

Case report

Birt-Hogg-Dubé syndrome presenting with spontaneous pneumothorax and extensive pulmonary cysts in the absence of skin lesions or renal pathology

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SUMMARY

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant condition which classically manifests with skin lesions such as fibrofolliculomas, pulmonary cysts that predispose to spontaneous pneumothorax and an increased risk of developing renal cell carcinoma. We describe the case of a patient who presented with a spontaneous pneumothorax on a background of multiple lung cysts, in the absence of cutaneous fibrofolliculomas and renal tumours. A germline mutation in the folliculin FLCN gene was subsequently identified, confirming BHD syndrome. Our case highlights the importance of considering a broad differential diagnosis for the cause of a spontaneous pneumothorax in the presence of unexplained cystic lung disease and emphasises the value of maintaining a high index of clinical suspicion for inherited causes of pneumothoraces.

BACKGROUND

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant condition which classically manifests with skin lesions, pulmonary cysts that predispose to spontaneous pneumothorax, and up to a 30% increased risk of developing renal cell carcinoma (RCC).¹ It is caused by a germline mutation in the folliculin (FLCN) gene, which has a tumour suppressor function.² Loss of folliculin function has been shown to result in enhanced cellular proliferation, which may contribute to oncogenesis.³

The manifestations of BHD syndrome may impose a significant clinical burden on patients. The pulmonary cysts seen in BHD are irregularly shaped, vary in size and are predominantly in the lower medial lung zones.⁴ The presence of these cysts predisposes patients to pneumothoraces. BHD accounts for up to 15% of cases of familial pneumothoraces and patients may have a 50-fold increased risk of developing a pneumothorax compared with the general population.^{5,6} The most common skin lesions are fibrofolliculomas, particularly on the head and neck, but may also include trichodiscomas and acrocordons.⁷ These lesions are typically benign. While the cutaneous manifestations and lung involvement in BHD do not require long-term follow-up per se, the significant risk of developing RCC mandates long-term renal surveillance. Renal tumours that may develop include hybrid oncocytic tumours, chromophobe RCCs and clear cell RCCs.⁸ Early recognition of BHD syndrome and

subsequent regular interval imaging of the kidneys improves the likelihood of early RCC diagnosis and treatment should malignancy develop.

Here, we describe the case of a patient who presented with a spontaneous pneumothorax on a background of multiple lung cysts, in the absence of cutaneous fibrofolliculomas and renal tumours. Subsequent genetic testing confirmed a mutation in the FLCN gene.

CASE PRESENTATION

A Moroccan man in his 50s was admitted to hospital with acute dyspnoea and left-sided pleuritic chest pain. Other than a previous history of very briefly smoking cigarettes, he had no previous medical history. Initial blood test results were unremarkable. An ECG showed incidental left bundle branch block and an echocardiogram was normal. Chest X-ray revealed a large left pneumothorax, which was treated with an intercostal chest drain. High-resolution CT imaging (figure 1) demonstrated: the left pneumothorax; multiple cysts throughout both lungs, some of which were located subpleurally; and a 4.8 cm cyst in the right kidney.

DIFFERENTIAL DIAGNOSIS

Based on the radiographic appearances (figure 1), differential diagnoses included BHD syndrome, lymphangioliomyomatosis, Langerhans cell histiocytosis and lymphocytic interstitial pneumonia. However, he did not initially appear to have the classic phenotype of any of these conditions.

TREATMENT

After 9 days, following reinflation of the lung and cessation of the air leak, the chest drain was removed. A subsequent chest X-ray revealed recurrence of the left pneumothorax, necessitating reinsertion of an intercostal chest drain. The left lung failed to reinflate despite maintaining the chest drain on low vac wall suction for seven further days. The patient underwent video-assisted thoracoscopic apicectomy, multiple bullectomies, parietal pleurectomy and diaphragmatic basal mechanical abrasion. Histology revealed multiple bullae and blebs but no evidence of atypia or malignancy. He recovered well and was discharged from hospital.



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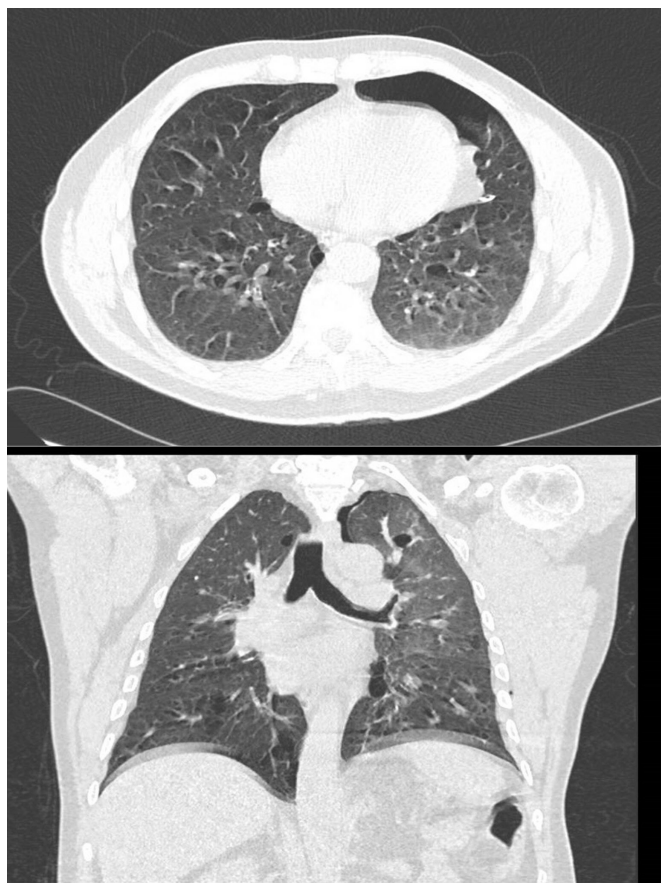


Figure 1 Axial (top) and coronal (bottom) views of HR CT chest scan demonstrating a left pneumothorax and widespread pulmonary cysts.

