Letter to the Editor

Two cases of Birt-Hogg-Dubé syndrome combined with congenital contractural arachnodactyly

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Introduction

Birt-Hogg-Dubé syndrome (BHD) is a rare disease caused by a mutation in the folliculin (*FLCN*) gene (1). The clinical manifestations of BHD mainly include skin fibrofolliculomas, pulmonary cysts, pneumothorax, and renal cancer (1). The syndrome can be easily misdiagnosed as primary spontaneous pneumothorax. In China, the average delay from first onset to final diagnosis is 10 years because of the high rate of misdiagnosis of the disease (2). Computed tomography (CT) is an important method for diagnosing BHD, and familiarity with the chest CT features of the syndrome can shorten the time to diagnosis (3). However, the mechanism of pulmonary cyst formation in BHD has yet to be fully elucidated.

Reduced elastin expression due to *FLCN* mutations may contribute to the formation of lung cysts in BHD (4). Congenital contractural arachnodactyly (CCA) is an autosomal dominant connective tissue disease caused by a mutation in the fibrillin-2 (*FBN2*) gene (5). Fibrillins are essential for elastin production and functional stability, and elastin is necessary for normal alveolar development (6). When *FLCN* and *FBN2* are mutated simultaneously, patients may exhibit more prominent lung manifestations.

Here, we report two cases of BHD combined with CCA from the same family. Both patients had heterozygous variants in the *FLCN* gene, c.1015C > T (p. Gln339Ter), and the *FBN2* gene, c.3485G > A (p. Cys1162Tyr) (7). These specific mutation loci have previously been reported by Qiu *et al.* (7). We focused on the lung CT manifestations of the two patients to further analyze whether their pulmonary cysts differed from those previously reported in patients with BHD.

Case report

Case A was a 58-year-old man. On October 27, 2020, the patient came to the First Affiliated Hospital of Henan University of Science and Technology for the first time for repeated spontaneous pneumothorax, which he had had four times in total. He had no history of smoking or occupational dust exposure. Multislice CT of the chest showed predominantly pulmonary cysts in the lower lungs and subpleural distribution (*Figure 1A,1B*). This patient has a total of 241 pulmonary cysts in both lungs. Pulmonary cysts in the lower lungs accounted for 63% (153/241), and subpleural cysts accounted for 68% (164/241). The largest cyst, measuring 52 mm ×48 mm ×112 mm in diameter, was located in the left lower lung. The large cysts near the spine of the bilateral lower lobes were fusiform (*Figure 1C*). Pulmonary vessels could be observed inside some cysts (*Figure 1D*). In the hand examination, the patient showed bilateral finger flexion contracture and could not extend the fingers fully. Digital radiography showed finger deformity and narrowing of the finger joint space (*Figure 2*). No substantial lesions were found in the heart and kidney ultrasound.

Case B was the 29-year-old son of case A. He first came to our hospital on May 19, 2014 with spontaneous

