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CASE REPORT

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A case report of Birt–Hogg–Dubé syndrome associated with severe airway obstruction in a 62-year-old female smoker

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Abstract

Birt–Hogg–Dubé syndrome (BHD) typically does not manifest airway obstruction despite the presence of multiple lung cysts. However, the long-term effects of cigarette smoking on lung function among individuals with BHD are unknown. We report a case of a smoking individual diagnosed with BHD syndrome complicated by spontaneous pneumothorax and severe airway obstruction. The patient presented with chronic dyspnea and productive cough. Further work-up revealed severe obstructive airflow limitation, and multiple lung cysts in both lungs, accompanied centrilobular emphysematous changes. Genetic testing confirmed a heterozygous deletion of exons 6–8 in the *folliculin* gene, confirming the diagnosis of BHD.

KEYWORDS
Birt–Hogg–Dubé syndrome, centrilobular emphysema, chronic obstructive disease, folliculin, paraseptal emphysema

INTRODUCTION

Birt–Hogg–Dubé syndrome (BHD) is a rare autosomal dominant genetic disorder caused by germline loss-of-function mutations in the *folliculin* (*FLCN*) gene, encoding the folliculin protein (FLCN). BHD is characterized by multiple pulmonary cysts, fibrofolliculoma, and renal tumours.[1] Diagnosis requires clinical features and *FLCN* gene mutation confirmation, but variability in manifestations and severity, even among family members, often leads to underdiagnosis.[1,2] Patients are at increased risk for recurrent spontaneous pneumothorax due to pulmonary cysts.[2,3] Unlike other cystic lung diseases or COPD, cough and dyspnea are uncommon in BHD, and pulmonary function typically remains normal or slightly impaired.[1,2] This report presents a rare BHD case with severe airflow limitation, diagnosable as severe COPD.

CASE REPORT

A 62-year-old female with a history of 45-pack years of cigarette smoking and spontaneous pneumothorax presents with dyspnea on exertion of 2–3 years of duration. She develops dyspnea on exertion, such as climbing up 2 flights of stairs. She also complained of chronic cough productive of clear to brownish sputum up to 10 times a day. Two months before the presentation, she developed left-sided pleuritic chest pain and worsening dyspnea, which prompted her to visit an emergency room. Chest X-rays revealed a small size of the left apical pneumothorax. She was released to home without any intervention, such as chest tube placement. She has a history of asbestos exposure approximately 30 years ago and marijuana use. Her other medical history was diabetes mellitus, osteoarthritis, hyperlipidemia, peptic ulcer disease, and depression, and she was subscribed to medications for these diseases. She has eight siblings, and four of them are affected with renal tumours (younger sister), lung cysts (another younger sister), spontaneous pneumothorax (younger brother), and fibrofolliculoma on the face (older brother).

Physical examination revealed that the patient is afebrile with normal heart rate and blood pressure, but her respiratory rate was increased to 18/min, and SpO_2 is 96% on room air. Her weight was 54.4 kg (body mass index, 19.3). Her

skin exam was normal. Scattered rhonchi were confirmed bilaterally. There was no clubbing, cyanosis, or edema.

The chest computed tomography images obtained 2 months after the resolution of pneumothorax showed multi-pulmonary cysts dominantly at the lung bases and calcified pleural plaques, and not only pulmonary cysts but also centrilobular emphysema was observed (Figure 1.). Abdominal CT without intravenous contrast showed no renal mass (data not shown). The pulmonary function test (PFT) showed the obstructive disorder and a lower diffusion capacity (FVC: 3.06 L, %FVC: 87%, FEV_1: 1.31 L, $\%FEV_1$: 49%, $FEV_{1\%}$ (Gaensler): 42.8%, TLC: 6.95 L, RV/TLC: 120%, DL_{CO}: 16.2 mL/min/mmHg, $\%DL_{CO}$: 67%). The level of alpha-1 antitrypsin was normal (168 mg/dL).

