Respir Case Rep 2023;12(1):7-10 DOI: 10.5505/respircase.2023.03708

A Rare Cause for Recurrent Pneumothorax: Birt-Hugg-Dubé Syndrome

Nadir Bir Rekürren Pnömotoraks Sebebi: Birt-Hugg-Dubé Sendromu

Merve Şengül İnan[1], Özgün Aran[2], Hakan Işık[1], Agbaba Ahmedov[1], Abdullah Sezer[3], Alper Gözübüyük[1]

Abstract

Birt-Hogg-Dube syndrome (BHDS) is a rare disease with autosomal dominant inheritance. A positive family history, recurrent pneumothorax, skin fibrofolliculomas, pulmonary cysts, and an increased risk of renal malignancy characterize it. The mutation in the folliculin gene is considered to be responsible for the development of this syndrome. This article aims to present a 40-year-old female BHDS patient with a recurrent pneumothorax, skin lesions, and positive family history.

Keywords: *Pneumothorax, recurrent pneumothorax, folliculin gene.*

Öz

Birt-Hogg-Dube sendromu (BHDS), otozomal dominant kalıtım gösteren çok nadir bir hastalıktır. Pozitif aile öyküsü, tekrarlayan pnömotoraks, deri fibrofolliküloları, pulmoner kistler ve renal malignite riskinde artış ile karakterizedir. Folikülin genindeki mutasyonun bu sendromun gelişiminden sorumlu olduğu düşünülmektedir. Bu yazıda tekrarlayan pnömotoraks, cilt lezyonları ve pozitif aile öyküsü ile başvuran 40 yaşında BHDS kadın hastayı sunmayı amaçladık.

Anahtar Kelimeler: *Pnömotoraks, tekrarlayan pnömotoraks, folikülin gen.*

[1]Department of Thoracic Surgery, Gülhane Training And Research Hospital, Ankara, Türkiye
[2]Department of Thoracic Surgery, Kırıkkale Yuksek Ihtisas Hospital, Kırıkkale, Türkiye
[3]Department of Medical Genetic, Dr. Sami Ulus Maternity And Child Health And Diseases Training And Research Hospital, Ankara, Türkiye

[1]Gülhane Eğitim ve Araştırma Hastanesi, Göğüs Cerrahisi Kliniği, Ankara
[2]Kırıkkale Yüksek İhtisas Hastanesi, Kırıkkale
[3]Dr. Sami Ulus Kadın, Doğum Ve Çocuk Hastalıkları Hastanesi, Tıbbi Genetik Anabilim Dalı, Ankara

Submitted (Başvuru tarihi): 16.11.2022 ***Accepted (Kabul tarihi):*** 05.01.2023

Correspondence (İletişim): Merve Şengül İnan, Department of Thoracic Surgery, Gülhane Training And Research Hospital, Ankara, Türkiye

e-mail: drmervesengul@hotmail.com

Birt-Hogg-Dubé Syndrome (BHDS) is a rare genetic disease with an autosomal dominant inheritance that occurs as a result of a mutation in the folliculin (FLCN) gene (1,2). Pulmonary air cysts, recurrent pneumothorax episodes, skin abnormalities, and an elevated risk of kidney cancer characterize it. Different clinical manifestations might be seen from patient to patient as a result of different organs being involved due to genetic variability. When young people and people with bullous lungs have recurrent pneumothorax, the cause of BHDS should be examined.

