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Cystic Lung Disease in Birt-Hogg-Dubé Syndrome

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match tissue perfusion with oxygen demand. NO activity results in vasodilation and antagonism of platelet aggregation and thrombosis. Hemoglobin binds NO rapidly, and essentially irreversibly, to produce nitrate and methemoglobin.[17,18] The avidity of ferrous heme for NO is so great that uncontrolled access of even small amounts of free hemoglobin to endothelial-derived NO serves as a substantial NO sink, leading to local vasoconstriction and platelet aggregation. Evolution of the RBC membrane and free-heme scavenging mechanisms for physiologic intravascular hemolysis prevent this toxic effect of hemoglobin while allowing its vital oxygen-carrying role.[17] When stroma-free hemoglobin solutions are infused as investigational blood substitutes in animals and humans, both systemic and pulmonary hypertension are predictably found.[18–21] Chronic intravascular hemolytic anemias, such as sickle-cell anemia and hereditary spherocytosis, are also associated with systemic and pulmonary hypertension. We hypothesize that the small but significant free hemoglobin released in the pulmonary circulation during PMT-induced hemolysis in our patient caused transient endothelial dysfunction and vasoconstriction. Additionally, it is possible that inhaled NO, a potent local pulmonary arterial vasodilator, could have been used to prevent or reverse this effect. Inhaled NO has previously been used to reduce right ventricular afterload in major PE and, in one report,[22] was effective in reversing sluggish pulmonary vascular reperfusion after PMT using both suction and rheolytic thrombectomy. Hemolysis was not reported in this latter case.[22]

Hemolysis was self limited in our patient, and she subsequently did well. However, had the complication of PMT been anticipated by the critical care team, unnecessary testing and delay in diagnosis may have been avoided. Controlled studies of PMT in PE should be performed to better define its risks and potential role, if any, in the multidisciplinary approach to major PE.

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Cystic Lung Disease in Birt-Hogg-Dubé Syndrome*

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Background: **To describe the clinical, radiologic, and histopathologic aspects of cystic lung disease occur-**

ring in patients with Birt-Hogg-Dubé (BHD) syndrome, a rare, inheritable, multisystem disorder.

Methods: We retrospectively reviewed five patients with BHD syndrome evaluated at the Mayo Clinic Rochester from 1998 through 2005.

Results: Mean age (± SD) at the time of pulmonary evaluation was 56.4 ± 4.8 years; four patients were men. Three patients had not received a diagnosis of BHD syndrome at the time of initial CT of the chest. Three patients had a smoking history, and two were nonsmokers. Two patients had a history of recurrent pneumothoraces. Pulmonary function tests available in four patients revealed normal results in one patient and mild airflow obstruction or nonspecific pattern of abnormalities in three patients. CT of the chest revealed cystic lung disease in all five patients; cysts were round to oval in shape, ranged widely in size, and were randomly distributed throughout the lungs, except for a predilection to involve the lung bases more extensively. Three patients with a smoking history had more severe cystic changes compared to nonsmokers and included both patients with recurrent pneumothoraces. Surgical lung biopsy available in one patient revealed emphysema-like changes. Follow-up CT scans available in four patients revealed relative stability over a median interval of 20 months (range, 3 to 66 months).

Conclusion: We conclude that cystic lung disease in BHD syndrome varies widely in severity, mimics pulmonary lymphangioleiomyomatosis, and may be worsened by smoking.

