ORIGINAL RESEARCH PAPER

Pulmonary Medicine

SIBLINGS IN SYNC: FAMILIAL BIRT-HOGG-DUBÉ SYNDROME REVEALED BY BILATERAL PULMONARY CYSTS AND SPONTANEOUS PNEUMOTHORAX

KEY WORDS: Birt-Hogg-Dubé syndrome; pulmonary cysts; spontaneous pneumothorax; FLCN mutation; familial; renal surveillance; xanthelasma.

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ABSTRACT

Birt-Hogg-Dubé (BHD) syndrome is a rare autosomal dominant disorder caused by pathogenic variants in the FLCN gene. It commonly manifests with cutaneous lesions, pulmonary cysts, spontaneous pneumothorax, and an increased risk of renal neoplasms. We describe two adult sisters who presented within 24 hours of each other with spontaneous pneumothorax. High-resolution CT (HRCT) demonstrated extensive bilateral thin-walled lung cysts in both patients. Dermatological evaluation revealed xanthelasma in each sibling, which—although not specific to BHD—prompted further work-up. Clinical exome sequencing in one sibling confirmed a heterozygous pathogenic frameshift mutation (FLCN c.1542del; p.Val515Ter). This familial cluster underscores the importance of recognizing subtle clinical and radiologic cues and highlights the need for genetic testing and lifelong renal surveillance in affected families.

1. INTRODUCTION

Birt-Hogg-Dubé (BHD) syndrome is an uncommon hereditary multisystem disorder resulting from pathogenic alterations in the FLCN gene, which encodes folliculin. The condition is classically associated with benign skin tumors, pulmonary cysts predisposing to recurrent pneumothorax, and a markedly elevated lifetime risk of renal cell carcinoma (RCC). Because its pulmonary findings can mimic other cystic lung diseases-such as lymphangioleiomyomatosis or pulmonary Langerhans cell histiocytosis-BHD is often overlooked in clinical practice [1–3].

Familial clustering and variable dermatologic expressions further complicate detection. We report two sisters who developed spontaneous pneumothorax almost simultaneously, with HRCT findings typical of BHD. Genetic confirmation in one sibling supported the diagnosis and enabled structured counseling and surveillance of additional family members.

2. CASE SERIES

Case 1 -

A 44-year-old woman presented with acute right-sided pleuritic chest pain, breathlessness, and productive cough. On examination, breath sounds were reduced over the right hemithorax. Dermatology referral revealed xanthelasma, without other cutaneous markers associated with BHD. Chest radiography and HRCT demonstrated a moderate right-sided pneumothorax and multiple thin-walled cysts scattered predominantly in the basal and subpleural regions of both lungs (Figure 1). An intercostal drainage (ICD) tube was inserted with full re-expansion of the lung and later ICD was removed.

The constellation of familial symptoms and characteristic imaging raised the suspicion of BHD. She was advised to undergo FLCN gene testing and renal imaging surveillance.

Case 2 -

A 40-year-old woman, the younger sister of Case 1, presented the following day with persistent dry cough, dyspnea, and left-sided chest pain. Clinical examination revealed diminished breath sounds on the left. Dermatological assessment again noted xanthelasma, without fibrofolliculomas or trichodiscomas.

HRCT showed a left-sided pneumothorax and widespread bilateral cystic lung disease with striking similarity to the elder sibling (Figure 2). An ICD was inserted for Pneumothorax which was resolved overtime and ICD was removed.

Clinical exome sequencing identified a heterozygous frameshift deletion in the FLCN gene (c.1542del; p.Val515Ter), confirming BHD syndrome. Additional imaging revealed Grade II fatty liver, mild hydronephrosis, and minimal pleural effusion and no evidence of RCC.

Additional Family History

A third sibling reportedly had chronic lung disease in adolescence and underwent bullectomy for extensive cystic changes. Genetic evaluation was not performed at that time. This raises the likelihood of wider familial involvement and the need for cascade screening of first-degree relatives.

3. DISCUSSION

BHD syndrome results from pathogenic variants of FLCN, located on chromosome 17p11.2, which disrupt folliculin-mediated cellular pathways implicated in tumor suppression [3,4]. Lung involvement—most prominently multiple thin-walled cysts—is often the earliest clinical manifestation. These cysts typically show a lower-lobe and subpleural predilection, a pattern clearly identified in our patients [5,6].

Simultaneous pneumothorax in siblings is highly suggestive of an inherited cystic lung disorder, with BHD being a key differential. Asia-Pacific reports indicate that dermatologic markers such as fibrofolliculomas may be absent or subtle in many patients, making HRCT findings crucial for diagnosis [7]. In our cases, xanthelasma—not directly related to BHD—served as an incidental clue prompting dermatology review and further genetic evaluation.

The confirmed FLCN c.1542del (p.Val515Ter) frameshift mutation in the younger sibling is a pathogenic variant documented in BHD literature [8]. Early identification is essential, as renal cell carcinoma represents the major long-term morbidity. Current guidelines recommend lifelong renal imaging every 1–2 years, ideally via MRI to minimize radiation exposure.

4. CONCLUSION

This familial case series illustrates the diagnostic value of combining HRCT findings, detailed family history, and genetic testing in suspected BHD syndrome. Early

recognition enables structured renal cancer surveillance and facilitates cascade screening for at-risk relatives.

IMAGES -

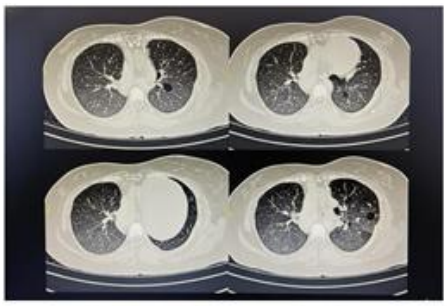

Figure 1 – multiple thin-walled cysts scattered predominantly in the basal and subpleural regions of both lungs

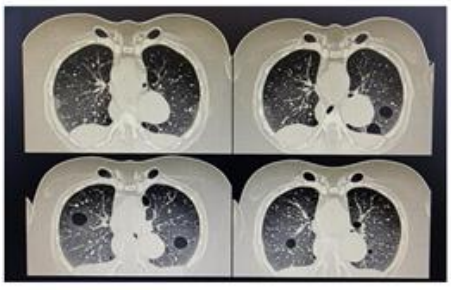

Figure 2 - widespread bilateral cystic lung disease

5. REFERENCES

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