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A Case Requiring a Multidisciplinary Approach: Birt-Hogg-Dube Syndrome

Multidisipliner Yaklaşım Gerektiren Bir Olgu: Birt-Hogg-Dube Sendromu

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Abstract

Birt-Hogg-Dubé Syndrome (BHDS) is characterized by benign cutaneous lesions in the head and neck region, pulmonary cysts or spontaneous pneumothorax. It is a rare disorder associated with a mutation in the folliculin (FLCN) gene. A 53-year-old male patient who presented with exertional dyspnea was identified with multiple cystic lesions in a computed tomography (CT) scan, as well as pneumothorax in the right lung. The patient presented again 2 years later complaining of left-side chest pain, and left-sided pneumothorax was identified on imaging. The patient had 2–3 mm papules on his shoulders, cheeks and forehead, and a pathological examination confirmed a diagnosis of trichodiscoma. The patient, who had bullous lung disease, trichodiscoma and a positive FLCN gene sequencing result, was diagnosed with BHDS. We share this case to emphasize the need to consider BHDS in the differential diagnosis of rare cystic lung diseases in patients presenting with recurrent pneumothorax and distinctive cutaneous findings.

Keywords: *Birt-Hogg-Dube Syndrome, Trichodiskoma, Pulmonary Cyst.*

Öz

Birt-Hogg-Dube Sendromu (BHDS); baş ve boyun bölgesi hamartomları, pulmoner kistler veya spontan pnömotoraks ile karakterizedir. Otozomal dominant geçiş gösteren nadir bir hastalıktır. Follikülin (FLCN) gen mutasyonu mevcuttur. Bizim olgumuz 53 yaşında erkek hasta efor dispnesi ile başvurdu. Görüntülemesinde sağ akciğerde pnömotoraks ve bilgisayarlı tomografide multipl kistik lezyonlar görüldü. İki yıl sonra, hasta sol göğüs ağrısı ile başvurdu. Sol akciğerde pnömotoraks görüldü. Hastada omuz, çene ve alın bölgesinde 2-3 mm papül saptandı. Lezyonların patolojisi trichodiscoma olarak sonuçlandı. Büllöz akciğer, trichodiscoma ve pozitif FLCN gen dizilimi olan hastaya BHDS tanısı konuldu. Bu olgu, tekrarlayan pnömotoraks ve belirgin kutanöz bulgularla gelen hastalarda nadir kistik akciğer hastalıklarının ayırıcı tanısında BDHS'nin düşünülmesinin gerekliliğini vurgulamak için paylaşıldı.

Anahtar Kelimeler: *Birt-Hogg-Dube Sendromu, Trichodiskoma, Pulmoner Kist.*

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Birt-Hogg-Dubé Syndrome (BHDS) is characterized by benign cutaneous lesions in the head and neck region, pulmonary cysts or spontaneous pneumothorax. It is a rare disorder with an autosomal dominant inheritance pattern that can be traced to a mutation in the folliculin (FLCN) gene (1,2). Pulmonary manifestations include multiple, irregularly shaped, thin-walled cysts located predominantly in the lower lobes and subpleural regions, along with secondary spontaneous pneumothorax (3). Fibrofolliculoma and trichodiscoma are among the specific cutaneous manifestations (4). Diagnosis is established based on clinical suspicion, imaging, skin biopsy and genetic testing. While BHDS is a rare condition, it should be considered in patients with recurrent spontaneous pneumothorax and characteristic cutaneous findings, as early diagnosis may help prevent complications. Given the potential complications associated with BHDS, clinicians should maintain a high index of suspicion in such patients. We share this case to emphasize the need to consider BHDS in the differential diagnosis of rare cystic lung diseases, particularly in patients presenting with recurrent pneumothorax and distinctive cutaneous findings.

CASE

A 53-year-old male patient presented with exertional dyspnea persisting for 2–3 days. His medical history included hypertension and undifferentiated spondyloarthritis, and he was an active smoker with a 20 pack-year smoking history. A physical examination revealed an absence of breathing sounds in the right lung. His general condition was moderate to good, his SpO_2 was measured at 91% in room air and other vital signs were within normal limits. Laboratory findings revealed pathological values of WBC: 12,310 $\times$ $10^3/\mu$L and CRP: 35.1 mg/L. Imaging revealed pneumothorax in the right lung (Figure 1), and so a tube thoracostomy was performed.

