

Multiple Cystic Lung Disease

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A lung cyst is an air-filled lucent structure surrounded by a thin wall. The presence of multiple intrapulmonary cysts is defined as cystic lung disease. Although cystic lung disease is rare, incidental detection has increased significantly in recent years by screening using computed tomography. There are many conditions that can mimic lung cysts and cause cystic lung disease. Clinical, radiographic, and histologic findings are all necessary for a proper diagnosis, and multidisciplinary approaches are frequently required. The aim of this report is to review the causes and characteristics of cystic lung disease to better understand and improve treatment.

Key Words: Cysts; Lung Diseases; Lymphangiomyomatosis; Histiocytosis, Langerhans-Cell; Birt-Hogg-Dube Syndrome

Introduction

A lung cyst is an air-filled lucent area with sharply demarcated thin walls (<3 mm), a well-circumscribed round structure surrounded by lung parenchyma¹. Cystic lung disease is characterized by multiple intrapulmonary cysts. Computed tomography (CT) scanning has enabled the detection of these abnormalities that often cannot be found on simple chest X-rays. However, many conditions can mimic lung cysts and these should be excluded first before making a diagnosis. For proper diagnosis and treatment, we review the conditions which can mimic lung cyst² and each disease that can be presented as cystic lung disease^{3,4}.

Air-Filled Lucencies that Mimic Pulmonary Cysts

1. Cavities

Cavities are intraparenchymal air-filled lucencies with definable walls that are thicker (>4 mm) than those of lung cysts¹. Common causes of cavities are bronchogenic carcinoma, lung metastasis, vasculitis, and infectious diseases such as lung abscess, septic emboli, tuberculosis, and fungal infection². Due to the prognostic and therapeutic influence of underlying disease, a definitive evaluation is required.

2. Emphysema

Emphysema is abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls⁵. Emphysematous destruction is classified as centrilobular, paraseptal, or panlobar, according to the location of the secondary pulmonary lobule involved.

Centrilobular emphysema is the destruction of the airway from the center of the secondary pulmonary lobule. This is mainly related to cigarette smoking, and appears predominantly in the upper lobes. Centrilobular emphysema shows low attenuation without definable

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walls on chest CT scans. The destruction of the pulmonary lobule begins from the center, but as the disease progresses, the entire secondary pulmonary lobule becomes affected, and the interlobular septum left between the destroyed lobules looks similar to a lung cyst. In emphysema, the air-filled space keeps the polygonal shape as secondary pulmonary lobules. Lung cysts, however, are usually round in shape.

Paraseptal emphysema involves the more distal part of the secondary pulmonary lobule, and usually presents as a single row of elongated, thin-walled, air-filled structures that are distributed in the subpleural areas.

Panlobular emphysema is the destruction of the secondary pulmonary lobule. Unlike centrilobular emphysema, it involves more diffuse lung parenchyma, especially in the lower lobes. Panlobular and centrilobular emphysema both show low attenuation areas without definable walls on chest CT scans.

Bulla is defined as well-demarcated emphysema that is ≥ 1 cm in diameter with a wall thickness of ≤ 1 mm¹. Bulla frequently presents as an aspect of paraseptal emphysema and is usually located in the subpleural area. Bleb is thin-walled (≤ 1 mm) emphysema that is smaller than 1 cm in diameter and is found in the apex region.

3. Bronchiectasis

Bronchiectasis is defined as focal or diffuse, irreversible dilatation of the bronchial tree¹. The most common cause is recurrent pulmonary infection, but it can also be part of hereditary syndromes such as cystic fibrosis, dysmotile cilia syndrome, immunodeficiency disorder, and connective tissue disease⁶. Bronchiectasis can be differentiated by following the dilated airway branching from the pulmonary cyst on multiple sequential chest CT scans. This branching pattern is better recognized on coronal or sagittal reconstructed images. Bronchiectasis is usually associated with bronchial wall thickening, centrilobular nodules, and air-trapping.

4. Honeycombing

Honeycombing is multiple rows of air-filled lucencies

with variable wall thickness that are clustered in the subpleural area¹. Honeycombing is associated with end-stage pulmonary fibrosis, predominantly distributed in the lower lobes and usually < 1 cm in diameter. Other features of pulmonary fibrosis, such as decreased lung volume, reticular opacities, architectural distortion, and traction bronchiectasis, accompany honeycombing. Honeycombing is differentiated from cystic lung disease because multiple air-filled spaces are distributed along the subpleural area, not within the lung parenchyma.

