

# Birt-Hogg-Dubé Syndrome: CT Findings of an Under Recognized Disease Requiring Multidisciplinary Approach

## Birt-Hogg-Dubé Sendromu: Az Tanınan ve Multidisipliner Yaklaşım Gerektiren Olgu Serisinde BT Bulguları

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### Abstract

Birt-Hogg-Dubé Syndrome (BHDS) is characterized by hair follicle hamartomas, renal tumors, and pulmonary cysts. In this case series, CT findings of two index patients with BHDS, and their family members, are presented. Differential diagnosis with other cystic lung diseases is discussed. The importance of follow-up and screening for the early detection of possible malignancies, as well as multidisciplinary approach, is emphasized. The course of BHDS requires not only annual patient follow-up but also care due to the risk of pneumothorax.

**Key words:** Birt-Hogg-Dubé syndrome, fibrofolliculoma, lung cysts, renal tumors, pneumothorax.

### Özet

Birt-Hogg-Dubé Sendromu (BHDS) deride fibrofolikü-lomalar, renal tümörler ve akciğer kistleri ile karakterizedir. Bu olgu serisinde, Birt-Hogg-Dubé sendromlu iki olgu ve aile üyelerinin BT bulguları sunulmaktadır. Diğer kistik akciğer hastalıkları ile ayrıncı tanı tartışılmaktadır. Olası malignitelerin tespit edilebilmesi açısından takip ve tarama ile multidisipliner yaklaşımın önemi vurgulanmaktadır. BHDS seyri sırasında yıllık hasta takibi yanı sıra pnömotoraks riski açısından özen gerekmektedir.

**Anahtar Sözcükler:** Birt-Hogg-Dubé Sendromu, fibrofoliküloza, akciğer kistleri, renal kitle, pnömotoraks.

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant genodermatosis caused by mutations in the FLCN gene, located on the 17p11.2 region (1). BHDS is a systemic disorder characterized by hair follicle hamartomas (fibrofolliculomas, trichodiscomas, acrochordons), renal tumors, and pulmonary cysts (2). Fibrofolliculomas are the most characteristic finding of BHDS and typically appear as multiple, 2-to4-mm, whitish skin-colored papules on the head, neck, face and upper body (3).

BHDS is associated with renal tumors such as chromophobe renal cell carcinoma (RCC), oncocytomas, and renal cysts. Pulmonary cysts are reported in 89% of affected members of BHDS families, and approximately 25-35% of subjects have a history of pneumothorax (4,5). Although many cases are clinically silent, older patients and those with severe lung involvement have symptoms like dyspnea, cough, and recurrent pneumothorax (5).

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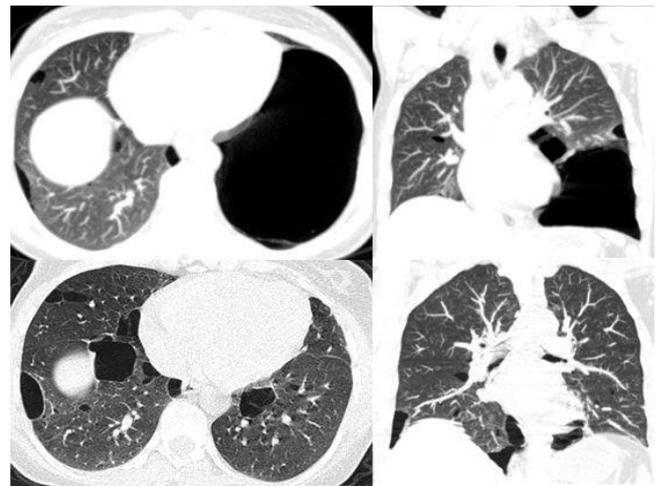
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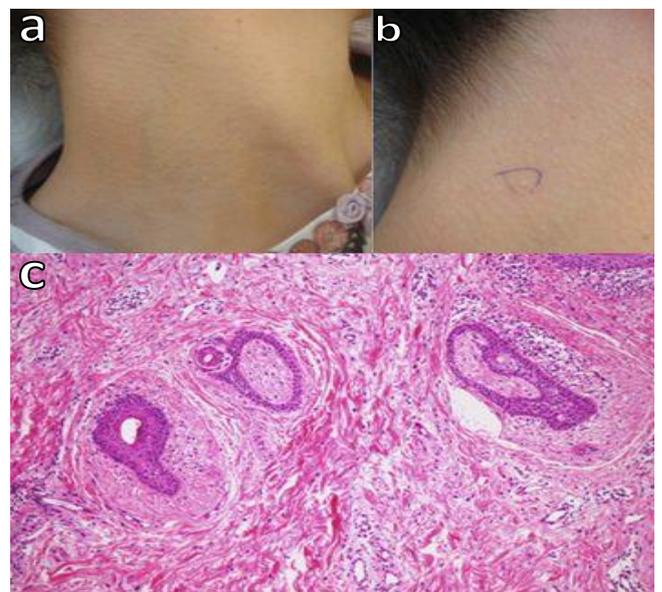
## CASE

