

A Japanese Family with Multiple Lung Cysts and Recurrent Pneumothorax: A Possibility of Birt-Hogg-Dubé Syndrome

Hiroshi Ishii¹, Hiroaki Oka¹, Yuka Amemiya¹, Atsuko Iwata¹, Satoshi Otani¹, Kenji Kishi¹, Ryo Shirai¹, Issei Tokimatsu¹, Katsunobu Kawahara² and Jun-ichi Kadota¹

Abstract

We herein report a Japanese family lineage, possibly demonstrating Birt-Hogg-Dubé (BHD) syndrome. A 29-year-old nonsmoking woman was admitted to our hospital due to spontaneous pneumothorax. A chest CT showed multiple lung cysts, and breast cancer was simultaneously detected that needed priority surgical treatment. In the family history, the patient's father and half brother also experienced recurrent pneumothorax, and both had similar findings in their chest CT. In a genetic analysis of her half brother, the mutation of the BHD gene was identified. BHD syndrome is a rare autosomal and dominantly inherited disorder, which has three characteristics: multiple lung cysts that may be associated with pneumothorax, skin fibrofolliculomas, and renal neoplasm. For multiple-cystic disease of the lungs with an unknown etiology, or pneumothorax, as seen in a family history, it is necessary to consider the possibility of BHD syndrome.

Key words: cystic lung disease, family history, spontaneous pneumothorax

(*Inter Med* 48: 1413-1417, 2009)

(DOI: 10.2169/internalmedicine.48.2144)

Introduction

Birt-Hogg-Dubé (BHD) syndrome, an inherited autosomal genodermatosis characterized by benign tumors of the hair follicle, has been reported to be associated with renal neoplasia, lung cysts, and spontaneous pneumothorax. The present syndrome was first reported as a hereditary skin disorder in 1977 (1), and the responsible gene was later identified in 2001 (2, 3). This gene is identified in the short arm of chromosome 17 (17p11.2), consists of 14 exons, and encodes folliculin proteins (FLCN) (3, 4). With the discovery of the mutation of this BHD gene (FLCN), genetic research has further advanced (5-9), and in association with this, the number of reports has also been increasing in the respiratory field (10-14). Most of these reports are from the U.S., and it is believed that the recognizability of the present syndrome in Asia is still low. In Japan, 5 cases in which gene abnormality was first identified were reported by Gunji, et al. in

2007 (15). They noted that there were differences from the perspective of genetics and clinical differences between existing reports and the cases of Japanese.

We encountered a Japanese family lineage possibly demonstrating BHD syndrome, according to the findings of genetics in one of the family members, in addition to the chest CT findings and the histories of recurrent pneumothorax in three family members.

Case Report

In 2006, a 29-year-old nonsmoking single woman was admitted to our hospital due to spontaneous pneumothorax. She did not have any previous medical history including epilepsy or mental retardation and had never any abnormality pointed out in previous medical checkups. No signs of respiratory or collagen-vascular diseases were present before the onset of pneumothorax. At the onset of pneumothorax, no crackles were heard on auscultation, and no other abnormal

¹Department of Internal Medicine II, Oita University Faculty of Medicine, Yufu and ²Department of Surgery II, Oita University Faculty of Medicine, Yufu

Received for publication February 9, 2009; Accepted for publication April 26, 2009