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Birt-Hogg-Dubé (BHD) syndrome is a rare, inheritable disorder (autosomal dominant) that was first described in 1977.[1] It is caused by germline mutations in the BHD (*FLCN*) gene that lies within the chromosomal band 17p11.2 and encodes for a tumor-suppressor protein, folliculin.[2] Folliculin is highly expressed in a variety of tissues, including the skin, kidney, and lung (stromal cells and type I pneumocytes).[3] BHD syndrome is characterized by the cutaneous triad of fibrofolliculomas (hamartoma of the hair follicle), trichodiscomas, and skin tags,

along with a propensity for renal tumors.[1,2] Characteristic skin lesions typically appear as firm, dome-shaped papules in adults during the third or fourth decades of life and occur predominantly on the face, scalp, neck, and upper chest (Fig 1).[1,4,5] Renal tumors associated with BHD syndrome have included oncocytic hybrid tumor, chromophobe renal cell carcinoma, clear cell carcinoma, and papillary renal cell carcinoma.[6]

In recent years, a relationship between BHD syndrome with pulmonary cysts and spontaneous pneumothorax has become recognized, but description of this lung disease has been limited.[5,7–13] In this study, we sought additional details of cystic lung disease in BHD syndrome, including the clinical presentation, radiologic features, pulmonary function correlates, histopathology, and clinical course.

MATERIALS AND METHODS

Study Population

A computer-aided search was conducted to identify all patients seen at the Mayo Clinic in Rochester, MN, during an 8-year period from January 1, 1998, to December 31, 2005, with a diagnosis of BHD syndrome or fibrofolliculoma. We identified seven patients with BHD syndrome, five of whom had CT of chest available for review and were included in this study. In all five patients, the diagnosis was confirmed clinically. Three patients chose to have genetic testing, and each patient was heterozygous for a *FLCN* mutation (Table 1). One of the excluded patients did not have any chest imaging, and the other patient had normal findings on chest radiography. The Mayo Foundation Institutional Review Board approved this study.

Clinical Data Collection

Data extracted from the medical records included demographics, clinical presentation, laboratory results, radiologic findings, and pulmonary function results. Presenting features were recorded from the first encounter at the Mayo Clinic that led to a diagnosis of cystic lung disease associated with BHD syndrome. Follow-up data were collected regarding subsequent clinical

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FIGURE 1. Photograph of fibrofolliculomas: multiple, firm, white papules on the jaw line and neck of a 50-year-old man.

Age, yr/ Gender	Smoking	Clinical Presentation	*FLCN* Gene Mutation	CT of the Chest	Pulmonary Function	Follow-up CT
54/male	Never	Skin lesions; no respiratory symptoms or renal tumors	Guanine to adenine substitution at nucleotide 1,098 in exon 20	5 to 10 cysts (3 to 8 mm in diameter) in each lung	Normal results	Stable CT findings at 27 mo
63/male	Never	Skin lesions; prior renal resections (clear cell renal carcinomas); no respiratory symptoms	Not tested	5 to 10 cysts (4 to 16 mm in diameter) in each lung	Not done	None
57/female	Previous, 10 pack-yr	Recurrent right pneumothorax; 12 previous episodes of ipsilateral pneumothorax; skin lesions present but no renal tumors	Not tested	10 to 15 cysts (5 to 25 mm in diameter) in each lung, and more extensive in bases	Mild nonspecific pattern*	Stable CT findings at 66 mo
58/male	Previous, 45 pack-yr	Renal mass; prior renal resections (chromophobe cell carcinomas, oncocytomas); two previous episodes of ipsilateral pneumothorax; no skin lesions.	Deletion of a single cytosine nucleotide in exon 11	Innumerable cysts (2 to 80 mm in diameter) bilaterally, more extensive in bases; emphysema	Mild nonspecific pattern*	Slight progression of CT findings at 13 mo
50/male	Previous, 80 pack-yr	Skin lesions; mild exertional dyspnea and chronic productive cough; clear cell renal cancer resected later	Duplication of a single cytosine nucleotide in exon 11	Innumerable cysts (6 to 35 mm in diameter) bilaterally; emphysema	Mild obstruction	Stable CT findings at 3 mo

*Mild nonspecific pattern on pulmonary function testing consisted of mildly reduced FEV_1 with a normal FEV_1/FVC ratio.

course, pulmonary function results, and imaging studies. Chest radiographs and CT scans of the chest were reviewed by a chest radiologist (G.L.A.). Four of five patients had both high-resolution and standard CT scans of the chest available; one patient had a standard CT only. Pulmonary function measurements included plethysmographically determined total lung capacity and residual volume, along with FVC, FEV_1, ratio of FEV_1 to FVC, and diffusing capacity for carbon monoxide. Spirometry and measurements of lung volumes and diffusing capacity were performed in our pulmonary function laboratory and were expressed as percentage of predicted normal values, using previously described techniques.[14] Surgical lung biopsy slides were available in one patient and were reviewed by a pulmonary pathologist (J.E.Y.).

