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Spontaneous Pneumothorax in Diffuse Cystic Lung Diseases

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Abstract

Purpose of review—Diffuse cystic lung diseases (DCLDs) are a heterogeneous group of disorders with varying pathophysiologic mechanisms that are characterized by the presence of air-filled lung cysts. These cysts are prone to rupture, leading to the development of recurrent spontaneous pneumothoraces. In this article, we review the epidemiology, clinical features, and management DCLD-associated spontaneous pneumothorax, with a focus on lymphangioleiomyomatosis (LAM), Birt-Hogg-Dubé syndrome (BHD), and pulmonary Langerhans cell histiocytosis (PLCH).

Recent findings—DCLDs are responsible for approximately 10% of apparent primary spontaneous pneumothoraces. CT screening for DCLDs (BHD, LAM, and PLCH) following the first spontaneous pneumothorax has recently been shown to be cost-effective and can help facilitate early diagnosis of the underlying disorders. Patients with DCLD-associated spontaneous pneumothorax have a very high rate of recurrence, and thus pleurodesis should be considered following the first episode of spontaneous pneumothorax in these patients, rather than waiting for a recurrent episode. Prior pleurodesis is not a contraindication to future lung transplant.

Summary—Although DCLDs are uncommon, spontaneous pneumothorax is often the sentinel event that provides an opportunity for diagnosis. By understanding the burden and implications of pneumothoraces in DCLDs, clinicians can facilitate early diagnosis and appropriate management of the underlying disorders.

Keywords

Lymphangioleiomyomatosis; Birt-Hogg-Dubé syndrome; Pulmonary Langerhans cell histiocytosis; Pneumothorax

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Introduction

Diffuse cystic lung diseases (DCLDs) are a heterogeneous group of disorders sharing a common radiographic feature of discrete air-filled cysts on high-resolution computed tomography (HRCT) scan of the chest. The differential diagnosis of DCLDs is quite broad (Table 1), and encompasses a wide set of underlying pathophysiologic mechanisms (1). While the clinical manifestations vary between the different DCLDs, the vast majority of these diseases share an increased propensity to cause recurrent spontaneous pneumothoraces. In this review, we will provide an overview of the epidemiology, clinical features, and management of spontaneous pneumothoraces in patients with DCLDs.

Lymphangioleiomyomatosis (LAM)

LAM is a low-grade metastasizing neoplasm primarily affecting women, and is characterized by infiltration of the lung interstitium with abnormal smooth muscle cells (2). LAM can occur sporadically (S-LAM), or occur as part of tuberous sclerosis complex (TSC-LAM) (1, 3). Both S-LAM and TSC-LAM develop as a result of mutations in one of the two TSC genes leading to abnormal activation of the mechanistic target of rapamycin (mTOR) pathway (1, 3). Increased mTOR activity drives proliferation of abnormal smooth muscle cells, which subsequently metastasize from their origin via blood and lymphatics and invade the pulmonary parenchyma. Left unchecked, progressive destruction and cystic remodeling of the pulmonary interstitium follows, ultimately culminating in respiratory failure (1, 3).

The clinical presentation of LAM can be quite variable and ranges from asymptomatic patients diagnosed incidentally, to young-middle aged females presenting with worsening dyspnea, pneumothorax, or chylothorax (4, 5). Most patients with LAM present in the mid-30′s to mid-40′s, however presentation in the teens and elderly has been described (1, 4, 6, 7).

HRCT in LAM reveals the presence of multiple, bilateral, uniform, thin-walled cysts devoid of septations or internal structures, present in a diffuse distribution with normal-appearing intervening lung parenchyma (Figure 1) (8). The diagnosis of LAM can be made in a non-invasive manner if one of the following is present in addition to characteristic HRCT features: 1) presence of TSC, 2) angiomyolipomas, or lymphangioleiomyomas on abdominal imaging, 3) chylous effusions, or 4) elevated serum vascular endothelial growth factor-D, greater than 800pg/ml (9, 10). Lung biopsy, transbronchial or surgical, may be needed if the diagnosis cannot be established non-invasively (10, 11).

Pneumothorax in LAM—55–73% of patients with LAM experience a pneumothorax in their lifetime (4, 5, 12–18), with pneumothorax leading to the diagnosis in approximately 40% of patients (4, 5, 16). On average, patients experience 2.2 pneumothoraces before the diagnosis of LAM is made (Table 2) (4, 15, 17, 19–23). Among patients with at least one pneumothorax, 73–85% will have multiple pneumothoraces (13, 15), with ipsilateral recurrence rates of approximately 70% (15). Patients with a history of pneumothorax average between 3.5–4.4 total pneumothoraces (4, 15), with over 10% developing more than

10 pneumothoraces (13). In patients who require lung transplant, post-transplant pneumothorax of native lung occurs in 7–12% of cases (24, 25).