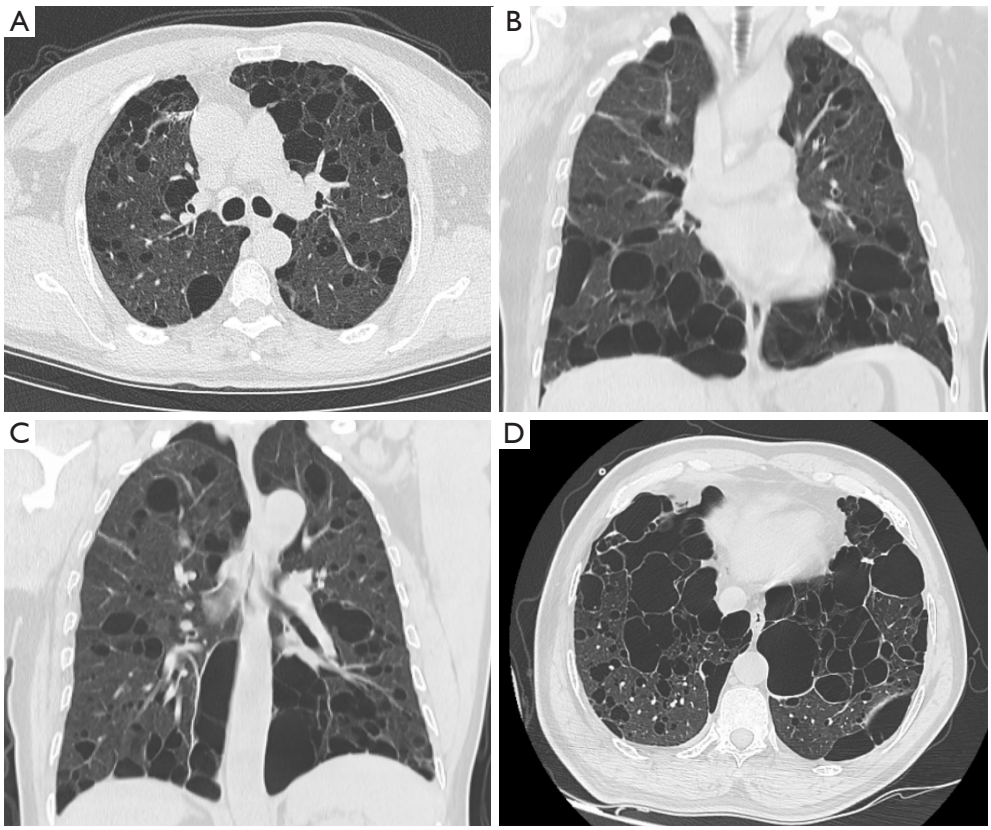

Figure 1 Chest computed tomography (CT) of case A. (A) Axial CT shows pulmonary cysts, mainly distributed in the subpleural regions. (B) A coronal CT scan showing multiple cysts with a basal predominance distribution. (C) A coronal CT scan showing fusiform pulmonary cysts near the spine of both lower lungs. (D) For the multiple pulmonary cysts in the basal segment of both lungs, the diameter of most cysts is >2 cm.

pneumothorax, which he had had three times in total. The patient had no history of smoking or occupational dust exposure. Chest CT showed pulmonary cysts, which were mainly distributed in the lower lung and bilateral subpleural lungs (*Figure 3A*). This patient has a total of pulmonary cysts in both lungs. Pulmonary cysts in the lower lungs accounted for 52% (43/82) and subpleural accounted for 71% (58/82). The largest cyst, measuring 35 mm ×21 mm ×44 mm in diameter, was in the left upper lobe (*Figure 3B*). In the hand examination, the patient showed double finger deformities similar to those of his father. The patient underwent bullae resection, and pathological examination of the resected specimens confirmed lung bullae (*Figure 4*).

The two patients' genetic sequencing maps are described in detail in the supplementary file (Figure S1). All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for the publication of the case reports and accompanying images was obtained from the 2 patients. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

In East Asian patients, BHD mainly presents as pulmonary cysts and spontaneous pneumothorax, while typical skin and kidney involvement are less common than in other groups (8). Pulmonary cysts are the most common radiological manifestation of BHD (8), and chest CT is an important method used for their evaluation. In BHD, pulmonary cysts are mainly located in the lower lobes of both lungs and the subpleural area (9,10). The cysts can include or be adjacent to blood vessels (11). Most large cysts (>20 mm) are irregular, while the cysts near the

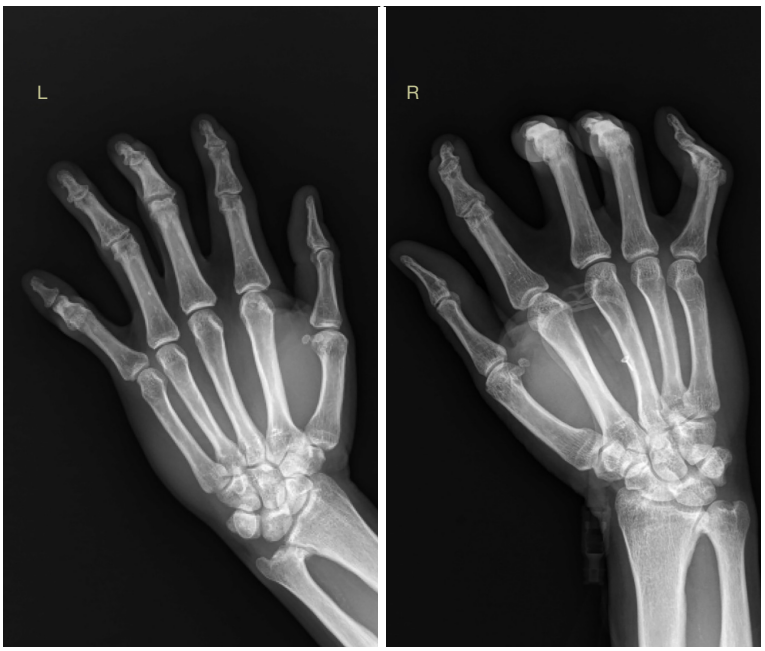

Figure 2 Digital radiography shows bilateral finger deformities and narrowing of the finger joint space with varying degrees of elevated bone cortical density in the middle and ring fingers of both hands.

