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CHEST IMAGING

PICTORIAL ESSAY

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 (BHD) syndrome is an uncommon, autosomal dominant, multiorgan systemic disorder characterized by the presence of fibrofolliculomas, lung cysts with or without spontaneous pneumothorax, and renal tumors (1). When lung cysts and spontaneous pneumothorax are detected incidentally on chest computed tomography (CT), BHD syndrome should be considered in the differential diagnosis because multiple lung cysts may be the only manifestation of BHD syndrome in its early stage (1). The early detection of BHD syndrome may improve the prognosis and quality of life of the patient by enabling regular follow-up and allowing the monitoring of family members for renal tumor and pneumothorax.

Here, we review BHD syndrome and describe its characteristic chest CT findings. We also point out the features that can help to differentiate this disorder from other diffuse cystic lung diseases.

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

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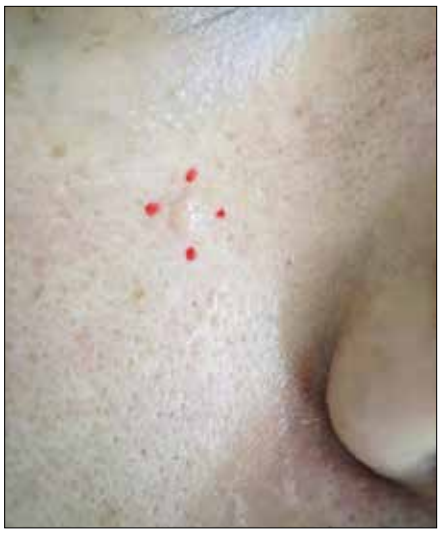


Figure 1. Fibrofolliculoma, a dome-shaped, yellowish papule on the cheek, in a 32-year-old male with Birt-Hogg-Dubé (BHD) syndrome.

lineage in patients with BHD syndrome. The risk of renal tumor is higher in patients with BHD syndrome, and renal cancer is the most threatening complication. The prevalence of renal tumors varies from 6.5% to 34% and one study revealed a sevenfold increase in the risk of renal cancer (5, 6). Most renal tumors in patients with BHD syndrome are malignant, although benign tumors such as oncocytoma may develop. Chromophobe renal cancer and a mixed pattern of chromophobe and oncocytic renal tumors are most common histologies. When these types of renal tumors are diagnosed, especially if multifocal or bilateral, evaluation of BHD syndrome should be done. Other subtypes include papillary carcinoma, clear cell carcinoma and oncocytoma (1, 7).

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.

BHD syndrome is diagnosed on the clinical presentations and the identification of a *FLCN* germline mutation in a genetic study. Disease management is primarily focused on the early detection and treatment of renal tumor, as well as prevention of pneumothorax. Once BHD syndrome is diagnosed, the algorithm developed in 2013 by the National Cancer Institute suggests baseline chest and abdominal imaging by CT or magnetic resonance imaging (MRI) with intravenous contrast. Lifelong surveillance for renal cancer is necessary, and renal imaging by MRI is recommended every 36 months for patients without renal tumors on initial examination. Clinical assessment, pedigree analysis, and *FLCN* mutation analysis are suggested in patients who have familial cystic lung disease, pneumothorax, familial renal cancer, or any combination of spontaneous pneumothorax and kidney cancer in an individual or family (1).

Chest CT findings of Birt-Hogg-Dubé syndrome

The morphology and distribution of the lung cysts, as well as the clinical presentation, may be helpful in the differential diagnosis of BHD syndrome and other diffuse cystic lung diseases. Lung cysts in BHD syndrome occur bilaterally with lower and medial lung predominance, and involve both costophrenic sulci (Fig. 2). The chest CT scan shows scattered, multiple, well-circumscribed and thin-walled cysts of variable size in both lungs (Figs. 2–4). The size of lung cysts varies widely from a few millimeters to 2 cm or more. While the majority of the cysts are small (<1 cm), large lung cysts (>2 cm) frequently coexist (8). Lung cysts of BHD syndrome are usually oval, round, lenticular, or irregular in shape. Among 198 patients with BHD syndrome evaluated by Toro et al. (9), the number of lung cysts ranged from 0–166, with a mean of 16. Agarwal et al. (10) reported that, among 15 BHD syndrome patients with lung cysts, 47% had fewer than 10 cysts, 20% had 10–20 cysts, and 33% had more than 20 cysts. In one study, cysts occupied less than 30% of the lung (8). Large cysts are multiseptated and irregular in shape, and usually located in the lung bases (8, 10). The surrounding lung parenchyma is usually normal. Subpleural and fissural cysts are among the other common CT findings in BHD syndrome (Fig. 3). The cysts may abut or include the proximal lower pulmonary veins or arteries (Fig. 4). Unlike other diffuse cystic lung diseases, the number and size of the lung cysts in BHD syndrome do not progress over time (8). 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 angiomyolipomas are typical of LAM. Skin involvement is also present in both diseases with facial angiofibromas in LAM. In contrast to BHD syndrome, lung

