CASE REPORT

A Rare Case of Spontaneous Pneumothorax Recurrence 30 Years After Surgery in a Patient with Birt-Hogg-Dube Syndrome: Case Presentation and Short Review of the Literature

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ABSTRACT

Background: Birt-Hogg-Dube syndrome (BHDS), also known as Hornstein–Knickenberg syndrome is a rare, autosomal dominant genetic disorder characterized by a triad of clinical manifestations: skin fibrofolliculomas, renal tumors, and multiple pulmonary cysts. The exact incidence of BHDS syndrome is unknown. This hereditary syndrome is caused by mutations in the folliculin (FLCN) gene, located on chromosome 17p11.2, which encodes the folliculin protein. **Objective:** This case report aims to highlight the importance of increased vigilance and long-term follow-up in BHDS patients, even decades after surgical intervention, to detect and manage potential pulmonary complications effectively. **Case presentation:** We present a unique case of spontaneous pneumothorax recurrence in a 63-year-old patient with a history of Birt-Hogg-Dube syndrome. The patient had undergone surgical treatment for pneumothorax 30 years ago and remained asymptomatic until presenting to our clinic with acute dyspnea and a dry cough. A recurrent pneumothorax was diagnosed and treated with a chest tube. Further chest imaging revealed extensive ground-glass opacities and cysts in both lungs. The patient was diagnosed with active pneumonia. A conservative approach was adopted due to the pneumonia diagnosis, and the patient showed a successful recovery without pneumothorax recurrence. **Conclusion:** This case highlights the importance of long-term follow-up in patients with Birt-Hogg-Dube syndrome and previous pneumothorax episodes.

Keywords: Spontaneous pneumothorax, pneumothorax recurrence, Birt-Hogg-Dube syndrome.

1. BACKGROUND

Birt-Hogg-Dube syndrome (BHDS), also known as Hornstein–Knickenberg syndrome is a rare, autosomal dominant genetic disorder characterized by a triad of clinical manifestations: skin fibrofolliculomas, renal tumors, and multiple pulmonary cysts (1, 2). The exact incidence of BHDS syndrome is unknown (2). This hereditary syndrome is caused by mutations in the folliculin (FLCN) gene, located on chromosome 17p11.2, which encodes the folliculin protein (3). The folliculin protein plays a crucial role in cellular signaling pathways, including the mechanistic target of rapamycin (mTOR) pathway, involved in cell growth and proliferation (1-3).

Pulmonary manifestations of BHDS are a significant concern, with the development of multiple lung cysts predisposing patients to spontaneous pneumothorax (SP), especially in individuals aged between 20 and 40 years. Spontaneous pneumothorax occurs due to the rupture of subpleural cysts, leading to the escape of air into the pleural space and lung collapse. The risk of pneumothorax recurrence in BHDS patients varies, and long-term follow-up is essential due to the potential for delayed recurrence even after surgical intervention (1- 2).

2. OBJECTIVE

We present an exceptional case of spontaneous pneumothorax recurrence in a 63-year-old patient with a history of BHDS. Despite the previous surgical management, the patient experienced a recurrent episode of pneumothorax, which required immediate medical attention. This case report aims

to highlight the importance of increased vigilance and long-term follow-up in BHDS patients, even decades after surgical intervention, to detect and manage potential pulmonary complications effectively. Through this report, we hope to contribute to the existing knowledge and promote awareness among healthcare professionals about this rare but clinically significant syndrome.

3. CASE PRESENTATION

A 63-year-old male patient presented to the emergency room of our clinic due to acute dyspnea and a dry cough. The patient had already received a one-week course of amoxicillin/clavulanic acid antibiotics from the general practitioner for suspected pneumonia. The patient, along with his brother, has a history of Birt-Hogg-Dube syndrome. The patient presented the typical skin lesions (fibrofolliculomas) in the head and upper torso.No history of renal problems was reported. Thirty years ago, the patient experienced two episodes of spontaneous pneumothorax, which were surgically managed through thoracoscopic partial pleurectomy and double extraanatomical wedge resection. Subsequently, he remained free of any pulmonary issues, and there has been no requirement for specific Birt-Hogg-Dube syndrome-related treatment.

Investigations

Chest X-ray revealed a right-sided pneumothorax, which was promptly managed by chest drainage, resulting in complete lung expansion (Figure 1). Computed tomography (CT) of the thorax showed extensive map-like ground-glass opacities with thickened interlobular septa, resembling a crazy-paving pattern, consistent with acute interstitial pneumonia, pulmonary alveolar proteinosis, or atypical infiltrates (Figure 2, 3). Multiple cysts were observed in both lungs, with the largest cyst measuring approximately 2.5 cm in the right lower lobe. Mild emphysematous changes were noted in the left lung without infiltrates. Bronchoscopy revealed signs of chronic bronchitis, and bronchoalveolar lavage culture showed evidence of Escherichia coli, leading to a change in antibiotic therapy to clarithromycin based on the antibiogram.

