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Birt-Hogg-Dubé syndrome with c.1579_1580insA variant in a Chinese family: a case report

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Birt-Hogg-Dubé (BHD) syndrome, is a rare genetic disease with heterogeneous manifestations in different populations. In this study, we reported a Chinese female BHD case and her family members with c.1579_1580insA variant in *FLCN* gene, who were characterized by diffused pulmonary cysts/bulla, and reviewed another five familial BHD cases in China. Based on these cases, recurrent spontaneous pneumothorax is likely to be the first symptom for BHD in Chinese patients, with particularly but not limited to c.1579_1580insA variant. Therefore, attention to the early diagnosis of BHD in China should focus on pulmonary signs, but skin or kidney lesions still can not be neglected.

KEYWORDS

Birt-Hogg-Dubé syndrome, case study, exome sequencing, genetic disease, spontaneous pneumothorax

Introduction

Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant genetic disease, which causes a clinical syndrome including benign skin tumors (fibrofolliculomas), renal tumors and pulmonary cysts/bulla via pathogenic variants at position 17p11.2 on chromosome, known as *FLCN* gene (1, 2). *FLCN* gene contains 14 exons and encodes a follicular protein consisting of 579 amino acids, which is mostly interfered through occurring code shifting or nonsense variants in *FLCN* gene, especially in organs including skin, kidney and lung (3, 4). In China, c.1285dup/delC in exon 11 of *FLCN* gene has been documented to be the most frequent variant in BHD (5, 6). Here, we reported a Chinese female BHD case and her family members with c.1579_1580insA variant in *FLCN* gene, who were characterized by diffused pulmonary cysts/bulla as well as spontaneous pneumothorax.

Case presentation

A 65-year-old woman was admitted to the West China Hospital (WCH) of Sichuan University because of a 13-year history of dyspnea and recurrent pneumothorax. In the past 13 years before admission, the patient experienced exertional dyspnea with unknown cause and suffered from spontaneous tension pneumothorax in both sides for several times, followed by the closed drainage of chest. Two years ago, she was diagnosed in the local hospital with chronic obstructive pulmonary disease (COPD) and pulmonary

bulla, and treated by budesonide formoterol powder inhaler but with poor outcomes. One day prior to admission, the symptom of dyspnea was suddenly worsened with a right-sided tension pneumothorax again. Therefore she was emergently admitted to the WCH for further treatment. The timeline of history of present illness was showcased in Figure 1. The patient has no history of smoking or other exposure. Her father, sister, brother and daughter all suffered from lung lesions (cysts or bulla).

On admission, body temperature: 36.8°C; heart rate: 108 times per minute; respiratory rate: 24 times per minute; blood pressure: 162/99 mmHg. Physical examination indicated a barrel-shaped chest, hyperresonance when percussing, a few moist crackles in both lungs. No abnormality was found in skin. In the laboratory test, percentage of neutrophil in blood was a little bit higher (77%). Liver and kidney functions were normal. α1 antitrypsin and autoimmune antibodies were negative. Chest CT scan revealed pneumothorax in the right thoracic cavity, emphysema with multiple pulmonary bulla and scattered inflammatory shadows in both lungs. The representative chest CT images of the patient (A) and her daughter (B) were shown in Figure 2. Abdominal CT did not show any significant abnormality. The patient was then treated with cephalosporin and closed drainage of the right chest. After 2-week treatment, the symptoms were significantly improved and the drainage tube was removed before discharge. During the 3-month follow-up, the patient stayed at home and felt not well because of progressive dyspnea, especially after movement, and unexpectedly suffered from another pneumothorax episode. This case report was approved by the Institutional Review Board of West China Hospital of Sichuan University. The informed consent was obtained from the patient.

In this case, combined the clinical manifestations with the pulmonary bullae-related family history, we considered there might be a family hereditary disease. Consequently, the whole exome sequencing showed an insertional variant (c.1579_1580insA) in 14 exon in *FLCN* gene (Figure 2C). The patient was eventually diagnosed with BHD syndrome and the pedigree of the family was shown in Figure 2D. In addition to the present patient and her family F6 in Table 1, there were another five familial BHD cases with c.1579_1580insA variant reported in China F1–F5 in Table 1. Based on these six familial BHD cases, pulmonary cysts and pneumothorax seemed to be much more common than injury in skin and kidney.

Discussion

In the present study, after analyses of BHD cases in six families, we established a "bridge" between c.1579_1580insA variant and typical clinical feature (pulmonary signs) in Chinese BHD patients, although no significant association of specific genotype with clinical phenotype in BHD patients has been reported previously.