Patient's are usually in their third or fourth decade at the time of their first pneumothorax (15). Concurrent chylothorax and pneumothorax can occur (26). The majority (~80%) of the pneumothoraces occur at rest or with minimal activity (15). Patients with larger cyst size on HRCT (>5mm) (13) and those with a history of smoking (27) are more likely to develop a pneumothorax. Pregnancy may be associated with increased risk of pneumothorax (28).

Pneumothorax accounts for significant morbidity among patients with LAM. It is the most common reason for unscheduled hospitalization, and patients with recurrent pneumothorax average 5 pneumothorax-related procedures each (4, 15, 29). In one study, a pneumothorax-related hospitalization averaged 8 days, resulting in approximately 29 days of total pneumothorax related hospitalization time per patient, and $75,000 in pneumothorax-related cost (15). Pneumothorax in LAM can occasionally be fatal (16).

It has been suggested that patients with LAM presenting with a pneumothorax have a more favorable prognosis compared to those presenting with dyspnea (16, 17). However, earlier diagnosis of the disease may account for the difference in prognosis rather than a true biological effect in these cases.

Management—Some of the management principles regarding pneumothoraces are applicable not only to LAM, but all patients with DCLDs. All patients with DCLDs should be counseled on the symptoms of pneumothorax, and advised to seek medical care immediately if those symptoms present. Smoking cessation should be encouraged. Whenever possible, pneumothorax should be managed by clinicians with expertise in addressing pleural complications of DCLDs.

Given the high rates of recurrence, pleurodesis should be performed after the first spontaneous pneumothorax in patients with LAM rather than waiting for a recurrence. Pleurodesis, while not perfect, reduces the recurrence risk substantially. In one study, the ipsilateral pneumothorax recurrence rate was 66% if managed conservatively, but this was reduced to 27% with chemical pleurodesis, and 32% with surgical pleurodesis (15). Post pleurodesis pain is a significant concern for patients with LAM; patient preferences regarding early pleurodesis differ markedly from the clinicians and should be taken into account when making decisions about pleurodesis (30).

It is important to note that while prior pleurodesis can lead to increased risk of bleeding and prolongation of the operative time, it does not impact outcomes such as mortality, or length of hospital stay (15, 25), and is not a contraindication for lung transplant (31).

Recently, the mTOR inhibitor sirolimus was shown to stabilize lung function decline and improve quality of life among patients with LAM (32). Sirolimus is now considered the first line treatment option for qualifying LAM patients (9), however the impact of sirolimus on future risk of pneumothoraces needs to be studied.

Pulmonary Langerhans Cell Histiocytosis (PLCH)

PLCH is a rare, smoking-associated, progressive DCLD, predominantly affecting young to middle-aged patients (19). Patients are often asymptomatic, but may present with cough, dyspnea, constitutional symptoms, or spontaneous pneumothorax (1). PLCH can occur as part of multisystem LCH, but most often occurs with solitary pulmonary involvement (33).

The central lesion in PLCH is the bronchiolocentric accumulation of Langerhans cells activated by exposure to cigarette smoke. These activated Langerhans cells attract other immune cells leading to destruction of bronchiolar walls with airspace enlargement, creating cystic changes (34). While traditionally believed to be a polyclonal disorder, recent discovery of BRAF, NRAS, and MAPK mutations in a large proportion of PLCH patients suggest that PLCH is an inflammatory, metastasizing neoplasm driven by smoking-induced recruitment and proliferation of circulating histiocytes containing growth-promoting mutations (1, 35, 36).

HRCT imaging in PLCH reveals upper and middle lobe predominant cystic and/or nodular abnormalities, along with characteristic sparing of the costophrenic angles (Figure 2) (1). Imaging findings vary from peribronchiolar nodules in early stages, to a combined nodular and cystic stage, or pure cystic change as the disease advances. In late stages, patients may have significant stellate-shaped interstitial fibrosis (34). The cysts in PLCH often have a unique morphology, frequently being irregular and bizarre shaped, and can have thicker walls as compared to the cysts in LAM (1). While the diagnosis of PLCH can be established based on characteristic imaging in typical cases, histopathological confirmation by lung biopsy (transbronchial or surgical) is often required in atypical cases (1, 37, 38).

