



Cystic lung disease in Birt-Hogg-Dubé syndrome. A case series

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ABSTRACT

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant inherited disease caused by mutations in the folliculin (FLCN) gene. It is characterized by lung cysts, skin fibrofolliculomas and an increased risk for the development of renal cancer, especially chromophobe. Lung cysts in the context of BHDS are typically lower lobe predominant, paramediastinal, in relation to the fissures and often elliptical shaped. Skin manifestations can easily go unnoticed. Respiratory physicians need to have a high degree of vigilance as they can be the first to suspect the disease in the setting of diffuse cystic lung disease. Meticulous skin examination and referral to a dermatologist is of utmost importance as it can establish the diagnosis in the least invasive way. Correct diagnosis is crucial as it may allow for genetic counseling to the affected family and the implementation of a monitoring strategy for early detection of renal cancer.

1. Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant inherited disease caused by mutations in the folliculin (FLCN) gene. Lung involvement is both frequent and characteristic of the disease. It is seen in up to 90% of patients. Typically, they are lower lung predominant and not as numerous as those seen in LAM or PLCH. They are of various sizes, can have an elliptical shape. The presence of lower lung predominant, paramediastinal, elliptical cysts in the absence of other radiological findings is considered quite characteristic of BHDS. Skin lesions are also frequent being present in approximately 90% of patients. They manifest as dome-shaped white papules and histologically they mainly correspond to fibrofolliculomas. In the presence of isolated diffuse cystic lung disease a meticulous clinical examination of the skin is of utmost importance. In this clinical scenario the histological confirmation of fibrofolliculomas secures the diagnosis of BHDS. Establishing the correct diagnosis has direct practical implications. Patients are informed about the possibility of pneumothorax and how to recognize it. Genetic counseling is offered to them and their family. Finally, they follow a lifelong surveillance program for early detection of renal neoplasms.

2. Case series

2.1. Case 1

A 64-year old man presented for evaluation of chronic shortness of breath associated with recurrent episodes of lower respiratory tract infections. He also reported two episodes of expectoration of frothy, bloody streaked sputum 3 days ago. He was a never smoker and worked as a constructor and welder. He denied having symptoms of dry eyes or dry mouth. There was a history of arterial hypertension, hypercholesterolemia and gastroesophageal reflux disease. His medication included nifedipine 5mg o.d., nebivolol 2.5mg o.d. and esomeprazole 40mg o.d. There was no family history of lung diseases.

On examination the patient was afebrile, with a heart rate of 63 beats/min, respiratory rate of 12 breaths/min, BP of 130/70 mm Hg and oxygen saturation of 97% on ambient air. Chest auscultation revealed expiratory wheezing. There were also multiple whitish papules in the face, nose and retroauricular area (Fig. 1). According to the patient they were attributed to his welding history and were considered a manifestation of allergic/photosensitive dermatitis. The rest of the physical examination was normal.

Complete blood count (CBC) revealed a mild increase in eosinophils ($420/\text{mm}^3$). Rest of CBC and metabolic panel were within normal limits. Pulmonary function test revealed an obstructive pattern with significant bronchodilator reversibility: FEV1/FVC ratio was of 69%. FEV1 pre

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bronchodilation was 2.82 lt (81% predicted), FVC was 4.09 lt (100% predicted) and FEV1 post bronchodilation was 3.28 lt (+460ml, +16.3%). DLco and TLC were within normal limits, 88% and 94% predicted respectively. Chest X-Ray was reported as normal but because of the history of hemoptysis multidetector Computed Tomography (MDCT) of the thorax was performed. It revealed multiple lung cysts with lower lung predominance. Some cysts appeared to be septated, elliptical and the majority of them were located in the subpleural and paramediastinal region (Fig. 2). Due to the reported hemoptysis bronchoscopy with BAL was performed. Airways were patent and there were no signs of active or recent hemorrhage. BAL revealed 74% macrophages, 21% lymphocytes, 1% eosinophils and 4% neutrophils. Cultures were negative for common pathogens, fungi, Mycobacterium Tuberculosis and Nontuberculous Mycobacteria.