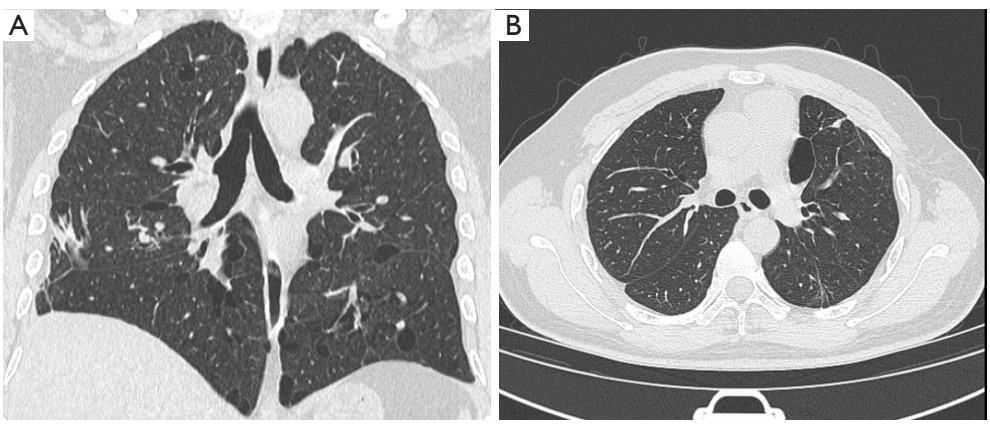

Figure 3 Chest computed tomography (CT) of case B. (A) Coronal CT shows pulmonary cysts, mainly distributed in both lower lungs. (B) The largest cyst is irregular and in the left upper lung.

spine can show plastic changes (9). In the present case report, the two patients presented with pulmonary cysts and pneumothorax without typical skin and renal lesions. Their pulmonary cysts were mainly distributed in the lower lobe of both lungs and the subpleural regions.

Among diffuse cystic lung lesions, BHD mainly needs to be distinguished from lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis, and lymphocytic interstitial pneumonia. Sporadic lymphangioleiomyomatosis almost exclusively occurs in women of childbearing age and also shows as multiple cysts in both lungs on CT. However, lymphangioleiomyomatosis cysts are smaller, rounder, and more uniformly distributed than those in in BHD (10). Pulmonary Langerhans cell histiocytosis is closely related to smoking. On chest CT, it shows as cysts with multiple nodules distributed mainly in both upper lungs, whereas pulmonary cysts in BHD are mainly distributed in the lower lungs (12). Lymphocytic interstitial pneumonia, which

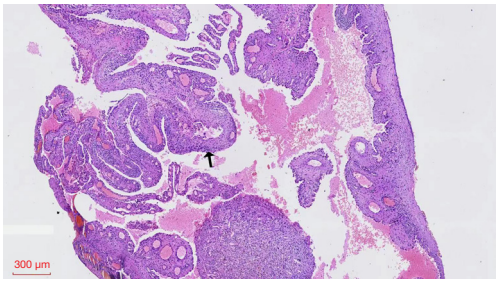

Figure 4 H&E staining of the resected lung cyst tissue in case B. The inner surface of the pulmonary cyst is covered with alveolar epithelium (black arrow), and red blood cells can be observed in the cyst.

is mostly secondary to desiccation syndrome, has more diverse manifestations than BHD on chest CT. In addition to pulmonary cysts, lymphocytic interstitial pneumonia can be accompanied by ground-glass shadows and centrilobular nodules (13).

The mechanism of the formation of BHD pulmonary cysts has yet to be fully elucidated. Previous studies have suggested that *FLCN* mutations lead to reduced mTORC1 and Wnt activity, which may reduce alveolar growth (14,15). Chu *et al.* (4) found that, after *FLCN* gene knockout in mouse pulmonary mesenchymal cells, the expression of elastin in the lung decreased, leading to alveolar destruction, which may be one reason for the formation of pulmonary cysts in BHD. *FBN2* is involved in the regulation of elastin synthesis (16). In this case, two patients had mutations in both FLCN and FBN2. Compared with data previously reported in China, we found that the average number of pneumothoraxes in these two patients was more remarkable than previously reported in China (3.5 *vs.* 1.8) and the diameter of the largest cyst was larger (112 *vs.* 85 mm) (2). Xu *et al.* (10) suggested that most patients with BHD had only a small number of pulmonary cysts (<50), while our two patients had a relatively large number of cysts (241 and 82). Both *FLCN* mutations and *FBN2* mutations lead to elastin dysfunction; therefore, we speculate that this provides the conditions for creating more and larger pulmonary cysts in the patient's lungs. Toro *et al.* (17) showed that pneumothorax was significantly associated with the number and size of cysts, which explains pneumothorax occurring a more significant average number of pneumothoraxes in the present cases.

The main clinical manifestations of CCA are joint contracture, arachnodactyly, crumpled ears, and kyphoscoliosis (18). Usually, CCA is not associated with lung abnormalities. In contrast, Marfan syndrome caused by *FBN1* mutations is associated with pulmonary maculopathy and pneumothorax, although at a low incidence (19). The generation of pulmonary cysts in BHD may involve a cooperative formation of mechanisms (20). *FBN2* mutations cause elastin dysfunction, which may not be a sufficient mechanism to cause pulmonary cysts alone but may contribute to the formation of pulmonary cysts at a later stage.