It was well-documented that Chinese BHD patients, compared to Caucasians, tended to have multiple pulmonary cysts, and similar to this case, spontaneous pneumothorax was often their first and even only symptom, and more than 95% of reported Chinese patients had pulmonary lesions, which was significantly higher than Caucasians (5, 7), which usually resulted in a misdiagnosis of COPD initially in China. Most of the pulmonary cysts were 0.5–6 cm in diameter, with multiple thin-walled pulmonary cysts that were lobulated and multi-segmented, and mainly located near the lower lobe of the lungs and mediastinum bilaterally (8, 9).

The pathogenic mechanisms of pulmonary cysts in BHD remain not fully understood. Previous studies indicated that BHD pulmonary cysts might be caused by dysregulations of not only epithelial-stromal interactions through *FLCN*-dependent mTOR signaling, leading to the formation of cystic alveoli (10, 11), but also cell-cell adhesions via *FLCN* interacting with P0071, a member of armadillo protein subfamily, which functioned in cell-cell adhesion by aggregating and stabilizing cadherins (12–14). Moreover, *FLCN* deficiency decreased the secretion of pulmonary surfactant through increasing permeability of alveolar epithelial cells and inducing apoptosis, leading to pathogenic changes of alveolar surface tension and decreased dynamic compliance, which indicated an increased resistance to mechanical stress (even respiratory movement), thus resulting in a potential for expansion of the cyst wall and rupture of the weak surface (15–17). Similarly, in BHD patients, rupture of the cyst wall initiated cyst formation and secondary pneumothorax, which were mainly distributed in the parts of greatest tensile force in lungs (18–20).

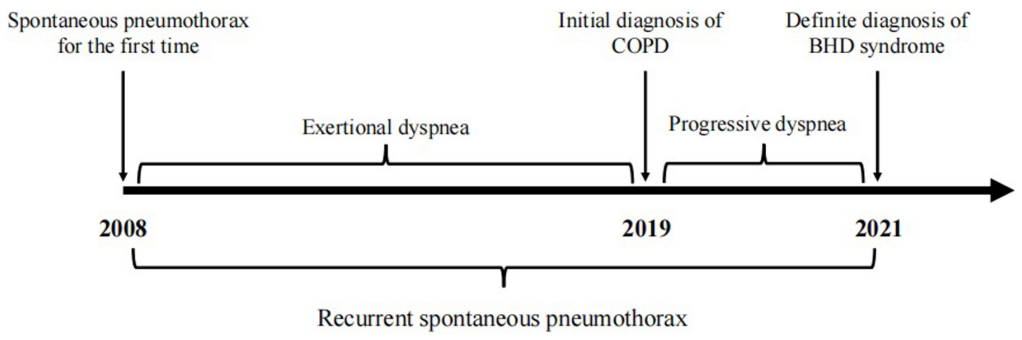

FIGURE 1
Timeline of the patient's history of present illness.

