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Birt-Hogg-Dubé syndrome — an unique case series

Abstract

Birt-Hogg-Dubé syndrome (BHDS) is an uncommon autosomal dominant syndrome. It is also known as Hornstein–Knickenberg syndrome. It is an inherited disorder culminating in mutations in folliculin coding gene (FLCN). The clinical exhibitions of the syndrome are multi-systemic, comprising of a constellation of pulmonary, dermatologic and renal system manifestations. The most common presentations include fibrofolliculomas, renal cell carcinomas, lung cysts and spontaneous pneumothorax. The treatment is conservative with regular monitoring of the renal and lung parameters. Fibrofolliculomas may require surgical excision and recurrent events of pneumothorax may warrant pleurodesis. We reported a case series of 2 patients presenting with symptoms of progressive breathlessness along with dermatological manifestations and subsequently showing radiological manifestations of Birt-Hogg-Dubé syndrome in the form of lung cysts.

Key words: autosomal dominant, lung cysts, fibrofolliculomas, FLCN gene

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Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare, inherited syndrome involving skin, lungs and kidneys [1]. It is also known as Hornstein-Knickenberg syndrome. BHDS is an autosomal dominant monogenic disorder caused by constitutional mutation in the folliculin coding gene (FLCN) [2–4]. Folliculin coding gene is a tumor suppressor gene, and it codes for the protein folliculin. Dermatological manifestations include fibrofolliculomas, trichodiscomas, and acrochordons, which primarily occur in the face, neck, and on the upper torso [1, 5]. Lung cysts are the hallmark of the lung involvement, causing an increased risk of spontaneous pneumothorax [6–9]. Birt-Hogg-Dubé syndrome increases the risk of kidney lesions like cysts, benign tumors, and kidney cancer. Many different types of kidney tumor (histologies) have been seen in people with BHDS, with the most common forms being hybrid oncocyctic tumors (HOTs), chromophobe, and oncocytoma. The most severe manifestation of the syndrome is the predisposition to renal cell carcinoma (RCC) [8]. Birt-Hogg-Dubé syndrome is a rare disorder that affects males and

females equally. A diagnosis of BHDS is based upon a thorough clinical evaluation, a detailed patient history, and identification of characteristic manifestations (symptoms), including 2 or more fibrofolliculomas, history of spontaneous pneumothorax or bilateral, multiple chromophobe or hybrid oncocyctic renal tumors. We herein report 2 cases of BHDS who fulfilled the diagnostic criteria after a thorough clinical, radiological, histopathological and genetic evaluation.

Case 1

A 34-year-old lady hailing from Kolkata followed up to our outpatient department with chief complaints of predominantly dry cough and progressive breathlessness of 3 years duration, with a progression of her symptoms over the last 4 months. There was a history of infective exacerbations about 2 episodes per year, managed with symptomatic treatment. The general examination was suggestive of the presence of multiple skin tags in the right axilla. The respiratory system examination was within normal limit. Her chest X-ray was suggestive of right lower zone fibrocystic opacity. Her baseline blood investigations

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Figure 1. High resolution computed tomography of the thorax showing bilateral widespread lung cysts

were within normal limits and viral markers were negative. High-resolution computed tomography (HRCT) of the thorax was suggestive of the presence of bilateral widespread lung cysts, with imperceptible walls with lower zone predominance (Figure 1). Her spirometry was normal with ratio of forced expiratory volume at the end of first second (FEV_1) to forced vital capacity (FVC) being 77%. She was evaluated with skin biopsy of the axillary tag, which was suggestive of the presence of acrochordon (Figure 2). Ultrasonography of the abdomen was normal; magnetic resonance imaging (MRI) of the abdomen was suggestive of the presence of left-sided simple renal cyst (Figure 3). In view of the multisystemic involvement, a diagnosis of BHDs was suspected. Hence genetic analysis for the FLCN gene mutation was done, which was positive for the FLCN gene, showing germline mutation of cytosine residue at C₈ tract in exon 11. Hence in light of her clinico-radiological and genetic analysis, a diagnosis of BHDs was made and the patient was counseled accordingly. She was managed with pulmonary rehabilitation.