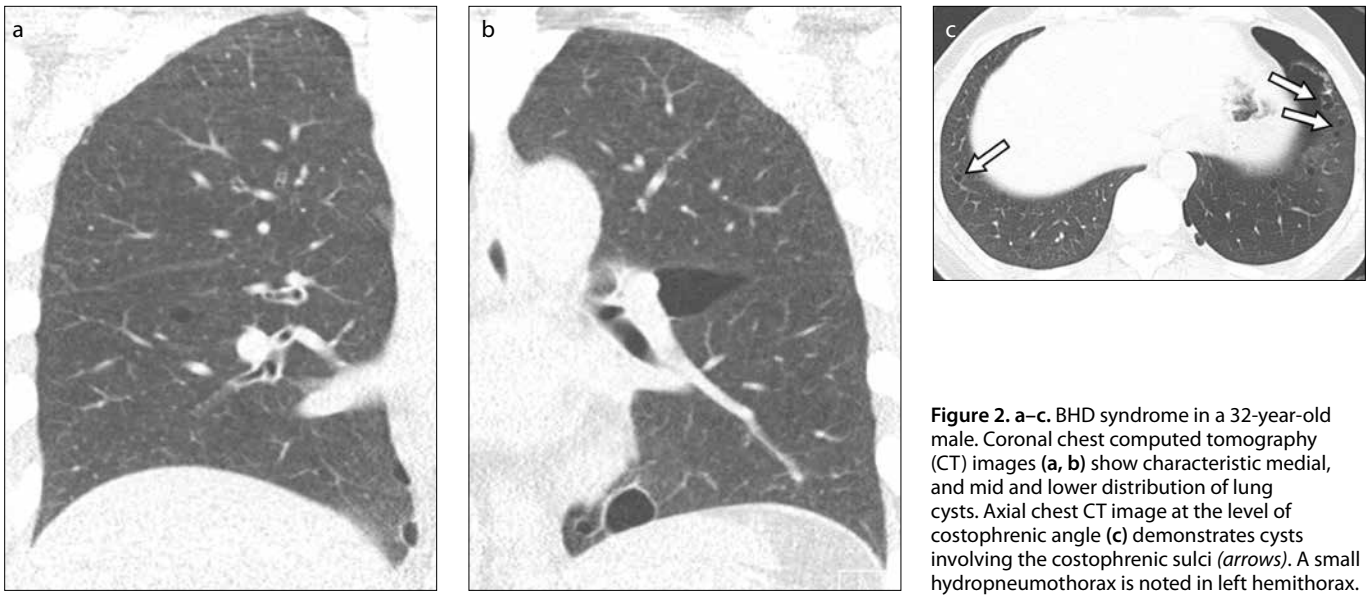


Figure 2. a–c. BHD syndrome in a 32-year-old male. Coronal chest computed tomography (CT) images **(a, b)** show characteristic medial, and mid and lower distribution of lung cysts. Axial chest CT image at the level of costophrenic angle **(c)** demonstrates cysts involving the costophrenic sulci *(arrows)*. A small hydropneumothorax is noted in left hemithorax.