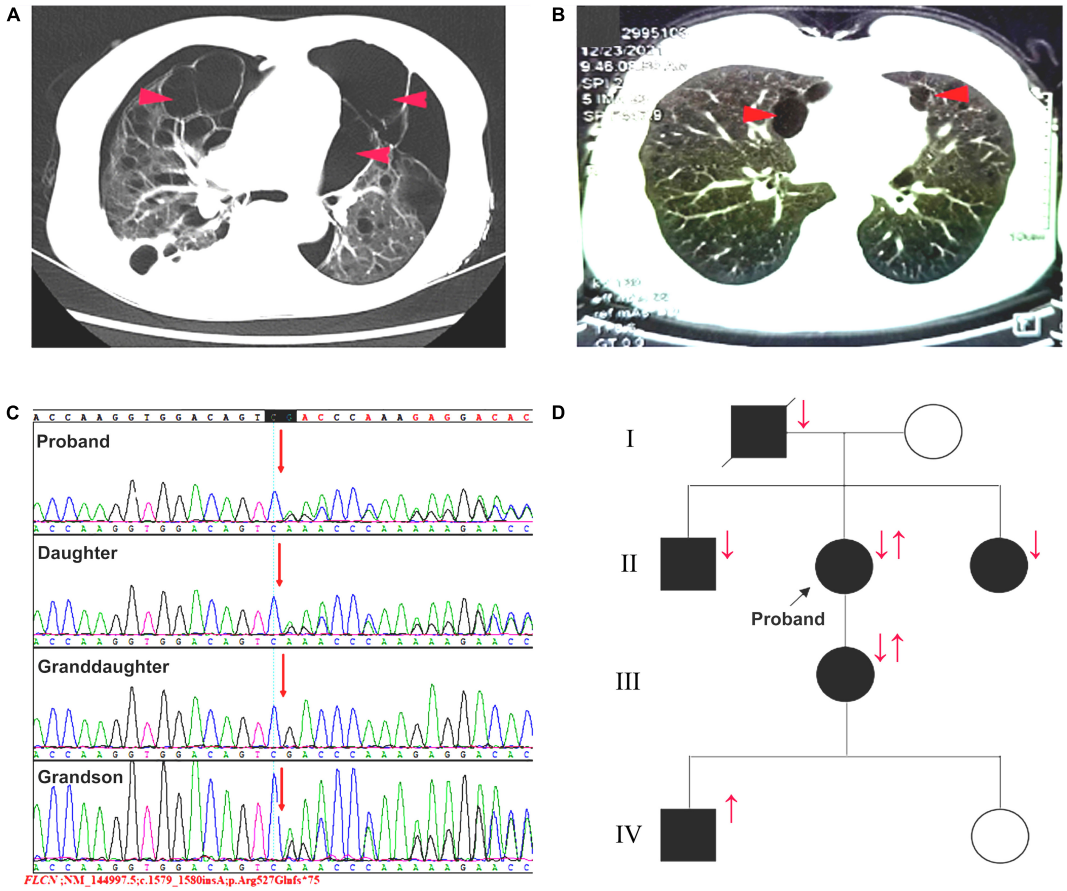

FIGURE 2
(A) The patient and **(B)** her daughter's representative chest CT images. red arrows: pulmonary bulla. **(C)** Sequence map for c.1579_1580insA in exon 14 of *FLCN* gene. **(D)** The pedigree of the patient and her family members. Squares: male members; circles: female members; ↓: pulmonary lesions; ↑: c.1579_1580insA variant.

TABLE 1 Clinical data of BHD patients (c.1579_1580insA) and their families in China.

Family ID	Age	Sex	Pneumo -thorax	Lung cysts	Kidney tumors	Skin lesion	c.1579_1580insA variant
F1	38	F	Yes	Yes	No	Yes	Yes
F1	–	F	Yes	Yes	–	–	–
F1	–	M	Yes	Yes	–	–	–
F2	77	F	No	Yes	–	–	Yes
F2	57	F	No	Yes	No	–	Yes
F2	55	F	Yes	–	No	–	Yes
F2	50	F	Yes	–	No	–	Yes
F2	48	F	Yes	Yes	No	–	Yes
F2	45	M	No	Yes	No	–	Yes
F2	41	F	No	Yes	No	–	Yes
F3	–	M	Yes	Yes	Yes	Yes	Yes
F3	–	M	Yes	Yes	Yes	No	Yes
F3	–	F	Yes	Yes	Yes	No	Yes
F3	–	F	Yes	Yes	Yes	No	Yes
F3	–	M	No	No	Yes	Yes	Yes

(Continued)

TABLE 1 (Continued)

Family ID	Age	Sex	Pneumo -thorax	Lung cysts	Kidney tumors	Skin lesion	c.1579_1580insA variant
F4	53	F	Yes	Yes	No	Yes	Yes
F4	48	F	Yes	Yes	Yes	No	Yes
F4	47	F	Yes	Yes	No	No	Yes
F4	28	M	Yes	No	No	Yes	Yes
F4	21	M	Yes	Yes	No	No	Yes
F4	18	F	No	No	No	No	Yes
F5	–	F	Yes	Yes	No	No	Yes
F5	–	F	–	–	–	–	Yes
F5	–	F	–	–	–	–	Yes
F5	–	F	Yes	–	–	–	–
F5	–	F	Yes	Yes	–	–	–
F5	–	F	Yes	Yes	–	–	–
F5	–	M	Yes	Yes	–	–	Yes
F5	–	M	Yes	Yes	–	–	–
F6	65	F	Yes	Yes	No	No	Yes
F6	–	F	No	Yes	No	No	–
F6	–	M	No	Yes	No	No	–
F6	–	M	No	Yes	No	No	–
F6	39	F	No	Yes	No	No	Yes
F6	–	M	No	–	No	No	Yes

F, female; M, male; –, not reported.

Conclusion

Overall, since recurrent spontaneous pneumothorax is likely to be the first clinical presentation for BHD in Chinese patients, with particularly but not limited to c.1579_1580insA variant, attention to the early diagnosis of BHD in China should focus on pulmonary signs. Hence, it is crucial for early differentiation of pulmonary cysts, especially in younger patients, caused by BHD from other diseases, such as lymphangioleiomyomatosis (LAM), lymphocytic interstitial pneumonia (LIP), COPD, cystic fibrosis, etc. Meanwhile, inquiry of patients' family history regarding lung lesion is also very important.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

This study was reviewed and approved by the Institutional Review Board of West China Hospital of Sichuan University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ST, CW, and XW: case report, literature review, and manuscript drafting. MX: data analyses. LC and FL: conception and draft revision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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