Follow-up computed tomography (CT) scans revealed multiple cystic lesions of varying sizes, predominantly in the subpleural regions of both lungs, with a greater distribution in the lower lobes (Figures 2). After a 2-year lapse in follow-up, the patient returned with new-onset left-sided chest pain, at which time, imaging confirmed a left-sided pneumothorax (Figure 3). A further tube thoracostomy was performed, followed by video-assisted thoracoscopic surgery (VATS). Pathological examination revealed a bullous formation, minimal congestion and inflammation, along with focal mesothelial hyperplasia on the pleural surface. Due to the recurrent pneumothorax and bullous lung involvement, pulmonary function tests (PFTs) were performed for differential diagnosis, revealing a restrictive pattern, and decreased diffusing capacity for carbon monoxide (DLCO) (FVC: 78%, FEV1: 80%, FEV1/FVC: 98%, DLCO: 68%). Alpha-1 antitrypsin levels were measured and found to be within the normal range (1.30 g/L, reference range: 0.9-2).

A physical examination revealed 2–3 mm papules on the shoulders, cheeks and forehead (Figure 4), and a pathological examination of the biopsied material confirmed the diagnosis of trichodiscoma. A FLCN gene analysis was then performed and found to be positive. As a result, the patient, who had bullous lung disease, cutaneous lesions diagnosed as trichodiscoma and a positive FLCN gene sequencing was diagnosed with BHDS. Due to the increased risk of renal malignancies, a renal ultrasound was performed, with normal results. The patient was placed under regular follow-up.

