Birt-Hogg-Dubé syndrome: characteristic CT findings differentiating it from other diffuse cystic lung diseases

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ABSTRACT
Birt-Hogg-Dubé (BHD) syndrome is an uncommon, autosomal dominant, multiorgan systemic disorder manifesting as cutaneous fibrofolliculomas, lung cysts with or without spontaneous pneumothorax, and renal tumors. Spontaneous pneumothorax and lung cysts on chest computed tomography (CT) should lead to the inclusion of BHD syndrome in the differential diagnosis, because these findings may develop earlier than other clinical manifestations. Here, we review and describe the characteristic findings of BHD syndrome. The number, shape, size, and distribution of the lung cysts can help to differentiate BHD syndrome from other diffuse cystic lung diseases. Knowledge of the chest CT findings of BHD syndrome may lead to a correct diagnosis and the initiation of an appropriate work-up in order to prevent pneumothorax and for the early detection of renal tumors.

Birt-Hogg-Dubé syndrome

The incidence of BHD syndrome is unclear and it can affect individuals at any age without definite sexual predilection (1, 2). The development of BHD syndrome has been ascribed to a germline mutation in the \( FLCN \) gene, which is on chromosome 17p11.2 and encodes a folliculin (1). Fibrofolliculoma, a benign tumor of the hair follicle, is the most characteristic finding of BHD syndrome (Fig. 1). Lung cysts have been described in more than 80% of BHD cases (1). Seventy-six percent of patients have at least one spontaneous pneumothorax during their lifetime, and 82% have multiple pneumothorax (3). Pleurodesis is generally performed after the second ipsilateral pneumothorax, reducing the recurrence rate by half (3). In addition, a relatively high incidence of pneumothorax is reported during or within the 24-hour period following air travel (8% per patient, and 0.12% per flight) (3). Despite multiple lung cysts, patients with BHD syndrome may have normal lung function or only mild airway obstruction. One study by Furuya et al. (4) reported that the morbidity from lung neoplasms in patients with BHD syndrome was 5%. Although cautious interpretation of the data is necessary as lung cancer is one of the most common malignancies, this study implies possible association between lung neoplasm and BHD syndrome suggesting that loss of heterozygosity of \( FLCN \) gene is frequently seen in lung neoplasms of adenocarcinomatous
Main points

- Birt-Hogg-Dubé (BHD) syndrome is an uncommon, autosomal dominant, multiorgan systemic disorder manifesting as cutaneous fibrofolliculomas, lung cysts with or without spontaneous pneumothorax, and renal tumors.

- When lung cysts and spontaneous pneumothorax are encountered on chest CT, radiologists should consider BHD syndrome as a differential diagnosis because these findings may be the initial clinical presentation of this disorder.

- Some characteristic chest CT findings of BHD syndrome can be helpful in differentiating this disorder from other diffuse cystic lung diseases. Common chest CT findings of BHD syndrome include multiple irregular shaped cysts of various size with medial and basal predominance, subpleural and fissural cysts, cysts abutting or including the proximal portion of the lower pulmonary veins or arteries, and spontaneous pneumothorax.

- The surrounding lung parenchyma is usually normal. Subpleural and fissural cysts are among the other common CT findings in BHD syndrome. The cysts may abut or include the proximal lower pulmonary veins or arteries. Unlike other diffuse cystic lung diseases, the number and size of the lung cysts in BHD syndrome do not progress over time. Spontaneous pneumothorax is often noted due to rupture of the cysts.