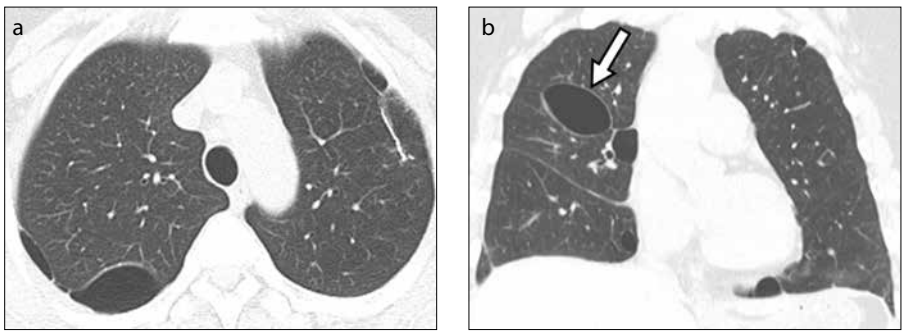


Figure 3. a, b. BHD syndrome in a 57-year-old female who has a first-degree relative with BHD syndrome. Axial chest CT image **(a)** shows the characteristic subpleural cysts. Linear surgical clips are noted in left upper lateral portion due to a previous operation. Coronal chest CT image **(b)** shows a fissural cyst in right minor fissure *(arrow)* and multiple small subpleural cysts in both mid and lower lungs.

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. Sirolimus is an immunosuppressant approved by the FDA, which inhibits cell proliferation and can be used in patients with abnormal 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 peribronchiolar 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).

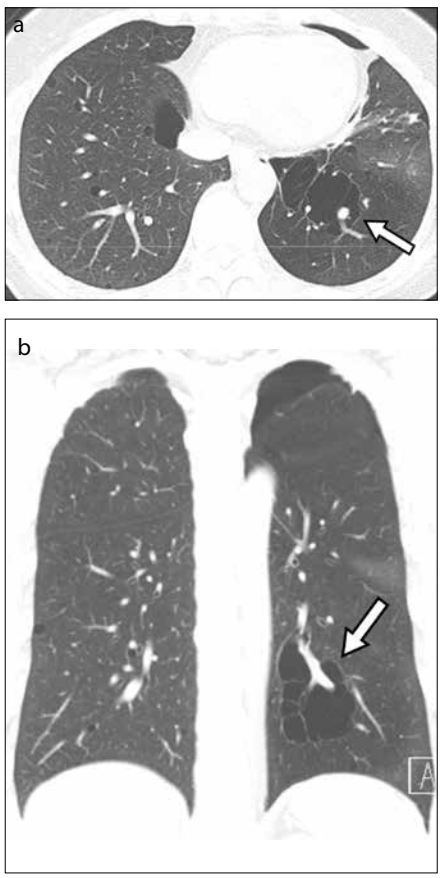
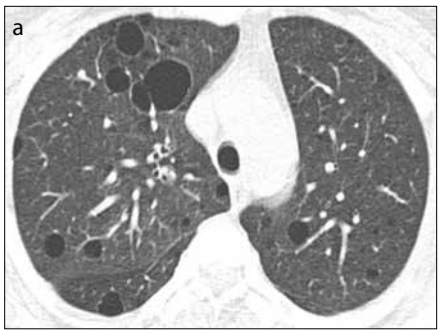


Figure 4. a, b. BHD syndrome in a 42-year-old female. Axial **(a)** and coronal **(b)** chest CT images show multiple well-circumscribed, thin-walled and variable sized lung cysts with round, oval, and irregular shapes. The lung cysts show the basal and medial distribution. The largest cyst in left lower lobe *(arrow)* is abutting or including the proximal portion of the lower pulmonary veins or arteries. A small pneumothorax is noted in left hemithorax. Patchy ground-glass opacities suggesting reexpansion pulmonary edema are seen in the left lung after insertion of a chest tube.



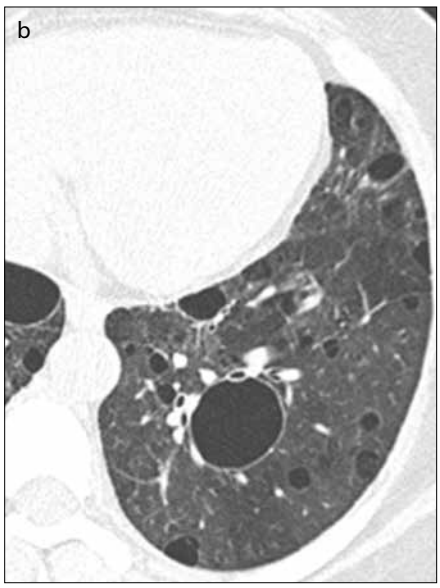


Figure 5. a, b. Lymphangioleiomyomatosis in a 39-year-old female. Axial chest CT images **(a, b)** show multiple smooth, thin-walled, round or oval cysts distributed evenly throughout the lung parenchyma.