In conclusion, this case report describes the first reported cases of an *FLCN* mutation causing BHD with an *FBN2* mutation causing CCA. Concurrent mutations in *FLCN* and *FBN2* may lead to more and larger pulmonary cysts in patients, suggesting that elastin has an important role in the formation of BHD pulmonary cysts.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-806/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the 2 patients to publish this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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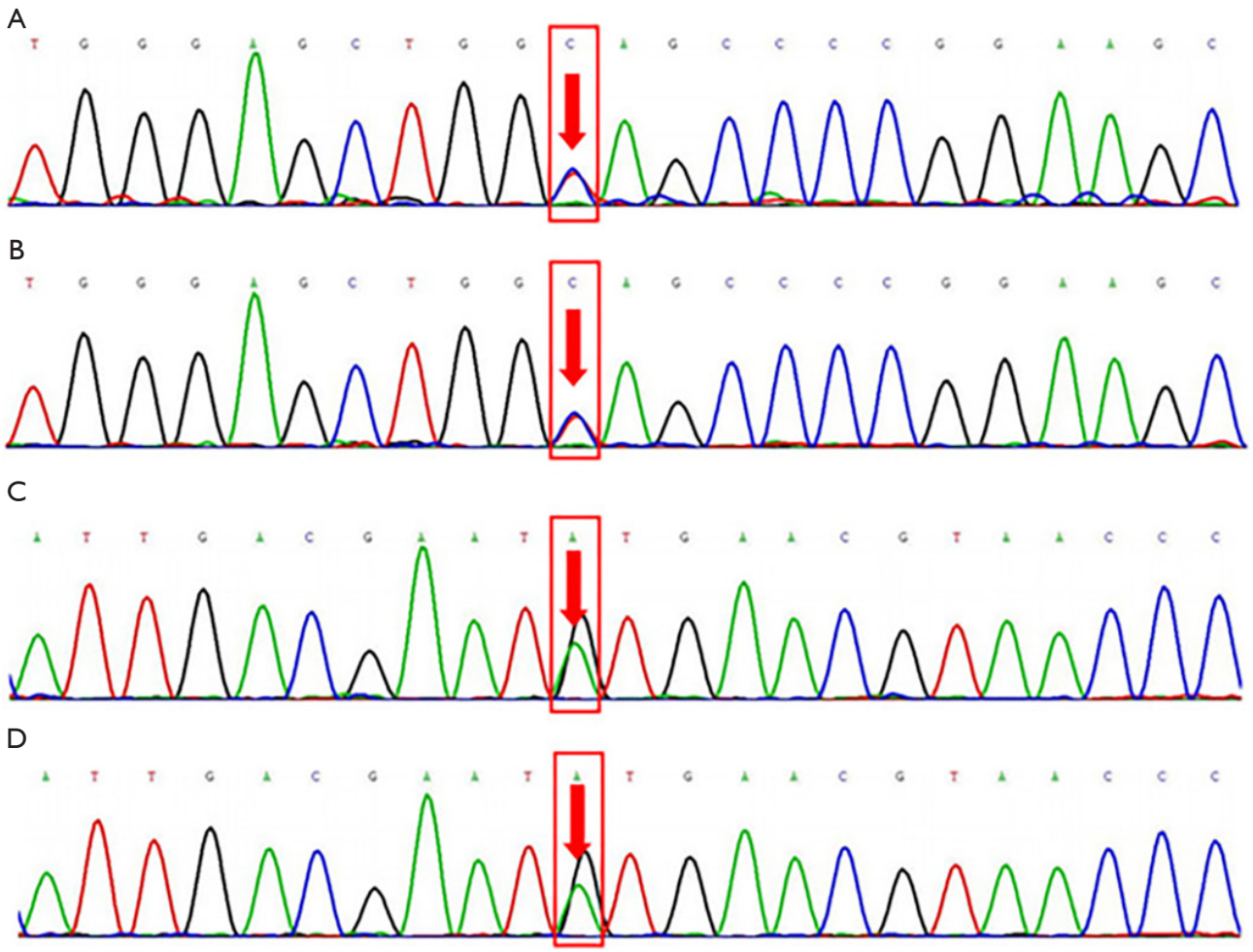

Figure S1 The whole exome sequencing results of case A and case B. *FLCN* gene c.1015C > T (p. Gln339Ter) mutation sequencing results of case A (A; heterozygous mutation) and case B (B; heterozygous mutation). *FBN2* gene c.3485G > A (p. Cys1162Tyr) mutation sequencing results of case A (C; heterozygous mutation) and case B (D; heterozygous mutation). Reproduced with the permission of Qiu *et al.* (7).

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