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Case Report

A novel *FLCN* gene mutation causing Birt–Hogg–Dubé syndrome in a Korean family

Jiyeon Bae [a], Jungwon Huh [b], Sung Shine Shim [c], Heae Surng Park [d], Yon Ju Ryu [e, *]

[a] *Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea*
[b] *Department of Laboratory Medicine, Ewha Womans University College of Medicine, Seoul, Republic of Korea*
[c] *Department of Diagnostic Radiology, Ewha Womans University Seoul Hospital, Seoul, Republic of Korea*
[d] *Department of Pathology, Ewha Womans University Seoul Hospital, Seoul, Republic of Korea*
[e] *Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea*

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ABSTRACT

Spontaneous pneumothorax is a common manifestation of Birt–Hogg–Dubé (BHD) syndrome, an inherited disorder caused by mutation of the *folliculin* (*FLCN*) gene. A 44-year-old female with a history of breast cancer was diagnosed with recurrent pneumothorax. Chest CT showed multiple cysts with left lung pneumothorax, and she received surgery for the diagnosis. Because the patient also had a family history of spontaneous pneumothorax, a *FLCN* genetic examination was conducted. A novel heterozygous, likely pathogenic variant (NM_144997.5:c.779 + 2T > C) was detected in the proband, her mother, and aunt. This is the first report of a new mutation of *FLCN* gene in a BHD syndrome patient.

1. Introduction

Birt–Hogg–Dubé (BHD) syndrome is caused by mutation of the *folliculin* (*FLCN*) gene that encodes the tumor suppressor protein folliculin [1]. The characteristic features of this rare autosomal dominant disease are fibrofolliculoma, pulmonary cysts, recurrent spontaneous pneumothorax, and renal cancer [2–4]. Not every patient presents with all manifestations; many initially complain of pulmonary symptoms such as lung cysts and spontaneous pneumothorax [5].

Herein we report an unprecedented *FLCN* mutation in intron 7 (NM_144997.5:c.779 + 2T > C) in a Korean family with BHD syndrome. As Asian patients with BHD syndrome are more likely to present with pulmonary symptoms at the beginning, BHD syndrome should be suspected in any patient with a familial history of cystic lung disease. Also, a genetic examination may help with the diagnosis.

2. Case presentation

A 44-year-old woman was admitted for the treatment of a spontaneous pneumothorax incidentally detected by chest computed tomography (CT) during her regular follow-up for breast cancer. The patient had been diagnosed with mucinous breast cancer eight years ago and had undergone a breast-conserving operation with adjuvant systemic chemotherapy and radiation therapy. Even

Abbreviations: BHD syndrome, Birt–Hogg–Dubé syndrome; *FLCN gene*, *folliculin* gene; LAM, lymphangioleiomyomatosis.

* Corresponding author. Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, College of Medicine, Ewha Womans University, 25, Magokdong-ro 2-gil, Ganseo-gu, Seoul, 07804, Republic of Korea.
E-mail address: medyon@ewha.ac.kr (Y.J. Ryu).

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though she was a never smoker, history taking revealed past diagnosis of pneumothorax six years previously during her routine follow-up for breast cancer. At that time, the radiologic findings included multiple, evenly distributed, thin-walled cysts in both lungs and pneumothorax. Such results in a female in a reproductive age suggested a diagnosis of lymphangioleiomyomatosis (LAM). A chest tube was inserted for treatment. The physician recommended surgical biopsy for the diagnosis, but she did not follow-up further.

When hospitalized due to second pneumothorax, she did not complain of any symptoms. Her initial vital signs were stable, including a respiratory rate of 20 breaths/minute. All the laboratory values were within normal ranges. However, the breath sound was diminished at her left lung. Chest CT scans also revealed variable multiple cysts that had increased in both number and size compared with the ones observed six years ago, along with the added complication of left lung pneumothorax (Fig. 1).

7L/min of oxygen was given via simple face mask. Also, a pigtail catheter was inserted into the left lung using Seldinger techinque instead of a conventional tube thoracostomy. Considering the recurrent pneumothorax and chest CT findings, we decided to perform a wedge resection of the left upper lobe of the lung via video-assisted thoracoscopic surgery (VATS). A VATS bullectomy and talc pleurodesis were conducted simultaneously to prevent recurrence of the pneumothorax. Histopathological examination showed multiple, small cysts in the subpleural and intra-parenchymal areas (Fig. 2). The cyst wall had a focal fibrosis and mild chronic inflammation. Aberrant spindle cell proliferation was absent, and immunohistochemical staining for HMB-45 was negative, thus excluding the pathological diagnosis of LAM. In addition, the patient had a family history of pneumothorax – her younger sister, mother and aunt had one, two, and five episodes of pneumothorax, respectively, but none had received genetic testing. Careful consideration of the patient's family history with recurrent pneumothorax suggested the possibility of BHD syndrome (Fig. 3), and genetic testing was initiated after obtaining the patient's consent.

