



Imaging Cystic Lung Disease

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Abstract

Purpose of Review Cystic lung disease is characterized by multiple air-filled spaces in the lung. Pulmonary cysts occur in a variety of diseases, including infectious, inhalational, genetic, and neoplastic conditions. The purpose of this report is to review the CT imaging patterns and appearances of the most common cystic lung diseases, and to highlight the differences between different cystic lung diseases and the unique qualities related to each condition.

Recent Findings Common cystic lung diseases include lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, Birt-Hogg-Dubé syndrome, and light chain deposition disease/amyloidosis. Infections or age-related change may also result in cystic lung disease.

Summary Cystic lung disease has multiple etiologies. CT imaging allows for characterization of lung cyst morphology, pattern, and distribution; familiarity with the imaging appearance of the most common cystic lung diseases allows for earlier identification, diagnosis, and disease management.

Keywords Imaging · Cystic lung disease · Radiology · Pulmonary radiology · CT imaging · Pulmonary cysts

Introduction

Pulmonary cysts are well-defined air-filled spaces in the lung that have a thin epithelial or fibrous wall surrounded by lung parenchyma [1]. Cystic lung disease has a variable clinical and radiologic appearance, with a wide variety of etiologies including inflammatory, genetic, inhalational, infectious, and neoplastic origins [2•, 3].

High-resolution computed tomography (HRCT) of the chest is the imaging modality of choice for initial diagnosis and evaluation of cystic lung disease [4]. HRCT allows for the characterization of pulmonary cyst size, shape, wall thickness, and distribution. HRCT also allows for characterization of surrounding lung parenchyma and identification of some extrathoracic findings. Initial evaluation with HRCT can narrow the differential diagnosis and exclude other considerations, although routine surveillance and follow-up may be performed

using thin-section computed tomography (CT). The radiologic appearance combined with thorough investigation of clinical history, demographics, family history, and exposures can help focus diagnostic work up and narrow the differential diagnosis. However, there is considerable overlap in clinical and radiologic findings, and surgical lung biopsy may still be necessary for definitive diagnosis in some patients.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a progressive cystic lung disease [4, 5] with multisystemic manifestations that affect the lungs and lymphatic system. LAM is also associated with mesenchymal tumors [6]. There are two forms of the disease. A sporadic form of LAM occurs almost exclusively in women of child-bearing age. A second form of LAM is associated with tuberous sclerosis complex (TSC-LAM) [2•, 3, 4, 7–9], occurring more frequently in women with TSC, but occurring in up to 13% of men with TSC [10]. Both sporadic LAM and TSC-LAM are associated with mutations with the *TSC* genes in the mTOR signaling pathway [11•, 12].

Clinical symptoms associated with LAM typically involve respiratory symptoms such as progressive dyspnea,

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hemoptysis, and cough [2••, 3, 6–9, 12]. The natural history of LAM is variable. Some patients may follow a slow, indolent course, while other patients may experience a more rapidly progressive course of disease [12].

Histopathologically, LAM cysts are characterized by proliferation of smooth muscle cells, which infiltrate around the cysts and the terminal bronchioles, alveolar walls, pulmonary vessels, and lymphatics [4, 8, 9, 13]. LAM is considered a low-grade neoplasm that occurs from proliferation of smooth muscle cells, resulting from loss of a tumor suppressor gene *TSC* [2••, 5, 6, 13]. Although mechanism is incompletely understood, LAM cells are thought to spread through the lymphatic system, resulting in obstruction of the lymphatics. Cyst formation is postulated to be due to a ball-valve mechanism related to obstruction of terminal bronchioles from proliferating LAM cells [2••, 8].

On CT, the pulmonary cysts in LAM are round and well-circumscribed, without internal septations or vessels [6]. On average, these pulmonary cysts measure 2–5 mm in size [3, 4], although larger cysts may measure up to 3 cm [8, 14]. There is usually no zonal predominance of the cysts [6, 11•, 15•] which are diffusely distributed throughout the lung parenchyma (Fig. 1a–c) and typically surrounded by normal lung [14].

Pulmonary nodules may be present. Generally, nodules are rare in sporadic LAM [4]. However, TSC-LAM may be associated with diffuse pulmonary nodularity [9] related to multifocal micronodular pneumocyte hyperplasia [16]. Pneumothorax occurs in up to 50% of patients [2••, 3, 14], and may be the presenting sign in some patients. Other

common intrathoracic findings associated with LAM include chylous pleural effusions (Fig. 1d) resulting from lymphatic obstruction in the interlobular septa and pleura [6, 14] and lymphangiomas [3, 7–9].