Pneumothorax in PLCH—Approximately 15–20% of patients with PLCH experience a pneumothorax (Table 2) (19, 20, 39, 40). Nearly 63% of those patients will have more than one pneumothorax, with ipsilateral recurrence rates approaching 56% (20). Pneumothorax leads to the diagnosis of PLCH in approximately 11% of patients (20). Simultaneous bilateral pneumothorax can occur, and may be fatal (41). In one study, patients with a history of pneumothorax averaged 2.3 total episodes (20). Another study showed that prior to lung transplant, PLCH patients had averaged 3.4 pneumothorax episodes, with as many as 17 in one patient (42). Pneumothorax of native lung has been reported post transplant (42). The age of diagnosis of PLCH is younger in those with pneumothorax, 27 versus 41.5 years old (20). Pulmonary function tests and survival in PLCH do not seem to be affected by pneumothorax (20).

Management—Due to high rate of recurrence, pleurodesis should be performed following the initial episode of pneumothorax rather than waiting for a recurrent event. Mendez et al. found a recurrence rate of 58% when managed conservatively, compared to 0% following surgical pleurodesis (20). Smoking status did not seem to impact pneumothorax rates (20). Nevertheless, treatment of PLCH must involve smoking cessation, which can stabilize, improve, or even resolve the disease (43).The role of steroids or chemotherapeutics such as cladribine on disease course is debated, and their effect on occurrence of pneumothorax is unclear (44). With the recent discovery of underlying MAP kinase mutations in PLCH, there

is potential for targeted treatment for these patients. The impact of targeted therapy on pneumothorax rates and overall disease course needs to be studied.

Other Neoplastic DCLDs

Sarcomas commonly metastasize to the lungs, resulting in cystic changes and pneumothorax (45). Prevalence of pneumothorax in sarcomas is 1.9%, varying by type, although higher rates (9.7%) are reported in patients on chemotherapy, likely due to necrosis of lesions following treatment (45, 46). The most common sarcomas associated with pneumothorax are osteogenic sarcoma, angiosarcoma, and synovial cell sarcoma (45). Pneumothorax recurrence rates are estimated to be 46% (45). In one study, 15% of the pneumothoraces were discovered incidentally, and in a similar proportion of patients discovery of pneumothorax led to the diagnosis of their underlying malignancy (45). Sarcoma-associated pneumothorax portends a very poor prognosis. More than 25% of patients die within a month and the 1-year survival rate is about 20% (45). Management of pneumothorax must be evaluated on a case-by-case basis based on overall prognosis and patient goals.

Other neoplastic processes such as Erdheim-Chester Disease (47), pleuropulmonary blastoma (48, 49), mesenchymal cystic hamartoma (50), adenocarcinoma and squamous cell carcinoma of the lung (51, 52) can rarely cause cystic lung changes and pneumothorax.

Birt-Hogg-Dubé syndrome (BHD)

BHD is an autosomal dominant disease characterized by pulmonary cysts, recurrent spontaneous pneumothoraces, hair follicle tumors, and renal neoplasms (53). It results from mutations of the Folliculin (*FLCN*) gene, a tumor suppressor gene (53, 54). The exact mechanism of pulmonary cyst formation is unclear, but may involve alterations in the mTOR pathway (55), altered cell-cell adhesion resulting in increased vulnerability to mechanical forces (56), impaired LKB1-AMPK signaling (57) and disordered extracellular matrix remodeling involving MMP's (58).

At least 80% of patients develop pulmonary cysts, which are typically thin-walled, irregular, elliptical-lentiform shaped in a basilar and subpleural distribution (Figure 3) (53). Spontaneous pneumothorax is the primary pulmonary manifestation of BHD; patients have well-preserved lung function, cysts do not appear to increase in size over time, and BHD does not typically result in progressive respiratory failure (53, 59). In the presence of compatible clinical and radiological features, the diagnosis of BHD can be confirmed by either a skin biopsy revealing fibrofolliculomas, or the detection of pathogenic *FLCN* mutations (59).

Pneumothorax in BHD—Patients with BHD have a 50-fold greater likelihood of pneumothorax as compared to age-matched controls (60). Recently, two separate studies have shown that BHD can be the underlying cause of 5–10% of apparent primary spontaneous pneumothoraces (61, 62). The prevalence of spontaneous pneumothorax in BHD varies substantially between different reports, based on the mode of ascertainment (renal and/or dermatologic cohorts versus pulmonary cohorts). While a pneumothorax prevalence ranging from 22.5–38% is reported in the renal/skin predominant centers (21, 54,

60, 63, 64), pneumothorax prevalence rates of 42–76% have been reported from patients in pulmonary cohorts (22, 65, 66). Pneumothorax is commonly the complaint that leads to diagnosis of BHD, and patients usually incur more than two episodes of pneumothorax before diagnosis is made (Table 2) (22).