The diagnosis of BHD syndrome was confirmed by *FLCN* genetic mutation analysis; a novel heterozygous and likely pathogenic variant of the *FLCN* gene (NM_144997.5:c.779 + 2T > C) was detected in the proband, her mother, and aunt. This variant was found in neither gnomAD exomes nor gnomAd genomes. Because this mutation lies in the splice region, it is predicted to create a truncated protein and likely to cause loss of protein function. Her younger sister did not undergo genetic testing, but she previously had a surgical biopsy at a different hospital after experiencing pneumothorax twice. The pathology did not reveal any typical findings of LAM, thereby excluding LAM from the list of possible cystic lung diseases. The doctor at that hospital suggested referral to a tertiary hospital for further evaluation and diagnosis one month ago, but she had not visited any hospital since then.

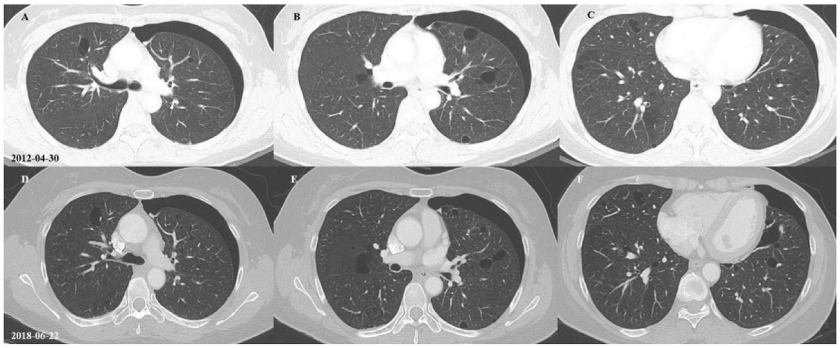

Fig. 1. Axial chest CT images. **(A)(B)(C)** Chest CT scans of the initial spontaneous pneumothorax of the left lung in 2012. **(D)(E)(F)** Chest CT scans of the proband six years after her second diagnosis as spontaneous left pneumothorax. In comparison with the previous CT findings, slightly larger, multiple, thin-walled cysts are observed in both lungs, suggesting multicystic lung disease.

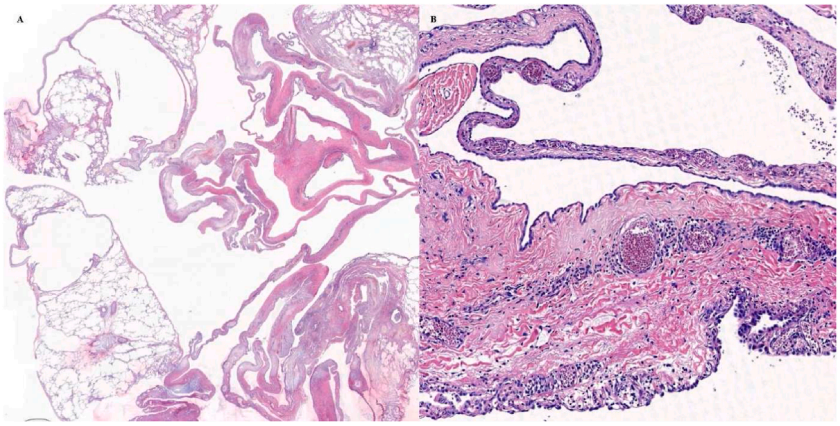

Fig. 2. Histopathological results. Histopathological examination of the lung specimen revealed multiple small cystic lung lesions in the subpleura and intra-parenchyma (**(A)**: Hematoxylin and eosin stain, original magnification 6 ×). Although the cyst wall showed focal fibrosis and mild chronic inflammation, abnormal spindle cell proliferation suggestive of lymphangioleiomyomatosis was absent (**(B)**: Hematoxylin and eosin stain, original magnification 100 ×).

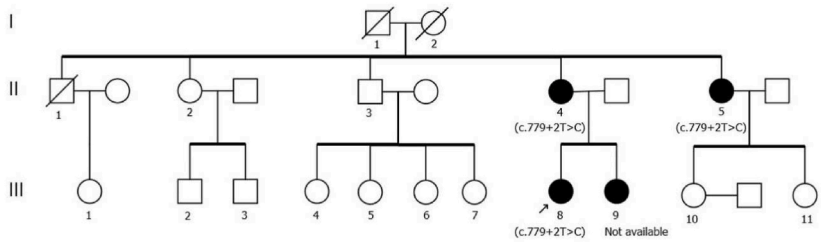

Fig. 3. Family Pedigree. The patient's pedigree for a history of pneumothorax; proband indicated by the arrow. Novel *FLCN* gene mutation in intron 7, c.779 + 2T > C heterozygous, was identified in the patient (III-8) and her mother (II-4) and aunt (II-5). Gene identification was not performed for her sister (III-9). ○, female without pneumothorax ●, female with pneumothorax □, male without pneumothorax ■, male with pneumothorax.

