Case Report

Birt–Hogg–Dubé syndrome presenting with bilateral pneumothorax, skin, kidney, liver, and brain lesions

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Abstract

Birt–Hogg–Dubé syndrome (BHDS) is a rare hereditary autosomal dominant condition characterized by benign cutaneous lesions, lung cysts, and increased risk of spontaneous pneumothorax and renal cancer. We report a case of a young Indian boy with bilateral pneumothorax as the first symptom of BHDS. Detailed history examination and investigation showed multiple facial lesions; his computerized tomography was suggestive of renal angiomyolipoma, hepatic angiomyolipoma, pulmonary cyst with pneumothorax, and small bilateral subependymal soft tissue density lesion with calcification in the brain, all of which were collectively suggestive of BHDS. Identification of the above commonly presented clinical features as a syndrome is important for even a primary care physician so as to ensure the timely management and if required referral to a higher center.

Keywords: Adenoma sebaceum, Birt–Hogg–Dubé syndrome, hepatic angiomyolipoma, pneumothorax, renal angiomyolipoma, renal cell carcinoma

Introduction

Birt–Hogg–Dubé syndrome (BHDS) is an autosomal dominant genodermatosis, which affects the skin, kidneys, and lungs, presenting as a triad of cancers. Confirmatory diagnosis involves genetic testing of the FLCN gene, coding for folliculin protein.[1,2] Renal neoplasms have significant histological variation and are bilateral and multi-focal. Oncocytic, chromophobic, or hybrid chromophobe-oncocytic tumors are the most common neoplasms.[3] Patients with BHDS have lung cysts, which are bilateral numerous, round or asymmetrical, are found in the lungs' basal regions, and present with spontaneous pneumothorax.[4] The median age of presentation is in the third decade of life.[2]

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Received: 02-09-2023 **Revised:** 10-01-2024
Accepted: 17-01-2024 **Published:** 24-05-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1451_23

Shortness of breath and chest pain are common presentations, with which patients present to primary care providers or family physicians. But having a high degree of suspicion is important to identify the larger syndrome in existence; hence, it becomes imperative for such physicians to look out for the other features, forming a part of syndromes like BHDS and tuberous sclerosis.

Case Presentation

A 16-year-old boy was admitted to the hospital with shortness of breath and pleuritic chest pain. Chest X-ray revealed left-side spontaneous pneumothorax, which was successfully treated with chest tube insertion [Figure 1]. A few days later, he again developed right-side pneumothorax; a chest computerized tomography (CT) was performed, showing bilateral cysts in the lungs primarily in the basal parts. Chest tube insertion was done. He also had complaints of pain in his abdomen for 3 days, which was insidious in onset and dull aching. The patient also complained of low-grade fever, which was on and

How to cite this article: Bajpai J, Roy S, Zanwar V, Kant S. Birt–Hogg–Dubé syndrome presenting with bilateral pneumothorax, skin, kidney, liver, and brain lesions. J Family Med Prim Care 2024;13:2164-7.

off in nature and which was relieved on medications for the same duration. There was no history of vomiting, constipation, loose motion, hematemesis, malena, hematochezia, hematuria or burning micturition, dysphagia, pain or lump in the abdomen, breathlessness, or dyspnea. He was not a known case of hypertension, diabetes mellitus, asthma, tuberculosis, or any other major illnesses.