Other diffuse cystic lung diseases

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is the closest mimic of BHD syndrome as it shares some of its clinical manifestations (lung, renal, and skin lesions), especially when it develops in young women. However, it is important to differentiate these diseases because their prognosis and management are quite different. LAM is an uncommon cystic lung disease characterized by the proliferation of immature smooth muscle cells in the pulmonary interstitium and along the axial lymphatic vessels, with resultant air trapping and cyst formation. This disorder predominantly affects women of reproductive age and may be developed in patients with tuberous sclerosis complex. Pulmonary function tests in LAM often show a chronic obstructive pattern, unlike BHD syndrome (11). The lung cysts in LAM are usually smaller and more uniform in size and shape. LAM cysts are round or oval in shape, have smooth, thin walls, and are more numerous than the cysts seen in BHD syndrome. Their diffuse distribution throughout both lungs, without zonal predominance, is also distinct from the findings in BHD syndrome with basal and medial lung predominance (Fig. 5). Involvement of the costophrenic angles and normal surrounding lung parenchyma are common findings in both diseases, but small centrilobular nodules, interlobular septal thickening and focal areas of ground-glass opacity (GGO) are only noted in LAM (12). Spontaneous pneumothorax is a common manifestation in both diseases. Pleural effusions occur in 10% to 20% of patients with LAM and they are often documented as chylous unlike BHD syndrome. Both diseases involve the kidney, but angiomylipomas are typical of LAM. Skin involvement is also present in both diseases with facial angiofibromas in LAM. In contrast to BHD syndrome, lung...
cysts in LAM progress slowly increasing in size and number and leading to respiratory failure within a decade after diagnosis in 10% to 20% of patients (11). Conservative management or treatment of complications such as pneumothorax or pleural effusion are usually suggested in patients with normal or mildly impaired lung function. However, for advanced stages of the disease and severe airway obstruction, lung transplantation remains the best treatment option (11).

**Pulmonary Langerhans cell histiocytosis**

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare lung disease of interstitium caused by the monoclonal proliferation of Langerhans cells. It is mainly seen in young cigarette smokers. Although the clinical manifestations are nonspecific, patients with PLCH usually complain of dyspnea or cough and may present with pneumothorax in up to 25% of patients, while patients with BHD syndrome only present with skin fibrofolliculoma or pneumothorax (13). The peribronchial proliferations of Langerhans cell make stellate nodules that, with progression, cavitate to form thick- and thin-walled cysts. Subsequently enlarged air spaces are surrounded by fibrotic tissue (13). The distinction between PLCH and BHD syndrome is relatively easy because PLCH presents multiple ill-demarcated small nodules characterized by a centrilobular and peribronchiolar distribution in addition to lung cysts. Lung cysts in PLCH have a bizarre shape and unequal size, involving the upper and middle lung zones, but relatively sparing the lung bases including both costophrenic sulci (Fig. 6) (13, 14).
Lymphocytic interstitial pneumonia

Lymphocytic interstitial pneumonia (LIP) is caused by diffuse interstitial proliferation of lymphocytes and plasma cells. It is associated with autoimmune diseases, such as Sjögren syndrome, acquired immune deficiency syndrome, and systemic lupus erythematosus (15). Chest CT findings are thin-walled lung cysts with lower lung predominance in nearly two-thirds of patients. Lung cysts may vary in size, but they are typically small (<3 cm), less numerous than those in LAM and PLCH, and usually located within areas of GGOs. The presence of ancillary parenchymal abnormalities, including bilateral GGOs and poorly defined centrilobular nodules, frequently in a subpleural distribution, can reinforce the diagnosis of LIP (Fig. 7).

Cystic lung metastasis

In rare cases, metastatic cancer presents as diffusely scattered multiple lung cysts. Primary cancers, such as squamous cell cancer especially in the head and neck, angiosarcoma, endometrial stromal sarcoma and adenocarcinoma of the lung, stomach, and colon, have been reported as causes of cystic lung metastasis (16). The appropriate clinical history of a primary malignancy is essential for this diagnosis. In cystic metastasis, cystic lesions develop by thinning of cavitary walls with inflation by a check valve mechanism. Cystic metastasis in squamous cell carcinoma may be caused by central cornification of squamous epithelium in the lesion followed by liquefaction and evacuation into airways (16). In addition, novel chemotherapeutic agents, such as anti-angiogenic drugs, have been known to cause cavitation in primary and metastatic lung cancer by central necrosis of tumor representing therapeutic response. Therefore, several authors proposed to consider cavitation as a feature of response to specific treatments (i.e., EGFR tyrosine kinase inhibitor therapy) (17). Chest CT findings of cystic metastasis usually show multiple thin-walled cysts with or without nodules (Fig. 8). These cysts may rupture causing pneumothorax. GGOs surrounding the cysts and air-fluid level in thin-walled cysts are also observed in cystic lung metastasis. The lung cysts in cystic pulmonary metastasis usually increase in size and their walls become thicker during the course of disease, while the cysts in BHD syndrome do not progress.

