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# Rare cystic lung disease: Birt-Hogg-Dubé syndrome

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## Abstract:

Birt-Hogg-Dubé syndrome is a rare autosomal dominant disorder characterized by fibrofolliculomas, renal tumors, and lung cysts of varying sizes that exhibit a lentiform appearance. The cysts are typically small (less than 1 cm), thin-walled, and irregularly shaped, with a higher prevalence in the basal and mediastinal regions of the lungs. Approximately 30% of patients experience one or multiple pneumothoraces before reaching 40 years of age. Unlike in other cystic lung diseases, lung cysts in this condition do not show progression. Malignant renal tumors manifest in 12–35% of individuals before the age of 50, with surgical intervention being the preferred treatment option. As mortality frequently results from these renal tumors, expert consensus often advocated for screening starting at 21 years of age. Herein, we present a 68-year old male patient who presented with shortness of breath and cough. He had a history of pneumothorax 30 years ago. Computed tomography of the thorax revealed lentiform (lens-shaped) cysts of various sizes in the basal regions of the lungs. Since multiple fibrofolliculomas on the face and neck, Birt-Hogg-Dubé syndrome was considered, and genetic screening was performed. A mutation in the Folliculin (FLCN) gene was identified. Abdominal Magnetic Resonance Imaging (MRI) was performed to assess for kidney tumors, but no pathology was identified. Although this patient does not have a renal tumor, we want to emphasize the need for MRI screening for renal tumors in patients with Birt-Hogg-Dubé syndrome. Additionally, due to autosomal dominant inheritance, genetic screening is recommended for relatives.

## Keywords:

Birt-Hogg-Dubé syndrome, cystic lung disease, fibrofolliculoma, kidney cancer, pneumothorax

## Introduction

**B**irt-Hogg-Dubé (BHD) disease is an autosomal dominant disorder characterised by widespread lung cysts, fibrofolliculomas, trichodiscomas, and kidney tumors. First described in 1977, mutations in the folliculin gene have since been identified in affected families worldwide. [1] Fibrofolliculoma, a benign skin tumor, typically appears in affected individuals in

their third decade of life. Bilateral multiple lung cysts are observed, with pneumothorax often occurring around age 30. Furthermore, kidney tumors can develop in individuals before they reach the age of 50.[2]

## Case Report

A 68-year-old male patient presented to our clinic with complaints of shortness of breath and cough. The patient had been

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treated for pneumothorax 30 years prior and experienced occasional shortness of breath since then. The patient neither smoked nor consumed alcohol. A physical examination revealed small, transparent papules/nodules measuring 1–2 mm on the face and nose, as well as small fibromas in both axillae and neck [Fig. 1]. Systemic examination yielded no specific findings, and blood biochemistry was within normal limits. Pulmonary function testing indicated restrictive respiratory insufficiency: Forced Vital Capacity (FVC) (1.46L) 35%, Forced Expiratory Volume in 1 second ( $FEV_1$ ) (1.46) 38%,  $FEV_1$ /FVC (78.1) 100%. A posteroanterior chest X-ray revealed reticular infiltration in both lower zones with blunt costovertebral angles. Thoracic Computed Tomography (CT) highlighted irregularly shaped cystic lesions with indistinct borders, measuring 2×3 cm in the basal areas, predominantly on the left [Fig. 2]. A facial papule biopsy taken five years prior showed fibrofolliculoma [Fig. 3]. Genetic screening was performed to diagnose Birt-Hogg-Dubé syndrome, and a mutation in the Folliculin (FLCN) gene was identified, confirming the diagnosis. An abdominal Magnetic Resonance Imaging (MRI) was performed to assess for kidney tumors, but no pathology was identified. Two sisters also presented with fibrofolliculomas and mutations in the FLCN gene; however, their kidney screening were negative. The patient was discharged with instructions to undergo an abdominal MRI annually.

## Discussion

BHD syndrome is a rare autosomal dominant disease caused by mutations in the FLCN gene, which encodes the folliculin protein. This condition is characterized by irregular lung cysts, spontaneous pneumothorax, fibrofolliculomas on the skin, and renal tumors.<sup>[1,2]</sup> Genetic testing is recommended for family members at risk of BHD syndrome starting at the ages of 20 to 21 years.<sup>[3]</sup> Birt-Hogg-Dubé (BHD) syndrome arises from germ cell-specific autosomal dominant pathogenic variants found in the folliculin (FLCN) gene, located on chromosome 17p11.2.<sup>[4]</sup> The folliculin protein plays a crucial role in cell growth and metabolism. FLCN, in combination with FLCN-interacting protein 1 (FNIP1) and FNIP2 (also known as FNIPL), forms a complex that interacts with signaling molecules like the 5'-AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR). A homozygous deletion of the FLCN gene proves embryologically lethal in mice, while het-



