Birt–Hogg–Dubé – a rare case of cystic lung disease

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Abstract

The differential diagnosis of cystic lung disease in adults includes inherited genetic syndromes and several acquired conditions. Birt–Hogg–Dubé syndrome (BHD) is a rare inherited cystic lung disease associated with an increased risk of renal cell carcinoma, pulmonary cysts, and spontaneous pneumothorax that is not typically included in the differential diagnosis. Early recognition of this potentially life threatening syndrome is important and may help prevent complications associated with this disease entity. The presence of spontaneous pneumothorax in this patient population is estimated at 30 %, and 12–34 % of patients with BHD are eventually diagnosed with renal cancer, usually by age 50 years.

Keywords: Cystic lung disease, Birt–Hogg–Dubé, spontaneous pneumothorax

Introduction

We describe a patient referred to the pulmonary service for progressive dyspnea on exertion. Her evaluation revealed fibrofolliculomas on her face and neck, pulmonary cysts on thoracic imaging, and FLCN genetic mutations on chromosome 17 with genetic testing. These results confirmed the diagnosis of Birt–Hogg–Dubé syndrome.

Case

A 60-year-old Caucasian woman with a past medical history of anxiety and hypertension was referred to the pulmonary service with a 24-month history of progressive exertional dyspnea. She was able to perform activities of daily living, could walk daily without significant limitations, but noted dyspnea walking up a flight of stairs or walking briskly. She had never smoked, denied second hand smoke exposure and occupational exposures, and had no history of asthma.

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Physical examination revealed BP 138/84 mmHg, BMI 22 kg/m^2, $Sp0_2$ 97% on room air, and pulse rate 73 bpm. Skin examination revealed multiple firm, non-tender, papules over the cheeks and nasolabial folds (Figure 1). Her lungs were clear to auscultation, and no dullness to percussion was noted. Cardiac

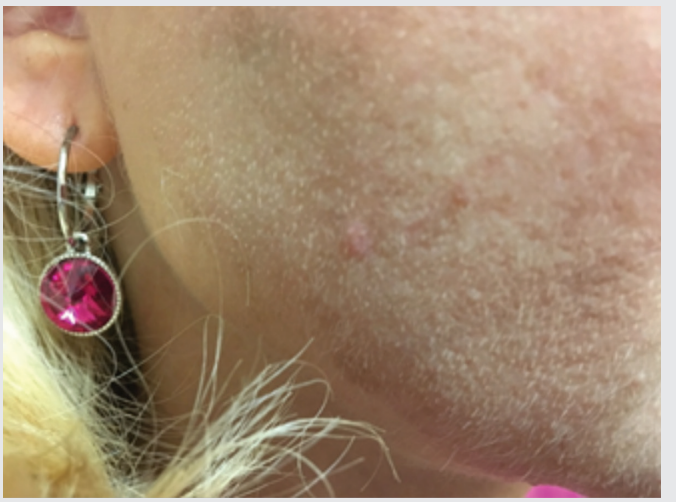

Figure 1. Multiple firm, non-tender, papules over the cheeks and nasolabial folds are seen on physical examination.

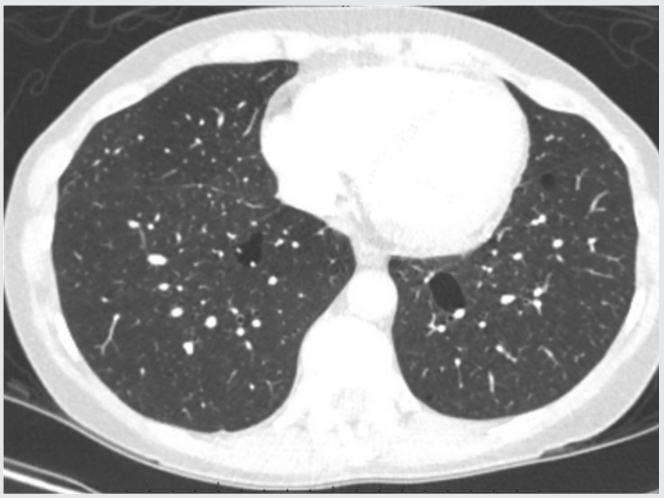

Figure 2. Computed tomography of thorax with contrast demonstrates cystic lesions of various sizes noted in both lung fields.