The results of the various pathological tests are summarized in Table 1. All the viral markers were negative. Electrocardiography revealed normal results. A dermatology reference was taken for the multiple facial lesions. A diagnosis of adenoma sebaceum was established [Figure 2]. Following this, he was referred to the Urology department, where his examination was suggestive of a soft, ballotable 8 × 6 × 3 cm lump in the right lumbar region. Contrast-enhanced computerized tomography (CECT) of the abdomen and pelvis revealed a large heterogeneously enhancing cortical-based mass lesion with necrotic areas within, predominantly involving the mid and lower poles of the right kidney, measuring 9.6 × 7.9 × 13.4 cm. Multiple vascular channels were seen within the lesion. A large exophytic component was seen along the inferior and posterior aspects of the kidney. There was no infiltration into the vessels, but the vessels were engorged and tortuous. The lesion was seen extending into the perineal space but did not extend beyond the anterior and

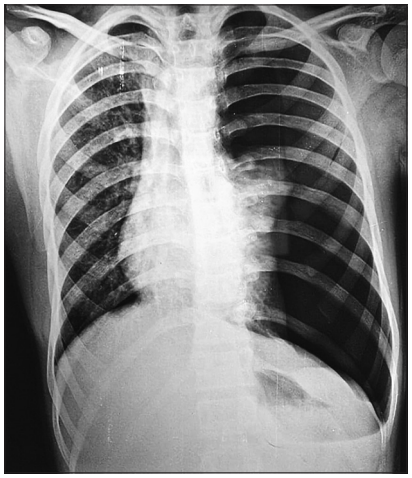

Figure 1: Chest X-Ray PA view showing left-sided pneumothorax

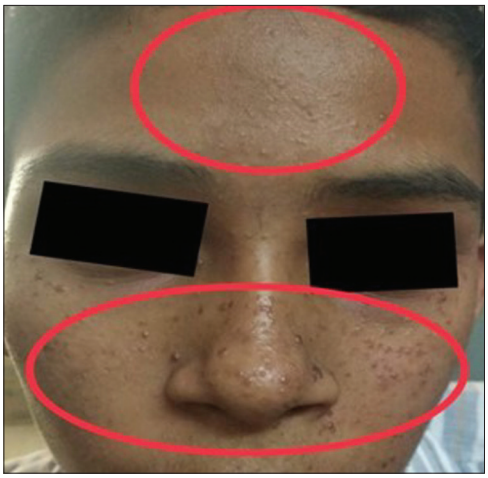

Figure 2: Multiple skin-colored tiny papule-like follicular lesions of the paranasal area and face

Table 1: Laboratory Parameters of Patients

Lab Parameter	Patient's Value	Normal Values
Hemoglobin (g/dL)	10.1	14-16
RBC count (million/mm^3)	3.01	4-6
Packed Cell Volume (%)	25.2	35-45
Mean Corpuscular Volume of RBC (fL)	83.72	80-99
Mean Corpuscular Hemoglobin of RBC (pg)	33.55	28-32
Mean Corpuscular Hemoglobin Concentration (%)	40.08	30-34
Red cell Distribution Width (fL)	13.5	9-17
Total Leukocyte Count (/mm^3)	9700	4000-11000
N/L/E/M/B (%)	76/17/6/1/0	40-75/20-45/0-6/0-10/0-1
Platelet (mm^3)	318000	150000-450000
Prothrombin Time (s)	16	11-13.5
INR	1.39	<=1.1
Random Blood Sugar (mg%)	69	<=140
Na+ (mEq/L)	138	135-149
K+ (mEq/L)	4.6	3.5-5.5
Alkaline Phosphatase (IU/L)	58.2	15-112
Total Bilirubin (mg/dL)	0.58	0.1-1.2
Direct Bilirubin (mg/dL)	0.27	0.1-0.4
Indirect Bilirubin (mg/dL)	0.31	0.1-0.7
Serum Urea (mg/dL)	17.8	10-50
Serum Blood Urea Nitrogen (mg/dL)	8.32	5-23
Serum Creatinine (mg/dL)	0.65	0.6-12
Serum Glutamate Oxaloacetate Transaminase (U/L)	26.8	<=46
Serum Glutamate Pyruvate Transaminase (U/L)	19.5	<=49

posterior renal fascia. The lesion indented and displaced the pelvicalyceal system medically. Minimal free fluid was seen in the perineal space. Anterosuperiorly, it abutted the liver, anterior lay the anterior abdominal wall, and posterior lay the right psoas muscle and paravertebral muscles without over-infiltration. There were multiple non-necrotic enhancing enlarged lymph nodes in the pre, right para-aortic, and right iliac visas regions, with the largest measuring 1.3 × 1.1 cm. All these were suggestive of renal angiomyolipoma [Figure 3].

