *BRAF* pathway have been identified in over 50% of ECD cases (102), and treatment with the *BRAF* inhibitor, vemurafenib, has resulted in clinical improvement in a few cases (103, 104).

Cystic Lung Disease Associated with Primary and Metastatic Neoplasms

Cystic lung disease develops rarely as a result of a frank malignant process, typically secondary to metastases from peripheral sarcomas and mesenchymal tumors. Cystic metastases due to sarcomas are often complicated by pneumothoraces and portend a poor prognosis (105). Hoag and colleagues (105) studied 153 patients with sarcomas of various cell types who suffered a pneumothorax, and found cystic or cavitory changes in 25% of

patients by chest radiography. Tateishi and colleagues (106) evaluated CT findings in 24 patients with metastatic pulmonary angiosarcoma and found that 21% (5/24) of patients had multiple thin-walled pulmonary cysts with a mean diameter of 46 mm (range = 8–71 mm). All five patients with cystic lung disease developed pneumothoraces, and follow-up studies showed an increase in cyst size and wall thickness. Endometrial stromal sarcomas can result in cystic pulmonary metastases that closely mimic LAM (107, 108). Synovial sarcomas have also been reported to cause metastatic cystic pulmonary lesions (109).

Pleuropulmonary blastoma (PPB), the most common primary pediatric lung neoplasm, typically presents in children under 6 years of age, and can manifest as a multilocular cystic neoplasm designated type I PPB (110) (Figure 3). PPB can also present as a mixed solid and cystic tumor

(type II) or a purely solid, high-grade sarcoma (type III) (111, 112). Low-grade mucosa-associated lymphoid tissue lymphomas rarely present as cystic lesions (113). Pulmonary cysts have also been reported in a variety of other metastatic and primary lung malignancies (105–109) (Table 2).

Smoking-related DCLDs

Exposure to cigarette smoke can cause a variety of diffuse lung diseases, many with a diffuse cystic pattern, including PLCH, DIP, and RB-associated ILD (RB-ILD) (114). RB is a nearly ubiquitous pulmonary process in smokers (114) that is characterized by bronchial metaplasia and the accumulation of pigmented macrophages in distal airways. The pathology of DIP is similar, though the intra-alveolar accumulation of pigmented macrophages is more profuse (115). The radiologic features of RB-ILD and DIP

Figure 4. Diffuse cystic lung disease associated with smoke exposure. (A) Chest computed tomography (CT) showing thin-walled cysts interspersed with areas of ground-glass attenuation and paraseptal emphysema in a patient with desquamative interstitial pneumonia. (B) Chest CT showing round, thin-walled cysts with intervening normal lung parenchyma mimicking lymphangioleiomyomatosis in a patient with small airway damage secondary to cigarette smoke exposure.

overlap significantly, with common abnormalities including bronchial wall thickening, centrilobular nodules, and ground-glass attenuation (116). Although ground-glass attenuation is the most common radiographic abnormality in DIP, cystic changes have been reported in 32–75% of patients (117, 118). The cysts in DIP are typically lower lung zone predominant, involve less than 10% of the parenchyma (118), and often appear within areas of ground-glass attenuation (Figure 4A). Smoking can also lead to small airway destruction, producing a diffuse cystic pattern on chest imaging that can mimic LAM and other DCLDs (Figure 4B) (119).

Infectious Etiologies of Cystic Lung Disease

Infectious diseases can occasionally present with diffuse cystic changes. The parenchymal lucencies in these cases are often referred to as pneumatoceles. *Pneumocystis jiroveci*-associated pneumatoceles are the most characteristic of this group of diseases. *Pneumocystis* pneumonia usually manifests as bilateral ground-glass attenuation and reticulation; however, a minority of cases (10–34%) can present with a predominant DCLD pattern associated with pneumothoraces (120). Cysts associated with *Pneumocystis* are usually numerous, bilateral, diffusely distributed or upper lobe predominant, and of variable size and wall thickness (Figure 5A). Diagnosis is confirmed by identification of microorganisms with appropriate staining (Figures 5B and 5C). The cysts can shrink or completely resolve with treatment of *Pneumocystis* pneumonia (121). Formation of pulmonary cysts is more commonly seen in *Pneumocystis* infections associated with acquired immune deficiency syndrome (~56%) compared with other immune-suppressed states (~3%) (122).

Diseases caused by *Staphylococcus* species can present with multiple pneumatoceles, most often in pediatric populations (123). Effective antibiotic therapy has dramatically reduced this disease presentation, but it is still occasionally reported in cases of septic emboli, especially in immunosuppressed patients (124). Coccidioidomycosis and other endemic fungal microorganisms are infrequently associated with cystic lung disease (125).