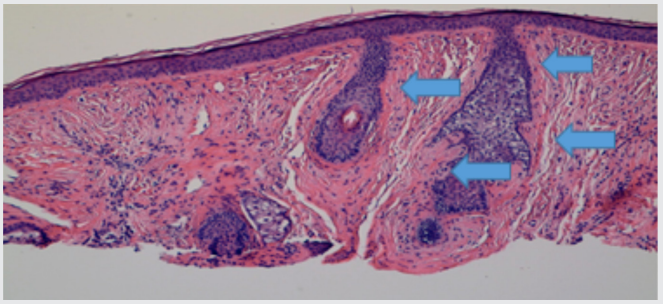

Figure 3. Histopathology of the skin lesion reveals proliferation of follicular epithelium surrounded by a perifollicular fibrous sheath consistent with a fibrofolliculoma. The blue arrows point to epithelial cells, and the stroma surrounding the epithelium is densely fibrous and sclerotic (hematoxylin-eosin, original magnification × 200).

auscultation revealed normal S1 and S2 heart sounds. Abdominal examination revealed no hepatosplenomegaly, and her extremities had no edema or clubbing.

Laboratory studies included hemoglobin 12.9 g/dL, serum creatinine 0.70 mg/dL, NT-pro BNP 147 pg/ml, and TSH 0.92 mIU/L. ECG was significant for normal sinus rhythm. Prior cardiac stress test was negative for inducible wall abnormality. A pulmonary function test revealed normal spirometry and lung volumes. Computed tomography of the thorax with contrast (Figure 2) demonstrated cystic lesions of various sizes in both lung fields.

Referral to the dermatology clinic was made to evaluate her skin lesions. Histopathology of the skin lesion revealed proliferation of follicular epithelium surrounded by a perifollicular fibrous sheath that was consistent with a fibrofolliculoma. Epithelial strands were composed of thin cords of epithelial cells and the stroma surrounding the epithelium was densely fibrous and sclerotic (Figure 3, hematoxylin-eosin, original magnification × 200). The patient was then referred to the medical center genetic counselor; she had blood tests that revealed a heterozygous profile for the folliculin gene (FLCN) that confirmed the diagnosis of Birt–Hogg–Dubé syndrome.

Discussion

Birt–Hogg–Dubé (BHD) syndrome was initially described in 1977 by a dermatologist (Burt), a pathologist (Hogg), and an internist (Dubé). It is a rare autosomal dominant disorder characterized by the development of hair follicle hamartomas (primarily affecting the face, neck, and upper trunk), pulmonary cysts that may give rise to a spontaneous pneumothorax, and renal cell carcinoma. Birt–Hogg–Dubé syndrome is caused by a loss of function mutation in the BHD gene, FLCN located on chromosome 17p11.2. The FLCN gene is thought to encode for folliculin a probable tumor suppressor protein resulting in dysregulation of mTOR signaling. The function of folliculin in maintenance of pulmonary structural integrity is not well established. Cystic lung lesions typically present in the fourth to fifth decade of life, and renal tumors can occur as early as young adulthood. The rate of progression of pulmonary disease in these patients is unknown; BHD does not usually result in respiratory failure.[3]

Pulmonary assessment is recommended for patients with BHD syndrome undergoing surgery, and excessive positive pressure ventilation should be avoided intraoperatively to avoid rupture of a pulmonary cyst and to

avoid pneumothoraces. Renal evaluation is particularly important for patients with BHD syndrome given the potential for multiple renal tumors and the risk of developing chronic renal failure following surgery. Lifelong surveillance for renal cancer is needed for patients with BHD. However, there is no clinical consensus on the optimal surveillance interval.

The prognosis of BHD depends primarily upon the penetrance of renal cancer and histologic type of renal cancer that develops. Deaths from renal cancer in BHD syndrome are uncommon, and the majority of cancer deaths are secondary to metastatic clear cell carcinoma. Asymptomatic family members should be counseled about the importance of screening and offered genetic testing.[5]

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