Causes of Cystic Lung Disease

1. Lymphangiomyomatosis (LAM)

LAM is an idiopathic multisystem disorder in which immature smooth muscle and spindle cells (LAM cell) proliferate along the axial lymphatics, leading to progressive cystic lung destruction, lymphatic obstruction, and abdominal tumors⁷. Peribronchiolar LAM cell infiltration leads to bronchiolar obstruction and air trapping by the check-valve mechanism; it destroys lung parenchyma and finally results in lung cysts. Tiny pulmonary nodules can appear due to the focal proliferation of type II pneumocytes. Histologic and pathologic features include the proliferation of atypical smooth muscle cells that replace lung parenchyma with thin-walled cysts, renal angiomyolipomas (AMLs), lymphadenopathy, and lymphangiomyomas.

LAM is almost exclusively found in women of child-bearing age and arises in 1–5 per million women. It mainly affects the lungs, promoting cystic destruction, but it can also affect other organs like angiomyolipoma or LAM. Dyspnea upon exertion is the most common symptom, and fatigue, coughing, chest pain, wheezing, abdominal bloating, edema of the arms and legs, hemoptysis, chyloptysis, and weight loss can be shown. Spontaneous pneumothorax can occur in 40–80% of patients and up to 50% experience kidney angiomyolipoma. Chylothorax or chylous ascites can be associated with or without lung lesions. Around 10–20% of patients eventually progress to respiratory failure within 10 years.

LAM can arise sporadically or in association with tuberous sclerosis complex (TSC), an autosomal inherited syndrome characterized by hamartoma-like tumor growth with pathologic findings similar to those of LAM. TSC mainly affects the brain, kidneys, skin, and lungs. Characteristic triads are mental retardation, seizures, and adenoma sebaceum⁸. TSC is caused by germline mutations in two genes, *TSC1* on chromosome 9q34 and *TSC2* on chromosome 16p13. Both genes are tumor-suppressor genes and encode hamartin and tuberlin, respectively⁹. Hamartin and tuberlin affect signaling in the phosphatidylinositol 3-kinase/serine-threonine kinase protein kinase B(Akt)/S6 kinase pathway, which controls cell growth and protein translation. Non-phosphorylated tuberlin has guanosine triphosphatase GTPase-activating protein (GAP) activity for Ras homolog enriched in the brain; it maintains an inactive state and inhibits the mammalian target of rapamycin (mTOR). Genetic mutations cause the absence or dysfunction of hamartin and tuberlin, silence GAP activity, and then activate the mTOR pathway. Evidence suggests that sporadic LAM is associated with *TSC2* loss of heterozygosity mutation, explaining the common disease pathway between sporadic LAM and TSC-associated LAM.

Radiographic evidence of LAM in women with TSC varies, ranging from 26–40%. According to the National Heart, Lung, and Blood Institute (NHLBI) LAM registry¹⁰, 15% of those registered have TSC-associated LAM. Radiographic and pathologic features cannot be distinguished in the two diseases. Tuberous sclerosis is an autosomal dominant inherited disorder that affects both sexes equally. However, lung involvement in TSC occurs nearly exclusively in women of childbearing age, similar to sporadic LAM. TSC-associated LAM patients are typically younger and show milder respiratory symptoms, but are combined with renal angiomyolipoma more frequently than with sporadic LAM. Patients with TSC-associated LAM have a family history of TSC (25–50%), but the detailed clinical manifestation may vary, even within families. Such patients also present with other systemic abnormalities of TSC.

The plain radiographic feature of LAM is nonspecific

and varies according to disease severity. Symmetric reticular, reticulonodular interstitial infiltrates can be found, but lung volumes are usually normal or increased. Pneumothorax or pleural effusion, and in advanced stages, honeycombing, may be seen on chest radiography. However, many patients with documented LAM have normal chest radiographs. Chest CT scans are more useful in the diagnosis and follow-up of LAM. Chest CT scans reveal numerous, symmetric, uniformly round, thin-walled lung cysts surrounded by relatively normal lung parenchyma. These cysts are diffusely distributed in all regions of the lungs, and the size and number tend to increase with disease progression¹¹. Other findings are small nodules, patchy ground-glass opacity with septal thickening, and hilar/mediastinal lymphadenopathy.

Pulmonary function tests usually reveal a restrictive pattern in the early stages and an obstructive pattern in the advanced stages. The radiological extent of disease is well correlated with decrement of forced expiratory volume in one second and a diffusing capacity for carbon monoxide (DLCO%)^{12,13}. Exercise tests, including a six-minute walking distance test, are useful to quantify the functional impairment.