Correspondence to Dr. Hiroshi Ishii, hishii@med.oita-u.ac.jp

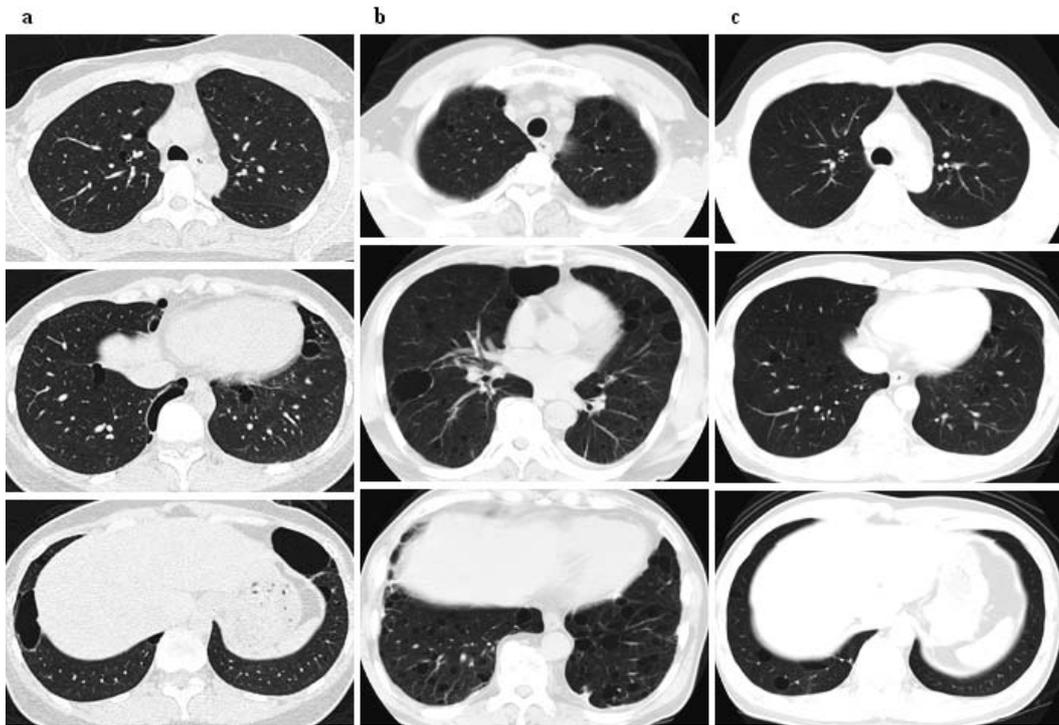


Figure 1. Chest CT, showing multiple thin-walled cysts of varying sizes, which are predominantly distributed in the basilar and mediastinal regions of the lungs (29 yo/female after the treatment for pneumothorax in Fig. 1a, 72 yo/male in Fig. 1b, 40 yo/male in Fig. 1c).

findings were observed in physical examination of chest, abdomen and skin. Her laboratory findings including inflammation markers, autoantibodies, tumor markers, the liver and kidney functions, the serum protein fraction, a blood gas analysis, and urinalysis were also normal. A chest CT showed multiple cysts with different sizes in the lung field (Fig. 1a), and therefore it was determined that surgery for pneumothorax and a surgical lung biopsy would be necessary in order to differentiate these from cystic lung diseases including lymphangioleiomyomatosis (LAM). However, the pneumothorax improved after only advising the patient to rest. Bronchoalveolar lavage fluid, transbronchial biopsy specimens obtained from the lung that were free of the cysts in order not to develop iatrogenic pneumothorax, and an abdominal CT did not show any abnormalities. In addition, breast cancer was simultaneously detected by the chest CT, and therefore priority was given to treat the breast cancer. In 2007, she developed a second pneumothorax, but this also improved with rest. As of 2009, although she has received chemotherapy for the recurrent breast cancer, the lung cysts on a chest CT have not changed since 2006.

In the family history, it was found that the patient's 72-year-old father and a 40-year-old half brother also experienced recurrent pneumothorax (Fig. 2). We obtained a chest CT of her father from a medical checkup in 2006. He had a previous history of two surgeries for pneumothorax in his youth. He was a current smoker who smoked 20 cigarettes per day for 50 years. The number of lung cysts in his chest CT (Fig. 1b) was clearly higher than that of his daughter, however, some kind of cystic lung disease rather than typi-

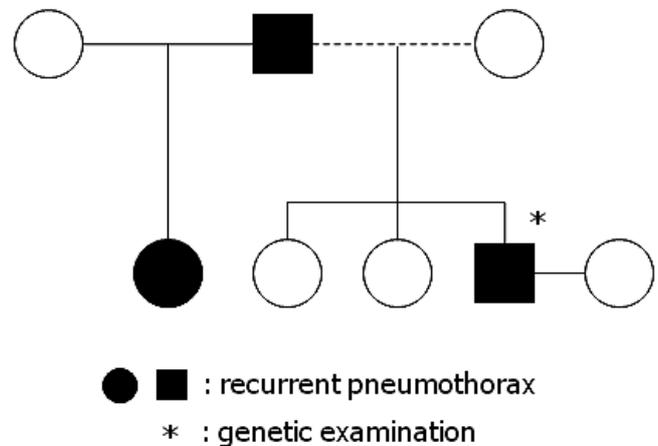


Figure 2. Family pedigree of the present patients.

cal pulmonary emphysema was suggested. He had never had skin lesions, renal tumors, or any other diseases pointed out.