Recurrent respiratory papillomatosis (RRP) can rarely present with a DCLD pattern on chest radiography. This predominantly pediatric disorder is caused by the human papilloma virus, and mainly affects the upper airways (126). Respiratory papillomas most commonly occur in the larynx, but can spread to involve the trachea and upper airways, causing mural irregularities, nodule formation, and airway obstruction

in severe cases (127, 128). Bronchopulmonary spread of RRP is rare (2–5% of cases) (128, 129), but is typically present in cases associated with cystic lung disease. The pulmonary lesions of RRP are characterized by multiple cavities, thin-walled cysts, and lower-zone-predominant nodules (Figure 5D). Cysts vary from round to irregular in shape, are usually less than 5 cm in diameter, and can contain air–fluid

Figure 5. Diffuse cystic lung disease associated with infectious etiologies. (A) Chest computed tomography (CT) showing multiple thick-walled cysts (pneumatoceles) and ground-glass opacities in a patient with *Pneumocystis jiroveci*. (B) Cytologic preparations of the bronchoalveolar lavage specimen showing frothy lavage fluid (*). (C) Fungal microorganisms are highlighted in the bronchoalveolar lavage specimen by Gomori methenamine silver (GMS) stain (arrow). (D) Chest CT showing thick-walled cysts along with nodules and ground-glass attenuation in a patient with recurrent respiratory papillomatosis. CT image of recurrent respiratory papillomatosis courtesy of Dr. Jonathan Chung (National Jewish Hospital, Denver, CO). Original magnifications: 100× (B and C).

levels. Cysts can increase in size and number with disease progression. The disease can be fatal, but improvement in cysts and nodules has been reported in a few cases after treatment with cidofovir (127, 130).

Paragonimiasis is a parasitic zoonosis caused by the oriental lung fluke, *Paragonimus westermani*. The infection is acquired after ingestion of freshwater crabs, and is endemic in Southeast Asia. After ingestion, the larvae of *P. westermani* migrate through the abdominal cavity to the pleural space and lungs, causing a variety of pleuropulmonary complications (131, 132). The radiographic findings of pulmonary paragonimiasis include formation of nodules, areas of consolidation, and cysts. Cysts are thought to form as a result of ischemic infarction caused by obstruction of an arteriole or a vein by the worm, and have been reported in 15–100% of pulmonary paragonimiasis cases (131, 133, 134). Cysts vary in size from 5 to 15 mm in diameter, and can have variable wall thickness. They are frequently present within areas of consolidation but can also be seen in isolation (133). Migration tracks can sometimes be visualized on chest radiography, and are considered a specific finding of paragonimiasis (131). Diagnosis can be established by serology and detection of eggs in sputum or bronchoalveolar lavage. Praziquantel is the drug of choice and is effective in over 90% of patients (131).

ILDs with a Cystic Component

ILDs, such as idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis (HP), and sarcoidosis, can present with cystic changes in the lung parenchyma, although cystic change is rarely the dominant feature. Subacute HP (135), as well as chronic HP (136), can present with a cystic lung disease pattern. In fact, the presence and nature of cysts can help distinguish chronic HP from IPF. Cysts in chronic HP are usually seen within areas of ground-glass attenuation (Figure 6A) (136). Centrilobular nodules and areas of decreased lobular attenuation are almost always seen in conjunction with cysts in patients with chronic HP (136).

Cysts in IPF vary from 3 to 10 mm in size, often have thick, fibrous walls, and

are invariably associated with other fibrotic features, such as reticulation, traction bronchiectasis, architectural distortion, and honeycombing (Figure 6B) (125). The distribution of lucencies can suggest the underlying diagnosis. Cysts in IPF and other ILDs have a peripheral, subpleural, and basilar predominance, whereas cysts in sarcoidosis tend to have a perihilar distribution (125).

Conclusions

DCLD is an uncommon clinical and radiographic presentation with a broad differential diagnosis. Neoplastic etiologies, especially LAM and PLCH, are the most common DCLDs seen in clinical practice. Chest HRCT remains the diagnostic

modality of choice, and can be sufficient to establish the diagnosis in some cases. The use of serum biomarkers, such as VEGF-D, has further reduced the need for a tissue biopsy. Bronchoscopy with transbronchial biopsy can be helpful in establishing the diagnosis in cases of LAM and PLCH, but surgical lung biopsy may be required when the diagnosis is not obtained by less-invasive means. Numerous other diseases, such as metastatic malignancies, smoking-related lung diseases, infectious etiologies, and ILDs, can have a predominantly cystic presentation. Clinicians should consider a broad differential diagnosis when evaluating patients with DCLD. ■

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Figure 6. Diffuse cystic lung disease associated with interstitial lung diseases. (A) Chest computed tomography (CT) showing multiple cysts of varying sizes in the left lower lobe associated with traction bronchiectasis, ground-glass attenuation, and areas of decreased lobar attenuation in a patient with chronic hypersensitivity pneumonitis. (B) CT showing cystic changes in a peripheral, subpleural distribution associated with reticulations and honeycombing in a patient with idiopathic pulmonary fibrosis.

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