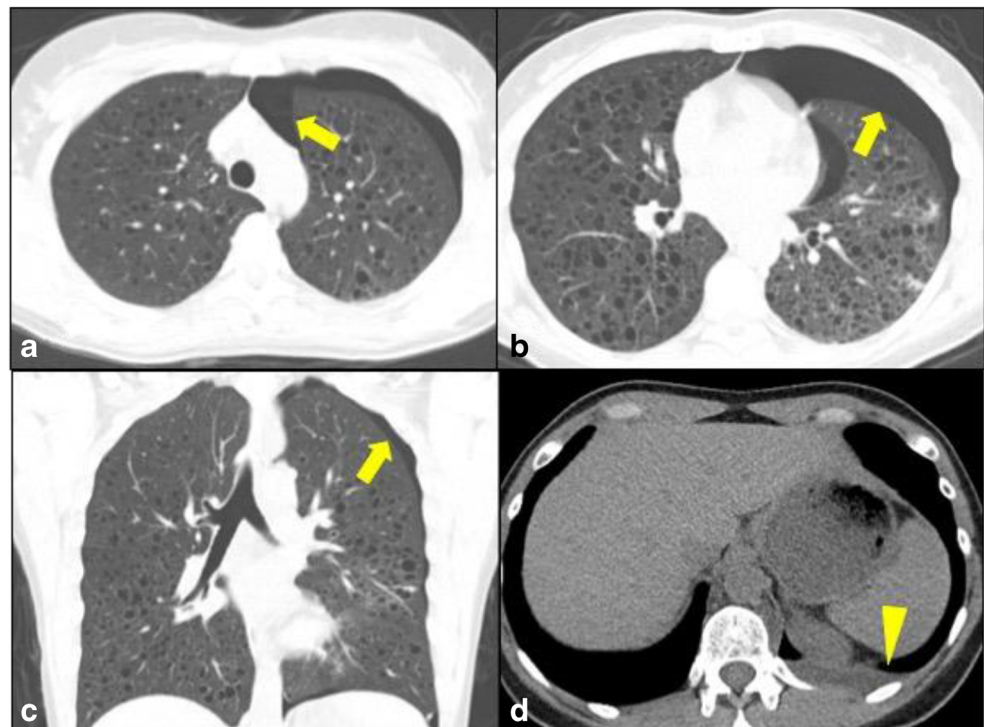
TSC is a multisystemic disorder. In addition to TSC-LAM, it is associated with neurologic abnormalities (subependymal nodules, subependymal giant cell astrocytomas), skin lesions (ash-leaf spots, facial angiofibromas), and cardiac rhabdomyomas [17]. Abdominal findings of TSC include abdominopelvic angiomyolipomas, chylous ascites, renal cysts, and meningiomas [4, 6, 8, 11•, 15•].

Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis (PLCH) has a strong association with cigarette smoking, with 90% of affected patients having a history of current or prior tobacco use [2••, 4]. It primarily affects younger adults, most commonly between 20 and 40 years of age [2••, 3, 14], with a slight male predominance [8].

Symptoms of PLCH are typically related to pulmonary disease, and the most common symptom is progressive dyspnea on exertion [2••]. PLCH has a variable course of disease. Pneumothorax occurs in up to 19% of individuals with PLCH [18] and can be the presenting sign or a recurrent issue [19]. Older age, baseline lung dysfunction, and continued smoking in the setting of PLCH are associated with progressive pulmonary decline [18].

Fig. 1 A 39-year-old woman with sporadic LAM. **a, b** Axial noncontrast CT images demonstrate diffuse, bilateral well-circumscribed thin-walled cysts. There is also a left pneumothorax (arrow). **c** Coronal noncontrast CT image demonstrates the bilateral pulmonary cysts with a diffuse craniocaudal distribution. Left pneumothorax is again seen (arrow). **d** Axial noncontrast image in soft tissue windows shows a pleural effusion, presumably chylous (arrowhead)



On CT, PLCH is characterized by upper lung predominant irregular and stellate nodules, which can be in either a centrilobular or peribronchiolar distribution [2••, 4, 7, 8]. In later stages of disease, these nodules cavitate into cavitary/cystic lesions [2••] which typically measure from 1 to 5 mm in size, although can measure up to 20 mm [9, 20]. As PLCH progresses, the cysts become bizarre and variable in shape, size, and thickness, and can coalesce into larger cysts [2••, 3, 8]. Depending on the stage of disease, the radiologic appearance can have nodules, cysts, or a combination of both [4, 9]. Pulmonary nodules and cysts in PLCH are upper and mid-lung predominant, generally sparing the costophrenic angles (Fig. 2) [2••, 3, 14, 20]. In addition, given its strong association with smoking, concomitant findings of emphysema [21•] and respiratory bronchiolitis may be present. Patients with PLCH may also develop pulmonary hypertension [22], which can be severe and unrelated to the degree of lung disease [23].

