**CASE REPORT**

**Birt-Hogg-Dubé Syndrome with Multiple Cysts and Recurrent Pneumothorax: Pathological Findings**

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**Abstract**

A 39-year-old woman presented with right-sided pneumothorax. Partial lung resection was done via thoracoscopy. Five years later, left-sided pneumothorax occurred, and she underwent thoracoscopy again. However, air leakage continued, and pleurodesis was performed. Although she had no skin eruptions or renal tumors, Birt-Hogg-Dubé (BHD) syndrome was suggested by radiographic findings. BHD gene analysis was performed, which revealed the BHD gene mutation. Reevaluation of pathological findings showed elastic fibers in the alveolar walls with fine granular changes and accumulation of macrophages. BHD syndrome should be considered in patients presenting with multiple pulmonary cysts with or without skin eruption, or kidney tumor.

**Key words:** multiple lung cysts, Birt-Hogg-Dubé syndrome, pneumothorax, pathology

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**Introduction**

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant disease first reported in 1977 that was characterized pathologically at the time by skin lesions termed fibrofolliculoma (1). Later, a relation to renal tumors was discovered, and now the characteristics of BHD syndrome include renal tumors, lung cysts, and spontaneous pneumothorax (2).

We encountered a patient with recurrent pneumothorax and suspected BHD syndrome on the basis of radiological findings although this patient did not present with skin eruptions or renal tumors. Recurrent pneumothorax is one characteristic of BHD syndrome, and the patient will generally present to the respiratory medicine department. Therefore, we consider this syndrome whenever we encounter such symptoms. Patients with BHD syndrome may be included with those diagnosed as having idiopathic spontaneous pneumothorax. Here, we report a case of BHD syndrome along with pathological findings of lung tissue resected via thoracoscopy.

**Case Report**

A 39-year-old woman with no past history of pulmonary problems was found to have a right-sided pneumothorax at a regular medical checkup in May 2001, and she was admitted to our hospital for treatment. She did not complain of any symptoms. Her height was 154 cm, and body weight was 53 kg. There was no family history of pneumothorax. She did not smoke or have a history of exposure to dust. She had no cardiac murmurs, and respiratory sounds were mildly attenuated in the right side. She had no skin rash or abnormal neurological findings. Laboratory findings including those for autoantibodies were normal. Chest X-ray showed moderate right-sided pneumothorax (Fig. 1), and chest CT showed multiple 7- to 20-mm diameter round, thin-walled cysts distributed predominantly in the subpleural and mediastinal area without apical scarring (Fig. 2). After we inserted a chest tube, the pneumothorax improved immediately, and we removed the tube. However, pneumothorax recurred 4 days later, and she was transferred to the Department of Thoracic Surgery for treatment under video-assisted thoracic surgery.

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Chest X-ray on admission. Chest X-ray showed right-sided pneumothorax.

Figure 2. Chest computed tomography performed on admission. Chest computed tomography showed right-sided pneumothorax. Pulmonary cysts were found predominantly in the subpleural and mediastinal areas of the lower lobes. A pulmonary vessel was found running across one cyst (arrow). A pulmonary nodule was also detected (arrow).

Partial resection of the lung was performed. The resected lung specimen showed multiple cysts distributed predominantly in the middle and lower lobe, and no site for an air leak was evident. After the operation, pneumothorax did not recur, and she was discharged. Differential diagnoses included lymphangioleiomyomatosis (LAM), Langerhans cell granulomas (LCG), and Sjögren’s syndrome because of the occurrence of pneumothorax in a young woman with multiple lung cysts. However, the resected lung specimen did not show characteristic findings of LAM cells or LCG. The resected lung specimen showed thin-walled, epithelial-lined cysts with elastosis and protrusion of arteries into cysts (Fig. 3). No LAM cell clusters were noted. On pathological examination, the nodules seen on chest CT were found to be scars. Clinically, the patient showed no symptoms of dryness characteristic of Sjögren’s syndrome, and both anti-SS-A and SS-B antibodies were negative. The probability of alpha-1 antitrypsin deficiency syndrome, Marfan syndrome, Ehlers-Danlos syndrome, and cystic fibrosis were discussed. Although we did not measure the serum alpha-1 antitrypsin level, the characteristic CT finding in alpha-1 antitrypsin deficiency syndrome of lower lobe predominance of panlobular emphysema was not found. Characteristic physical signs of Marfan syndrome or Ehlers-Danlos syndrome were also not found, and there were no airway symptoms related to upper or lower respiratory abnormalities such as sinusitis or bronchiectasis. The cause of the pneumothorax and multiple lung cysts could not be diagnosed clinically or pathologically, but radiological findings did not change and she continued to be observed on an outpatient basis.