Pneumothoraces due to BHD usually occur in the patient's mid-late 30′s (59), however they have been reported in pediatric (67) as well as geriatric patients (68). The presence of lung cysts and cyst burden including cyst number, size, and total cyst volume are associated with increased risk of pneumothorax (21). Interestingly, there are reports of pneumothorax in patients without radiographically apparent cysts on CT imaging (69). Family history of pneumothorax is associated with higher risk of pneumothorax (63), however smoking and the presence and/or severity of kidney tumors or fibrofolliculomas are not associated with an increased risk of pneumothorax (21, 60). Pneumothorax recurrence rates in BHD are estimated to be 75–80% (21, 22). Patients with BHD-associated pneumothorax experience an average of 3.6 total episodes of pneumothorax (22).

Management—Given the high recurrence rate (>75%), pleurodesis should be performed following the first pneumothorax rather than waiting for a recurrence. Pleurodesis, although not perfect, can reduce the recurrence rates of ipsilateral pneumothorax in half (~30% after pleurodesis as compared to >60% with conservative management) (22). Importantly, BHD does not typically result in progressive respiratory failure and thus concerns regarding pleural complications arising from pleurodesis during future lung transplantation are not applicable to this patient population (68).

Marfan Syndrome

Marfan syndrome is an autosomal dominant syndrome characterized by increased height, long limbs and digits, aortic root dilation, subluxation of the eyes, and apical pulmonary blebs (70). It results from mutations in the gene encoding fibrillin-1, an important constituent of elastic fibers (71). In addition to apical blebs, emphysematous and cystic changes have been reported (71, 72). Pneumothoraces occur in 4–11% of patients (70), which can be bilateral and recurrent (72). Apical blebs or bullae predispose patients to pneumothorax, although pneumothoraces can occur in patients without these changes (71). Some authors recommend definitive recurrence prevention with bullectomy or pleurodesis after first episode of pneumothorax (73). In an effort to reduce the risk of pneumothorax, patients with Marfan syndrome are often advised to avoid breathing against resistance (e.g. playing brass instrument), scuba diving, high altitude sports like skydiving, or flying in an unpressurized cabin (74).

Other Congenital or Genetic DCLDs

Ehlers-Danlos Type IV (vascular subtype) is an autosomal dominantly inherited disorder of collagen characterized by thin skin, abnormal facial appearance, as well as vascular, intestinal or uterine rupture (70, 75). Pulmonary complications include cystic or bullous changes, as well as pneumothorax in up to 16% of patients (75, 76). Congenital pulmonary airway malformation (CPAM) is the most common congenital lung lesion, which can lead to

cystic changes and pneumothorax (77). Bronchogenic cysts can also rarely cause pneumothorax (78).

Pneumocystis Jiroveci Pneumonia (PJP)

PJP manifests as cystic lung changes in 10–34% of patients (79). Cysts are usually bilateral, with a diffuse or upper lobe predominant distribution (79). Cystic changes can occur in PJP associated with HIV or in other immunosuppressive states, and treatment of PJP can shrink or resolve cysts (1).

Pneumothorax occurs in 4–12% of those with PJP (80). The mechanism for pneumothorax involves necrotizing alveolitis with eventual replacement of subpleural parenchyma by necrotic cysts and pneumatoceles that can rupture leading to pneumothorax (81). Cystic PJP is associated with a higher rate of spontaneous pneumothorax as compared to non-cystic PJP (79). Pneumothorax recurrence rates with conservative treatment are 35% (82). Bilateral spontaneous pneumothoraces occur frequently in patients with HIV-related PJP (81, 83). Patients who develop pneumothorax with PJP have a higher mortality than those with PJP without pneumothorax (79).

Patients with PJP and pneumothorax are prone to develop prolonged air leaks and treatment failure (81). As such, early aggressive therapy with surgical referral and/or pleurodesis is recommended, along with medical management of HIV and PJP (80, 81).

Other Infectious DCLDs

Recurrent respiratory papillomatosis (84), paragonimiasis (85), endemic fungal infections (1, 86), staphylococcus and other gram negative infections can also result in formation of lung cysts and spontaneous pneumothorax (87, 88).

