Case report

Recurrent spontaneous pneumothoraces and bullous emphysema. A novel mutation causing Birt-Hogg-Dube syndrome

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ABSTRACT

Birt-Hogg-Dube syndrome (BHDS) is a rare form of classically cystic lung disease that may present with spontaneous pneumothorax. The associated skin manifestations (fibrofolliculomas) are not always present. This article describes a case of spontaneous pneumothorax secondary to bullous emphysema in an otherwise healthy gentleman caused by a novel mutation in the folliculin (FLCN) gene.

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1. Case presentation

In November 2012, a 46 year old man was referred for assessment of spontaneous pneumothoraces pending an upcoming bullectomy by thoracic surgery. This gentleman had a past medical history of recurrent pneumothoraces, asthma diagnosed in childhood, eczema, depression and anxiety. His only current medication was duloxetine 30mg daily. His pneumothoraces began 24 years ago, the first of which was a tension pneumothorax he developed after contact in a rugby game at the age of 22. He has had 7 spontaneous pneumothoraces in total, 3 of which were treated with a chest tube. He underwent a right bullectomy in 1996 and, after being assessed in our clinic, proceeded with left bullectomy with subtotal parietal pleurectomy later in November 2012. At time of assessment, he was asymptomatic. He had no cough, dyspnea, chest pain, or exercise limitations.

He is a lifelong non-smoker and has no work place or hobby exposures. His family history is positive for a mother with colon cancer diagnosed at the age of 45 and a sister with spontaneous pneumothoraces. There was no history of renal neoplasms in the family.

His physical exam was normal with no evidence of skin lesions, abdominal masses, or hypertension.

Pulmonary investigations included pulmonary function tests (PFTs), thoracic computed tomography (CT), and surgical lung biopsy. PFTs demonstrated a total lung capacity of 6.65 L (93% predicted), a reduced forced vital capacity (FVC) of 3.44 L (68% of predicted [normal >80%]), and a reduced forced expiratory volume in 1s (FEV1) of 1.96 L (49% of predicted [normal >80%]); there was evidence of airflow obstruction, with a FEV1/FVC ratio of 57% (normal >70%). Post bronchodilator, his FEV1 improved to 2.70 L (67% predicted) which is a 38% improvement. His diffusing capacity for carbon monoxide (DLCO) was normal at 74% predicted.

A CT scan showed multiple, bilateral cysts in varying sizes and shapes with the largest measuring 10 cm within the left lower lobe (Fig. 1). With regards to craniocaudal distribution, there was a basal predominance. With regards to axial distribution, the cysts were diffuse with no central or peripheral predominance. The cysts demonstrated variable morphology with many of the larger subpleural cysts within the lower lobes demonstrating lobulated, septated appearance. Intervening parenchyma appeared unremarkable without nodules, ground glass, septal thickening or honeycombing.

The patient was diagnosed with asthma and started on budesonide/formoterol fumarate turbuhaler 200/6 mcg 2 inhalations twice daily, sent for asthma education, and referred to a Geneticist. The patient was counselled that his uncontrolled asthma may be contributing to bullae enlarging and risk of spontaneous pneumothorax. Pathological samples of lung tissue obtained during his left bullectomy showed benign lung parenchyma with subpleural...
bulla and benign pleural tissue with evidence of chronic inflammation. No cystic lesions were identified despite two large samples being obtained from the left upper and lower lobes.

Based on the clinical presentation, family history, and CT results, the patient’s diagnosis was most compatible with Birt-Hogg-Dube syndrome (BHDS) syndrome. Genetic testing revealed a deleterious mutation (c.1219delA) in his folliculin (FLCN) gene. He has had no post-surgical complications and abdominal CT showed normal sized kidneys with no renal lesions. His immediate family members were referred to a Geneticist for consideration of screening.

2. Discussion

BHDS is a rare autosomal dominant genodermatosis that described in 1977 as the triad of multifocal kidney cancer, pulmonary cysts, and fibrofolliculomas by three Canadian physicians [1]. While the fibrofolliculomas are classical of BHDS, only two thirds of BHDS patients will develop these lesions [2]. Lung involvement is seen in 80% of BHDS patients and spontaneous pneumothorax is the presenting feature in 25% of patients [3]. Renal cancer has variable penetrance in BHDS with 30% of patients developing solitary or multi-focal lesions [4]. Although not classically described in the triad, the original case reports of a BHDS like syndrome included generalized fibrofolliculomas and colonic polyps [5,6] and one case series found an incidence of colonic lesions (polyps or CI cancer) in 30% of BHDS patients [2].

The radiological lung findings in classical BHDS vary in severity but, if present, may show lentiform-shaped cysts that predominate in the lung bases and periphery and abut or include the proximal portions of the lower lobe pulmonary arteries and veins [7,8]. In the absence of extra-pulmonary manifestations that may help confirm BHDS, the lower zone location of cysts abutting vessels, lentiform cysts with or without septae, and absence of emphysema strongly suggest BHDS [7]. A family history of spontaneous pneumothorax should also raise strong suspicion for BHDS among the other causes of familial spontaneous pneumothorax which include Marfan syndrome, Homocystinuria, Ehlers-Danlos syndrome, and α1-Antitrypsin deficiency [9]. This patient had multiple large bullae with septae in addition to smaller, more typical, cysts and we hypothesized that his untreated airflow obstruction from asthma predisposed bullae formation. Regardless of etiology, the pleuropulmonary pathology of multiple pleural blebs and large subpleural bullae with pleural changes consistent with pneumothorax has been described [10] and, while not specific, these changes are rare in the absence of emphysematous changes outside of BHDS.

Molecular genetic testing for BHDS is the gold standard and can detect 88% of the mutations thought to cause BHDS [11]. Genetic testing to confirm the disease should be considered, even in highly suspicious cases, unless the patient has the other major criteria for diagnosis of BHDS (at least 5 adult onset fibrofolliculomas) [12]. In addition, The European BHDS Consortium suggests it is reasonable to order genetic testing on any patients with characteristic skin lesions, cystic lung disease of no apparent cause, spontaneous pneumothorax, early onset renal cancer, or a first degree relative with any of the prior features. A clinical diagnosis of BHDS can be made if a patient fulfills 1 major or 2 minor criteria from Table 1.
Table 1
Criteria to diagnose BHDS [12].

| Major criteria |
|----------------|
| At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset |
| Pathologic FLCN germline mutation |
| Minor Criteria |
| Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous pneumothorax |
| Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology |
| A first degree relative with BHDS |

A clinical diagnosis can be made of BHDS if a patient fulfills 1 major or 2 minor criteria.

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3. Conclusion

The present report described an unusual cause of spontaneous pneumothorax in the setting of bullous lung disease caused by BHDS and reports a novel mutation in the FLCN gene causing this clinical syndrome. We recommend genetic testing for BHDS in any patient with unexplained lower lobe bullous lung disease even in the absence of cystic lesions on pathological specimen.

Written informed consent was provided by the patient to submit this manuscript and can be provided at the editor's request.

Conflict of interest

None. The authors have no conflicts of interest to declare.