The combination of isolated diffuse cystic lung disease (with the aforementioned morphological and distribution characteristics) and skin findings raised suspicion of BHDS. Biopsy of the skin lesions revealed follicular epithelium proliferation surrounded by perifollicular fibrous sheaths, diagnostic of fibrofolliculomas (Fig. 3). Thus, the diagnosis of BHDS was established.

2.2. Case 2

A 55-year old man presented for evaluation of abnormal findings on his thorax CT. The latter was performed for investigation of chronic cough. He was an ex-smoker (quitted 7 months ago) with a total of 45 pack years. He denied xerostomia or xerophthalmia. He reported a history of arterial hypertension under treatment with irbesartan 150 mg o.d. There was no family history of lung or kidney diseases.

On examination the patient was afebrile, with a heart rate of 76 beats/min, respiratory rate of 14 breaths/min, BP of 110/60 mm Hg and oxygen saturation of 98% on ambient air. Chest auscultation was clear. There were limited white dome shaped papules on the forehead and the temporal region of the face (Fig. 4). The patient never conceived the presence of these “white spots” as a sign of skin disorder. Complete blood count (CBC) revealed and metabolic panel were within normal

limits. Pulmonary function test was normal: FEV1/FVC ratio was of 77%, FEV1 was 85% predicted, FVC was 88% predicted, DLco was 73% predicted and TLC was 91% predicted.

Thorax MDCT revealed multiple thin wall cysts, some of which were bilobated and in relation to the fissures (Fig. 5). Skin biopsy revealed fibrofolliculomas and the diagnosis of BHDS was made.

3. Discussion

BHDS is a rare autosomal dominant inherited disease caused by mutations in the folliculin (FLCN) gene that is located on chromosome 17p11.2 [1]. It is considered a tumor suppression gene that encodes folliculin. Although the function of folliculin is largely unknown, there is increasing evidence that it acts as a tumor suppressor by controlling the interactions between the folliculin-interacting proteins 1 and 2 (FNIP1, 2) and the mTOR signaling pathway [2,3]. There is no gender predilection. Diagnosis is usually made during the third or fourth decade; however a wide age range has been reported (20–85 years). Clinically BHDS is characterized by the presence of skin hamartomas (mainly fibrofolliculomas), lung cysts with episodes of spontaneous pneumothorax and a high risk of renal epithelial neoplasms, especially chromophobe renal cell carcinomas [3].

Lung involvement is quite frequent in patient with BHDS as it is seen in almost 90% of patients. It consists of pulmonary cysts with normal intervening parenchyma. Given the fact that patients with BHDS rarely present with respiratory symptoms (with the exception of pneumothorax) accurate description of radiologic findings is very important. BHDS is part of the differential diagnosis of cystic lung diseases that include Pulmonary Langerhans Cell Histiocytosis (PLCH), Lymphangioleiomyomatosis (LAM), Lymphocytic Interstitial Pneumonia (LIP), Light Chain Deposition Disease (LCDD), amyloidosis, cystic metastatic disease, and neurofibromatosis type 1 [4]. The location of lung cysts in BHDS is strikingly different from the apical location seen in PLCH or emphysema or the diffuse distribution in LAM [5]. Typically, they are lower lung predominant and can be erroneously characterized as bullae or blebs. Usually, lung cysts in BHDS are not as numerous as