Histopathologically, PLCH is characterized by peribronchiolar infiltration of Langerhans cells and other inflammatory cells in the lungs [2••, 4]. These infiltrative LCH cells represent monocyte and macrophage progenitor cells with impaired antigen presentation functionality. These clusters of LCH cells lead to granuloma and nodule formation [4].

Lymphocytic Interstitial Pneumonia

Lymphocytic interstitial pneumonia (LIP) is a cystic lung disease that is characterized as a benign lymphoproliferative

disorder of the lungs [24]. LIP most commonly occurs secondary to another disease process, such as connective tissue disease (Sjogren syndrome, systemic lupus erythematosus), infection (human immunodeficiency virus and Epstein-Barr virus), or immunodeficiency states (common variable immunodeficiency) [2••, 8, 24]. Idiopathic or primary LIP can also occur but is relatively rare [2••, 8]. LIP is more common in women, typically between the ages of 40 and 70 years [2••, 3].

Histopathologically, LIP is a lymphoproliferative disorder with a lymphocytic/plasma cell infiltration largely affecting the lymphatic system along the interlobular septa and peribronchiolar regions [8, 14, 24]. Cyst formation is postulated to be the result of air trapping and airway dilatation secondary to peribronchiolar cellular infiltration [8].

On CT, LIP is characterized by bilateral thin-walled cysts, which are present in approximately 66 to 80% of cases [2••, 4]. Cysts are more common in the setting of secondary LIP than idiopathic LIP [25]. LIP cysts are usually lower lung predominant and perivascular [2••, 4, 7–9], although they may also have a diffuse distribution [3, 4, 7]. The cysts are typically thin-walled and variable in shape, measuring up to 30 mm (Fig. 3) [2••, 3, 8, 14].

Additional pulmonary findings include consolidation, interlobular septal thickening, and bronchovascular thickening [4]. In addition, ground glass and centrilobular nodules may also be present in the lung parenchyma surrounding lung cysts [2••, 4].

Fig. 2 A 23-year-old female smoker with pulmonary Langerhans cell histiocytosis. **a–c** Axial noncontrast CT images of the lungs demonstrate bilateral, irregular cysts (arrows) and few irregular pulmonary nodules (arrowheads) with an upper lung predominant distribution. **d** Coronal noncontrast CT image shows the upper lung predominant distribution of findings, with relative sparing of the costophrenic angles

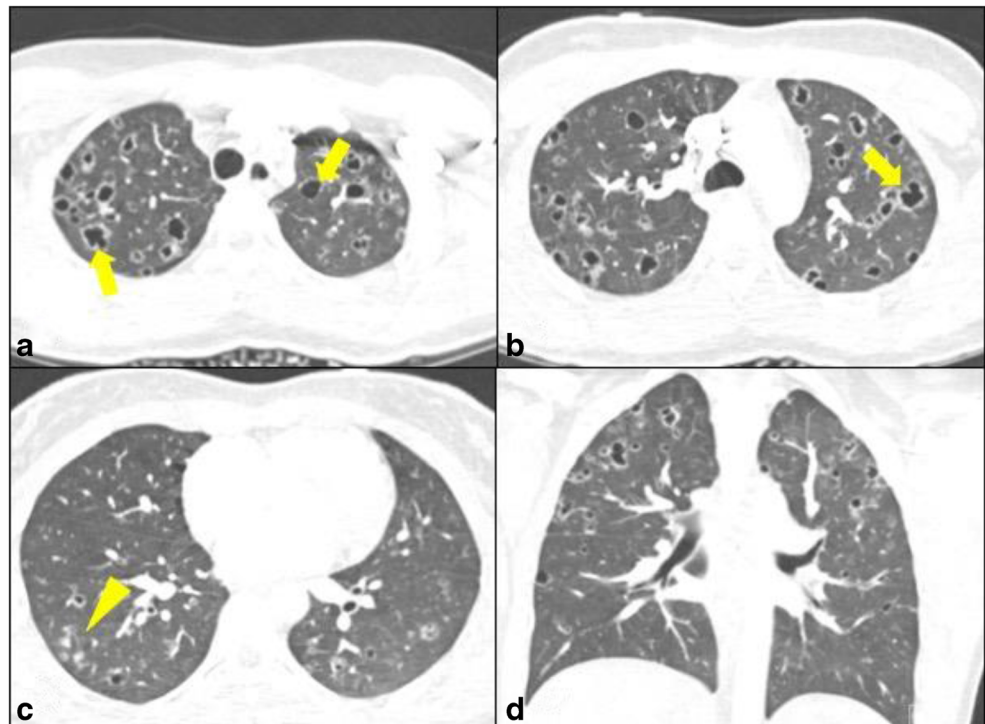
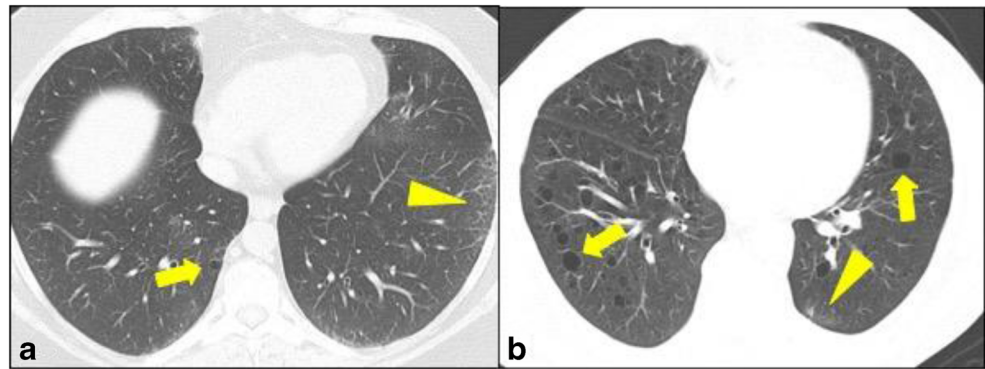