Multiple well-defined hypodense lesions of various sizes showing microscopic fat within and a few of them showing central enhancing areas were seen in both lobes of the liver, the largest of them being 1.8 × 1.6 cm in Segment VI, which was suggestive of hepatic angiomyolipoma. There was minimal free fluid in the pelvis and bilateral paracolic gutter. Splenomegaly was seen (11.9 cm). In the lung, multiple thin-walled cysts of varying sizes were seen scattered throughout the lower thoracic sections. A provisional diagnosis of BHDS was made. Next, a CECT of the brain was done. It revealed small bilateral subependymal soft tissue density lesions with calcification. A magnetic resonance imaging (MRI) of the brain was done, but it showed no significant abnormality. A CECT of the thorax was also done, which showed multiple thin-walled cysts of varying sizes throughout the bilateral lung parenchyma and mild right-sided pneumothorax [Figure 4].

Following this, the patient was planned for right nephrectomy with plication of right renal venous aneurysm. The excised right kidney was sent for histopathological examination, which confirmed the diagnosis of renal cell carcinoma and was graded as pT2bpNx.

Discussion

BHDS is also known as Hornstein–Birt–Hogg–Dubé syndrome, Hornstein–Knickenberg syndrome, and fibrofolliculomas with trichodiscomas and acrochordons. The most common feature is fibrofolliculoma on the face, neck, and upper chest in the second or third decade. These fibrofolliculomas appear like acrochordons in many cases. Other tumors commonly associated with BHD include trichodiscomas, angiofibromas, and perifollicular fibromas and rarely collagenomas. Around 40% of patients have papules in their mouths. Pulmonary cysts are seen in 84% of patients, while spontaneous pneumothorax is relatively less common. Renal cancers are relatively less common. Hybrid oncocytoma, chromophobe renal carcinoma, renal oncocytoma, clear cell renal carcinoma, papillary renal cell carcinoma, and renal cysts are the most commonly seen in BHDS patients. Thyroid nodules have been noted in 65% of individuals. The confirmatory test for BHDS is a genetic sequencing for the FLCN gene (tumor suppressor gene expressed strongly in the skin, distal nephrons, and type 1 pneumocytes and also to some extent in the parotid gland, brain, breast, pancreas, prostate, and ovaries) mutation, which codes for follicular protein. Haploinsufficiency of the gene is enough to cause BHDS in these patients. Other diseases, with similar features, need to be ruled out before making a diagnosis of BHDS—tuberous sclerosis complex, Marian syndrome, Ehlers–Danlos syndrome, and Von Hippel–Lindau disease.[5,6] A 2023 case report from USA showed that a patient of BHDS can also present with chorioretinopathy and nyctalopia to the ophthalmology department.[7] Another 2023 study from Munich, Germany, led to the finding that pregnancy in patients with BHDS might act as a risk factor for multiple pneumothoraces, seen as a significantly higher number of pneumothoraces in pregnant over non-pregnant patients with BHDS.[8]

In a 2022 study by Ray *et al.*,[9] 76 variants of FLCN gene mutation were seen, out of which six were pathogenic and two of them were novel: a stop-gain (c. 634C > T) and a 4-nucleotide duplication (c.1329_1332dupAGCC). In a systematic review, it was seen that Chinese BHDS patients presented more with pulmonary symptoms as compared to dermatologic lesions and malignancies of the kidney, which appeared to be in stark contrast when compared with patients of Caucasian descent. In them, c. 1285depC/delC was seen to be the most common mutation.[10]