Results

Patient Characteristics

None of the patients had a diagnosis of BHD syndrome at the time of the initial evaluation at our institution for skin lesions (three patients), renal mass (one patient), and recurrent pneumothorax (one patient). Mean age ($\pm$ SD) at the time of pulmonary evaluation was 56.4 ± 4.8 years; four of five patients were men (Table 1). Three patients did not have BHD syndrome diagnosed at the time of the initial CT scan of the chest. Further examination after initial presentation revealed characteristic skin lesions in

all five patients. Three patients had confirmed fibrofolliculomas, and two had trichodiscomas. One patient had the complete triad of trichodiscomas, trichofolliculomas, and skin tags. Mean age at the time of BHD syndrome diagnosis was 57.2 ± 5.4 years.

None of the patients were current smokers, but three had a smoking history. Two patients had respiratory symptoms, including exertional dyspnea (two patients) and chronic productive cough (one patient); three patients were asymptomatic. One of the symptomatic patients had a right pneumothorax on presentation; this patient had a previous personal history (12 episodes over 24 years) and a strong family history (father, uncle, sister, daughter, and nephew) of spontaneous pneumothoraces. One additional patient had a history of recurrent pneumothoraces (two episodes) for which surgical stapling and pleurodesis had been performed. Two patients with previous pneumothoraces were both ex-smokers.

Chest radiographs were available in all patients and revealed a right-sided, loculated hydropneumothorax in one patient; another patient had detectable cysts. No cysts were appreciable by chest radiography in the three remaining patients. CT scan of the chest revealed cystic lung disease in all five patients (Table 1); one patient had a right-sided pneumothorax (Fig 2). These cysts were round

FIGURE 2. High-resolution CT of the chest of a 57-year-old woman, an ex-smoker, with undiagnosed BHD syndrome and recurrent right-sided pneumothoraces. There is a right pneumothorax with small cysts in both lungs. Pleural thickening on the right anteriorly is due to prior pleurodesis.

to oval in shape and ranged widely in size (a few millimeters to several centimeters). The cysts were randomly distributed in the cross-sectional dimension as well as in the cephalocaudal axis, with the exception of more extensive involvement in the lung bases for two patients (Fig 3, *top*, *A*, and *bottom*, *B*). Two of three patients with a smoking history had evidence of emphysema by CT. Two nonsmokers had relatively mild lung involvement with small scattered cysts (3 to 16 mm in diameter), while those with a smoking history had more severe extensive disease with larger cysts (Table 1). The main indication for the initial CT of the chest included evaluation of BHD syndrome (two patients), assessment for possible metastatic disease from prior renal cancer (two patients), and recurrent pneumothorax (one patient). Follow-up CT scans available in four patients revealed minimal progression in only one patient over a median interval of 20 months (range, 3 to 66 months).

Pulmonary function results available in four patients revealed normal results in one patient (nonsmoker), mild airway obstruction in two patients, and nonspecific pattern of abnormalities (mildly reduced FEV_1 with a normal FEV_1/FVC ratio) in one patient. Three patients with abnormal pulmonary function results were previous smokers. Follow-up pulmonary function results were available in two patients and revealed no evidence of significant worsening over intervals of 42 months and 49 months, respectively.