Lymphoproliferative DCLDs

Light chain deposition disease (LCDD) is a rare pulmonary lymphoproliferative disorder characterized by the accumulation of monoclonal, nonamyloid immunoglobulin deposits (89). Patients with LCDD can have a primarily cystic imaging pattern that can mimic other common DCLDs such as LAM and PLCH, and also predispose patients to development of pneumothoraces (89). Spontaneous pneumothorax has also been reported in DCLD secondary to Sjögren syndrome and lymphoid interstitial pneumonia (90, 91).

Recent Advancements—Recent publications regarding safety of atmospheric pressure changes, HRCT screening, and alternative techniques for management of pneumothorax have important implications for clinicians and patients.

Atmospheric pressure changes and risk of pneumothorax

Atmospheric pressure changes encountered during activities such air travel and diving, may lead to cyst expansion, and predispose patients with DCLDs to a higher risk of cyst rupture and development of pneumothorax. The risk of pneumothorax associated with air travel has been studied in LAM and, more recently, BHD. In LAM, rates of pneumothorax related to air-travel are approximately 1.1–2.2% per flight (92, 93). Importantly, some patients in these

cohorts had symptoms consistent with a pneumothorax prior to boarding, thus the actual incidence of flight-related pneumothorax may be lower. Johannesma et al recently conducted a retrospective analysis of 158 patients with BHD and found a flight-related pneumothorax rate of 0.63% per flight. However, in this study a pneumothorax occurring within 30 days of the flight was considered as a flight-related pneumothorax, raising the concern for over estimation of the risk (65). In another recent analysis of 104 patients with BHD, the flight-related pneumothorax risk was estimated to be 0.12–0.27% per flight, with flight-related pneumothorax defined as a pneumothorax that occurred either during air travel or within 24 hours of landing (22). The risk of pneumothorax was lower for patients with prior pleurodesis (22). The risk of flight-related pneumothorax is currently being evaluated for patients with PLCH (ClinicalTrials.gov, NCT03052101). In summary, it is safe for most patients with DCLDs to undertake air travel. Patients should be educated about the signs and symptoms of a pneumothorax and counseled not to fly and to seek medical evaluation in the presence of new onset/unexplained chest pain and/or dyspnea prior to boarding an airplane.

Limited disease-specific data is available regarding the safety of diving in patients with DCLDs. In a recent study involving 158 patients with BHD, the pneumothorax rate associated with diving was estimated to be 0.33% per session (65). However, given the paucity of disease-specific data, we recommend that patients with DCLDs avoid diving in accordance with the British Thoracic Society guidelines (81).

CT Screening for DCLDs in patients presenting with a spontaneous pneumothorax

Recent data suggests that BHD, LAM, and PLCH likely cause approximately 10% of apparent primary spontaneous pneumothoraces in the general population (61, 62, 94, 95). Current guidelines do not recommend screening CT for first time pneumothoraces (10). However, in a recent study, performing a screening HRCT to facilitate early diagnosis of LAM, BHD, or PLCH followed by pleurodesis was found to be cost-effective with a marginal cost-effectiveness ratio of $1,427 per quality-adjust life-year (QALY) gained, which is substantially lower than the commonly accepted threshold of $50,000/QALY (95). Based on these results, we recommend that all patients with an apparent primary spontaneous pneumothorax be screened with HRCT for the presence of underlying DCLDs.

Alternative Techniques for Pneumothorax Management

Due to the persistent risk of pneumothorax recurrence after pleurodesis, as well as the risk of adhesions complicating future lung transplant, alternate management techniques are being explored. Total Pleural Covering (TPC), which involves wrapping the visceral pleura in a bioabsorbable mesh, has shown promise in preventing pneumothorax without severe impairment of lung function or formation of severe pleural adhesions (96). In a recent study involving 43 patients with LAM, TPC resulted in a pneumothorax recurrence rate (26%) that was comparable to traditional pleurodesis (15, 96). Successful use of TPC has also been reported in PLCH, BHD, bronchiolitis obliterans, and Ehlers-Danlos Syndrome (97, 98). Blood patch pleurodesis, whereby a patients own blood is instilled through an existing chest tube, has emerged as an effective option for treatment for pneumothorax with reported pneumothorax recurrence rates of 15.6–18.2% (99). The advantage of this technique is the almost complete absence of typical pleurodesis-associated side effects such as pain and fever

(100). The introduction of blood in an otherwise sterile cavity may, however, lead to an increased risk of infectious complications. These alternative techniques need to be better studied before widespread use can be recommended in patients with DCLDs.