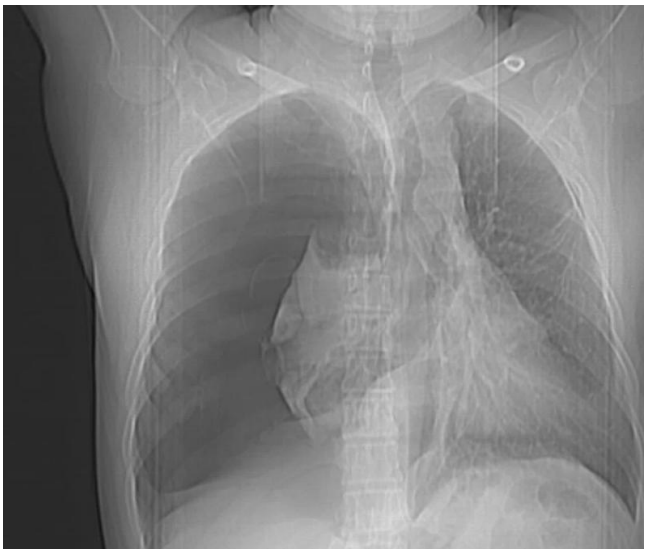

Figure 1: Posteroanterior (PA) chest radiograph showing right-sided pneumothorax

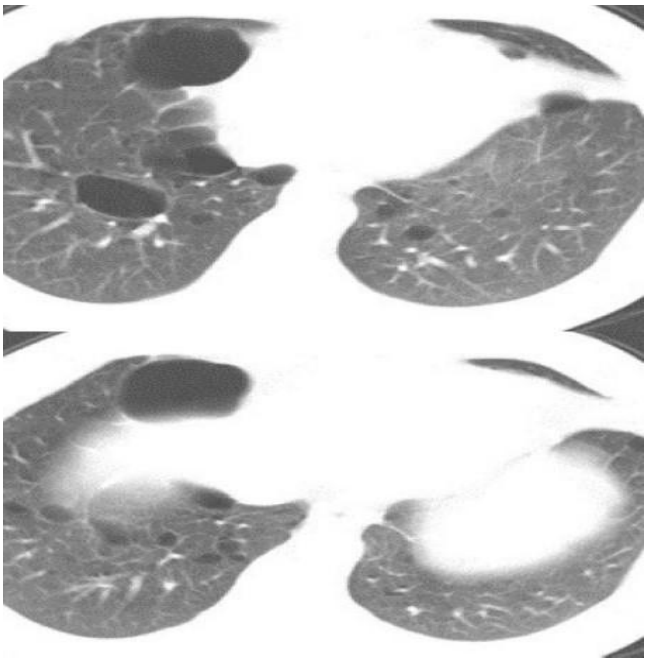

Figure 2: Chest CT demonstrating bilateral pulmonary cysts

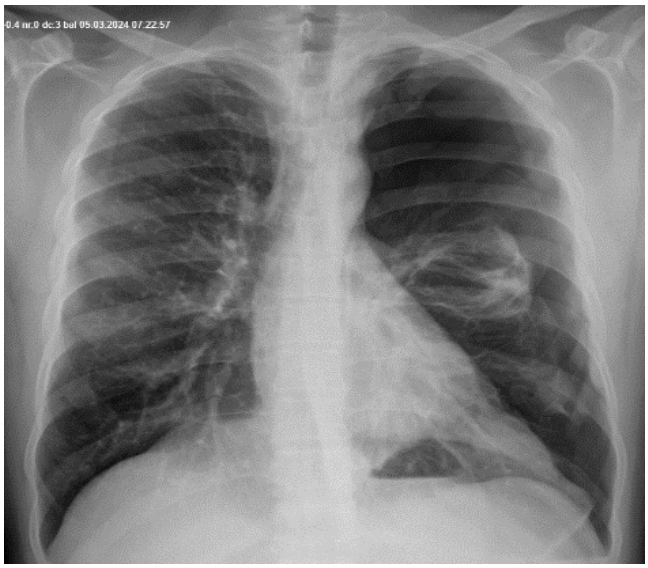

Figure 3: Posteroanterior (PA) chest radiograph showing left-sided pneumothorax

DISCUSSION

BHDS is a rare autosomal dominant disorder characterized by benign cutaneous lesions in the head and neck region, pulmonary cysts or spontaneous pneumothorax, and an increased risk of renal malignancies. A folliculin (FLCN) gene mutation is present in BHDS (1,2). Our patient was found to have trichodiscomas in the head and neck region, along with pulmonary cysts. The FLCN gene mutation was detected as positive. Among the pulmonary manifestations, multiple, irregularly shaped, thin-walled cysts located predominantly in the lower lobes and subpleural regions may be observed, along with secondary spontaneous pneumothorax (3). In our case, bilateral diffuse multiple thin-walled cysts were identified predominantly in the lower lobes, and recurrent pneumothorax episodes were also noted.

BHDS should be considered in the differential diagnosis of cases where pneumothorax is accompanied by bullae, predominantly in the lower lobes and subpleural regions. Patients should be informed about the potential risk of new pneumothorax episodes, and should be advised to avoid activities that involve pressure changes, such as scuba diving and air travel. The presented case highlights the importance of considering BHDS in patients who present with recurrent spontaneous pneumothorax.

Fibrofolliculoma and trichodiscoma are among the specific cutaneous manifestations of BHDS, and in the presented case the pathological diagnosis was confirmed as trichodiscoma. Acrochordons are common skin lesions observed in both the general population and BHDS (1). Acrochordons are not specific for BHDS, and their high prevalence in the general population may lead to delayed diagnosis in the affected. Patients should thus be evaluated for additional symptoms, and further investigations should be carried out when necessary.