A surgical lung biopsy specimen was available in one patient; wedge biopsies were performed from the right lower lobe of the lung at the time of surgical stapling and pleurodesis (Table 1). Histologic sections showed benign lung parenchyma with widespread emphysematous changes (Fig 4, *top*, *A*). The visceral pleura and interlobular septa demonstrated patchy areas of fibrosis, mesothelial hyperplasia, and eosinophilic pleuritis, findings consistent with the patient's clinical history of recurrent episodes of spontaneous pneumothorax. There was no apparent intraparenchymal air cyst or air-filled intrapleural bleb in the pleural surface. However, a focus of air accumulation

was noted in the interlobular septa that displaced a vein to the opposite side (Fig 4, *bottom*, *B*). Incidentally, a 1-mm focus of low-grade atypical adenomatous hyperplasia was found in a random section.

Clinical follow-up was available in all five patients over a median duration of 36 months (range, 13 to 76 months) following the initial CT of the chest. No pneumothorax or other respiratory events occurred during this period. Two patients required partial nephrectomy for chromophobe carcinoma (58-year-old man) and clear renal cell cancer (50-year-old man), respectively. One of these patients had already undergone renal resections for chromophobe cell carcinoma and oncocytoma (58-year-old man).

DISCUSSION

In this study, cystic lung disease was seen by CT in all five middle-aged patients with BHD syndrome; two of these patients had recurrent pneumothoraces. All five patients had
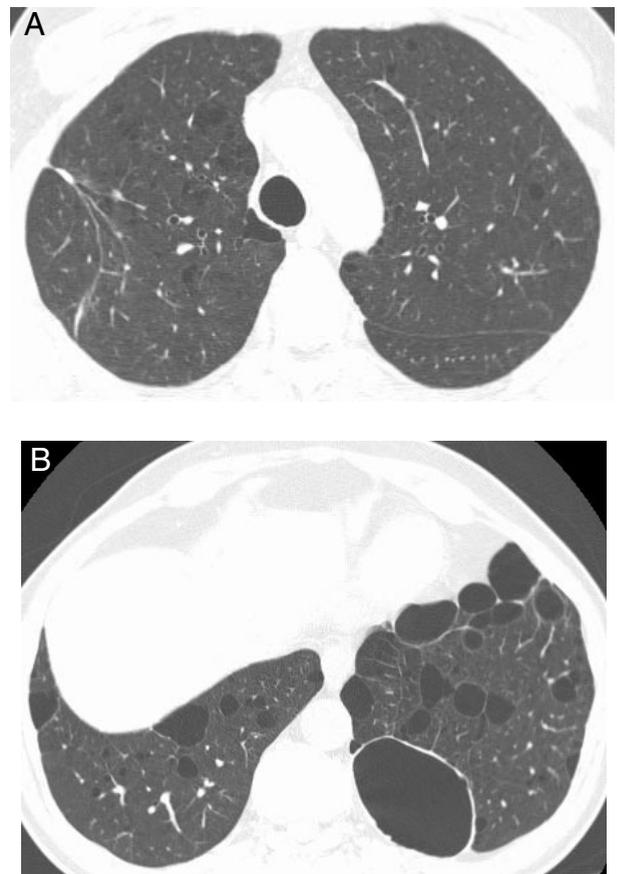