Figure 1: White-domed fibrofolliculoma on the sides of the nose

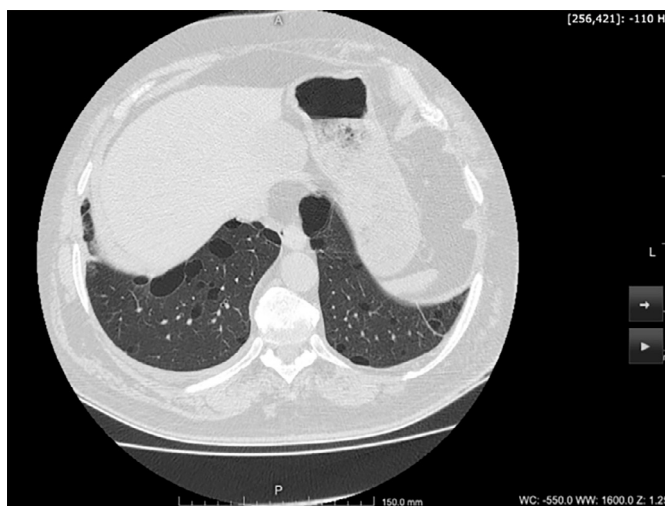


Figure 2: Cystic lesions of varying sizes in the lung bases

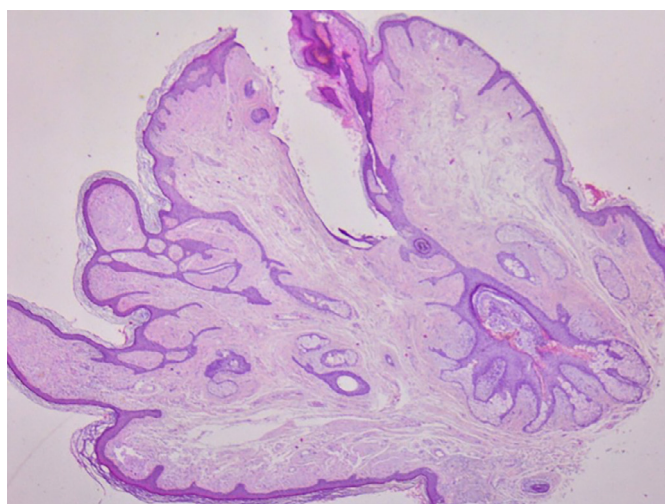


Figure 3: Solid epithelial cords extending from the central hair

**Table 1: Diagnostic criteria**

Diagnostic criteria			
Major criteria	At least five fibrofolliculomas or trichodiscomas	Minor criteria	Multiple lung cysts
	Histologically confirmed Folliculin (FLCN) gene mutation		Renal tumor before the age of 50
			Birt-Hogg-Dubé syndrome in first-degree relatives

erozygotes develop renal cancer without any pulmonary pathology.<sup>[5]</sup> The FLCN gene plays a pivotal role in post-natal lung development, but it has no prenatal effects.<sup>[6]</sup> Fibrofolliculomas and trichodiscomas are generally benign lesions that usually do not require treatment. Patients with multiple fibrofolliculomas may opt for cosmetic treatments, which can include carbon dioxide (CO<sub>2</sub>) or erbium:yttrium aluminum garnet (Er:YAG) laser ablation. However, only a few patients benefit from these treatments, and recurrence is common.<sup>[7]</sup> The topical solution of rapamycin (sirolimus), an mTOR inhibitor containing 0.1% did not lead to a reduction in the size or number of fibrofolliculoma lesions compared to placebo.<sup>[8]</sup> BHD syndrome is the most common genetic disorder in patients with familial pneumothorax. Pulmonary cysts typically present as irregularly shaped, thin-walled cysts below the diaphragm, rather than the apical bullae and blebs that cause primary pneumothorax.<sup>[9]</sup> The treatment of pneumothorax aligns with general population guidelines. Patients should avoid smoking and exposure to high atmospheric pressure. Surgical BHD patients should specifically avoid increased positive pressure ventilation.<sup>[3]</sup> In BHD disease, cysts of various sizes, and occasionally large bullae, can develop. If surgery is required for these bullae, low Positive End-Expiratory Pressure (PEEP) should be administered to protect patients from pneumothorax and ensure pain control.<sup>[10]</sup> BHD syndrome is associated with a sevenfold higher risk of kidney tumors compared to the general population.<sup>[11]</sup> Renal cell carcinoma develops in one-third of these patients and can be lethal if untreated. In BHD syndrome, the most commonly encountered tumor types are chromophobe tumors and hybrid chromophobe/oncocytic tumors. Clear cell carcinoma, papillary carcinoma, and mixed-type carcinoma are rarer.<sup>[12]</sup> In addition to renal tumors, patients with BHD syndrome present with colon polyposis, colon tumors, melanoma, parathyroid, thyroid, and parotid tumors than the general population.<sup>[13]</sup> The European Birt-Hogg-Dubé Consortium defines a