Other diseases with lung cysts

Lung cysts are encountered in various pulmonary infections. Pneumocystis Jirovecii pneumonia (PJP) is one of the most common opportunistic infection in immunocompromised patients. Chest CT findings of PJP include extensive GGO with septal wall thickening or reticular densities. Lung cysts occur in up to 34% of patients in areas of GGO and varying in shape, size, and wall thickness. Cysts are multiple and show upper lung predominance and may rupture causing pneumothorax. The cysts usually resolve or decrease in size as infection improves (Fig. 9). In patients affected by tuberculosis cavities that usually resolve with treatment are seen; nevertheless, they usually resolve or decrease in size as infection improves (Fig. 9). In patients affected by tuberculosis cavities that usually resolve with treatment are seen; nevertheless, they usually resolve or decrease in size as infection improves (Fig. 9). In patients affected by tuberculosis cavities that usually resolve with treatment are seen; nevertheless, they usually resolve or decrease in size as infection improves (Fig. 9). In patients affected by tuberculosis cavities that usually resolve with treatment are seen; nevertheless, they usually resolve or decrease in size as infection improves (Fig. 9). In patients affected by tuberculosis cavities that usually resolve with treatment are seen; nevertheless, they usually resolve or decrease in size as infection improves (Fig. 9).
can persist as cystic lesions (16). Other fungal and parasitic infections such as coccidiodomycosis, paragonimiasis, echinococcosis also cause lung cysts (16).

Tracheobronchial papillomatosis, which usually affects larynx and occasionally extends into the trachea and proximal bronchi, rarely involves lung parenchyma. In the lung, they manifest as homogeneous solid or cystic round nodules with thick or thin walls. As they progress, they cavitate and finally appear as cystic lesions scattered in both central and peripheral portions and occasionally in subpleural portion. Combined multiple small intraluminal nodules or diffuse nodular thickening of airway is another characteristic chest CT finding (18).

Amyloidosis is characterized by extracellular deposition of abnormal proteins and may involve various organs. Pulmonary amyloidosis, a rare manifestation of amyloidosis, can manifest as cystic lung disease besides tracheobronchial, nodular, and diffuse interstitial form. In amyloid-associated cystic lung disease, cysts are usually multiple, small-to-moderate sized and round or lobulated in shape sometimes having internal septa or bronchiocentric nodules. Peribronchovascular and subpleural cysts are commonly seen and cysts either show even distribution in longitudinal dimension or lower lung predominance (Fig. 10). Accompanying multiple small nodules, especially calcified nodules, are characteristic chest CT findings and usually have association with collagen vascular disease such as Sjögren syndrome (19).

Light-chain deposition disease (LCDD) is a rare disease due to deposition of monoclonal immunoglobulin light chain. About 75% of LCDD is associated with macroglobulinemia or multiple myeloma. Pulmonary involvement of LCDD is rare and manifests as multiple thin-walled cysts with irregular pulmonary nodules and no zonal predominance. Vessels transversing the cysts may be identified (20).

Erdheim-Chester Disease (ECD) is an uncommon non-Langerhans' cell form of histiocytosis. Pulmonary involvement occurs
in 50% of the patients (21). Interlobular septal thickening (30%) and centrilobular micronodular opacities (20%) are the most common lung manifestations; however, thin walled cysts predominant in the upper lobes may be seen (5%) (21).

**Conclusion**

Chest CT findings of BHD syndrome are characterized by multiple, irregular shaped cysts of various sizes with medial and basal predominance. Subpleural and fissural cysts as well as cysts abutting or including the proximal lower pulmonary veins or arteries are helpful in the diagnosis of BHD syndrome. Spontaneous pneumothorax is also commonly noted. Familiarity with the characteristic chest CT findings of BHD syndrome will allow its early diagnosis, appropriate management, and work up in order to prevent pneumothorax and for the early detection of renal tumors.

**Conflict of interest disclosure**

The authors declared no conflicts of interest.

**References**