CASE

A 40-year-old female patient had a history of pneumothorax after an in-vehicle traffic accident and tube thoracostomy 20 years ago. Due to prolonged air leakage, she had undergone bullae wedge resection and partial pleurectomy. The patient recovered without complications; the patient had occasional chest pain and mild shortness of breath until now. Due to the increase in her shortness of breath, the patient sought medical help, and pneumothorax and fibrosis in the apical regions and cystic areas were detected in her chest X-rays (Figure 1). On her chest CT, bilateral multiple pulmonary cystic lesions on the pleural surfaces and more on the left side were observed, the largest of which was 8.6 x 5.5 cm (Figure 2). Her physical examination revealed painless, visible lesions in her forehead and brow region measuring 2 to 3 millimeters in diameter. On detailed interrogation, it was learned that her father had been operated on for a renal tumor and later for a traumatic pneumothorax. BHD syndrome was suspected with these clinical findings, and heterozygous FLCN gene c. 1405–1406 deletion was detected in the genetic analysis of the patient, so the diagnosis was confirmed. Pleurodesis and pleurectomy operations are recommended for these patients to prevent recurrences. Surgical treatment was not planned for the patient due to a history of previous left-sided pneumothorax surgery. The patient underwent a urological examination and was given detailed information about her disease because her first-degree relative had a renal tumor and pneumothorax history. In the radiological follow-up of the patient, the pneumothorax was resorbed entirely (Figure 3).

DISCUSSION

BHD was defined in 1977 by Canadian author Birt et al. (3) as a genodermatosis inherited as autosomal dominant. The follicle protein, acting as a cytoplasmic guanine exchange factor, is associated with different signaling pathways (mTOR, AMPK, EGFR, and HIF1α) that are important for both tumorigenesis and cellular metabolism (2).

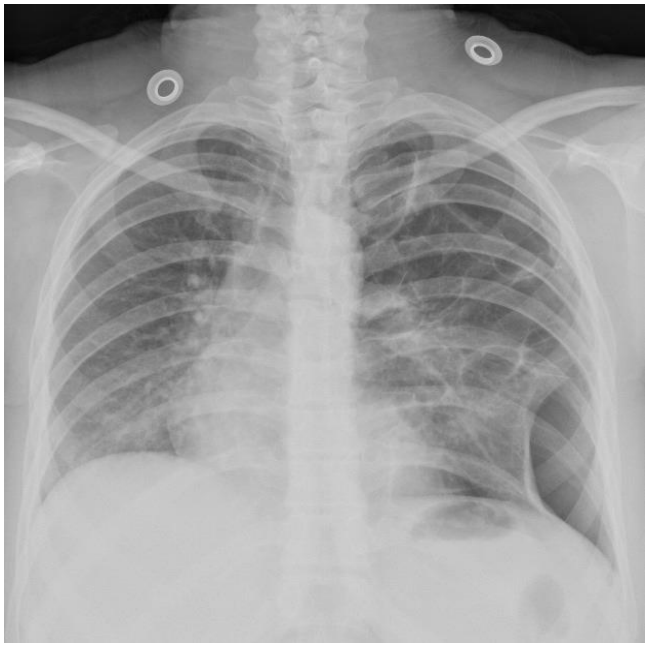

Figure 1: *A chest X-ray reveals pneumothorax, apical fibrosis, and cystic areas*

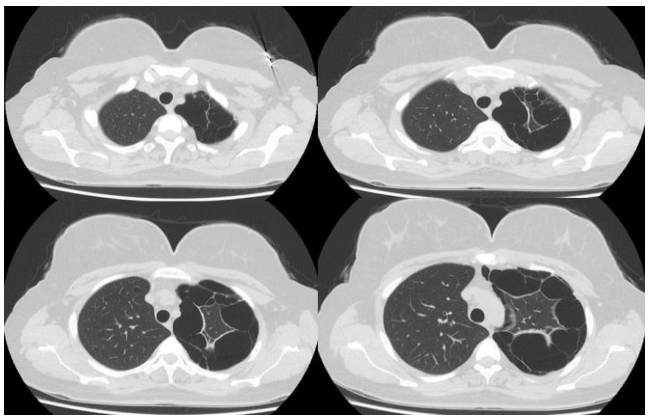

Figure 2: *A CT scan of the thorax showed multiple cystic lesions on the pleural surfaces of both lungs, with most of them on the left side*

Skin lesions usually present as fibrofolliculoma and trichodiscoma originating in hair follicles on the neck, face, and upper body. Renal tumors associated with BHD syndrome can be of different histopathological types, from benign oncocytomas to clear renal cell carcinomas (1-4).