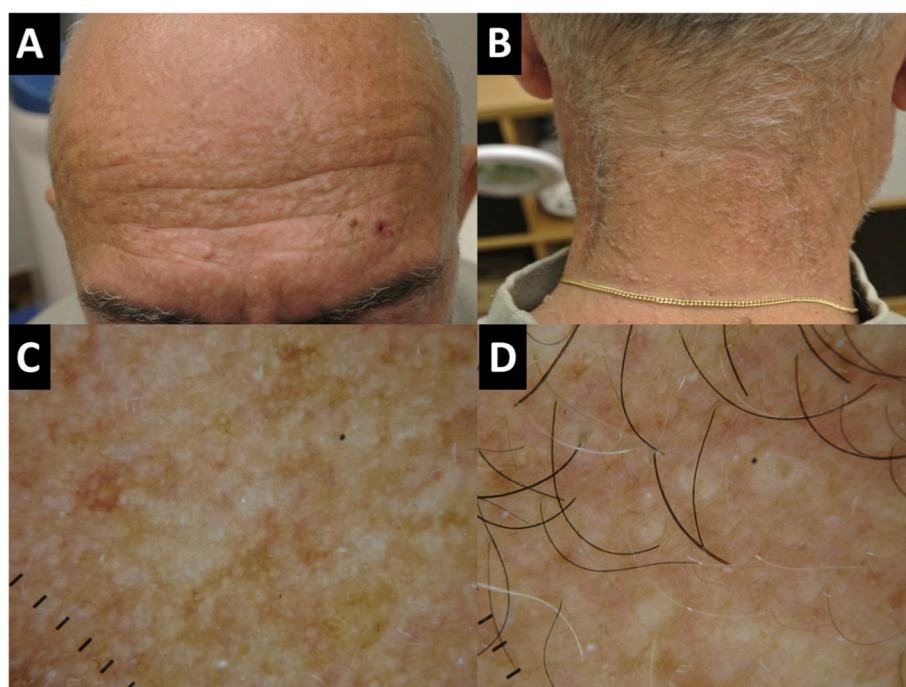


Fig. 1. White dome-shaped papules (A–B). Dermatoscopically the lesions show a structure-less pale white coloration, roundish contour and well-demarcated borders. Clues of chronically sun-exposed skin such as solar lentigos (brown spots) can also be detected at the peri-lesional skin (C–D). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

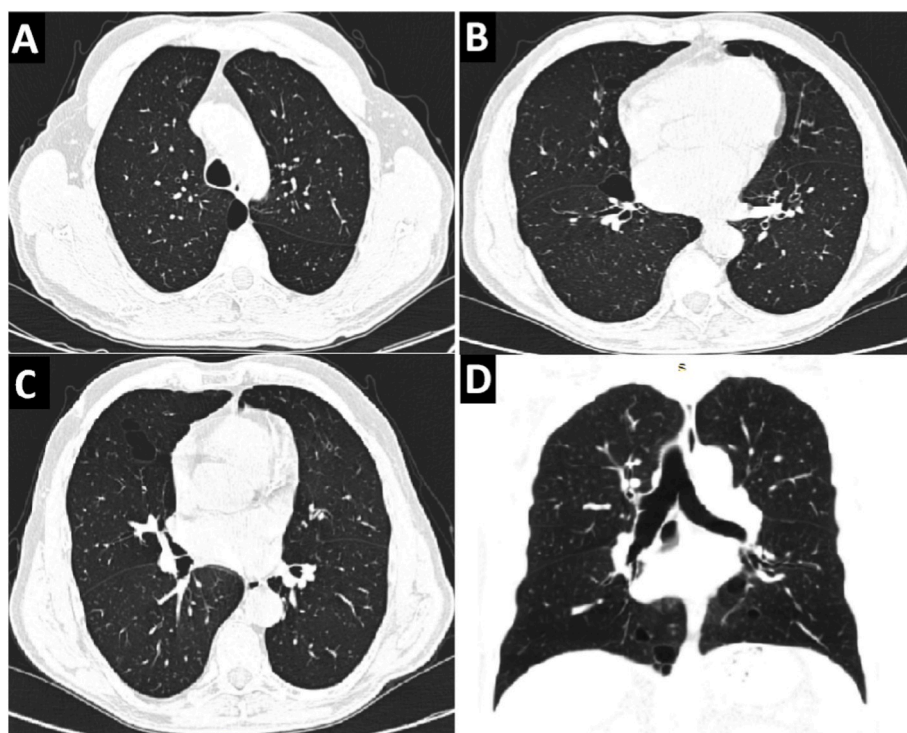


Fig. 2. Multiple bilateral cysts are noted with normal intervening parenchyma. Some of the cysts are paramediastinal and in relation to the fissures with an elliptical shape (A–B). An elliptical bilobated cyst is noted in the right middle lobe (C). The cysts are predominantly located in the lower lobes (D).