Fig. 3 Lymphocytic interstitial pneumonia. **a** A 55-year-old woman with Sjogren syndrome and LIP, and **b** 58-year-old man with rheumatoid arthritis and LIP. Axial noncontrast images demonstrate scattered pulmonary cysts (arrows) with additional areas of ground glass and interlobular septal thickening (arrowheads)



Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia (DIP) is an uncommon form of cystic lung disease. It is usually considered a smoking-related lung disease, with the majority of cases associated with active smokers. However, a minority of cases arise in nonsmokers [26]. Approximately 10–42% of patients with DIP have no smoking history, with associations including occupational exposures to metal particulates, connective tissue disease, and drug toxicity [27]. DIP most commonly occurs between the ages of 40 and 60, with a slight male predominance [9, 21•, 26]. Clinical symptoms and signs are nonspecific and include chronic cough and crackles on physical examination [26, 27]. Bronchoalveolar lavage typically shows increased macrophages, and surgical lung biopsy demonstrates an

inflammatory infiltrate with pigmented macrophages in a diffuse and uniform distribution [26, 27]. Histologically, DIP occurs along a spectrum with respiratory bronchiolitis [27, 28], and surgical lung biopsy demonstrates an inflammatory infiltrate with pigmented macrophages in a diffuse and uniform distribution [26, 27].

DIP is usually accompanied by other radiologic findings associated with smoking, such as emphysema or centrilobular nodules in respiratory bronchiolitis [21•, 28]. On CT, DIP is characterized by extensive ground glass opacities, with lower lung predominance [9, 26]. Furthermore, cystic disease may develop in these areas of ground glass (Fig. 4) [9]. These may represent either true pulmonary cysts or air-filled spaces due to coexistent emphysema [21•, 28]. Coexistent fibrosis may also be present [28].

Fig. 4 A 48-year-old woman with a long history of smoking and DIP. **a, b** Axial images demonstrate widespread ground glass and numerous areas of cystic change. **c** Coronal CT image shows overlap of emphysema and pulmonary cysts