Pulmonary cystic lesions are usually thin-walled, pleural-based, and show bilateral and multiple localizations with different sizes and shapes. Unlike other pulmonary cystic diseases (such as lymphangiomyomatosis, pulmonary Langerhans cell histiocytosis, and emphysema), respiratory functions are within normal limits in BHD syndrome patients (5,6). Patients are usually asymptomatic, but sometimes they complain of dyspnea that increases with exercise (7). While our case did not experience any shortness of breath in her daily life, she did describe shortness of breath during moderate to strenuous exercise.

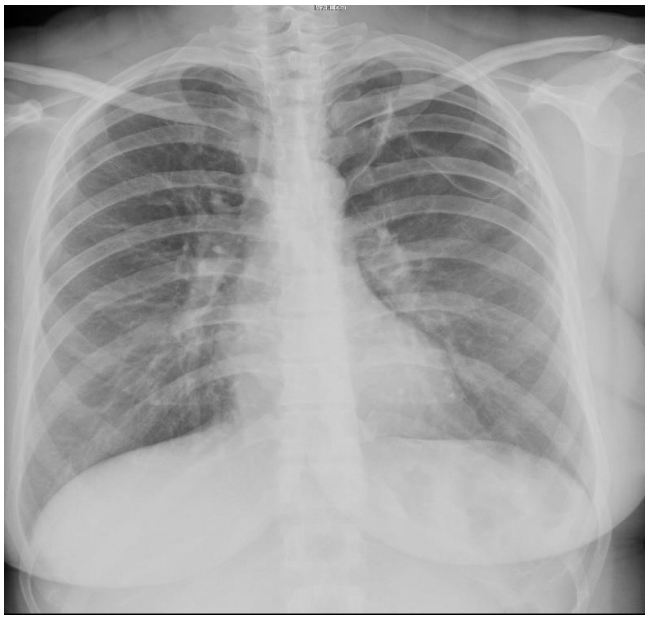

Figure 3: The pneumothorax was found to be resorbed in the X-ray taken at the control appointment

The effect of the FLCN mutation on the epithelial layer inside the pleural cysts could explain pathogenesis. It is possible that the downregulation of folliculin results in increased cell–cell adhesion. If the increased cell–cell adhesion of cells in the epithelial surface results in less potential to stretch, this might lead to rupture at the weakest spot of a continuous surface if the stretching force is strong enough (5). The incidence of pneumothorax is 50 times higher in patients with BHD syndrome (8). It was observed that smoking, age, and gender were not the determining factors in the first attack and recurrences (6). Chemical and surgical pleurodesis, or partial or total pleural coating, is performed after the first pneumothorax attack in these patients to prevent recurrent attacks (6,9).

According to the diagnostic criteria of the European BHDS consortium, the primary criteria are five fibrofolliculomas or trichodiscomas, at least one of which has been diagnosed histopathologically in adulthood and has genetically revealed FLCN germline mutations. Minor criteria are multiple pulmonary cysts, early-onset multifocal or bilateral renal cancer, and BHDS in a parent or sibling. One major or two minor criteria are sufficient for diagnosing BHDS (10). There were three papular lesions on the face of the patient, but a histopathological diagnosis could not be obtained because the patient did not consent to a biopsy. The diagnosis was made by detecting a deletion in the FLCN gene in the patient's genetic analysis, which was consistent with the significant criteria.

Skin lesions, which are among the primary criteria, do not affect the prognosis; since these patients are usually first presented to the dermatology units, dermatologists should be cautious about anamnesis and have the ability to combine renal and pulmonary findings (11). Thus, early diagnosis of renal malignancies can be possible.

Family history is of great importance, especially in the differential diagnosis of pulmonary lymphangioleiomyomatosis, which has radiologically similar findings to BHDS. In patients who had their first pneumothorax attack due to trauma, as was the case with our patient, thoracic CT findings may be shadowed due to trauma, and the diagnosis may be delayed. Johannesma et al. (5), in their survey of patients diagnosed with BHDS, found that pneumothorax was detected more frequently in patients after flying and diving activities compared to the general population. In that survey, the risk of pneumothorax in patients with BHDS was 0.63% per flight and 0.33% per dive session.