Subsequently, in a chest CT of her half brother who was a never smoker but had a history of two surgeries for pneumothorax at ages of 25 and 28, similar multiple lung cysts were detected (Fig. 1c). He did not have any previous medical history and had never any abnormality pointed out in previous medical checkups. No signs of respiratory or collagen-vascular diseases were present. His laboratory findings including α 1-antitrypsin, inflammation markers, autoantibodies, tumor markers, the liver and kidney functions, the serum protein fraction, a blood gas analysis, and urinalysis were all normal. There were no abnormal skin findings, and no abnormal findings in the abdominal radiological images.

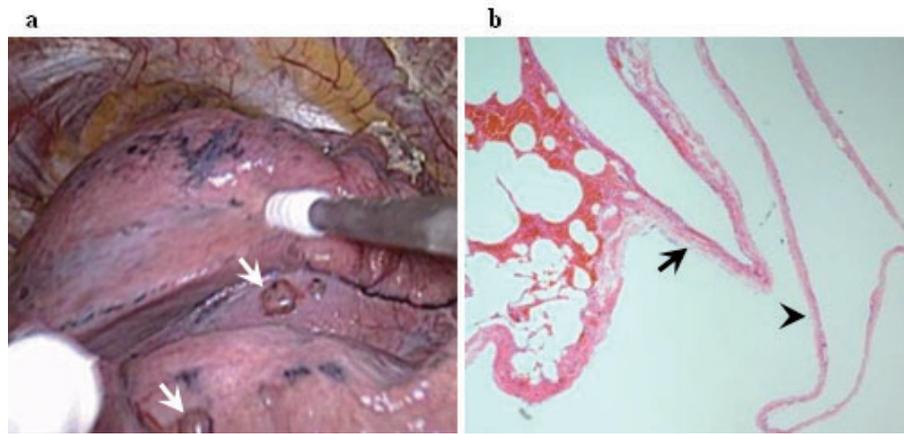


Figure 3. (a) Thoracoscopic view (40 yo/male) shows the cysts on the surface of the lung (white arrows). (b) Microscopic finding of the resected lung specimen shows a bulla (arrow head) and a bleb (arrow) consisting of collection of air within the pleura (Hematoxylin and Eosin staining, ×40).

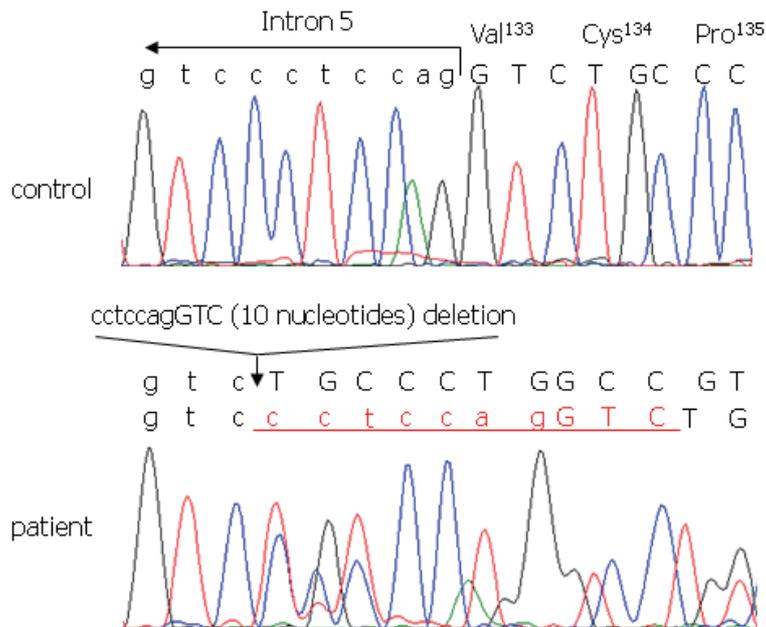


Figure 4. Sequence chromatogram of exon 6 of the BHD gene shows the deletion of 10 nucleotides from intron 5 to exon 6 of the BHD gene compared with control.