The first index patient was seen as an outpatient with a cough and occasional purulent sputum. She had normal bilateral auscultation findings, did not have dyspnea, and family history was clean for tuberculosis. The chest x-ray showed hyperlucent areas and a CT scan was performed to evaluate the extent of the disease. HRCT images of the chest revealed multiple cysts of various sizes with irregular contours, spread in the upper and lower zones of both lungs. The left lower lobe was completely replaced with cysts. The patient had a left lower lobe wedge resection and the specimen was histopathologically reported to have chronic inflammation and intraalveolar hemorrhage, as well as smooth muscle proliferation of the vessel walls with areas of fibrosis and myxoid degeneration. She was discharged uneventfully and reported to the same clinic eleven months later with similar symptoms. Alfa-1-antitrypsin deficiency was ruled out with PiMM genotype. The repeated CT revealed a relatively normal left lower lobe parenchyma following resection, as well as new cysts in the right lung (Figure 1). BHDS was suggested as a radiological diagnosis and the patient was referred to dermatology for a thorough examination of the skin. Multiple skin colored bright papules were detected on the neck (Figure 2a and b). The patient had no complaint about these papules, which could only be seen with a careful and close inspection of the skin. She said that they had been present since adolescence. A skin biopsy revealed fibrofolliculoma (Figure 2c.) The patient was diagnosed as BHDS and abdominal US was performed to evaluate the kidneys, which revealed no abnormal findings. The patient's immediate family members were called in for screening and chest x-rays were obtained. The patient's mother had hyperlucent areas, suggesting cysts in bilateral lung areas and CT was performed, revealing multiple cysts scattered in both lungs, similar to her daughter (Figure 3a and b). The mother also had skin lesions suggestive of fibrofolliculomas on her face and neck (Figure 3c and d). These were more clinically pronounced than her daughter's skin lesions and biopsy confirmed the diagnosis of fibrofolliculoma (Figure 3e). She had abdominal US screening for possible renal tumors and no abnormal findings were detected. The second index patient with dyspnea had hyperlucent areas on the chest x-ray. A CT scan was performed and scattered lung cysts of various shapes and sizes suggested the possibility of BHDS as a diagnosis. The patient was referred to the dermatology department and skin lesions were detected, a biopsy revealed fibrofolliculoma. The

patient's family was called in for screening. His mother and two children had similar skin lesions and lung cysts. His mother had history of pneumothorax and his son had asymptomatic pneumothorax at the time of CT scanning. Skin biopsies of these family members confirmed the diagnosis of fibrofolliculoma. Abdominal US were also performed and simple renal cysts were detected in the index patient and his mother (Figure 4).