OUTCOME AND FOLLOW-UP

The patient was reviewed in the pleural disease clinic following discharge from hospital. There was no personal history of skin lesions, malignancy or breathlessness on exertion. There was no known family history of pneumothoraces, renal cancer or facial papules. Tests for antinuclear antibody and HIV infection were negative. An ultrasound scan of the kidneys confirmed the presence of an avascular cortical cyst in the right kidney measuring 48×50×48 mm. Subsequent blood sent for genetic analysis identified the heterozygous variant c.1176+1dupG at a splice donor site of the folliculin *FLCN* gene, thus confirming BHD syndrome.

Arrangements were made for renal surveillance imaging, long-term pleural disease clinic outpatient follow-up and genetic counselling of first-degree relatives (the outcome of which is currently unknown). Eighteen months following his initial presentation to hospital, the patient remains well with no pneumothorax recurrence.

DISCUSSION

The prevalence of pneumothoraces among BHD patients ranges between 24% and 38%.⁹ *FLCN* mutations resulting in a primary spontaneous pneumothorax in the absence of skin lesions and renal pathology have previously been reported in the literature. In an American study of 12 families where there were at least two first-degree relatives who had experienced a spontaneous pneumothorax, members of two families demonstrated mutations in the *FLCN* gene; but none of the affected family members exhibited cutaneous manifestations of BHD syndrome

or renal tumours.¹⁰ A Finnish study of a large family in which several members had experienced one or more primary spontaneous pneumothoraces demonstrated a deletion mutation in the *FLCN* gene in all affected family members; no skin or renal involvement was identified in any cases.¹¹ Additionally, a Chinese study has identified multiple novel mutations in the *FLCN* gene among patients with both sporadic and familial isolated primary spontaneous pneumothoraces.¹² While clinical scoring systems have been developed to attempt to predict which patients presenting with primary spontaneous pneumothoraces may have BHD syndrome, these currently require clinical validation and further study.¹³

Although the pulmonary cysts in our patient were located throughout both lungs, pulmonary cysts in BHD syndrome typically exhibit a basal distribution, with cysts frequently seen in the lower medial and subpleural regions of the lung.^{4 14 15} Identifying the radiological distribution and characteristics of pulmonary cysts can help to differentiate between the various causes of cystic lung disease. Cysts in lymphangioleiomyomatosis are regular and distributed diffusely; cysts in Langerhans cell histiocytosis are irregular and tend to be in the upper zones; and cysts in lymphocytic interstitial pneumonia are diffusely distributed in the lower lobes.¹⁵

Long-term renal surveillance in BHD patients is essential to detect renal malignancies that may arise. Although our patient initially underwent an ultrasound scan of the renal tract to screen for renal pathology, it has been suggested that ultrasonography may miss small or isoechoic lesions associated with BHD syndrome and that abdominal CT or MRI using intravenous contrast would be the preferred imaging modalities to detect BHD-associated renal lesions.^{16 17} As renal cancer in BHD syndrome usually occurs between the ages of 25 and 75 years, surveillance from the age of 20 years has been advocated.¹⁸ There is no consensus on the frequency of renal imaging; it has been suggested that interval scans should take place every 2 years if no tumours are seen, but more frequently if small tumours are identified.⁵

Learning points

- ▶ Birt-Hogg-Dubé (BHD) syndrome may initially present exclusively with pulmonary involvement and without the classical dermatological or renal pathology that is typically seen in the condition.
- ▶ The presence of widespread pulmonary cysts of unclear aetiology, or the occurrence of a spontaneous pneumothorax in the context of cystic lung disease, should prompt genetic testing for an underlying inherited cause.
- ▶ The distribution and characteristics of pulmonary cysts may provide a clue as to their underlying aetiology; cysts in BHD syndrome are typically basally distributed and they are frequently seen in the lower medial and subpleural regions of the lung.
- ▶ Long-term renal surveillance of BHD patients should be undertaken by abdominal CT or MRI using intravenous contrast, as ultrasonography may miss small or isoechoic renal lesions; there is currently no consensus on the time interval between scans.
- ▶ The potential risk of BHD syndrome in relatives of affected individuals should be assessed in the clinical history and genetic testing should be offered to first-degree relatives.

Our patient did not have any family history suggestive of BHD syndrome. It is important to assess the potential risk of BHD syndrome affecting first-degree relatives of BHD patients. Given the phenotypic variability of the condition among affected family members, it should be remembered that relatives may present with just one or any combination of the pulmonary, cutaneous or renal manifestations of the disease.¹⁹

Our patient did not have the classical skin lesions associated with BHD and had only a single, simple renal cyst. This case therefore highlights the importance of considering a broad differential diagnosis for the cause of a spontaneous pneumothorax in the presence of unexplained cystic lung disease and emphasises the value of maintaining a high index of clinical suspicion for inherited causes of pneumothoraces.

Contributors KK and CR were both directly involved in the clinical care of the described case. KK and CR both planned the format of the article. KK drafted the initial manuscript. CR critically revised the manuscript for content. KK and CR both approved the version of the manuscript that was submitted for publication.

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