He was married but did not have any children (Fig. 2). In 2007, he was admitted to our hospital because of the spontaneous pneumothorax. During thoracoscopic surgery, multiple cysts on the surface of the lung were macroscopically observed (Fig. 3a). No LAM cells, proliferation of smooth muscle, or any other findings that indicated specific diseases, were microscopically detected in the resected specimen, and they were diagnosed to be pathologically nonspecific bulla and blebs (Fig. 3b). According to the results of a genetic analysis that was performed after obtaining consent, he was suspected to have BHD syndrome because a 10 nucleotide deletion was detected from intron 5 to exon 6 of the BHD gene (Fig. 4). This genetic examination was approved by the ethics committees of Juntendo University, and performed at the same university as described previously

(15) using isolated genomic DNA from peripheral leukocytes. Unfortunately, we have not been able to obtain permission from the other two patients or their relatives for genetic testing. The other 2 half sisters (Fig. 2) had no previous history of pneumothorax. However, a chest CT for them was not actually performed.

Discussion

BHD syndrome is a rare autosomal and dominantly inherited disorder, which has three characteristics: multiple lung cysts that may be associated with pneumothorax; skin fibrofolliculomas; and renal neoplasm. The development of the clinical features of BHD syndrome is thought to be age dependent. Skin fibrofolliculomas are reported to occur after

the age of 25-35 years (9, 10, 16), while renal neoplasms predominantly develop after the age of 40 years (10, 16). In 2007, the results of a large-scale study of 198 people (89 families, 51 family lines) with BHD syndrome were reported by Toro et al in the U.S. (14). According to that report, skin lesions were observed in most of the cases, and multiple lung cysts were detected at a high rate of 84%, but a previous history of pneumothorax was seen in only 24%. Renal tumors were detected in 25 family lineages, and 13 family lineages showed all of the three characteristics. The progression of the development of lung cysts in BHD syndrome is gradual and it rarely reaches respiratory insufficiency without specific treatment, but it is believed that smoking worsens this condition (13).

In a report by Gunji et al (15) in 2007 from Japan, the mutation of the BHD gene was observed in 5 of 8 cases with multiple lung cysts with an unknown etiology, but no skin or renal lesions were detected in any of the patients. In addition, all detected mutations were insertions or deletions, including one splice donor site mutation, and four of them were novel (15). There is a possibility that these patients, including the present cases, may develop renal neoplasms in the future, but according to the above observations, BHD syndrome seems to be increasingly recognized as a considerable heterogeneous disease.

BHD syndrome should be considered in the differential diagnosis for spontaneous pneumothorax, especially in patients with a family history (6, 11) and those with cystic lung diseases, such as LAM, Langerhans cell histiocytosis, and lymphoproliferative lung diseases. Gunji et al (15) noted that LAM, particularly in the early stages, needs to be carefully distinguished from BHD syndrome because it may have several clinical features in common with BHD syndrome: facial skin lesions, renal tumors and recurrent pneumothorax, even in the early stage when the number of lung cysts is still limited (17). However, in patients with LAM, especially those associated with tuberous sclerosis complex, facial skin lesions and renal tumors are usually angiofibromas and angiomyolipomas, respectively (16). In addition, BHD syndrome appears to have no gender difference (10,

18), whereas LAM occurs entirely in women (16). In the previous reports, chest CT in patients with BHD syndrome showed thin-walled cysts of varying sizes with normal intervening lung parenchyma (19), and the predominant distribution of cysts is in the basilar and mediastinal regions of the lungs (8). We confirmed these findings in the present three patients (Fig. 1). Moreover, the pathological findings of the lung lesions in BHD syndrome are nonspecific (20), which also was true in the half brother (Fig. 3b).

According to the family history of a woman patient with multiple lung cysts, we discovered that her father and half brother had a previous history of recurrent pneumothorax. Because the half brother demonstrated a BHD gene mutation in a genetic analysis and other possible cystic lung diseases were serologically, radiologically or pathologically excluded in one to three of the family members, this family was thus suggested to possibly demonstrate BHD syndrome. As an interesting genetic feature of BHD syndrome, a reduced penetrance has been cited, whereas a relatively late age of onset of the disease has also been noted (5). Therefore, in the present family lineage, it is necessary to be aware of the complications of skin fibrofolliculomas and renal neoplasm in addition to the development of pneumothorax, and it is desirable to advise such individuals to quit smoking and to provide genetic counseling.

In conclusion, pulmonologists should be aware that BHD syndrome can occur as an isolated phenotype with pulmonary involvement. Furthermore, in patients with multiple lung cysts that show characteristic findings in a CT as well as patients with familial pneumothorax, it is recommended to consider the possibility of BHD syndrome and to perform a genetic analysis.