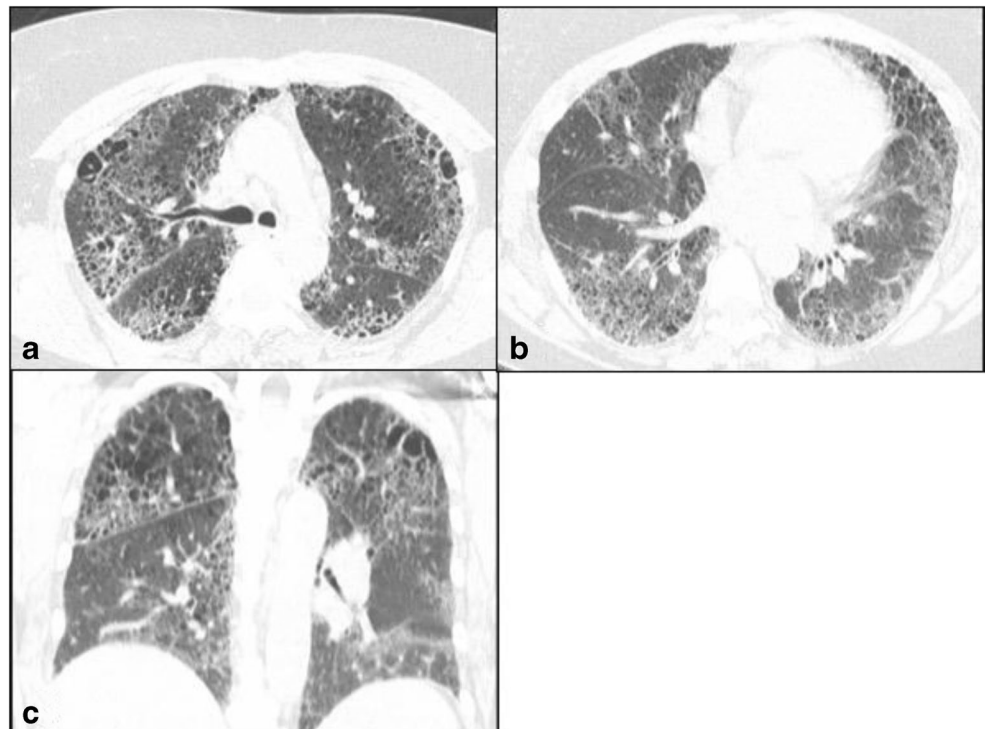
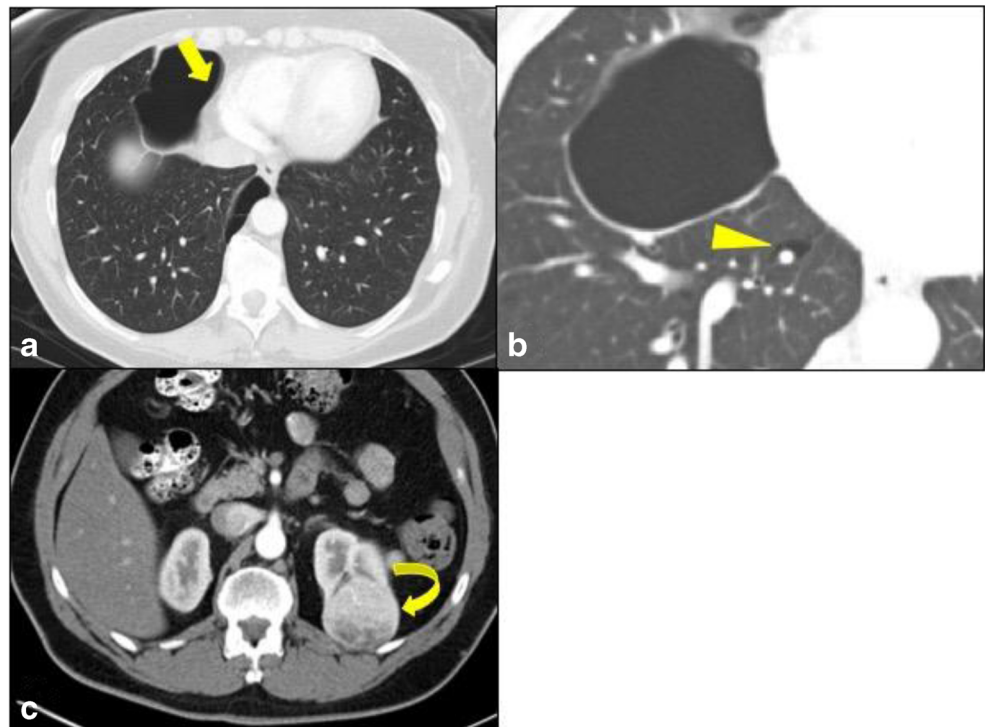


Fig. 5 Birt-Hogg-Dube syndrome. **a** Axial noncontrast CT image of a patient with BHD demonstrates multiple subpleural cysts, one of which indents the mediastinal fat (arrow). **b** Noncontrast axial CT image in a different patient shows a paramediastinal cyst (arrow) and a cyst surrounding a bronchovascular bundle (air-cuff sign, arrowhead). **c** Contrast-enhanced image of the upper abdomen demonstrates a left renal mass (curved arrow), later proven to be a renal cell carcinoma



Birt-Hogg-Dube Syndrome

Birt-Hogg-Dubé syndrome (BHD) is a multisystemic, autosomal dominant disorder caused by a mutation of the folliculin (*FLCN*) gene on chromosome 17 [2•, 9, 29]. *FLCN* is expressed in type 1 pneumocytes, in the distal nephron of the kidneys, and in the skin [30]. As such, BHD is characterized by the clinical triad of pulmonary cysts, renal neoplasms, and follicular tumors of the skin [3, 8, 29, 31].