In June 2006, left-sided chest pain and cough developed, and she presented again to our hospital. Chest X-ray showed left-sided pneumothorax. A chest tube was inserted, and good lung expansion was obtained; however, pneumothorax recurred 2 weeks after tube removal. Partial lung resection was performed by thoracoscopy. Cystic changes were noted at the lingual and lower lobe apices. The resected lung showed an increase in elastic fibers in the cyst walls, but the lung tissue surrounding the cysts was normal, and the origin of the cysts remained unclear. After the procedure, air leakage did not stop, and pleurodesis was performed that resolved the air leak, and the patient was discharged.

Later, we recognized the characteristic radiologic findings of BHD syndrome and reviewed reports indicating that BHD syndrome is associated with spontaneous pneumothorax and lung cysts (3, 16). We therefore suspected BHD syndrome in this patient on the basis of chest CT findings of thin-walled cysts existing predominantly in the subpleural and mediastinal areas and in the lower and basal segments of the lung, and because a pulmonary vessel protruded into one cyst. In 2007, we performed BHD gene analysis in this patient with her informed consent, and deletion of 4 bases (GATG) in exon 13 was discovered (Fig. 4). We therefore diagnosed the patient as having BHD syndrome. Since discharge, she has been followed as an outpatient in our hospital, and pneumothorax has not recurred. It was initially difficult to suspect BHD syndrome on the basis of pathological findings at the time of thoracoscopy, but because the patient showed mutation of the BHD gene, we reevaluated the lung specimen resected by thoracoscopy. The inner surface of the lung cyst was lined with pulmonary alveolar epithelial tissue. The cyst wall was composed of an increased amount of elastic fibers (mild elastosis). However, discontinuous and small granular changes in the elastic fibers were confirmed. Alpha-1 antitrypsin is frequently positive in the elastic fibers
of centrilobular emphysema, but it was negative in this case. The alveolar border composing the cystic wall showed accumulation of macrophages and neutrophils. In addition, a pulmonary artery was exposed in the cyst as a result of destruction of the alveolar wall. Matrix metalloproteinase (MMP)-1, -2, and -9 and tissue inhibitor of matrix metalloproteinase (TIMP)-2 immunostaining, and especially that of MMP-9, was positive in the cells composing the alveolar wall such as alveolar epithelial cells, macrophages, and neutrophils (Fig. 5).

Figure 3. Pathology of the resected lung obtained via thoracoscopy in 2001. a. Panoramic view of the resected lung. A round, thin-walled subpleural cyst is shown. b. Keratin staining (×20). The wall of the cyst was lined with alveolar epithelial cells (arrow). c. Elastica van Gieson staining (×20). An increased number of elastic fibers had accumulated on the wall of the cyst (arrow). d. Hematoxylin and Eosin staining (×20). One artery protruded into the cyst.

Figure 4. BHD gene sequence analysis. Mutation analysis identified a GATG deletion in exon 13.
Figure 5.  a. Elastica-Masson stain shows the accumulation of elastic fibers in the wall of the cyst (×200). b. On high magnification, elastic fibers located in cyst wall were discontinuous and showed a small granular appearance (×400). c. Immunohistochemistry for CD68 showed accumulated macrophages in the wall of the cyst (×400). d. Immunohistochemistry for MMP-9 showed that the alveolar epithelial cells and inflammatory cells including neutrophils and probable macrophages located in the wall of the cyst were positive for MMP-9 (×400).

Discussion

In 2002, the gene responsible for BHD syndrome was reported to reside on chromosome 17p11.2 and was named the BHD gene (4). The BHD gene codes a protein named folliculin, which is expressed in skin tissue, nephrons, and type I pulmonary alveolar epithelial cells (5). Its functions are unknown, although it is reported to be involved in cell growth (6) and as a cancer-inhibitory gene on the basis of renal tumor analysis (7, 8). The BHD gene is composed of 14 exons, and exon 11 includes a hot spot that easily develops gene mutation due to the continuous residence of a cytosine base at C8. Deletion of exon 13 was found in the present patient, and only 3 such cases were included in 30 cases of BHD gene abnormalities reported by Kunogi et al (9). Phenotype and genotype relations have not been reported, and further cases must be accumulated to clarify these relations.

Characteristic pulmonary findings of BHD syndrome are lung cysts and spontaneous pneumothorax. The lung cysts are reported to be round, to contain blood vessels, and to exist predominantly subpleurally, mediastinally, and in the lung bases and lower lobes (10). The round, thin-walled lung cysts in the present patient were located predominantly in the lower lobes, and these findings were compatible with the previous report. According to previous report of the National Cancer Institute in the United States (10), lung cysts were present in 75 (84%) of 89 patients with BHD syndrome, and 34 (38%) of these 89 patients had histories of spontaneous pneumothorax. In Japan, all patients with BHD syndrome who presented to a Department of Respiratory Medicine had lung cysts. In addition, 21 of these patients had no skin lesions or renal disease; therefore, BHD syndrome cannot be excluded simply because no renal disease or skin lesions are found (9). The differential diagnosis of patients with multiple lung cysts includes LAM, LCG, and lymphocytic interstitial pneumonia. These diseases can all be distinguished by pathological findings. If there are no pathological findings suggestive of these diseases, BHD syndrome should be suspected.