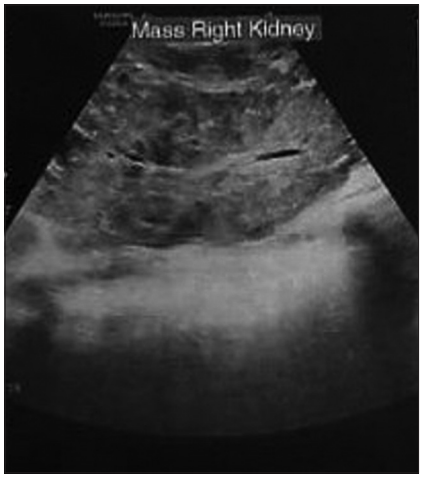

Figure 3: USG KUB showed right renal mass

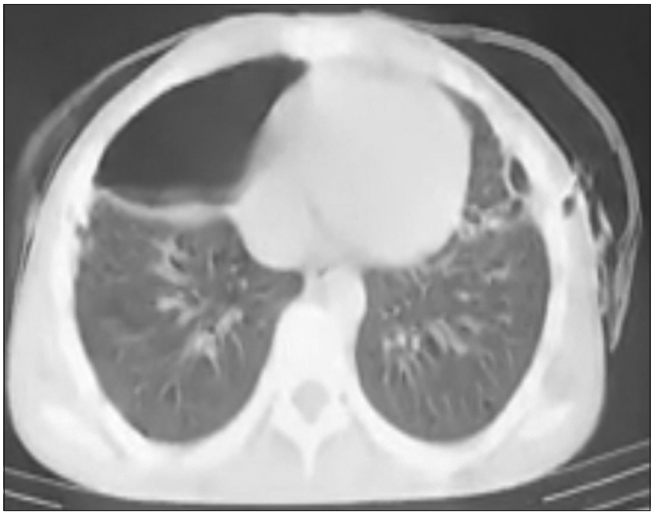

Figure 4: CECT of the thorax showing multiple thin-walled cysts of varying sizes throughout the bilateral lung parenchyma and mild right-sided pneumothorax

The importance of reporting this case lies in both the practice of family physicians (primary care givers) and those seeing to patients at a tertiary care center. Patients very commonly present with shortness of breath and chest pain, which might be pleuritic in origin. Physicians at the primary level should inculcate a habit of looking out for other features which might form a part of syndromes like BHDS, and that comes only with possession of high degrees of suspicion. The severity of the pulmonary symptoms may sometimes outweigh the skin and abdominal complaints and may be missed by both the patient and the primary care physician at the first visit. Many a times, patients present with complaints of individual organ systems at different times, leading to not being assessed together. The importance of detecting the syndrome as a whole at the primary level lies in the fact that timely referral to a tertiary care center, after providing basic emergency care available at the primary level, can be lifesaving for the patient. Hence, it is of paramount significance for the family physician to know who and when to refer to a higher center.

Respiratory physicians are becoming increasingly familiar with diseases like Langerhans cell histiocytosis, BHDS, lymphoid interstitial pneumonia, and lymphangioleiomyomatosis. However, a precise and comprehensive examination enhances diagnostic precision and may reveal other exceptionally rare conditions such as light chain deposition disease, cystic pulmonary amyloidosis, low-grade metastatic neoplasms, or infections. Failure to thoroughly investigate diagnostic details often results in uncertainty regarding the disease progression and appropriate treatments.[11]

Conclusion

Young patients with lung cysts and bilateral pneumothorax should be suspected of having BHDS. The classical triad of spontaneous pneumothorax, lung cysts, skin lesions, and renal neoplasms give high suspicion of BHDS, and it is rare to find. A detailed history and examination play an important role in diagnosing these rare cases. The diagnosis is crucial for treating the patient, and it has also had significant effects on the family.

Declaration of patient consent

Informed consent had been taken from the patient's parents and assent from the patient to publish the data in an anonymous manner, along with anonymous images in this journal, by the authors.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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