Suspicion is important in diagnosis (especially in recurrent pneumothorax or chylothorax in young women) as the diagnosis of LAM is often delayed. Typical clinical and image findings with extrapulmonary manifestations, such as angiomyolipoma, thoracic or abdominal chylous effusion, biopsy-proven lymph nodes involved by LAM, and combined features of TSC, are also sufficient to confirm the diagnosis¹⁴. When a differential diagnosis is needed, a surgical lung biopsy should be performed. Immunohistochemistry staining for human melanoma black-45 and smooth muscle actin-positive smooth muscle cells is the gold standard for LAM diagnosis.

At present, there is little effective treatment for LAM. Since LAM occurs in pre-menopausal women and is reported to be worse during pregnancy or estrogen replacement therapy, various hormonal strategies have been tried. The efficacy of bilateral oophorectomy is

controversial, and there is no consistent evidence regarding anti-estrogen therapy^{15,16}. Lung transplantation is the only curative therapy for end-stage LAM, and recurrent LAM in the graft is rarely reported. Recently, data from the Multicenter International Lymphangiomyomatosis Efficacy of Sirolimus (MILES) trial has been published, according to which sirolimus slows down the annual decline rate of forced expiratory volume in one second, decreases the level of vascular endothelial growth factor D, and improves symptoms and the quality of life¹⁷. Treatment with an mTOR inhibitor could be promising; however, tolerance and safety issues should be considered. Conservative treatment for complications is frequently necessary. Pleurodesis is performed for pneumothorax or chylothorax, and occasionally thoracic duct ligation or a long-acting somatostatin analogue (octreotide) is used. Symptomatic AML could be treated by embolization or nephron sparing surgery.

2. Pulmonary Langerhans cell histiocytosis (LCH)

LCH is a rare clonal proliferative disease characterized by the accumulation of pathologic Langerhans cells (LCs; LCH cell) in a single organ or in multiple organs, specifically the lungs, bones, pituitary gland, skin, mucous membranes, lymph nodes, and the liver¹⁸. LCs are divided from dendritic cells, which defend and regulate the immune response. LCH cells and LCs look similar and both express Birbeck granules, but LCH cells have a more rounded appearance and lack dendritic cell extensions. LCH cells express CD1a, Langerin, and S100, but fail to express mature markers like CD83. The incidence of LCH is 1–2 per million of the adult population, and 2–10 cases per million for children. LCH is considered a malignant process due to clonality, but others though as reactive condition secondary to immature dysregulation. About 40% of LCH patients have pulmonary involvement, and 28% present isolated pulmonary involvement¹⁸. Pulmonary LCH (PLCH) is a smoking-related disease¹⁹ that is prevalent in the second and fourth decades of life. Most cases of adult onset LCH are a form of isolated PLCH, but combined extrapulmonary involvement is reported in up to 15% of

cases.

Patients have nonspecific symptoms, including dry cough and dyspnea, but around 15% present with spontaneous pneumothorax as an initial manifestation and 25% of all instances are incidentally detected on routine chest CT scans without any symptoms²⁰. Abrupt onset of chest pain or worsening dyspnea usually indicates pneumothorax, but could be due to rib involvement. Constitutional symptoms such as fever, weight loss, and malaise can occur. Advanced PLCH is associated with pulmonary hypertension by direct arterial invasion, which also contributes to significant exercise limitations.

Pulmonary function tests for PLCH are variable and exhibit restrictive, obstructive, or mixed patterns with decreased DLCO. The radiological features are bilateral, symmetrical nodules up to 1 cm in size that are predominantly distributed in the upper- and mid-lung zones. The cysts are often irregularly shaped and have a coalescence of nodules that extend to the lower lobe as the disease progresses. However, the costophrenic angles are typically spared, except in very severe cases. In the advanced stage, reticular and cystic changes can be observed without reduced lung volume. Chest CT scans can be diagnostic in determining PLCH, and a combination of cysts and nodules in the upper lung zone is a pathognomonic finding. Advanced PLCH may progress to include honeycombing and fibrotic changes^{3,20}.

If clinical characteristics are well correlated with imaging findings, a lung biopsy is not required. However, this typical finding is relatively uncommon. Most patients have either cysts or nodules alone, and a surgical lung biopsy might be needed, which could be performed during pleurodesis to treat pneumothorax. Pathologic findings have revealed LCH cells stained for CD1a and S100 infiltrate the bronchiolar wall and epithelium in the early stage, and characteristic stellate fibrotic scars can be seen in the later stage. Electron microscopy can reveal the presence of Birbeck granules, specific to LCH cells.