To date, no reports have mentioned specific pathological findings of the cysts in BHD syndrome, and the mechanism of cyst formation is unknown. There have also been no reports showing hematoma formation in the lung similar to that in Ehlers-Danlos syndrome, and pulmonary fragility is not suggested.

One hypothesis is that cyst formation is related to development of the lungs (6). In humans, the growth of bronchi and lungs continues for several years after birth. For exam-
ple, the bronchus divides 17 times during the final 6 months of the prenatal period, and 6 additional divisions occur after birth. In addition, the number of primary alveoli increases during the last 2 months of pregnancy and for several years after birth. Type-I alveolar cells gradually become thinner. BHD mRNA is expressed on type-I alveolar cells, and the BHD gene is known to regulate cell growth (6). Mature alveoli develop after birth, but folliculin dysfunction obstructs this development, and immature alveoli may then result in cyst formation. There is peripheral lung growth after birth. Lung cysts in BHD syndrome often reside in subpleural areas, and it is hypothesized that folliculin dysfunction induces incomplete lung growth, which results in the formation of lung cysts (14). Koga et al also hypothesized that the pulmonary cysts in BHD syndrome represent an aberrant cystic alveolar formation, and deranged interaction between alveolar epithelial structures and the surrounding mesenchyme in the peripheral lobular compartment results in the formation of cysts without stromal reaction (15). Another report hypothesized that dysfunction of macrophages and fibroblasts causes cyst formation. BHD mRNA is most strongly expressed in the stromal cells (macrophages and fibroblasts) and alveolar macrophages. The hypothesis has been proposed that BHD gene mutation induces dysfunction of macrophages and fibroblasts that induces imbalance among cytokine, chemokine, and protease, which causes inflammation or degeneration of substrates that result in cyst formation (13). The walls of the lung cysts in the present patient were lined with epithelial tissue along with an accumulation of elastic fibers showing elastosis; however, fine granular changes were also present, indicating that some additional mechanism was damaging the elastic fibers. Nevertheless, the accumulation of elastic fibers was mild and alpha-1 antitrypsin was negative, which is different from what is found in emphysema (11) or LAM (12); thus, the probability of serine protease and alpha-1 antitrypsin involvement seemed low in the present patient. MMP/TIMP immunostaining showed MMP-9 to be especially was positive in the cells in the alveolar wall of the cyst and in macrophages and neutrophils, indicating involvement of these cells. In addition, an apparently undamaged pulmonary artery was also exposed in the lung cyst. We believe an active mechanism of pulmonary tissue damage with a background of folliculin dysfunction occurred in which the alveoli suffered more damage than did the pulmonary vessels. The degree to which folliculin is expressed predominantly in the alveoli versus the blood vessels may explain these pathological findings.

Patients with BHD syndrome have a 50 times greater risk of pneumothorax than do normal people (16), and 24% of 198 patients in 89 family strains developed pneumothorax (17). Another report indicated that 10% of the patients studied had a family history of spontaneous pneumothorax (10), and it is well known that patients with alpha-1 antitrypsin inhibitor defect, Marfan syndrome, Ehlers-Danlos syndrome, tuberous sclerosis, LAM, and cystic fibrosis have a family history of pneumothorax. BHD syndrome should also be added to the list of differential diagnoses of patients with a family history of pneumothorax. In addition, the pneumothorax that occurs with BHD syndrome often develops during age 20 to 40 years, and spontaneous pneumothorax may be an indicator of BHD syndrome. However, there are patients with BHD syndrome without a family history of pneumothorax, as in the present case, so BHD syndrome should not be excluded simply because there is no family history of pneumothorax. Pneumothorax often develops as a result of bleb rupture, and bleb formation was also detected in our patient. However, the mechanism of bleb formation in BHD syndrome remains unknown.

Although the patient with BHD syndrome may repeatedly develop pneumothorax, it is different than that in LAM in that pulmonary function is preserved, and the patient will not progress to respiratory failure (10). The present patient developed pneumothorax, so partial lung resection was performed. But in cystic lung disease without pneumothorax and when BHD syndrome is suspected by radiological findings, BHD gene analysis with the informed consent of the patient may be useful because once the diagnosis of BHD is established, pulmonary function can be preserved, and patients who present with pneumothorax may avoid the pleurodesis we performed in our patient. In addition, the specific pathological findings of BHD syndrome are not clear, and lung biopsy can be avoided. Now that the radiologic characteristics of BHD syndrome are known, reports of this syndrome are expected to increase. Our patient’s disorder was also limited to the lungs, but regular follow-up will continue to be required.

We reported a case of BHD syndrome with recurrent pneumothorax. We suspected the diagnosis of BHD syndrome from the CT findings; multiple thin-walled lung cysts were located predominantly in the subpleural and mediastinal areas. The prognosis of pulmonary function in patients with this syndrome is reported to be good, but the presence of cancer, especially that of the kidney, can be problematic. Thus, such patients should be regularly followed on an outpatient basis.

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