Acknowledgement

We would like to thank Dr. K. Seyama (Department of Respiratory Medicine, Juntendo University School of Medicine) for performing the mutation analysis of the BHD gene and Dr. Y. Kawabata (Division of Pathology, Saitama Cardiovascular and Respiratory Center) for valuable assistance in the pathological diagnosis.

References

1. Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol* **113**: 1674-1677, 1977.
2. Schmidt LS, Warren MB, Nickerson ML, et al. Birt-Hogg-Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet* **69**: 876-882, 2001.
3. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. *Cancer Cell* **2**: 157-164, 2002.
4. Warren MB, Torres-Cabala CA, Turner ML, et al. Expression of Birt-Hogg-Dubé gene mRNA in normal and neoplastic human tissues. *Mod Pathol* **17**: 998-1011, 2004.
5. Khoo SK, Giraud S, Kahnoski K, et al. Clinical and genetic studies of Birt-Hogg-Dubé syndrome. *J Med Genet* **39**: 906-912, 2002.
6. Painter JN, Tapanainen H, Somer M, Tukiainen P, Aittomäki K. A 4-bp deletion in the Birt-Hogg-Dubé gene (*flcn*) causes dominantly inherited spontaneous pneumothorax. *Am J Hum Genet* **76**: 522-527, 2005.
7. Baba M, Hong SB, Sharma N, et al. Folliculin encoded by the *bhd* gene interacts with a binding protein, *fnip1*, and *ampk*, and is involved in *ampk* and *mtor* signaling. *Proc Natl Acad Sci USA* **103**: 15552-15557, 2006.
8. Adley BP, Smith ND, Nayar R, Yang XJ. Birt-Hogg-Dubé syndrome: Clinicopathologic findings and genetic alterations. *Arch Pathol Lab Med* **130**: 1865-1870, 2006.
9. van Steensel MA, Verstraeten VL, Frank J, et al. Novel mutations in the *bhd* gene and absence of loss of heterozygosity in fibrofol-

- liculomas of birt-hogg-dube patients. *J Invest Dermatol* **127**: 588-593, 2007.
10. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev* **11**: 393-400, 2002.
 11. Graham RB, Nolasco M, Peterlin B, Garcia CK. Nonsense mutations in folliculin presenting as isolated familial spontaneous pneumothorax in adults. *Am J Respir Crit Care Med* **172**: 39-44, 2005.
 12. Chiu HT, Garcia CK. Familial spontaneous pneumothorax. *Curr Opin Pulm Med* **12**: 268-272, 2006.
 13. Ayo DS, Aughenbaugh GL, Yi ES, Hand JL, Ryu JH. Cystic lung disease in Birt-Hogg-Dubé syndrome. *Chest* **132**: 679-684, 2007.
 14. Toro JR, Pautler SE, Stewart L, et al. Lung cysts, spontaneous pneumothorax, and genetic associations in 89 families with Birt-Hogg-Dubé syndrome. *Am J Respir Crit Care Med* **175**: 1044-1053, 2007.
 15. Gunji Y, Akiyoshi T, Sato T, et al. Mutations of the Birt-Hogg-Dubé gene in patients with multiple lung cysts and recurrent pneumothorax. *J Med Genet* **44**: 588-593, 2007.
 16. Ryu JH, Moss J, Beck GJ, et al. The nhlbi lymphangiomyomatosis registry: Characteristics of 230 patients at enrollment. *Am J Respir Crit Care Med* **173**: 105-111, 2006.
 17. Yamazaki A, Miyamoto H, Futagawa T, et al. An early case of pulmonary lymphangiomyomatosis diagnosed by video-assisted thoracoscopic surgery. *Ann Thorac Cardiovasc Surg* **11**: 405-407, 2005.
 18. Schmidt LS, Nickerson ML, Warren MB, et al. Germline bhd-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. *Am J Hum Genet* **76**: 1023-1033, 2005.
 19. Souza CA, Finley R, Muller NL. Birt-Hogg-Dubé syndrome: A rare cause of pulmonary cysts. *AJR Am J Roentgenol* **185**: 1237-1239, 2005.
 20. Butnor KJ, Guinee DG Jr. Pleuropulmonary pathology of Birt-Hogg-Dubé syndrome. *Am J Surg Pathol* **30**: 395-399, 2006.