Conclusions

DCLDs are increasingly being recognized as the cause of spontaneous pneumothoraces. Early diagnosis of DCLDs has management implications from both a pneumothorax as well as the underlying disease perspective. Performing a HRCT scan at the first episode of spontaneous pneumothorax to screen for underlying DCLDs can be cost-effective. In general, air travel is safe for most patients with DCLDs. Due to the high recurrence rate of pneumothoraces, pleurodesis should be considered following the sentinel event in patients with DCLDs. The impact of pneumothoraces on the natural history of these diseases, the efficacy of alternative techniques to reduce recurrence risk of pneumothoraces, and the impact of targeted pharmacologic therapy on future risk of pneumothoraces are some of the major unanswered questions that should be addressed in future studies.

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Key Points

1. Diffuse cystic lung diseases are a common cause of spontaneous pneumothorax, and can represent approximately 10% of the patients presenting with an apparent primary spontaneous pneumothorax.
2. Performing a screening high-resolution CT scan in patients presenting with a first episode of spontaneous pneumothorax is cost-effective and can help facilitate timely diagnosis and appropriate management of these patients.
3. Patients with underlying diffuse cystic lung diseases and a sentinel pneumothorax have a very high rate of recurrence, if managed conservatively.
4. Due to the high recurrence rate, pleurodesis should be considered following the initial episode of pneumothorax in patients with diffuse cystic lung diseases rather than waiting for a recurrent event.
5. Prior pleurodesis is not a contraindication to lung transplant.

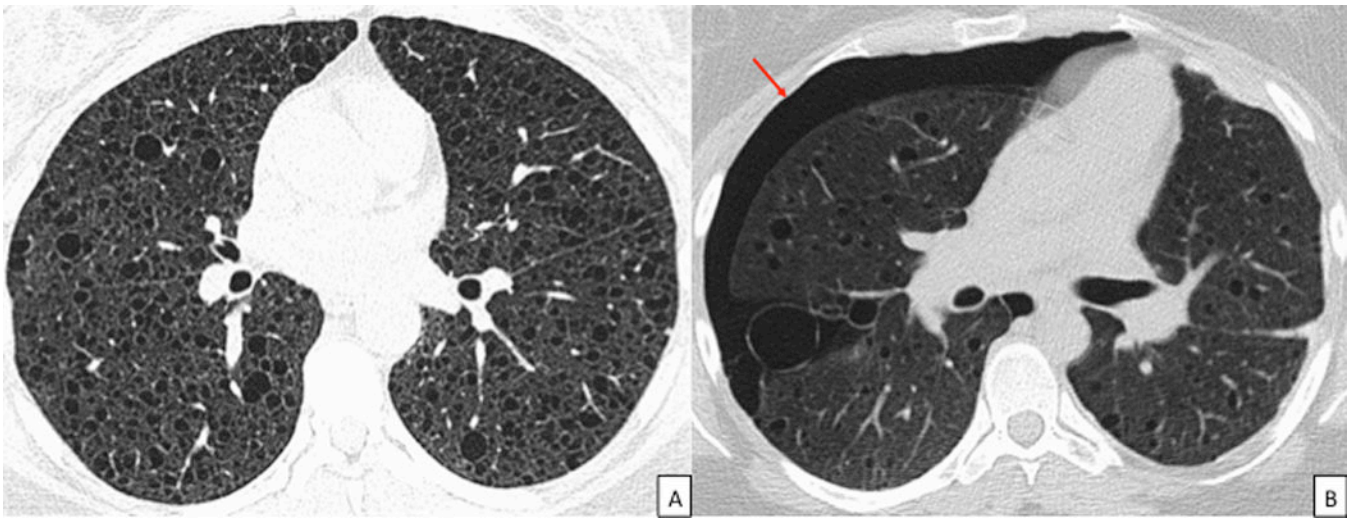

Figure 1.

CT images in a patient with LAM. 1A: Axial CT chest demonstrating the uniform, round, thin-walled cysts characteristic of LAM. 1B: CT chest demonstrating a right sided pneumothorax in a patients with LAM (arrow). Notice the presence of characteristic LAM cysts in addition to the pneumothorax. CT = Computed Tomography, LAM = Lymphangioleiomyomatosis.