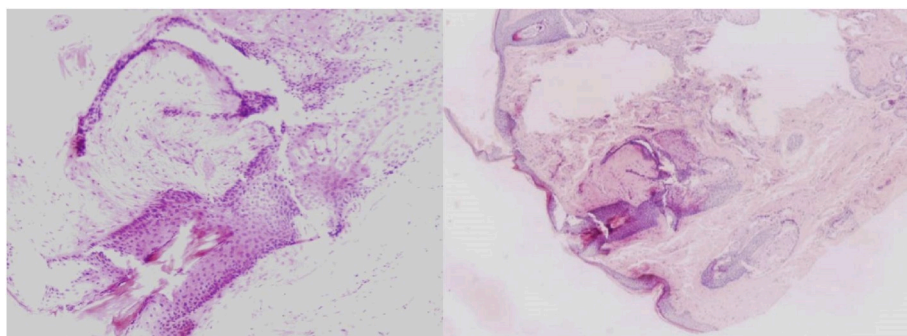


Fig. 3. Proliferation of follicular epithelium surrounded by a perifollicular fibrous sheath.

those seen in LAM or PLCH; they are of various sizes, and can have an elliptical shape. The presence of lower lung predominant, paramediastinal, elliptical cysts in the absence of other radiological findings is considered quite characteristic of BHDS [5]. BHD patients have a 50-fold increased risk of spontaneous pneumothorax which is observed in about 40% of patients [6]. The maximum diameter of cysts is an independent risk factor for spontaneous pneumothorax [7]. A family history of spontaneous pneumothorax should raise suspicion of BHDS. On the other hand, the absence of such history should not by any means discourage from the diagnosis in the right clinical context.

Cutaneous lesions are also quite frequent being present in almost 90% of patients. They usually appear after the age of 20 years as dome shaped, white papules usually in the face, neck, retroauricular area and upper torso. Histologically, the vast majority of the skin lesions are fibrofolliculomas and infrequently trichodiscomas, and acrochordons [8,9]. In the appropriate clinico-radiological setting, the histological confirmation of fibrofolliculomas secures the diagnosis of BHDS [1,3]. Otherwise, diagnosis is confirmed with genetic testing positive for a germline *FLCN* mutation [3].

It is important to establish a correct diagnosis because patients with

BHDS have an increased risk (x7) of kidney tumors compared with the general population [10]. Histologically the most common subtypes are chromophobe and hybrid oncocytic/chromophobe tumors. However, other subtypes have been reported as well (e.g. clear cell and papillary carcinoma) [11]. BHD patients should follow a lifelong surveillance program [12]. Patients with BHDS might present with multiple recurrences of renal cancer, thus early diagnosis is also important to allow for nephron-sparing surgery. The main methods for surveillance are annual renal MRI or renal ultrasonography. Computed tomography is not recommended as it would result in an unacceptable radiation dose over the years. Renal ultrasonography has a smaller sensitivity for smaller renal lesions compared to MRI. Smoking cessation is of utmost importance as it can increase the risk of pneumothorax and renal cancer. Since *FLCN* seems to have tumor suppressor activity, high vigilance is required for early diagnosis of other tumors as well depending on relevant symptoms.