FIGURE 3. High-resolution CT of the chest of a 58-year-old man, an ex-smoker, with undiagnosed BHD and a history of recurrent right-sided pneumothoraces. *Top*, *A*: Focal low-attenuation areas without walls in the upper lungs consistent with emphysema. One probable cyst is seen in the right lung posterior to the trachea. Postoperative changes are shown in the right lung. *Bottom*, *B*: Numerous cysts in the lung bases including one dominant cyst measuring 8 × 5 cm in the left lung. Cystic walls are difficult to appreciate for some of these lesions.
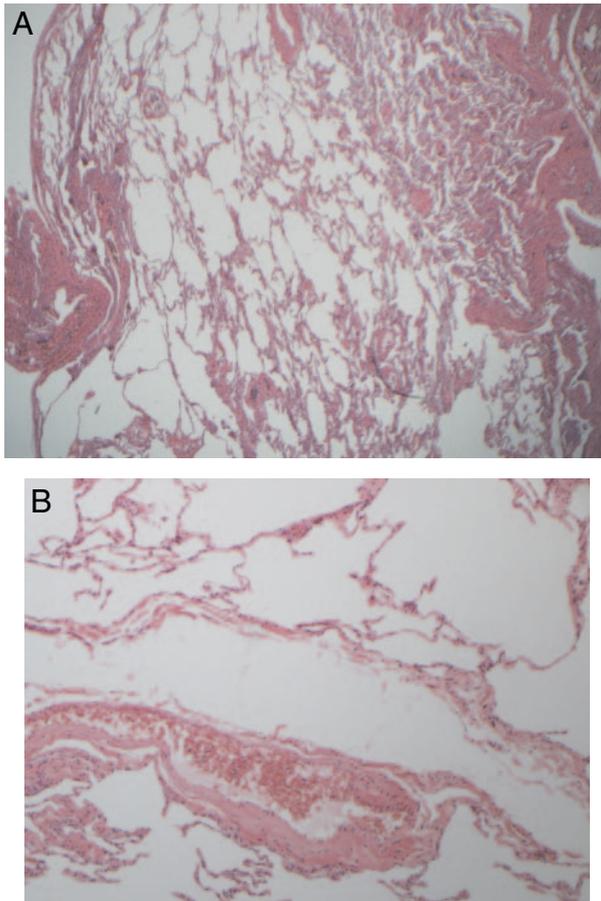
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FIGURE 4. Histopathology of cystic lung lesions obtained from a 57-year-old woman at the time of redo thoracotomy for mechanical pleurodesis and pleurectomy for management of recurrent pneumothoraces despite a previous pleurodesis elsewhere. *Top*, *A*: Severe emphysema involving the most alveolar parenchyma (hematoxylin-eosin, original × 20). *Bottom*, *B*: An interlobular septum is replaced by interstitial air, which results in the displacement and compression of the venous wall (left lower corner) on the side abutting the air-filled space (hematoxylin-eosin, original × 200).

skin lesions characteristic of BHD syndrome; two patients had previously undergone resection of renal tumors (clear cell and chromophobe renal cancers, respectively) associated with BHD syndrome. Pulmonary function was only mildly impaired and may have been affected by smoking and pleural complications as well as the cystic lung disease. Cystic lung disease associated with BHD syndrome varied in severity and appeared to be more extensive in patients with a smoking history but remained relatively stable on follow-up CT scans over an interval ranging up to nearly 6 years.

In a case report, Chung and colleagues[15] described a 60-year-old man who presented with numerous papules on the face, neck, and upper trunk that began to appear in his early 20s along with a history of recurrent pneumothoraces. No additional information was provided regarding this patient's pulmonary disease. In 1999, Toro and colleagues[7] reported an association between cystic lung disease and BHD syndrome. Four of 28 patients (14%) with

BHD syndrome and at-risk relatives had pulmonary cysts detected by chest radiography; one of these patients had a history of pneumothorax. In a study of 223 members of BHD syndrome families, Zbar and colleagues[8] noted 26 subjects (11.7%) to have had spontaneous pneumothorax. CT scanning detected pulmonary cysts in 83% of affected member of BHD syndrome families. In this study, the odds ratio of pneumothorax in BHD syndrome-affected subjects, adjusted for age, was 50.3.

Mutations in the *FLCN* gene are responsible for BHD syndrome as well as the syndrome of dominantly inherited spontaneous pneumothorax.[10,16] In the latter condition, nonsense mutations and a 4–base-pair deletion in exon 4 of *FLCN* gene have been identified.[10] Affected family members have cystic lung lesions that are scattered randomly throughout the lungs.[10] The function of folliculin and how mutations of *FLCN* gene gives rise to pulmonary cysts and pneumothorax remain unknown, but association with cutaneous hamartomas and renal neoplasia suggests tumor suppressor function.[10]

Pulmonary pathology in BHD syndrome was described in two patients by Butnor and Guinee.[12] Histopathologic features were nonspecific and included intraparenchymal air-filled spaces surrounded by normal parenchyma or a thin fibrous wall. Lung tissue adjacent to the cysts appeared normal. Both of these patients were nonsmokers. Similar nonspecific findings were noted in our patient.