**Figure 1:** HRCT of the first index patient. Axial and coronal images showing the left lower lobe completely replaced with multiseptated cysts (top). Relatively normal left lower lobe parenchyma after wedge resection, as well as new cysts of various shapes in the right lower lung (bottom). Costophrenic sinus is also involved with cysts

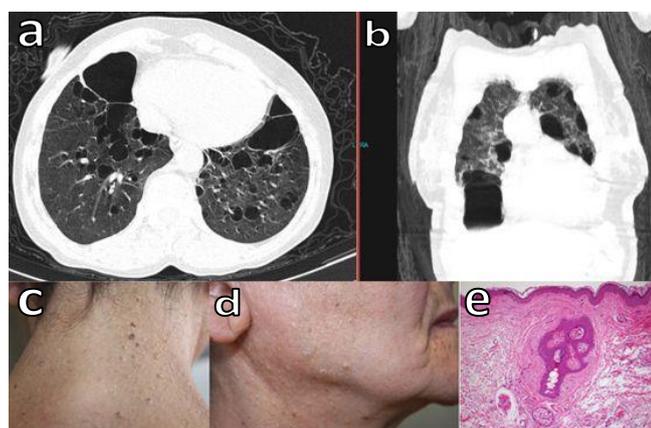


**Figure 2a, b, c:** Skin-colored bright papules in the neck (a,b). Histopathologic features consisted with fibrofolliculoma: Anastomosing epithelial strands and cords of basaloid cells, arising from the infundibulum, in a dense stroma (HEx100) (c)

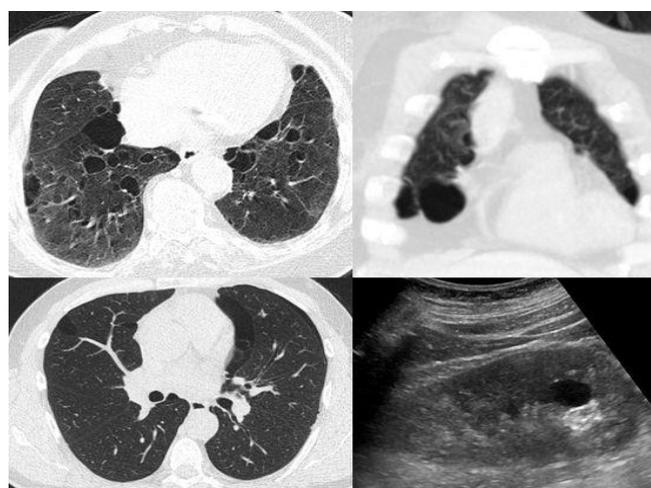
## DISCUSSION

BHDS must be differentiated from other more common cystic lung diseases. In our case series, the distribution

and morphology of cysts in BHDS helped us to differentiate the syndrome from other well-known cystic lung diseases. The patients had bilateral lung cysts except in one case. Cysts were seen to be diffusely scattered or predominantly in the middle or lower zones. Most of them showed no central or peripheral predominance. The thin walled cysts varied in size and shape (oval, round, septated). Most of the patients had more than 20 cysts. Lymphangioliomyomatosis (LAM) is a disease almost exclusively seen in women of childbearing age. Since there is an association of LAM with tuberous sclerosis, lesions of the lung and kidney makes LAM more difficult to differentiate from BHDS (3,6). However, the medium sized cysts in LAM have uniform distribution in both lungs with no preferential area, whereas the cysts in BHDS are generally of irregular shapes and sizes with a predilection for mid to lower lobes.



**Figure 3:** HRCT scan, revealing multiple confluent cysts scattered throughout both lungs. Note septations in the large cysts (a,b). Multiple fibrofolliculomas on the face and neck (c,d). Biopsy revealed anastomosing a few cell-thick, epithelial strands, arising from the infundibulum, forming a fenestrated pattern, in a fibrotic stroma (HEx200)(e)



**Figure 4:** HRCT findings of the second family: Scattered lung cysts of various sizes and shapes (top), left lung pneumothorax (bottom right), renal ultrasonography revealing simple cortical cyst (bottom left)

Langerhans cell histiocytosis (LCH) is a virtually exclusive disease of cigarette smoking young adults with no gender predilection. The cysts in LCH have upper lobe distribution with sparing of the costophrenic areas and nodules also noted (6). In our case series, costophrenic sinuses were not spared in four out of six patients.