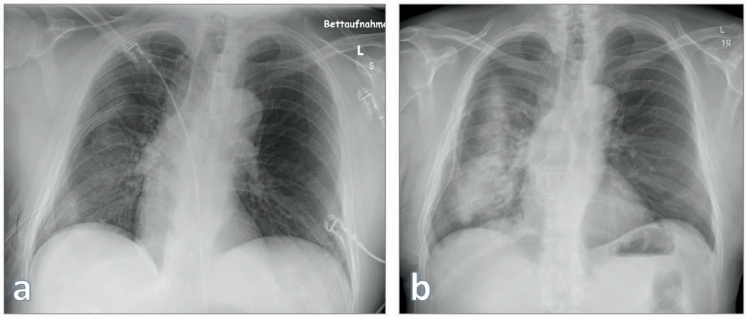

Figure 1. Chest X-Ray a. directly after the insertion of the chest tube showing the complete expansion of the lung and b. one day after revealing the manifestation of pneumonia.

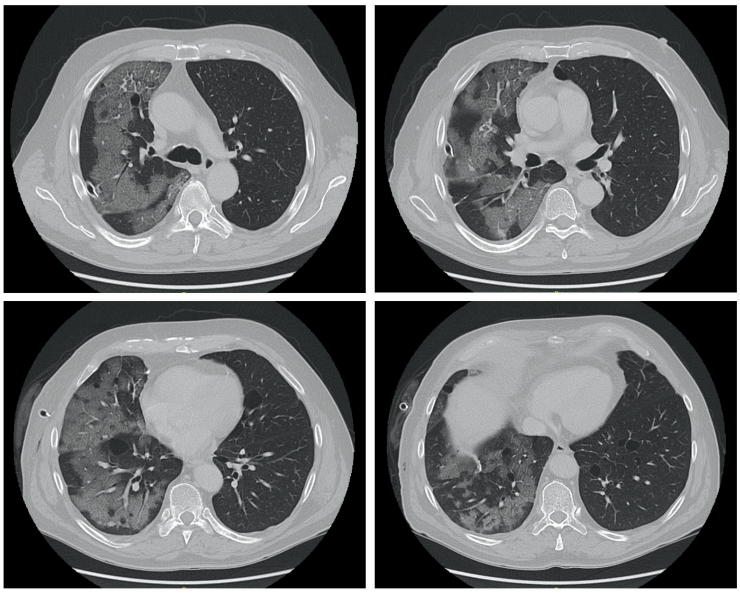

Figure 2. Chest computed tomography images revealing the map-like ground-glass opacities and the crazy-paving pattern, consistent with acute interstitial pneumonia. The multiple cysts in both lungs are obvious, as well as mild emphysematous lesions.

Treatment and Management

Histological examination ruled out pulmonary alveolar proteinosis and malignancy, supporting the diagnosis of active pneumonia. Given the diagnosis of active pneumonia, operative treatment was not advised, and conservative therapy was initiated. The chest drainage was removed after 4 days, and the patient's inpatient course was uneventful (Figure 4). After 8 days of hospitalization, the patient was discharged with no signs of pneumothorax recurrence.

Follow-up and Outcomes

Follow-up appointments after one week and one month showed no evidence of pneumothorax recurrence, and the patient remained asymptomatic.

4. DISCUSSION

This case highlights the importance of recognizing the potential for SP recurrence in patients with BHDS, even decades after previous surgical intervention. The presence of ground-glass opacities and cysts on imaging necessitates a comprehensive diagnostic evaluation to differentiate between various pulmonary conditions. In this case, active pneumonia was successfully managed conservatively, resulting in a favorable outcome.

As previously mentioned, BHDS presents as a rare and highly diverse disease, often leading to undiagnosed or misdiagnosed cases. This syndrome can frequently be mistaken for primary spontaneous pneumothorax or emphysema, further complicating the diagnostic process. Unfortunately, the time between symptom onset and BHDS diagnosis can be considerable and is influenced by gender, posing significant health risks to both patients and their families. The exact prevalence of BHDS remains uncertain, with only a few hundred families reported to date with FLCN mutations, and the initial symptoms can vary widely among affected individuals. Although the syndrome's diagnosis and treatment rely on its three primary classic manifestations, rare presentations such as pericardial cysts, parotid oncocytomas, and even colorectal cancer have also been reported (4-5).

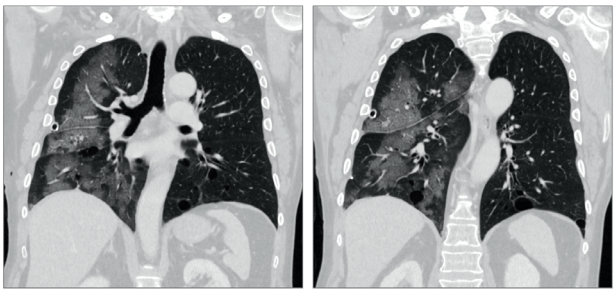

Figure 3. Coronary reconstruction of the CT images demonstrating the interstitial pneumonia and the multiple pulmonary bullae.