Case 2

A 61-year-old nonaddict man, with comorbidities in the form of ischemic heart disease and systemic hypertension, on medical management for the same presented with complaints of right-sided chest pain and exertional dyspnea of 10 months duration. On general examination, multiple skin tags were noted over bilateral axillary areas and on the neck. On examination of the respiratory system, his breath sounds were decreased in right inframammary, infraaxillary, lowerinterscapular and infrascapular areas. In

Figure 2. Histopathological skin biopsy image consistent with findings of acrochordon showing papillary dermis [H & E stain 10x power]

Figure 3. Magnetic resonance of the abdomen showing left-sided renal cyst

view of the above complaints, he was evaluated with chest X-ray suggestive of right-sided loculated pneumothorax. He was hospitalized on our side for a detailed evaluation. His baseline blood investigations were within normal limits and viral markers were negative. High-resolution computed tomography (HRCT) of the thorax was suggestive of bilateral diffuse thin-walled cysts of various

Figure 4. Computed tomography of the thorax showing right-sided loculated pneumothorax (lung window)

Figure 5. Skin tags in axillary area

size, predominantly in the upper lobe with partly loculated hydropneumothorax (Figure 4). Spirometry showed a restrictive abnormality with ratio of FEV_1/FVC being 72% and FVC of 52% predicted; two-dimensional echocardiography was suggestive of ischemic heart disease with concentric left ventricular hypertrophy showing increased global left ventricular wall thickness and pulmonary artery systolic pressure (PASP) by the tricuspid regurgitation (TR) velocity demonstrating normal findings. Dermatologist's opinion was taken for skin tags (Figure 5), which on skin biopsy was proven to be acrochordon. Hence on basis of clinico-radiological and skin biopsy reports, provisional diagnosis of Birt-Hogg-Dubé syndrome was made, and genetic analysis for the same was processed, the reports of which are awaited.

Discussion

Birt-Hogg-Dubé syndrome is a unique genetic condition, associated with multisystemic involvement in the form of benign skin lesions, lung cysts and an increased risk of benign kidney tumors. BHDS is a rare complex genetic skin disorder (genodermatosis), characterized by the development of skin papules generally located on the head, face and upper torso. These benign tumors (hamartomas) of the hair follicle are called fibrofolliculomas. Birt-Hogg-Dubé syndrome also predisposes individuals to the development of benign cysts in the lungs, repeated episodes of a collapsed lung (pneumothorax), and an increased risk for developing kidney neoplasia. It emanates from heterozygous loss-of-function mutations in the BHD tumor suppressor gene on chromosome 17p11.2, which encodes the novel protein folliculin. Fluorescent in situ hybridization of Birt-Hogg-Dubé mRNA has shown expression in many normal tissues, most commonly the skin and its appendages, the distal nephron of the kidney, stromal cells, and type 1 pneumocytes of the lung [1]. In 1977, Birt, Hogg, and Dubé reported a study of 70 members of three generations, 15 of whom exhibited multiple small skin-colored to grayish-white dome-shaped papules distributed over the face, neck, and the upper trunk. Histologic analysis revealed fibrofolliculomas, trichodiscomas, and acrochordons [2]. The triad of these lesions has been named “Birt-Hogg-Dubé syndrome”, which exhibits an autosomal-dominant trait pattern of inheritance. The folliculin gene locus is within chromosome 17p11.2, in an unstable genomic region, which is associated with a number of diseases [3, 4].

Both cases presented with pulmonary and dermatological manifestations of BHDS with initial symptoms of progressive dyspnea.

Skin manifestations

The skin manifestations are the most conspicuous and often presenting features of the syndrome. They occur in the form of skin fibrofolliculomas and less commonly, trichodiscomas and acrochordons [3, 5–7]. Papules, varying in number from a few to several hundred, with a histological diagnosis of fibrofolliculoma, are the hallmark of the syndrome [2, 3]. They are asymptomatic and develop during the third or fourth decade of life, increasing in number and size as patients grow older. Our both cases were showing the presence of acrochordons proven on

skin biopsy reports, the first case presented with skin tags on the right axilla, while the second one had it on bilateral axilla and the neck.

Renal manifestations

Along with skin manifestations, patients with BHDS also have renal system affection in the form of renal tumors [3, 5, 7–9], ranging from benign oncocytomas to malignant renal carcinomas. Familial kidney tumors have bilateral predilection and multifocal involvement and are usually asymptomatic in the initial stages. It is therefore recommended that affected patients and family members undergo abdominal computed tomography and renal sonography screening for renal cancer [5, 7–9]. Our first case also had a renal cyst detected on her MRI of the abdomen, although her ultrasound of the abdomen was normal. Other systemic conditions associated with BHDS include colonic polyposis and ophthalmologic disorders, such as progressive flecked chorioretinopathy and chorioretinal scars [4].