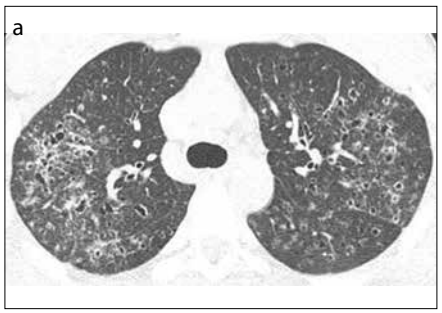
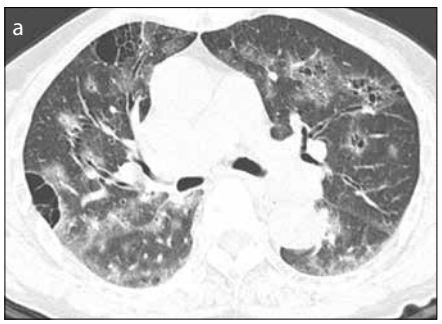


Figure 6. a, b. Pulmonary Langerhans cell histiocytosis in a 21-year-old male smoker. Axial chest CT image at the level above carina **(a)** demonstrates multiple small centrilobular nodules and oval and bizarre shaped cysts predominant in the upper and middle lung zones. Axial chest CT image at the level of costophrenic angle **(b)** shows sparing of both costophrenic angles.



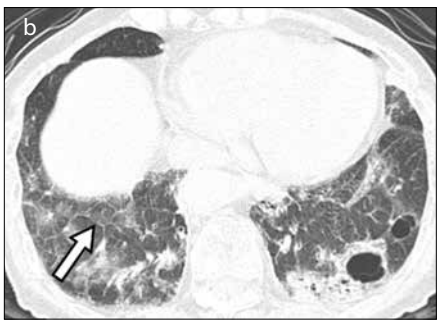


Figure 7. a, b. Lymphocytic interstitial pneumonia in a 71-year-old female. Axial chest CT images **(a, b)** reveal multiple thin-walled cysts. Peribronchial and subpleural ground glass opacities (GGO) are seen in both lungs and some cysts are located within GGOs. Interlobular septal thickening *(arrow)* is also noted in right lower lung.

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. Additional chest CT findings of LIP are thickening of peribronchovascular bundles and interlobular septae and lymphadenopathy (Fig. 7). Unlike BHD syndrome, pneumothorax is not a common finding in LIP (15).

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

can persist as cystic lesions (16). Other fungal and parasitic infections such as coccidiomycosis, 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 bronchiolocentric 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

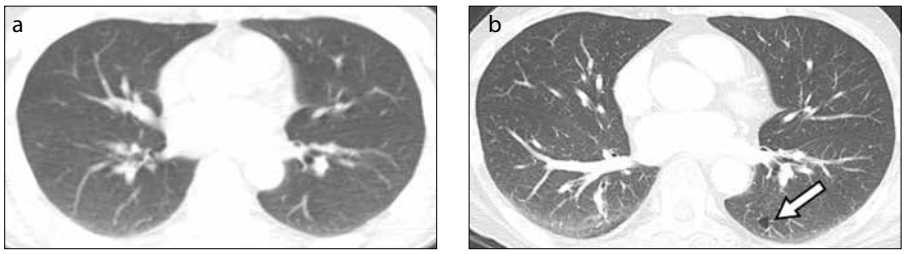


Figure 8. a, b. Cystic pulmonary metastasis in a 50-year-old male with advanced gastric cancer. Initial axial chest CT image **(a)** shows no abnormal parenchymal lesion. Axial chest CT image two years later at the same level **(b)** shows a newly developed small thin-walled cyst *(arrow)*.

