

CASE REPORT

A novel mutation of the folliculin gene causing Birt–Hogg–Dubé syndrome as rare cause for secondary pneumothorax

Melanie Vogl¹, Axel Scheed^{1,2}, Gernot Seebacher^{1,2,*},
Elisabeth Stubenberger¹ and Bahil Ghanim^{1,2}

¹Division of General and Thoracic Surgery, University Hospital Krems, Karl Landsteiner University of Health Sciences, Krems an der Donau, Austria, ²Institute of Clinical Surgery, Karl Landsteiner Society, Krems an der Donau, Austria

*Correspondence address. Division of General and Thoracic Surgery, University Hospital Krems, Karl Landsteiner University of Health Sciences, Dr. Karl-Dorrek-Straße 30, 3500 Krems an der Donau, Austria. Tel: +43-2732-9004-2501; E-mail: gernot.seebacher@kl.ac.at

Abstract

The Birt–Hogg–Dubé syndrome is an orphan genetic disease characterized by the development of renal neoplasms, fibrofolliculomas, pulmonary cysts and spontaneous pneumothoraces. Here, we report on the case of a 21-year-old man presenting with a primary event of a persistent spontaneous pneumothorax. Computed tomography images and a positive family history for pneumothoraces led to the suspicion of Birt–Hogg–Dubé syndrome. Genetic testing then confirmed the suspected clinical diagnosis, however with a mutation that has not yet been reported.

INTRODUCTION

The Birt–Hogg–Dubé (BHD) syndrome is a rare genetic disorder caused by an autosomal dominant inherited mutation of the folliculin gene (*FLCN*), a tumor suppressor located on chromosome 17p11. BHD patients present in 80–100% with pulmonary cysts and pneumothoraces in about 40–80% with a significant tendency for recurrence [1–4]. Gupta et al. [1] found a recurrence rate of 82%, with 73% having at least one recurring pneumothorax ipsilateral and 48% contralateral. The frequency of familial pneumothorax for patients with BHD is up to 41% compared to 10–12% for patients with primary spontaneous pneumothorax [2, 4].

Extrapulmonary manifestations include cutaneous fibrofolliculomas as well as renal cysts and early-onset renal neoplasms [1, 3–5].

CASE REPORT

Here, we report on a 21-year-old male patient presenting with thoracic pain and dyspnea. An initial chest X-ray showed a completely collapsed right lung. Hence a thoracic drain was placed successfully. A repeated X-ray showed a fully expanded lung without any residual pneumothorax, and the patient was admitted for observance to our department.

However, after clamping the chest tube, the patient presented a persisting pneumothorax.

The young man additionally had a positive family history of pneumothorax—his mother and aunt had each one episode of pneumothorax but without genetic testing. Hence a thoracic computed tomography (CT) was organized for our patient. The typical apical bullae, usually present in patients with spontaneous pneumothoraces, were not found. Instead the CT images

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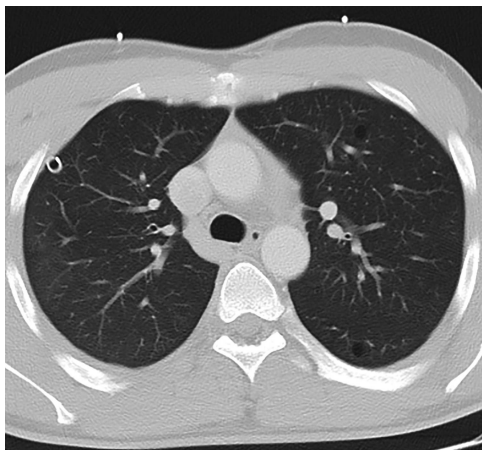


Figure 1: Intraparenchymal cysts of both lungs.

showed intraparenchymal cystic alterations of both lungs, in line with the pulmonary manifestation of the BHD (Fig. 1).

After consenting the patient, genetic testing was initiated. In view of the persisting pneumothorax and considering the high recurrence rate of pneumothoraces in patients with BHD, we decided to perform a right-sided video-assisted thoracoscopy with wedge resection of the right upper lobe and subtotal pleurectomy. The postoperative course was uneventful. The patient was pain-free with pain medication and the chest tube was removed on the third postoperative day. A minor apical pneumothorax disappeared spontaneously after removal of the chest tube and the patient was discharged home in good clinical condition on the fifth postoperative day.

The final results of the genetic analysis arrived some weeks later and confirmed a mutation of the *FLCN* and thus the suspected BHD. Our patient was found to have a base exchange mutation in position c.1432+1G>T, which is not listed in neither the ExAC nor the 1000 Genomes Database. Thus, we report a currently unpublished genetic alteration leading to BHD.

DISCUSSION

The development of a spontaneous pneumothorax often represents the first clinical symptom of the BHD, an autosomal dominant disease. The underlying mutation can also cause skin lesions, renal cysts and early-onset renal neoplasms with severe consequences for the patient and his family. Although the

syndrome is rare, it is advisable to keep it in mind as a cause for primary pneumothoraces. Ebana et al. [6] defined five criteria when a physician should question the diagnosis of a typical spontaneous pneumothorax and raise the suspicion of BHD: previous events of bilateral pneumothorax, a positive family history for pneumothoraces, age 25 years or older at first diagnosis, body mass index ≥ 18.5 and female sex. An early diagnosis of the underlying genetic syndrome could then lead to earlier screening for extrapulmonary manifestations. Regular magnetic resonance imaging or CT screening should be conducted to enable an early diagnosis of possible renal neoplasms not only of the patient diagnosed with BHD but also of the patient's family members.

Due to the family history, the patient's brother was tested as well and diagnosed positive for BHD. Until now, he has been symptom-free, and a CT scan of the thorax and abdomen showed no pulmonary or renal cysts or neoplasms. Follow-up examinations are scheduled for our patient as well as his brother.

CONFLICT OF INTEREST STATEMENT

None declared.

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