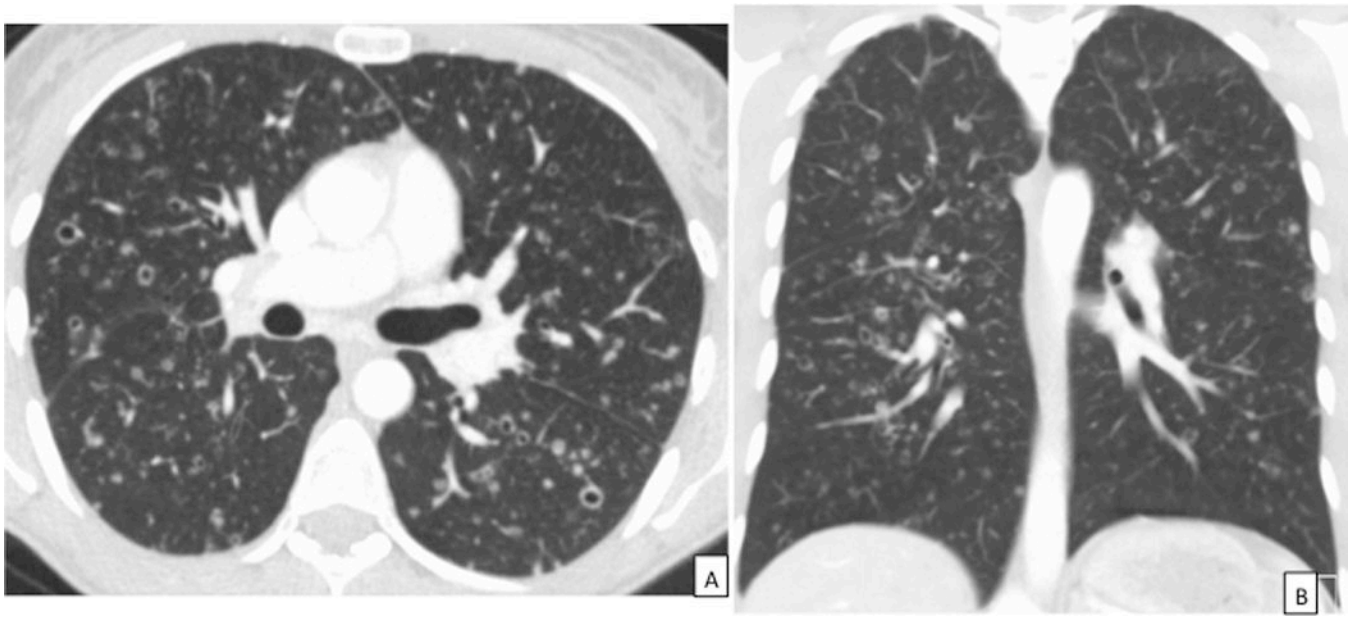

Figure 2.

CT images in a patient with PLCH. 2A: Axial CT chest demonstrating the characteristic thin-walled cysts, thick-walled cavities, and nodules in a patient with PLCH. 2B: Coronal view of the CT scan in the same patient highlighting the upper lobe predominance of radiographic abnormalities with sparing of the costophrenic sulci characteristic of PLCH. CT = Computed Tomography, PLCH = pulmonary Langerhans cell histiocytosis.