In conclusion BHDS is a rare autosomal dominant inherited disease caused by mutations in the folliculin (*FLCN*) gene. Clinically it is characterized by the presence of skin fibrofolliculomas, lung cysts, history of familial pneumothorax and a high risk of renal epithelial neoplasms,

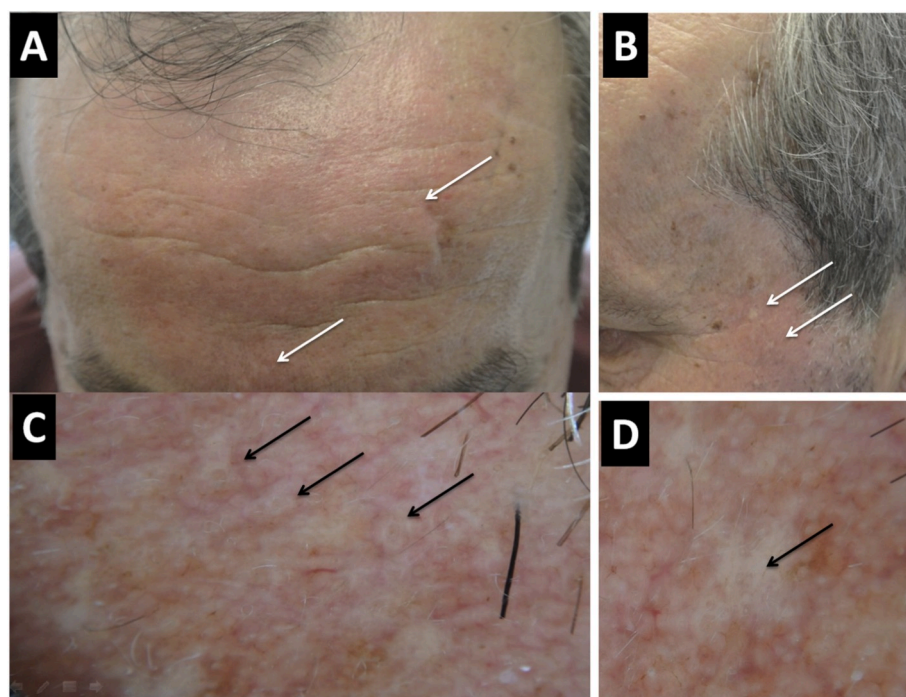


Fig. 4. A few numbers of white, dome-shaped papules on the frontal and lateral face are noted (white arrows) (A–B). Dermatoscopic examination reveals lesions with pale white areas and a hint of circular structures correlating with follicular openings (black arrows). Dermatoscopy was very helpful both in terms of diagnosis and as a guide for the selection of the precise site of skin biopsy (C–D).

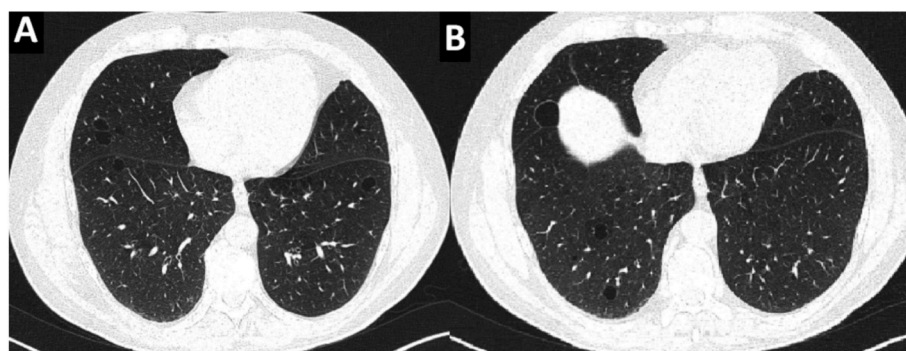


Fig. 5. Multiple bilateral cysts are noted with normal intervening parenchyma. A bilobated cyst is noted (A). A cyst in the right middle lobe is in relation to the major fissure (B).

especially chromophobe renal cell carcinomas. BHDS should be included in the differential diagnosis of isolated cystic lung diseases. Lung cysts in BHDS are usually of various sizes, have elliptical form and are mainly located in the lower, subpleural and paramediastinal regions. The absence of a history of familial or recurrent pneumothorax should not discourage from the diagnosis. Correct diagnosis is essential as it leads to lifelong surveillance for early detection of renal cancer and genetic counseling to the affected family.

Declaration of competing interest

All authors have no conflicts of interest to disclose.

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