BHD usually presents in the 3rd to 4th decades of life [4]. There is no known gender predilection or proven relationship to cigarette smoking in the development of lung disease [29]. However, there is significant phenotypic variability in the clinical features associated with each case of BHD [31], with variable expressivity. The presenting symptoms are largely based on the systems involved; follicular tumors may be the

presenting sign in a patient with skin involvement, while pneumothorax may be presentation in a patient with pulmonary cysts [8]. Histopathologically, the cysts are lined with epithelial cells and pneumocytes, without evidence of proliferative or inflammatory features [4, 30].

Chest CT is the imaging modality of choice for the evaluation of pulmonary disease in BHD. Up to 80% of patients with BHD have pulmonary cysts [14, 32]. BHD cysts are typically thin-walled and predominantly located in the medial lung bases [2•, 31]. Cysts are of variable size and shape, and can be round, oval, lenticular, or irregular in shape [33]. In the axial plane, the cysts have a perivenous distribution and can be subpleural or intrapulmonary in location (Fig. 5) [3, 9, 29, 33]. The cysts often have internal septations, which contain interlobular septa and venules [34]. Additionally, the cysts may entirely encircle the bronchovascular bundle (air-cuff sign, Fig. 5a) or

Fig. 6 A 29-year-old woman with amyloidosis and Sjogren syndrome. **a, b** Axial contrast-enhanced CT images demonstrate multiple pulmonary nodules (arrows) and pulmonary cysts (arrowheads). The largest pulmonary cyst in the right middle lobe is subpleural

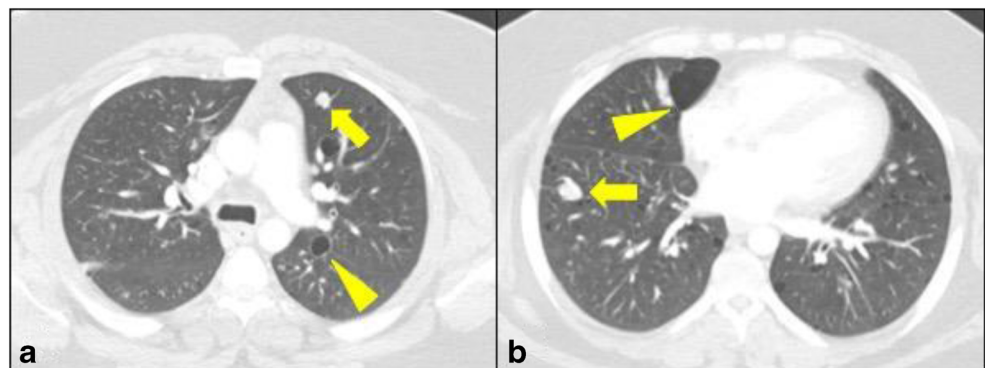
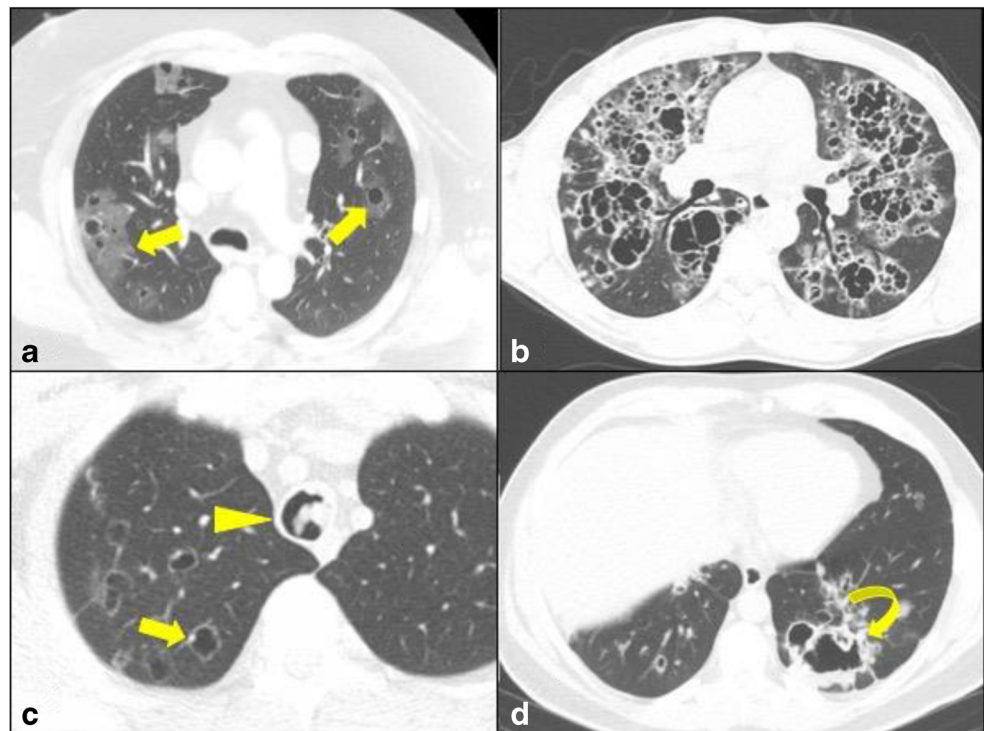