There was no significant bronchodilator response. The diagnosis of severe COPD was made, and the patient has developed 2 episodes of mild exacerbation within the 12 months. She then received the triple inhaler therapy (budesonide 160 mcg/glycopyrrolate 9.0 mcg/formoterol 4.8 mcg per puff, 2 puffs twice a day).

From the physical examination, images, and her family history, BHD was suspected strongly, and the genetic test (next-generation sequencing and Sanger sequencing) was performed from a peripheral blood sample. The heterozygous deletion of exons 6–8 in the *FLCN* gene was detected and considered likely pathogenic, and she was diagnosed with BHD (Met one major criterion: a pathogenic *FLCN* germline mutation, and one minor criterion: multiple lung cysts, as proposed by the European Birt–Hogg–Dubé Consortium[1,4]).

We recommended that the patient pursue smoking cessation and participate in pulmonary rehabilitation and annual low-dose CT lung cancer screening for lung cancer due to the facts that she is over 60yo, heavy smoker, with asbestos exposure, in addition to continuing inhaler therapy. Additionally, we advised a consultation with thoracic surgery for a definitive intervention, such as surgical or medical pleurodesis, due to her high risk of recurrent pneumothorax. Additionally, the annual kidney cancer screening by an abdominal MRI scan alternating with abdominal ultrasound was recommended, since patients with BHD have a high risk of kidney cancer.[1]

DISCUSSION

BHD is a rare genetic disease characterized by multiple lung cysts, skin lesions, and kidney tumours and is diagnosed through a combination of clinical symptoms, family history, and genetic testing.[1,2]