Pulmonary manifestations

The pulmonary involvement in BHDS generally occurs in the form of lung cysts of varying sizes and incidentally picked up episodes of pneumothorax. The presence of lung cysts in association with Birt-Hogg-Dubé syndrome was first described by Toro *et al.* [7] in 1999 in a study of 152 individuals from 49 families with familial renal neoplasms syndromes. Among these patients, three of the 13 who had BHDS exhibited pulmonary cysts, and one of these three patients developed pneumothorax [5]. A few additional cases of lung cysts and spontaneous pneumothorax have subsequently been reported in the literature [3, 4, 6, 8, 9]. Bullous emphysema has also been described [3, 4]. The increased frequency of reports on pulmonary cystic abnormalities in these patients strongly suggests that they are manifestations of BHDS rather than chance associations. The location and profusion of the cysts may vary in individual cases. Our first patient had multiple scattered bilateral cysts with a lower zone predominance, while the second one had scattered lung cysts with upper lobe predilection and an incidentally detected loculated pneumothorax too.

Differential diagnosis

Before making diagnosis of BHDS, it is necessary to rule out the following differential di-

agnosis like *PTEN* hamartoma tumor syndrome (PHTS), which is a spectrum of disorders caused by mutations of the *PTEN* gene characterized by multiple hamartomas that can affect various areas of the body, tuberous sclerosis complex, including skin and lung hamartomas and angiomyolipomas of the kidney (and rare renal neoplasia) that are similar to BHD. Other differential diagnoses to BHD are other cystic lung diseases, such as Langerhans' cell histiocytosis, lymphangioleiomyomatosis (LAM), or other diseases with a high risk of secondary spontaneous pneumothorax, i.e. Marfan syndrome, chronic obstructive lung disease or emphysema.

Diagnosis

Diagnosis of BHDS is based on a combination of genetic analysis and the systemic manifestations. Major and minor criteria have been defined for the diagnosis [10]. The two major criteria include the presence of fibrofolliculoma, trichodiscoma or acrochordon, confirmed histologically on at least 5 cervical or facial areas and the folliculin gene mutation on DNA analysis [11]. The minor criteria include multiple lung cysts localized in the basal regions of no other identified etiology, with or without an evidence of pneumothorax, a history of renal cancer or renal cysts and a diagnosis of BHD syndrome in the first degree relatives. Diagnosis is confirmed by the presence of one of major criteria or two of minor criteria. Our first patient was a genetically proven case while the second one also satisfied the other required criteria whilst awaiting the genetic mutation report.

Prognosis

Prognosis of Birt-Hogg-Dubé syndrome depends on associated comorbid factors, particularly the occurrence of renal cell carcinoma. It also depends on tumor histology, size, and metastatic spread. Of BHDS kidney cancers, 80–85% are slow growing with a low potential for metastasizing and a favorable prognosis. The typical dermatologic lesions are of benign etiology and could be relevant only from cosmetic concerns. Pulmonary component of the disease is not generally aggressive, and patients need to be kept under observation for the lung cysts and the occurrence of spontaneous pneumothorax. A thorough counseling should be done pertaining to the benign nature of these cysts to avoid unwarranted surgeries and interventions. Genetic

counselling is advocated, considering autosomal trait of the syndrome.

Treatment

In the literature, no specific treatment for BHD syndrome is mentioned. The fibrofolliculomas can be resected surgically if bothersome from cosmetic angle. In patient with BHD syndrome with renal cancer, total or partial nephrectomy may be required [12]. Pleurodesis that may be offered for recurrent episodes of pneumothorax, can be either chemical or mechanical. Pleurodesis works by symphysis between parietal and visceral pleura by administration of sclerosing agents or mechanical process causing secretion of various mediators — most commonly used is talc (*magnesium silicate*). Chemical pleurodesis can be performed during surgery or via a chest tube.

Follow-up

Patients are kept under a regular follow-up from the perspective of early detection of complications. The renal and pulmonary systems are followed on the basis of clinical symptoms and with regular follow-up with the help of CT of the thorax, ultrasound of the abdomen, or MRIs of the kidneys annually. As MRI harbours a lesser risk of radiation complication than CT scans and is more sensitive than ultrasounds, it is the preferred method for observation of the kidneys in the patient with BHD.

Conclusions

It is crucial to keep BHDS as a differential diagnosis while evaluating a patient with cystic lung disease; and the key to the diagnosis of this uncommon syndrome is a due index of suspicion and a multidisciplinary workup.

Conflict of interest

None declared.

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