Fig. 7 Other causes of cystic lung disease. **a** A 64-year-old man with metastatic angiosarcoma, with CT chest demonstrating multiple cysts and surrounding ground glass (arrows), likely representing hemorrhage. **b** Axial CT images of a man with recently HIV and *Pneumocystis jirovecii* pneumonia. Axial CT images demonstrate widespread cystic change and surrounding ground glass. **c, d** Axial CT images of a 37-year-old man with respiratory papillomatosis. CT images demonstrate a papilloma in the trachea (arrowhead) and multiple pulmonary cysts (arrows). Additionally, an irregular cavity in the left lower lobe (curved arrow) was biopsied and found to represent squamous cell carcinoma, compatible with malignant transformation



indent the mediastinal fat (Fig. 5b) [35]. Surrounding lung parenchyma is typically normal [31, 33]. Over time, the number of cysts can decrease while overall cyst size increases, suggesting fusion or coalescence of cysts [34].

Recurrent pneumothoraces are common in the setting of BHD [31]. Although the cystic lung disease itself is typically not symptomatic, up to 75% of patients have a history of pneumothorax [3], and patients often have a family history of spontaneous pneumothorax [8, 29].

The clinical course of disease is variable, but largely based on behavior of renal neoplasms and pneumothoraces [4]. Recurrent pneumothorax associated with BHD can be treated by pleurodesis [3, 31]. Renal malignancies pose the most life-threatening complication of BHD (Fig. 5c) [32], and routine imaging surveillance for and management of renal masses is of utmost importance in the follow up of BHD.

Light Chain Deposition Disease/Amyloid

Light chain deposition disease (LCCD) and amyloid represent diseases in which insoluble proteins are deposited in the extracellular space. Both light chain deposition disease and pulmonary amyloid occur in middle-aged to older patients [36, 37]. Light chain deposition disease is characterized by eosinophilic deposits of monotypic immunoglobulin light chain deposits [36], and 75% of cases of light chain deposition disease occur in the setting of multiple myeloma or macroglobulinemia [2]. Amyloid is also eosinophilic on H&E staining,

with Congo red-stained deposits and apple-green birefringence on polarized microscopy [38]. Pulmonary amyloidosis has a strong association with myeloma or monoclonal gammopathy [37]. The cystic form of amyloid commonly occurs in the setting of collagen vascular disease, particularly Sjogren syndrome [2, 37].

Light chain deposition disease appears on CT as multiple round, thin-walled cysts measuring up to 2 cm in size; the cysts may have a diffuse distribution or a lower lung predominance [36]. Nodules are present in most cases [39]. Additional findings include consolidation, and mild reticular or linear opacities are also possible [36]. Pulmonary amyloidosis may have a variety of radiologic appearances. In its cystic form, pulmonary cysts measure up to 3 cm in size [37, 38]. Cysts in amyloidosis are typically irregular and subpleural in distribution (Fig. 6) [37]. Coexistent nodules and calcifications are a common finding, and superimposed ground glass is also possible [37]. Both LCDD and cystic pulmonary amyloid are slowly progressive over time, with increasing size and number of pulmonary cysts [37, 39].