Cystic lung disease seen in BHD syndrome needs to be distinguished from other lung diseases characterized by multifocal or diffuse cystic changes, including lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, lymphocytic interstitial pneumonitis, and Pneumocystis pneumonia.[17,18] Lymphocytic interstitial pneumonia and Pneumocystis pneumonia both cause parenchymal changes aside from cysts such as ground-glass opacities, consolidation, nodules, and reticular opacities.[17,18] In addition, both of these disorders are usually symptomatic and are associated with specific clinical contexts. Pulmonary Langerhans cell histiocytosis encountered in adults is usually a smoking-related interstitial lung disease and is characterized by irregular cystic lesions and nodules predominantly affecting the upper and mid lung zones with relative sparing of the bases.[17–19] This pattern of distribution, irregular shape of the cysts, and architectural distortion seen in the intervening lung parenchyma are characteristics of pulmonary Langerhans cell histiocytosis, and distinguishable from cystic lung disease seen in BHD syndrome. Rarely, metastatic neoplasms, including adenocarcinomas and low-grade sarcomas, can present with cystic lung lesions.[18,20]

Pulmonary lymphangioleiomyomatosis may be more difficult to separate radiologically from cystic lesions of BHD syndrome since both disorders are characterized by scattered cystic lesions that are randomly distributed throughout the lungs with no appreciable changes in the intervening lung parenchyma.[17,18,21] Furthermore, both disorders can present with lung cysts and renal masses, although the fatty component of renal angiomyolipomas associated with pulmonary lymphangioleiomyomatosis can usually be distinguished radiologically from solid renal tumors of BHD syndrome. Pulmonary lymphangioleiomyomatosis almost exclusively affects women and typ-

ically presents in the third and fourth decades of life,[21] earlier than patients with BHD syndrome described in this report. However, both of these disorders can be associated with recurrent spontaneous pneumothoraces, although a known family history of BHD syndrome would obviously be helpful in the differential diagnosis. Additional evaluation including biopsy of lung, skin lesions or renal tumor may help distinguish these two disorders. In some patients, BHD syndrome may be mistaken for tuberous sclerosis because the latter disorder is also associated with lung cysts (almost exclusively in women) and facial skin lesions.[21,22]

BHD syndrome is associated with renal tumors of various histologic types, including clear cell, chromophobe, and papillary types of renal cell cancers, as well as oncocytomas.[6,23] Thus, patients with BHD syndrome should be screened for renal tumors and carefully followed up at periodic intervals. Similarly, family members of patients with BHD syndrome should be screened for renal tumors and offered genetic counseling.

In conclusion, we find cystic lung disease in BHD syndrome to vary in severity in patients affected with this rare disorder. Although our data are limited by small number of patients, smoking appears to be associated with more severe lung disease compared to nonsmokers, a relationship not previously explored in BHD syndrome. Limited follow-up of our patients suggests a relatively slow rate of progression for this lung disease.

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Nonfatal Systemic Air Embolism Complicating Percutaneous CT-Guided Transthoracic Needle Biopsy*

Four Cases From a Single Institution

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Background: Systemic air embolism is recognized as a potentially fatal but extremely rare complication following percutaneous transthoracic needle biopsy. However, its incidence might be underestimated by missing systemic air in patients without cardiac or cerebral symptoms.
Methods: This study was based on four cases (one man and three women; age range, 54 to 75 years) of systemic air embolism complicating CT scan-guided transthoracic needle biopsy, which were encountered among 1,010 procedures performed at our institution

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