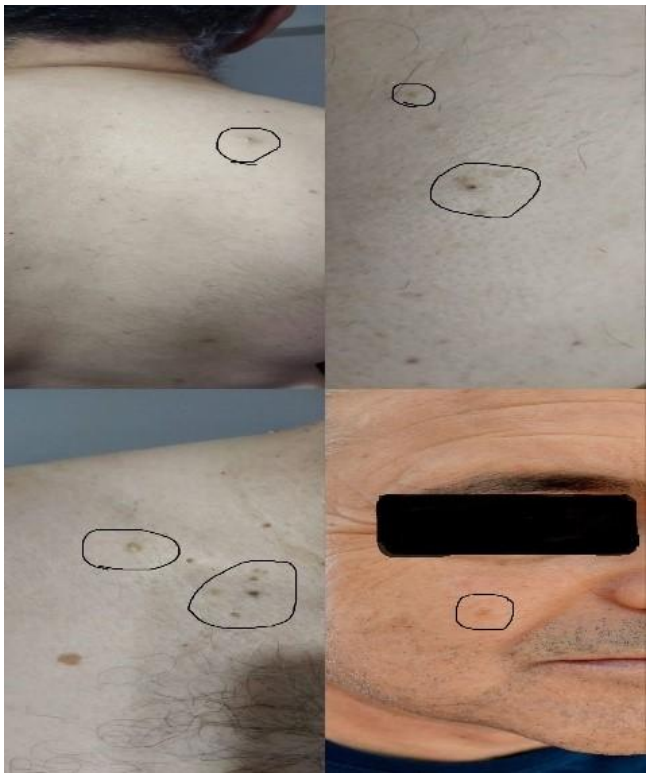

Figure 4: Clinical image showing 2–3 mm papules on the patient's shoulders, cheeks and forehead. The diagnosis of trichodiscoma was confirmed by a histopathological examination

Table 1: Diagnostic criteria of BHDS

BHDS Diagnostic Criteria
For a diagnosis of Birt-Hogg-Dubé Syndrome (BHDS), patients must meet either one major criterion or two minor criteria
Major Criteria
1. Presence of five or more fibrofolliculomas or trichodiscomas, at least one of which is confirmed by histopathology, developing in adulthood.
2. Presence of a pathogenic folliculin (FLCN) gene mutation.
Minor Criteria
1. Presence of multiple, bilateral, and basally located lung cysts, with or without spontaneous pneumothorax.
2. Diagnosis of renal cancer, characterized by early onset (before age 50), multifocal or bilateral presentation, or a mixed chromophobe and oncocytic histopathology.
3. Family history of BHDS in a first-degree relative

The clinical manifestation of greatest concern in BHDS is renal tumors. BHDS is commonly associated with chromophobe and hybrid chromophobe/oncocytic tumors (4). It has also been associated, albeit less frequently, with intestinal polyps, thyroid cysts and nodules, parathyroid adenomas, oncocytomas and melanomas (5). Given the potential presence of malignancies, screening tests were performed in the present case. Patients with BHDS should undergo periodic evaluations for malignancy risk. Diagnoses of BHDS are established based on clinical suspicion, imaging, skin biopsy and genetic testing. The diagnostic criteria determined by the European BHD Consortium are presented in Table 1. In the presented case, the

patient met two major criteria and one minor criterion, and since the diagnostic criteria were fulfilled, the patient was diagnosed with BHDS.

Given the potential complications associated with BHDS, clinicians should maintain a high index of suspicion in patients presenting with recurrent spontaneous pneumothorax and characteristic dermatological findings. Early diagnosis and long-term surveillance are crucial for the prevention of morbidity and appropriate management. BHDS should be considered in patients with cystic lung disease, especially those with a family history or those reporting skin lesions. Recognizing BHDS early can facilitate timely interventions and reduce the risk of severe complications, including renal malignancies, and close follow-up and periodic evaluations are recommended for optimal patient care.

CONCLUSION

BHDS should be considered in a differential diagnosis of rare cystic lung diseases in patients with recurrent pneumothorax and prominent skin findings. Recognizing BHDS early can facilitate timely interventions and reduce the risk of severe complications, including renal malignancies, and close follow-up and periodic evaluations are recommended for optimal patient care.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - H.A.U., O.Y., Ş.T.G., A.Y.; Planning and Design - H.A.U., O.Y., Ş.T.G., A.Y.; Supervision - H.A.U., O.Y., Ş.T.G., A.Y.; Funding - H.A.U., O.Y., Ş.T.G., A.Y.; Materials - H.A.U., O.Y., Ş.T.G., A.Y.; Data Collection and/or Processing - H.A.U., O.Y., Ş.T.G., A.Y.; Analysis and/or Interpretation - H.A.U., O.Y.; Literature Review - H.A.U., O.Y.; Writing - H.A.U., O.Y.; Critical Review - H.A.U.

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