No randomized trial for adult PLCH has been conducted yet. Because the majority of PLCH patients are current or former smokers (>90%), smoking likely

plays a central role in the pathogenesis, and smoking cessation frequently leads to improvement or resolution of the disease²⁰. Nevertheless, in cases of relapse or worsening after smoking cessation, corticosteroids are used for treatment, although evidence of their benefit is limited. Experts suggest corticosteroid therapy should be reserved for symptomatic patients with a predominantly nodular form of the disease. Typically, the initial dose of corticosteroid is 0,5–1,0 mg/kg/day, which is then tapered over the next 6–12 months^{21–23}. Cytotoxic agents are best reserved for multisystem LCH patients. Vinblastine, cyclophosphamide, methotrexate, cladribine, and etoposide have been used. Conservative treatment for complications, such as pneumothorax, is needed and pleurodesis is generally performed. When severe respiratory failure develops, lung transplantation is indicated, but PLCH is known to recur in allografts in 20,5% of transplantation cases. The risk factors for recurrence are the presence of extrapulmonary disease and the resumption of smoking^{24,25}.

3. Lymphoid interstitial pneumonia (LIP)

LIP is a rare, benign lymphoproliferative interstitial lung disease. Lymphocytes, plasma cells, and histiocytes infiltrate the airways and the pulmonary interstitium²⁶. LIP is usually associated with connective tissue disease (specifically, Sjögren's syndrome), autoimmune thyroid disease, human immunodeficiency virus, viral infections, and less commonly, Castleman's disease and lymphoproliferative disorders².

Patients usually have progressive dyspnea and coughing. Radiological findings are multiple thin-walled cysts distributed along the peribronchiolar interstitium. Additionally, ground-glass opacities, poorly defined centrilobular nodules, peribronchovascular/interlobular septal thickening, and lymphadenopathy can occur.

Most LIP patients initially respond well to corticosteroid therapy; however, the prognosis is not good and half of patients die within five years. Treatment of the underlying systemic disease is thus important²⁶.

4. Birt-Hogg-Dube syndrome (BHD)

BHD is a rare autosomal dominant inherited disorder caused by germline mutation of the gene that encodes folliculin (*FLCN*)²⁷. Folliculin is a tumor-suppressor protein thought to be involved in the mTOR pathway and is located on chromosome 17p11.2. Folliculin is highly expressed in stromal cells and type I pneumocytes of the lungs, skin, and kidneys. Affected patients could be asymptomatic, but common features of BHD are skin fibrofolliculomas, multiple lung cysts, spontaneous pneumothorax, and renal cancer²⁸. Characteristic skin lesions are multiple dome-shaped, whitish papules on the face or neck, which were previously essential for a diagnosis before the genetic study was available. Approximately 75% of carriers have fibrofolliculoma, but 25% do not have these skin lesions. On CT examination, more than 80% of adult BHD patients have multiple lung cysts, often in the basal lung region²⁹, which cause pneumothorax. However, chest X-rays generally appear normal and pulmonary function is usually unaffected. The most threatening complication of BHD is renal cancer, which can occur even at a young age.

BHD is known to show heterogeneity of penetrance among mutation carriers. The identification of families with BHD has varied and was mostly based on dermatological signs. However, patients might not have skin lesions or present with isolated lung cysts or isolated renal tumors. The current diagnosis is based on DNA testing for *FLCN* mutations. This can also be used for familial surveillance.

BHD should be differentiated from other syndromes, especially tuberous sclerosis complex. Patients with this disease often present with facial angiofibroma, lung cysts and pneumothorax, and renal cysts or tumors. Diffuse distribution of lung cysts, prominent central nervous system symptoms, and being female are characteristics that favor a diagnosis of TSC rather than BHD.

Treatment should be conservative, and active surveillance for kidney tumors is emphasized. No established guidelines for initial examination age, screening method, or intervals between procedures exist.

5. Cystic lung metastasis

Cystic pulmonary metastasis usually occurs in tumors of epithelial origin, and less frequently in tumors of mesenchymal or hematopoietic origin³⁰⁻³². Reported cystic lung metastasis from mesenchymal tumors originates from leiomyosarcoma, synovial cell carcinoma, epithelioid cell sarcoma, and endometrial stromal sarcoma. A history of previous malignancy is critical for diagnosis, and immunostains could be helpful³.

Conclusion

Cystic lung disease is defined as the presence of multiple air-filled lucent cysts in lung parenchyma. Conditions causing these cysts include cavities, emphysema, bronchiectasis, and honeycombing; can mimic lung cysts and should be excluded. Clinical, radiographic, and histologic findings are important to differentiate the causes of cystic lung disease, which frequently requires a multidisciplinary approach. Chest radiography is less sensitive in detecting lung cysts; therefore, clinicians should consider the possibility of these entities if suspected. Further studies about the characteristics of this disease and the therapeutic challenges involved are needed.

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