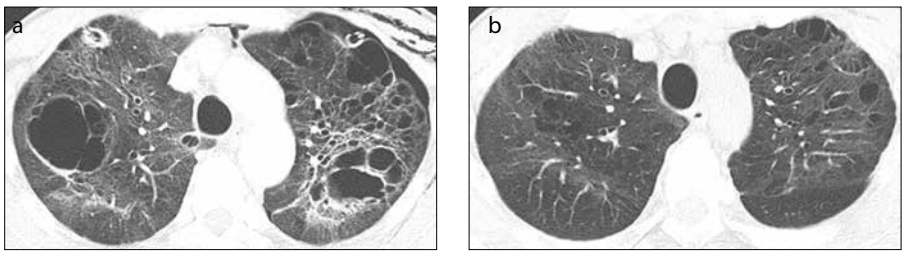


Figure 9. a, b. Pneumocystis Jirovecii pneumonia in a 46-year-old male with acquired immune deficiency syndrome. Axial chest CT image at the level of aortic arch **(a)** shows multiple small thin and thick-walled irregular shaped cysts. The cysts are located in the areas of ground-glass opacities with upper lung predominance. Small pneumothorax is noted in left hemithorax and chest tubes are inserted in both hemithoraces. Axial chest CT image at the same level after three months **(b)** shows remarkable decrease in size of lung cysts.

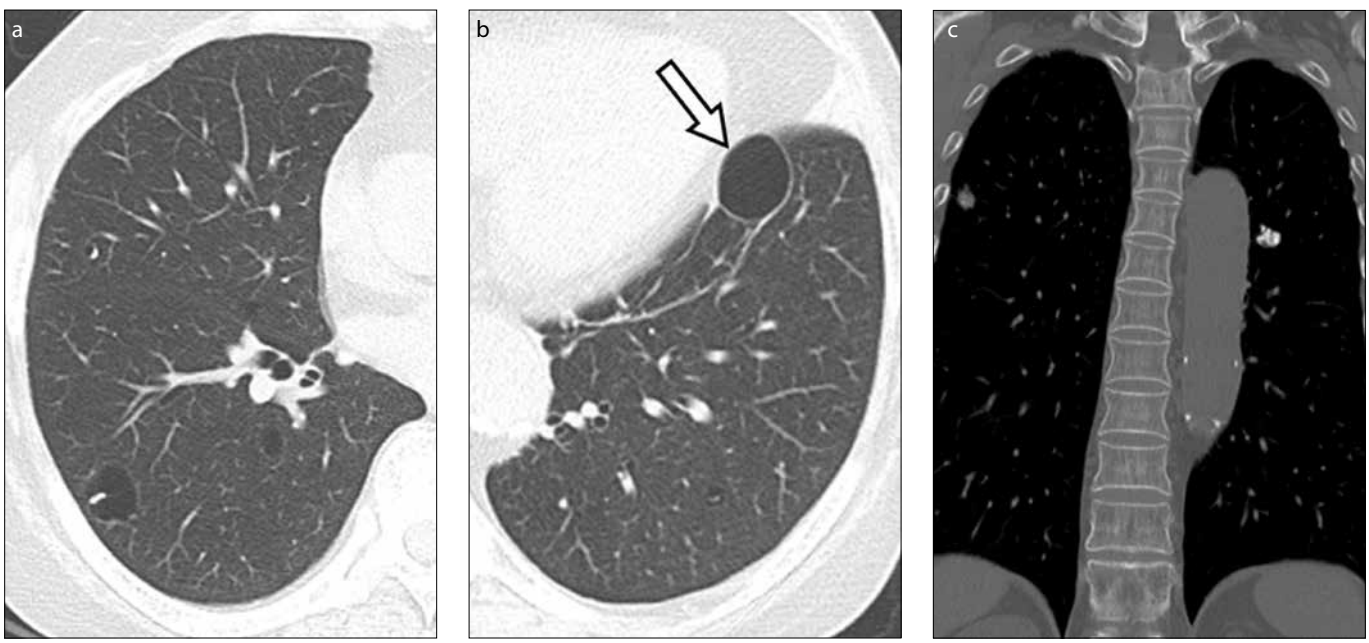


Figure 10. a–c. Amyloid-associated cystic lung disease in a 74-year-old female with Sjögren syndrome. Axial chest CT images **(a, b)** show several variable sized thin-walled cysts including subpleural cyst (**b**, *arrow)*. Coronal chest CT image on bone window settings **(c)** shows two lobulated calcified nodules in both upper lobes.

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.

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