The large and various shapes of the bullous lesions seen in emphysema are usually located at the upper lung areas and inexperienced physicians can confuse them with cysts. Most of the large cysts detected in our case series were noted in the lower zones.

Lymphocytic interstitial pneumonitis (LIP) is characterized by lymphocytic infiltration of the lungs, and scattered cysts in the lung parenchyma are accompanied with areas of ground glass opacity. In desquamative interstitial pneumonia (DIP) there are also ground glass opacities and nodules accompanied by cystic changes (7). In BHDS, no ground glass opacities or nodules are detected.

FLCN is a tumor suppressor gene associated with renal carcinogenesis and inactivating mutations are associated with BHDS. Renal tumors have been reported with a 27% incidence (8) and annual screening is warranted for this group of patients, preferably with US and MRI, as the risk of malignancy increases with age.

The characteristic skin lesions described in BHDS are hamartomatous hair-follicle tumors. Despite their description as a triad, fibrofolliculomas, trichodiscomas and achrochordons represent a spectrum of the same skin tumor. Fibrofolliculomas and trichodiscomas usually develop after 30 years of age and as Birt et al. (9) reported, all patients with fibrofolliculomas are over 25 years of age. The skin lesions are benign and may be overlooked unless a careful inspection is made. The dermatologist should consider a diagnosis of BHDS when a patient presents with an adult-onset of five or more fibrofolliculomas.

BHDS is diagnosed with clinical findings and molecular genetic testing. The criteria for genetic testing and diagnosis, which take into account variable manifestations, have recently been proposed by the European BHD Consortium. FLCN is the only gene known to be associated with BHDS. Sequence analysis detects pathogenic variants in FLCN in 88% of affected subjects. Hence, although approximately 7-9% of affected individuals who fulfill the clinical diagnostic criteria do not have an identifiable FLCN pathogenic variant that can be detected using current technology, mutations in another currently unknown gene could be responsible for a minority of cases (4,10,11). On behalf of the European BHD Con-

sortium, Menko et al. (2) proposed diagnostic criteria that are based on clinical manifestations and the outcome of DNA testing (4). Patients should fulfill one major or two minor criteria for diagnosis where the major criteria were as follows: 1- at least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset and 2- a pathogenic FLCN germline mutation. Minor criteria were listed as: a- multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax; b- renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer or renal cancer of mixed chromophobe and oncocytic histology; 3- a first-degree relative with BHD. All patients and their families suspected of having BHDS were offered genetic testing to confirm the diagnosis, but because of financial reasons the test for FLCN gene could not be performed. The diagnosis of BHDS in our case series was based on imaging findings and histopathological evaluations of skin lesions, which fulfilled the diagnostic criteria proposed by Menko et al. (2).

Currently, there are no published guidelines for screening pulmonary cysts or renal cancer in asymptomatic BHDS patients and their families (4,11). Provisional recommendations include screening for the early detection of renal cancer with US or MR, starting at age 20, and lung cysts with HRCT every three to five years. Patients diagnosed with BHDS should be reminded of the increased risk of pneumothorax and warned against air travel and general anesthesia. Cessation of smoking is the major available strategy to possibly prevent pneumothorax and also RCC. In conclusion, our case series emphasizes the importance of a thorough physical examination and its correlation with radiological imaging findings. CT findings of numerous cysts of various shapes and sizes, predominantly scattered throughout the lower zones of the lungs, may help in differentiating BHDS from other cystic lung diseases and the radiologist should be able to confidently suggest the diagnosis. The course of BHDS requires family screening and annual patient follow-up, as well as treatment for the risk of pneumothorax.

## CONFLICTS OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

Concept - C.C., E.E., N.C.C., D.S., C.D., S.O., M.H.S.; Planning and Design - C.C., N.C.C., E.E., D.S., S.O., C.D., M.H.S.; Supervision - C.C., E.E., N.C.C., D.S.,

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