Other Causes of Cystic Lung Disease

A variety of other disease may be associated with cystic lung disease. Metastases from squamous cell carcinoma or sarcoma may cavitate and resemble diffuse pulmonary cystic disease (Fig. 7a) [33, 40]. In addition, chemotherapy

Table 1 Imaging findings in cystic lung disease

Lymphangiomyomatosis	<p>Thoracic findings:</p> <ul style="list-style-type: none"> --Regular, thin-walled cysts --2–30 mm in size --Diffuse, bilateral distribution --Normal surrounding lung parenchyma --Pneumothorax --Chylous pleural effusions --Diffuse nodularity due to multifocal micronodular pneumocyte hyperplasia (TSC-LAM only) <p>Extrathoracic findings of TSC-LAM:</p> <ul style="list-style-type: none"> --Facial angiomas and ash-leaf spots --Subcortical tubers, subependymal giant cell astrocytomas in the brain --Cardiac rhabdomyomas --Chylous ascites --Abdominopelvic angiomyolipomas --Lymphangiomas
Pulmonary Langerhans cell histiocytosis	<ul style="list-style-type: none"> --Irregular, cysts, and centrilobular nodules --Cysts are 1–20 mm in size --Upper lung predominance --Spare costophrenic angles --Concomitant emphysema, respiratory bronchiolitis
Lymphocytic interstitial pneumonia	<ul style="list-style-type: none"> --Variable sized thin-walled cysts --Up to 30 mm in size --Diffuse or basilar predominant --Surrounding ground glass --Centrilobular nodules --Interlobular septal thickening --Peribronchovascular thickening
Desquamative interstitial pneumonia	<ul style="list-style-type: none"> --Basal predominant ground glass --Cystic lesions in areas of ground glass --Concomitant emphysema, respiratory bronchiolitis
Birt-Hogg-Dubé	<p>Thoracic findings:</p> <ul style="list-style-type: none"> --Variable sized thin-walled cysts --Lower lung predominant --Perivenous, subpleural distribution --Pneumothorax <p>Extrathoracic findings:</p> <ul style="list-style-type: none"> --Renal masses --Follicular skin tumors
Light chain deposition/cystic amyloidosis	<ul style="list-style-type: none"> --Round or irregular cysts --Up to 20–30 mm in sizes --Diffuse or basilar predominant --Nodules and calcifications are common --Consolidations and ground glass also possible

can result in cavitation of pulmonary metastases, as a result of tumor necrosis [2••].

Cystic lung disease may also occur secondary to infectious causes. *Pneumocystis jirovecii* infection occurs in immunocompromised patients. Pneumocystis pneumonia is associated with bilateral upper lung cystic lung disease, with cysts being variable in shape and size (Fig. 7b) [2••, 22]. Respiratory papillomatosis is a disease of the upper aerodigestive tract caused by infection with human papillomavirus [41, 42]. In this disease, nodular lesions form along the respiratory lumen and in the lung parenchyma (Fig. 7c) [42]. These nodules undergo central necrosis and

cavitation over time [41, 42], and a combination of both solid and cavitory nodules can be seen [43]. Long-term follow-up of nodules and cavities is necessary, as these lesions may undergo malignant transformation to squamous cell carcinoma (Fig. 7d) [43].

Finally, the incidence of lung cysts increases in age, even in asymptomatic patients. Basal predominant lung cysts occur in increasing size and number with age, generally seen after age 40 [44–46]. As these pulmonary cysts are associated with preserved lung function, these findings may represent a normal aging process of the lung [44].

Conclusion

Cystic lung disease occurs in the setting of multiple disease states including infectious, neoplastic, and inhalational disorders. There can be considerable overlap in the clinical and radiologic appearance of these entities, and a thorough understanding of the subtle differences between these diseases may aid in diagnosis.

For example, both LAM and BHD are associated with lung cysts, pneumothorax, skin lesions, and renal neoplasms. However, LAM cysts are more diffuse and smaller than those in BHD [35•]. BHD cysts are more likely to be in the lung bases with subpleural distribution and internal septations [35•]. In addition, a family history of pneumothorax or tuberous sclerosis may help differentiate these two entities.

In another example, LAM and LIP often occur in women of child-bearing age, and present with diffuse cystic lung disease. However, LAM is typically surrounded by normal lung parenchyma, while LIP is often associated with surrounding ground glass, nodules, and interlobular septal thickening. In addition, cysts in LIP are generally fewer in number than cysts in LAM [3].

Although there is considerable overlap in clinical presentation, high-resolution chest CT allows for detailed characterization of lung disease. Knowledge of cystic lung disease patterns, such as size, number, and distribution of lung cysts, as well as characterization of the surrounding lung parenchyma can better identify the type of cystic lung disease present (see Table 1). Additionally, familiarity with the extrapulmonary and extrathoracic findings associated with different types of cystic lung disease can allow the interpreter to better identify the underlying disease state and to direct therapy.

Compliance with Ethical Standards

Conflict of Interest Tami J. Bang, Thomas D. Suby-Long, and Daniel Vargas declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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