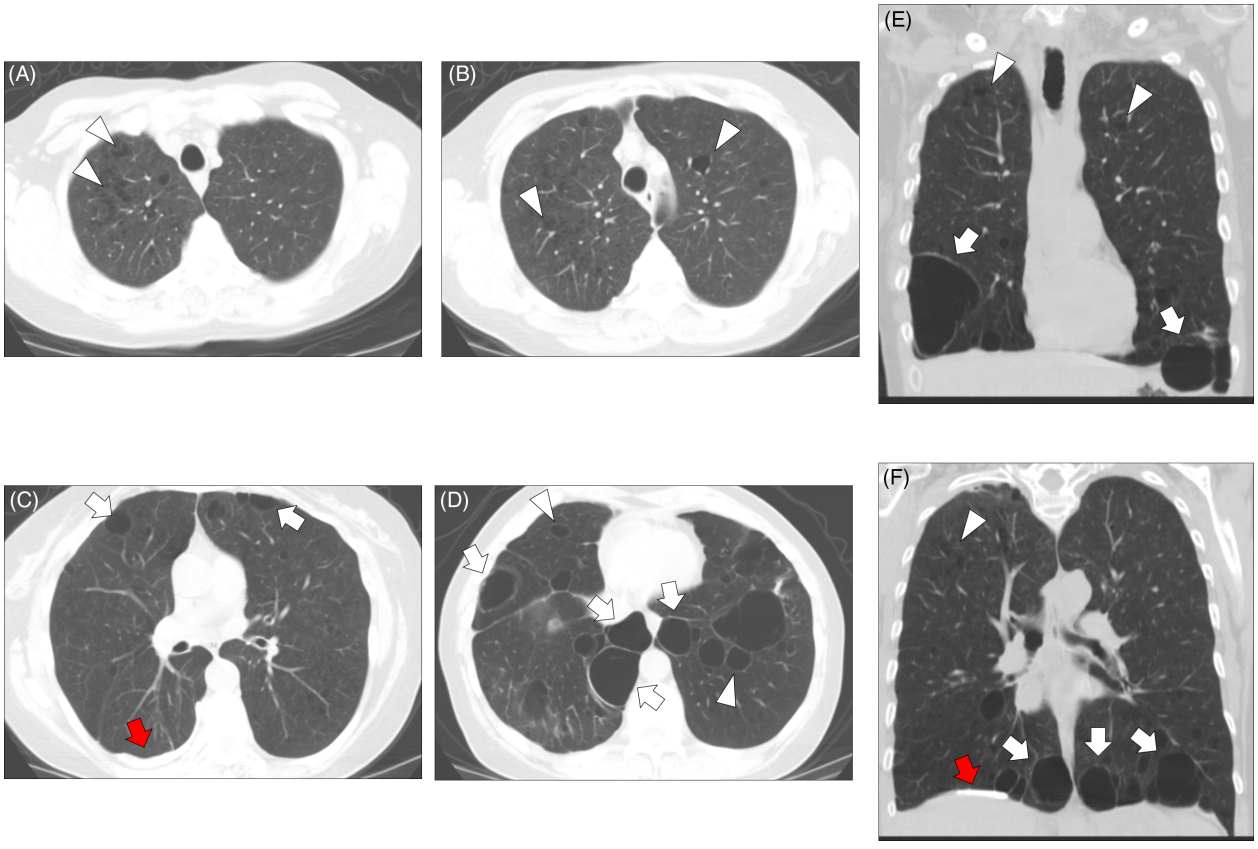

FIGURE 1 Chest computed tomography images showed mixed features of Birt-Hogg-Dubé syndrome (BHD) and centrilobular emphysema. Chest computer tomography images (A: apex region, B: upper region, C: middle region, D: lower region, E: coronal anterior section, F: coronal posterior section): Multiple lung cysts consistent with features of BHD are observed (white arrows), and centrilobular emphysema (white triangles) are observed. Calcified pleural plaques (red arrow) are also observed.

This patient had a heterozygous deletion of exons 6–8 in the *FLCN* gene, which is predicted to induce premature termination, leading to codon and nonsense-mediated *mRNA* decay. Thus, this extensive deletion is predicted to cause FLCN loss. Based on a current literature review, although this deletion has not been reported in affected individuals, a similar deletion of exon eight has been observed in FLCN-associated disease, supporting the diagnosis of BHD on this patient.[5]

Clinically, lung cysts in BHD often appear bilateral and multifocal, and the risk of spontaneous pneumothorax is high,[1] but individuals with BHD generally do not complain of severe respiratory symptoms and maintain normal lung function. In our case, the patient had chronic cough and dyspnea on exertion. Her PFT showed a severe obstructive ventilatory defect associated with impaired diffusing capacity, confirming the diagnosis of COPD. Additionally, her chest CT images had both pulmonary changes caused by BHD; pulmonary multiple cysts and cigarette smoking; centrilobular emphysema, suggesting that small airway injury and centrilobular caused by COPD may contribute to her respiratory symptoms and pulmonary dysfunction.

Currently, the knowledge of the protective role of FLCN against cigarette smoke-induced lung injury is limited. Whereas, our previous study showed that cigarette smoking is a secondary cause of folliculin loss and that FLCN protein expression in COPD lungs is depleted relative to smokers without COPD.[6] Therefore, it is possible that BHD individuals are more vulnerable to CS-induced lung function decline and have a higher COPD risk compared to non-BHD individuals. We need further studies to concrete the mechanisms of the FLCN on the formation of lung cysts and CS-induced lung injury.

In conclusion, individuals with BHD syndrome can be complicated by severe airway obstruction through long-term smoking. Further studies are needed to determine their susceptibility to smoking-induced COPD, but smoking cessation cannot be overemphasized to BHD individuals.

AUTHOR CONTRIBUTIONS

Kiyoshi Uemasu: Writing-original draft; review and editing; review of patient's medical file. **Toru Nyunoya**: Writing-review & editing; obtaining the informed consent of the patient described in the case report; review of patient's medical file; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This work was performed in accordance with local laws and ethical considerations. The patient described in this article has given written informed consent for publishing her case.

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