Birt-Hogg-Dubé syndrome: Report of a new mutation

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Birt-Hogg-Dubé syndrome is an autosomal dominant genodermatosis caused by germline mutations in the folliculin gene and characterized by facial papules, pulmonary cysts, kidney tumours and recurrent pneumothoraces. Several distinct mutations in the folliculin gene resulting in a truncated protein have been described. The present report describes a new mutation, which has not been reported in individuals with Birt-Hogg-Dubé syndrome but is of a type predicted to cause disease.

Key Words: *Fibrofolliculoma; Folliculin; Pneumothorax; Pulmonary cysts; Renal tumour*

Learning objectives

- Recognize different underlying familial causes of spontaneous pneumothorax.
- Understand the genetic basis of Birt-Hogg-Dubé syndrome.
- Comprehend the screening strategies in Birt-Hogg-Dubé syndrome.

Pre-test

- What are the clinical features of Birt-Hogg-Dubé syndrome?
- Give a differential diagnosis of familial syndromes of pneumothorax.

CASE PRESENTATION

A 47 year-old woman of French and Italian descent presented to the emergency room with increasing shortness of breath on exertion of a few days duration. She denied any chest pain, cough, fevers, orthopnea or paroxysmal nocturnal dyspnea. The patient weighed 121.5 kg. Her height was 165 cm and her blood pressure was 126/88 mmHg. Multiple pale yellow-white dome-shaped nodules were seen on her face, neck and upper trunk (Figure 1). She was tachypneic. Examination of her chest revealed hyper-resonance and reduced breath sounds over the right lung. No crackles or wheezes were audible. The trachea was deviated to the left. An x-ray of the chest showed a large right pneumothorax, complete collapse of the right lung and mediastinal shift to the left. The remainder of the physical examination was unremarkable. A Heimlich valve was placed, resulting in complete expansion of her right lung.

The patient's medical history was significant for recurrent pneumothoraces. She experienced her first pneumothorax on the right side at 41 years of age, which was treated with percutaneous drainage. Six years later, she experienced two additional pneumothoraces involving the right lung, which were treated with percutaneous drainage and placement of a Heimlich valve. A previously performed computed tomography (CT) scan of the chest revealed multiple thin-walled cysts in both lungs and a cyst along the pleural surface of the right upper lobe (Figure 2). Fibrofolliculoma was diagnosed on the basis of a skin biopsy seven years previously. She was not a smoker.

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Le syndrome de Birt-Hogg-Dubé : rapport d'une nouvelle mutation

Le syndrome de Birt-Hogg-Dubé est une génodermatose autosomique dominante causée par des mutations des cellules germinales du gène de folliculine et caractérisée par des papules faciales, des kystes pulmonaires, des tumeurs rénales et des pneumothorax récurrents. Plusieurs mutations distinctes du gène de folliculine responsable de la troncation d'une protéine ont été décrites. Le présent rapport décrit une nouvelle mutation, qui n'a pas été signalée chez les personnes ayant le syndrome de Birt-Hogg-Dubé, mais qui est d'un type prédit comme responsable de la maladie.

Figure 1) Facial nodules (fibrofolliculomas)

Family history was significant for facial lesions and pulmonary cysts in her father and a paternal uncle, and recurrent pneumothoraces in a paternal aunt. Her sister was diagnosed with breast cancer at 44 years of age and passed away at 60 years of age. Four maternal aunts and her maternal grandmother also had breast cancer. One paternal aunt who had a history of recurrent pneumothoraces died of cancer of the adrenal gland, and a paternal uncle died of renal carcinoma. Her paternal grandmother had died of lung cancer.

A clinical diagnosis of Birt-Hogg-Dubé syndrome (BHDS) was made. Further investigations revealed a normal CT scan of the abdomen and pelvis. Pulmonary function tests demonstrated normal spirometry, lung volumes and diffusion capacity.

A right thoracotomy was performed with wedge resection of three blebs and pleurectomy. Microscopic examination of the surgical specimen showed neutrophilic infiltration of the bleb walls. The pleural specimen also showed focal active inflammation.

Sequencing analysis of the folliculin (*FLCN*) gene identified one copy of a c.1117C→T (p. Q373X) nonsense mutation.

DISCUSSION

BHDS is an autosomal dominant genodermatosis caused by germline mutations in the *FLCN* gene and characterized by facial papules,

Figure 2 Computed tomography scan demonstrating multiple cysts in both lung fields

pulmonary cysts, kidney tumours and recurrent pneumothoraces. The genetic defect responsible has been mapped to a gene on chromosome 17p11.2, which encodes a tumour suppressor protein, folliculin (FLCN) (1). Folliculin is a protein expressed in a wide variety of tissues including skin, type-1 pneumocytes of the lungs and the distal nephron of the kidneys (2). Reduced expression of FLCN has been seen in renal tumours from patients with BHD.

The skin lesions, which are fibrofolliculomas, trichodiscomas and acrochordons, typically appear as firm, yellow-white, dome-shaped papules during the third and fourth decades of life. They appear predominantly on the face, scalp, neck and upper chest.