3. Discussion

BHD syndrome is an inherited disease characterized by skin, kidney, and lung lesions. Sex predilection does not exist [5], and a patient does not need to exhibit multiple symptoms for the diagnosis. Pulmonary cysts are the most common features, reaching 80%–100% of the patients with BHD syndrome [6–8]. Zbar et al. reported that patients with this syndrome are 50 times more likely to develop pneumothorax, after adjusting for age [8].

The diagnosis of BHD syndrome requires the fulfillment of one major or two minor diagnostic criteria. Major criteria include the following: 1) presence of five or more adult-onset fibrofolliculomas or trichodiscomas, of which at least one has been histologically confirmed; 2) pathogenic *FLCN* germline mutation. Minor criteria are as follows: 1) multiple, bilateral pulmonary cysts mainly found in the basilar region with no other specific cause, with or without spontaneous primary pneumothorax; 2) renal carcinoma that is either early onset (< 50 years), bilateral, multifocal, or of mixed chromophobe and oncocytic histology; and 3) family history of a first-degree relative with BHD syndrome [5]. In our case, the patient manifested one major and two minor criteria. She had multiple, bilateral pulmonary cysts, a history of recurrent spontaneous pneumothorax, and eventually, a family history of a first- and even second-degree relative with BHD syndrome. In addition, a *FLCN* mutation was confirmed by genetic testing.

Although no racial correlation has been confirmed, several studies have shown that Asian BHD syndrome patients tend to develop pneumothorax rather than renal or skin involvement. All the Korean patients studied by Lee et al. had pulmonary cysts, and 66.7% had pneumothorax which recurred in 75% of them [9]. In contrast, skin lesions were only confirmed in 25% of the patients. Another analysis of 26 Korean patients showed that 65.4% had at least one pneumothorax, whereas only 16% had fibrofolliculoma [10]. Similarly, 73.5% of 287 Chinese BHD syndrome patients presented with pneumothorax while skin lesions occurred only in 22.3% [11]. A report by Kunogi et al. showed that lung cysts without skin or renal involvement is the most frequent combination of phenotypes in Japanese BHD syndrome patients (70%) [12]. Another Japanese study found that 73.7% of 312 BHD family members experienced episodes of pneumothorax, whereas only 40 individuals among 115 *FLCN* mutation carriers over the age of 40 had renal cell carcinoma (34.8%) [13]. These findings differ from those of Toro et al., who found 93% of 198 patients confirmed with BHD syndrome had fibrofolliculomas, 45% had kidney tumors, and 24% had history of spontaneous pneumothorax [6]. The genetic, epidemiologic, and clinical characteristics of BHD syndrome need further evaluation to clinically validate the difference between Asian and Caucasian populations.

In our case, the patient had a history of breast cancer. There are several reported cases of BHD syndrome patients with breast tumors, but this possible association requires further study. In a review by Palmirotta et al., the authors demonstrated a range of germline *FLCN* mutations and phenotypic manifestations of BHD syndrome patients with breast cancers [14]. For example, there were two cases of breast fibroadenomatosis in a study of a large, six-generation Swedish family with BHD syndrome [15]. Leter et al. researched 20 families with BHD and observed two cases of breast cancer [16]. Breast cancer may be another feature among the various tumors associated with BHD syndrome [17]. However, since breast cancer is common in the general female population, additional clarifications are recommended.

The *FLCN* gene is a tumor suppressor gene located on chromosome 17p11.2 that encodes the folliculin protein [18]. Thus far, it is known to take a role in the signaling of mammalian target of rapamycin (mTOR) and 5′AMP-activated protein kinase (AMPK). Although the mechanisms are not completely understood, knowledge so far has shown several dysregulated signaling pathways such as mTOR and AMPK and impaired cellular adhesion contribute to the formation of pulmonary cysts [19]. Identified mutations are accumulated in databases like gnomAD, Leiden Open Variation Database, and European Birt–Hogg–Dubé Consortium. There is no clear association between mutation type or location and phenotypic manifestations of BHD syndrome [20].

A novel heterozygous, likely pathogenic variant of the *FLCN* gene (NM_144997.5:c.779 + 2T > C) was detected in the proband, her mother, and aunt who all had history of spontaneous pneumothorax. This mutation was neither found in gnomAD exomes nor gnomAD genomes. Thus, we report a currently unpublished pathogenic variant of the *FLCN* gene that leads to BHD syndrome. To provide early diagnosis of BHD syndrome, physicians should consider the possibility of BHD syndrome in patients with lung cysts and family history of pneumothorax and recommend *FLCN* genetic testing.

Statement of ethics

This case-report study abided by the Declaration of Helsinki. This study was approved by the Institutional Review Board of Ewha Womans University Hospital (EUMC 2018-12-017-002).

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Author contributions

Conceptualization: Ryu YJ. Writing – original draft preparation: Bae JY, Ryu YJ. Writing – review and editing: Bae JY, Ryu YJ, Huh JW, Sim SS, Park HS. Interpretation of genetic findings: Huh JW. Interpretation of radiological findings: Sim SS. Interpretation of pathological findings: Park HS. Approval of final manuscript: all authors.

Declaration of competing interest

The authors have no potential conflicts of interest to disclose.

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