BHD syndrome diagnosis by the presence of at least one histologically confirmed fibrofolliculoma or trichodiscoma in adulthood, a mutation in the FLCN gene, or one of these criteria combined with a family history of BHD syndrome, renal tumor before the age of 50, or bilateral widespread cysts in the lungs (Table 1).<sup>[14]</sup> Our patient exhibited fibrofolliculomas, a mutation in the FLCN gene, and multiple bilateral lung cysts. Additionally, the patient's 60-year-old sister also had fibrofolliculomas and a mutation in the FLCN gene. When patients present with dyspnea and bilateral cystic lesions in the lungs, BHD syndrome should be suspected. Dermatological examinations are essential for identifying fibrofolliculomas. It is also crucial to investigate similar findings in first-degree relatives. Patients should be counseled against smoking. Although not definitive, annual renal MRI is recommended for early detection of renal tumors. Ultrasonography may miss smaller tumors, and computed tomography presents radiation exposure risks.<sup>[15]</sup>

### Informed Consent

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

### Conflicts of interest

There are no conflicts of interest.

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Nil.

### Peer-review

Externally peer-reviewed.

## References

1. Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol* 1977;113:1674–7.
2. Nickerson ML, Warren MB, Toro JR, Matrosova V, Glen g, Turner ML, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumours of the hair follicle in patients with Birt-Hogg-Dube syndrome. *Cancer Cell* 2002;2(2):157–64.

3. Stamatakis L, Metwalli AR, Middleton LA, Marston Linehan W. Diagnosis and management of BHD-associated kidney cancer. *Fam Cancer* 2013;12(3):397–402.
4. Lim DH, Rehal PK, Nahorski MS, Macdonald F, Claessens T, Van Geel M, et al. A new locus-specific database (LSDB) for mutations in the folliculin (FLCN) gene. *Hum Mutat* 2010;31(1):E1043–51.
5. Marciniak SJ, Johnson SR. Pneumothorax and the biology of Birt-Hogg-Dube syndrome. *Thorax* 2020;75(6):442–3.
6. Chun J, Futami K, Petillo D, Peng J, Wang P, Knol J, et al. The deficiency of FLCN in mouse kidney led to development of polycystic kidneys and renal neoplasia. *PLoS One* 2008;3(10):e3581.
7. Farrant PB, Emerson R. Letter: hyfrection and curettage as a treatment for fibrofolliculomas in Birt-Hogg-Dube syndrome. *Dermatol Surg* 2007;33(10):1287–8.
8. Kim D, Wysong A, Teng JM, Rahman Z. Laser-assisted delivery of topical rapamycin: mTOR inhibition for Birt-Hogg-Dube syndrome. *Dermatol Surg* 2019;45(12):1713–5.
9. Gupta N, Seyama K, McCormack FX. Pulmonary manifestations of Birt-Hogg-Dubé syndrome. *Fam Cancer* 2013;12(3):387–96.
10. Özer E, Pampal HK, Mehmet Dakak. Multiple lung cysts and Birt Hogg Dube syndrome management of anaesthesia and surgery. *Gülhane Med J* 2012;54(4):302–5.
11. Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. *Cancer Epidemiol Biomarkers Prev* 2002;11(4):393–400.
12. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet Oncol* 2009;10(12):1199–206.
13. Mota-Burgos A, Acosta EH, Márquez FV, Mendiola M, Herrera-Ceballos E. Birt-Hogg-Dubé syndrome in a patient with melanoma and a novel mutation in the FLCN gene. *Int J Dermatol* 2013;52(3):323–6.
14. López V, Jordá E, Monteagudo C. Birt-Hogg-Dubé syndrome: an update. *Actas Dermosifiliogr* 2012;103(3):198–206. Spanish.
15. Jamis-Dow CA, Choyke PL, Jennings SB, Linehan WM, Thakore KN, Walther MM. Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. *Radiology* 1996;198(3):785–8.