Most patients with BHD have radiological evidence of pulmonary cysts and/or bullae. In the largest and most comprehensive study of individuals and families with BHD, 89% of patients had multiple pulmonary cysts (3). BHD patients have a 32-fold greater risk of spontaneous pneumothorax than an age-matched general population. Men and women are affected equally, and smoking does not seem to be a risk factor for spontaneous pneumothorax. Spontaneous pneumothorax may be the first presentation of BHD. It may also be the only manifestation of BHD in some patients.

Renal tumours are found in 15% of the patients, and may be clear cell carcinoma, papillary renal cell carcinoma, oncocytomas, chromophobe renal cell carcinoma or hybrid oncocytic/chromophobe tumours (4). BHD confers a seven-fold increased risk of developing renal neoplasia.

Colon and breast cancers might also be rare components of the spectrum of tumours associated with BHD (5). The presence of colon cancer and colonic polyposis has been reported in several families with BHD. However, an epidemiological study (6) showed no association between BHD and colon cancer or polyps. More recently, colorectal polyps were identified in 50% of BHD patients analyzed (7).

BHD should be differentiated from other syndromes in which cystic lung disease and pneumothorax are features. These include Marfan's syndrome, homocystinuria, Ehlers-Danlos syndrome type IV, Langerhans' cell granulomatosis (LCG), tuberous sclerosis complex (TSC) and lymphangioleiomyomatosis. TSC may sometimes be difficult to distinguish from BHD. Renal angiomyolipomas, epithelial cysts, polycystic kidney disease and renal-cell carcinomas may develop in patients with TSC. Cysts in BHD, LCG and lymphangioleiomyomatosis are all thin walled. They are found in all lung zones in

lymphangioleiomyomatosis and TSC, and have a basal and subpleural prominence in BHD, and are found in the upper and middle zones with sparing of costophrenic recesses in LCG (8).

More than 40 mutations in the *FLCN* gene in 200 families with BHD have been reported worldwide (9). Eighty-four per cent of the families with BHD have a germline *FLCN* mutation (10). Most of these mutations are frame-shift or nonsense mutations that lead to protein truncation (11).

Molecular analysis of the *FLCN* gene was performed in our patient. Sequence analysis of the entire coding region of the *FLCN* gene identified one copy of a c.1117C→T (p.Q373X) nonsense mutation in exon 10. The c.1117C→T mutation is predicted to result in the replacement of the codon for the amino acid glutamine with a premature translation stop at codon 373 (p.Q373X). This mutation has not been reported in individuals with BHD but is of a type predicted to cause disease.

The treatment of spontaneous pneumothorax in BHD is the same as for any patient with spontaneous pneumothorax. Given the high recurrence of pneumothorax, surgical intervention with resection and pleurodesis would be an acceptable option even in patients with a first episode of pneumothorax.

Patients should be cautioned about the increased risk of pneumothorax with scuba diving and air travel due to ambient pressure effects. Screening for renal tumours and careful follow-up should be performed. An estimated 25% of *FLCN* mutation carriers older than 20 years of age do not manifest skin lesions, and underlying *FLCN* mutations have been detected in families with apparently nonsyndromic pneumothoraces. Therefore, patients with familial pneumothorax without skin lesions or other evidence of BHD should undergo CT scan of the lungs and testing for *FLCN* gene mutations if multiple cysts are found in the basal lung regions (11). Annual mammography for breast cancer screening is recommended. Ophthalmological and dermatological assessment and follow-up should be arranged for ocular and cutaneous melanoma screening. A susceptibility to colonic polyps and colon cancer should be taken into account in the clinical follow-up. Family members should also receive genetic counselling.

Post-test

1. BHD is characterized by facial papules, pulmonary cysts, kidney tumours and recurrent pneumothoraces. The skin lesions, which are fibrofolliculomas, trichodiscomas and acrochordons, typically appear as firm, yellow-white dome-shaped papules predominantly on the face, scalp, neck and upper chest. Most patients with BHD have radiological evidence of pulmonary cysts and/or bullae. BHD patients have a 32-fold greater risk of spontaneous pneumothorax than the age-matched general population. Spontaneous pneumothorax may be the first presentation of BHD. It may also be the only manifestation of BHD in some patients. Renal tumours are found in 15% of the patients and may be clear cell carcinoma, papillary renal cell carcinoma, oncocytomas, chromophobe renal cell carcinoma and hybrid oncocytic/chromophobe tumors. BHD confers a seven-fold increased risk of developing renal neoplasia.
2. BHD should be differentiated from other syndromes of which cystic disease and pneumothorax are features. These include Marfan's syndrome, homocystinuria, Ehlers-Danlos syndrome type IV, LCG, TSC and lymphangioleiomyomatosis. TSC may sometimes be difficult to distinguish from BHD. Renal angiomyolipomas, epithelial cysts, polycystic kidney disease, and renal-cell carcinomas may develop in patients with TSC. Cysts in BHD, LCG and lymphangioleiomyomatosis are all thin walled. They are found in all lung zones in lymphangioleiomyomatosis and TSC, have a basal and subpleural prominence in BHD and are found in upper and middle zones with sparing of costophrenic recesses in LCG.

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