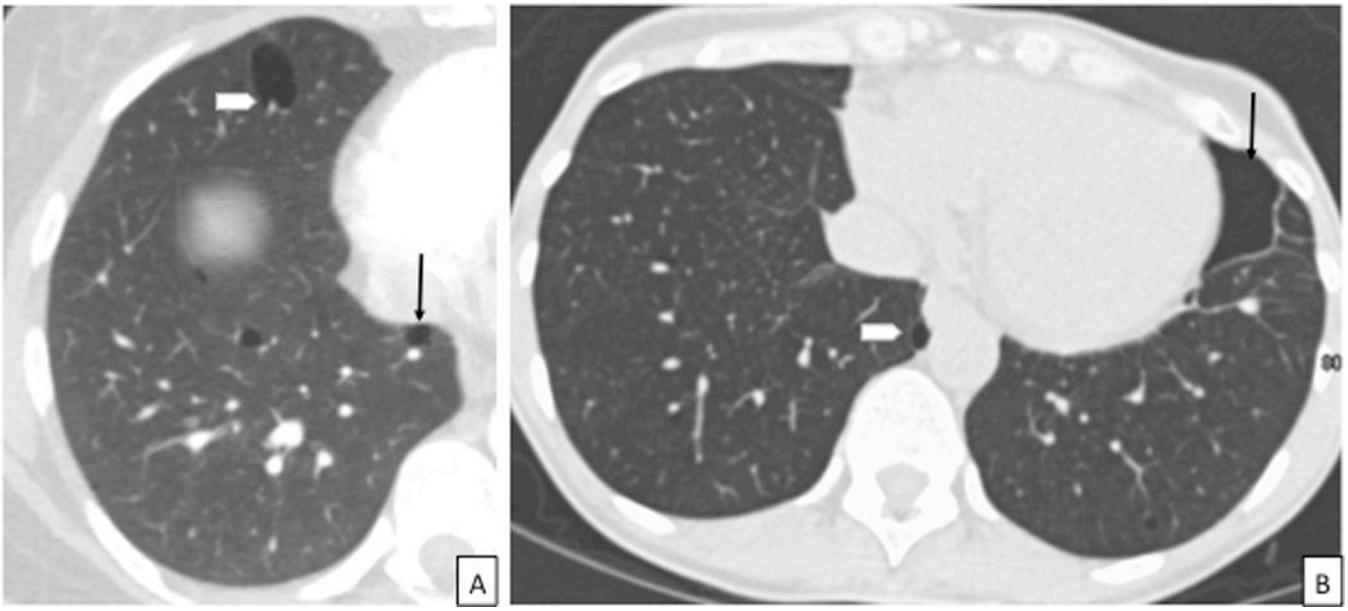

Figure 3.

CT images in a patient with BHD. 3A: Axial CT chest showing the characteristic thin-walled, lentiform cysts abutting the pleura (arrow) and pulmonary vasculature (arrowhead), in a lower lobe distribution. 3B: CT chest showing a chronic loculated left sided pneumothorax in a patient with BHD (arrow). Notice the presence of characteristic lentiform-shaped BHD cyst abutting the mediastinal pleura (arrowhead) in addition to the loculated pneumothorax. CT = Computed Tomography, BHD = Birt-Hogg-Dubé syndrome.

Table 1

Classification of diffuse cystic lung diseases (1)

Certain diseases have overlapping features and can be classified in more than one category. Pulmonary Langerhans cell histiocytosis is classified both as a neoplasm as well as smoking related cystic lung disease. Similarly, desquamative interstitial pneumonia is classified under the category of interstitial lung disease as well as smoking related cystic lung disease. Although classified as a lymphoproliferative disorder, light chain deposition disease can also be considered under the neoplastic category. Similarly, Hyper-IgE syndrome, although classified as other/miscellaneous, can also be classified under the category of infections causing cystic lung disease.

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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*** • Pneumocystis jiroveci • Staphylococcal pneumonia • Recurrent respiratory papillomatosis • Endemic fungal diseases especially coccidioidomycosis • Paragonimiasis
5	***Associated with interstitial lung diseases*** • Hypersensitivity pneumonitis • Desquamative interstitial pneumonia • Respiratory bronchiolitis
6	***Smoking related***

	• Pulmonary Langerhans cell histiocytosis • Desquamative interstitial pneumonia
7	***Other/Miscellaneous*** • Post-traumatic pseudocysts • Fire-eater's lung • Hyper IgE syndrome
8	***Cyst mimics*** • Emphysema • Alpha-one antitrypsin deficiency • Bronchiectasis • Honeycombing seen in late stage scarring interstitial lung diseases

Table 2

Comparative features of pneumothorax incidence and recurrence rates in patients with LAM, PLCH, and BHD (4, 15, 17, 19–23)

Clinical Variable	LAM	PLCH	BHD
Age at first pneumothorax	35 years	29 years	37 years
Proportion of patients who develop a spontaneous pneumothorax	55 – 73%	15 – 20%	24 – 76%
Pneumothorax as the presenting disease manifestation *	82%	69%	65%
Average number of pneumothoraces experienced per patient *	3.5 – 4.4	2.3	2.1 – 3.6
Average number of pneumothoraces per patient prior to diagnosis *	2.2	2.1	2.4
Proportion of patients who develop bilateral spontaneous pneumothorax *	4%	12.5%	5%
Ipsilateral pneumothorax recurrence rate *	71%	56%	73%
Contralateral pneumothorax occurrence rate *	74%	29%	48 – 71%
Ipsilateral recurrence rate after conservative management of first pneumothorax	66%	58%	63%
Ipsilateral recurrence rate following conservative treatment of second pneumothorax	60%	Unknown	93%
Ipsilateral recurrence rate after chemical pleurodesis	27%	Unknown	30%
Ipsilateral recurrence rate after surgical pleurodesis	32%	0 – 20%	35%

* Among patients with at least 1 pneumothorax

Abbreviations: BHD = Birt-Hogg-Dubé syndrome, LAM = Lymphangioleiomyomatosis, PLCH = Pulmonary Langerhans cell histiocytosis