Patients should be informed in detail about their disease and be aware of the symptoms that may develop during these activities. Unlike LAM, cystic lung disease in BHDS does not cause severe lung function impairment at the six-year follow-up, despite the increased residual volume and slightly decreased DLco. Although its effect on the prognosis of the disease is low, smoking cessation should be encouraged to reduce the risk of pneumothorax in patients diagnosed with BHDS. Although spontaneous pneumothorax is typically seen in tall, young male patients, the fact that patients with BHDS are primarily middle-aged and normal-weight females should also suggest secondary pneumothorax. If there is, an indication for bulla wedge resection in patients with pneumothorax, in addition to this procedure, covering the surgical area on the lung with oxidized regenerated cellulose (ORC) meshes used as a hemostatic agent in surgery may eliminate the recurrence of pneumothorax. Patients diagnosed with BHDS should be followed up with an MRI once a year for possible kidney malignancies, and other family members should be called to the hospital to screen for this disease.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - H.I., Ö.A., A.A., M.Ş.İ., A.S., A.G.; Planning and Design - M.Ş.İ., Ö.A., H.I., A.A., A.S., A.G.; Supervision - A.G., A.S., A.A., M.Ş.İ., Ö.A., H.I.; Funding - A.G.; Materials - A.S., M.Ş.İ.; Data Collection and/or Processing - A.A., Ö.A.; Analysis and/or Interpretation - H.I., A.S.; Literature Review - A.A., Ö.A.; Writing - M.Ş.İ.; Critical Review - H.I., M.Ş.İ.

REFERENCES

1. Daccord C, Good JM, Morren MA, Bonny O, Hohl D, Lazor R. Birt-Hogg-Dubé syndrome. Eur Respir Rev 2020; 29:200042.[CrossRef]

2. Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [updated 2020 Jan 30]. In: Adam MP,

Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2022.

3. Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 1977; 113:1674-7. [CrossRef]

4. Gupta N, Sunwoo BY, Kotloff RM. Birt-Hogg-Dubé Syndrome. Clin Chest Med 2016; 37:475-86. [CrossRef]

5. Johannesma PC, Houweling AC, van Waesberghe JH, van Moorselaar RJ, Starink TM, Menko FH, et al. The pathogenesis of pneumothorax in Birt-Hogg-Dubé syndrome: a hypothesis. Respirology 2014; 19:1248-50. [CrossRef]

6. Gupta N, Seyama K, McCormack FX. Pulmonary manifestations of Birt-Hogg-Dubé syndrome. Fam Cancer 2013; 12:387-96. [CrossRef]

7. Daccord C, Cottin V, Prévot G, Uzunhan Y, Mornex JF, Bonniaud P, et al. Lung function in Birt-Hogg-Dubé syndrome: a retrospective analysis of 96 patients. Orphanet J Rare Dis 2020; 15:120. [CrossRef]

8. Johannesma PC, van de Beek I, van der Wel JW, Paul MA, Houweling AC, Jonker MA, et al. Risk of spontaneous pneumothorax due to air travel and diving in patients with Birt-Hogg-Dubé syndrome. Springerplus 2016;5:1506. [CrossRef]

9. Mizobuchi T, Kurihara M, Ebana H, Yamanaka S, Kataoka H, Okamoto S, et al. A total pleural covering of absorbable cellulose mesh prevents pneumothorax recurrence in patients with Birt-Hogg-Dubé syndrome. Orphanet J Rare Dis 2018; 13:78. [CrossRef]

10. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. Birt-Hogg-Dube syndrome: diagnosis and management. Lancet Oncol 2009; 10:1199-206. [CrossRef]

11. Cesar A, Baudrier T, Mota A, Azevedo F. A case of Birt-Hogg- Dube syndrome presenting with a single pedunculated fibrofolliculoma and a novel FLCN gene mutation. Actas Dermosifiliogr 2016; 107:541-3. [CrossRef]