Historical references to the syndrome

BHDS, named after its discoverers the Canadian physicians Arthur R. Birt, Georgina R. Hogg, and James Dubé in 1977 (6), is characterized by fibrofolliculomas, trichodiscomas, and acrochordons on the scalp, forehead, face, neck, and upper torso in some family members after turning 25. The hereditary nature of these skin manifestations follows an autosomal dominant inheritance pattern. However, as early as 1927, Burnier and Rejsek published a case, possibly the first instance of BHDS, describing perifollicular fibromas on a 56-year-old woman's face. Hornstein and Knickenberg later described the first instance of BHD with systemic symptoms in a family, including two siblings and their father, all exhibiting colon polyps and characteristic fibrofolliculomas. The father also had lung and kidney cysts (7).

In 1999, Toro et al. established the autosomal dominant inheritance of skin manifestations and renal cell carcinoma (RCC) in BHDS while studying patients with renal tumors, who showed an overrepresentation of lung manifestations (7). Subsequent research provided crucial genetic insights, locating the BHDS gene locus on chromosome 17 and linking the syndrome to the FLCN gene on the same chromosome, which encodes the folliculin protein. Patients with BHDS were found to have a sevenfold increased risk of RCC development and a 50-fold risk of SP (8).

Further studies revealed FLCN's significance and its interacting proteins. Common mutations in the FLCN gene led to premature termination and loss of function of folliculin, identifying FLCN as a tumor suppressor gene (9). Additionally, FLCN was found to participate in various metabolic pathways, cellular processes, and signaling pathways, including its modulation of the energy-sensing mTOR pathway, regulation of PGC1α and mitochondrial biogenesis, influence on cell-cell adhesion and Rho A signaling, control of TFE3/TFEB transcriptional activity, role in amino acid-dependent activation of mTORC1 on lysosomes through Rag GTPases, and regulation of autophagy (3). The complexity of FLCN's role in cellular function and signaling highlights the need for further research to understand and potentially develop therapeutic strategies for BHDS.

Pulmonary manifestations

Pulmonary manifestations are a very significant aspect of the syndrome. Lung cysts are prevalent in a substantial number of BHDS patients (67-90%)and are typically located in the basal regions of the lungs.The presence of lung cysts can increase the risk of SP in affected individuals and about 40% of them experienceSP (10). SP risk in BHDS patients is 50 times higher compared to the general population, and around 40-75% of these patients may experience recurrent SP (10). SP usually manifests in adults, with a median age of 38 at presentation. The development of cysts or SP is generally not considered to be associated with gender, smoking, or other risk factors, but recent studies have indicated that sex, smoking history, and skin manifestations at BHDS diagnosis may influence clinical features of BHDS-associated pneumothorax. Lung function is generally unaffected (11).

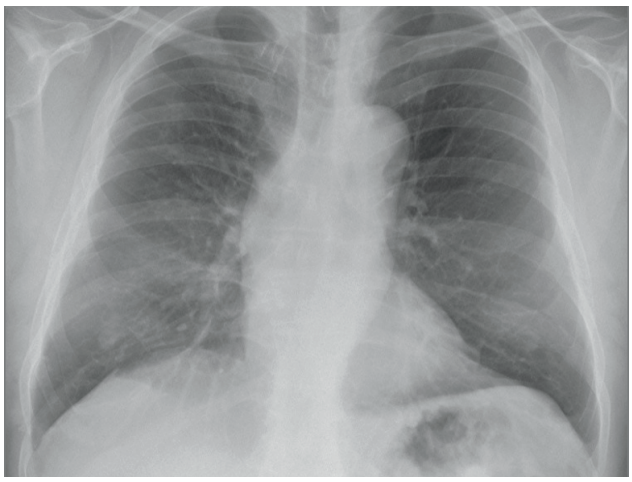

Figure 4. Chest X-ray before the discharge of the patient showing a remission of the pneumothorax and pneumonia.

Diagnosis of lung cysts involves computed tomography (CT), revealing variable cyst numbers, typically bilateral, irregularly shaped, and located in the lower basal lung zones. Larger cysts and basal localization correlate with a higher SP risk (11). Reliable CT features, such as cyst size > 2.1 cm predominantly in bilateral basal lungs, suggest the need for FLCN gene mutations screening (24). Differential diagnoses include other cystic lung diseases like Langerhans cell histiocytosis, lymphangioleiomyomatosis (LAM), or conditions with high secondary spontaneous pneumothorax risk (Marfan syndrome, chronic obstructive lung disease, emphysema). The role of BHDS in chronic obstructive pulmonary disease (COPD) development remains inconclusive (12).

Sasso et al. categorized pulmonary manifestations into Definite, Probable, and Possible pulmonary BHDS based on HRCT findings, skin biopsy, family history, and genetic testing (13):

Definite pulmonary BHDS: The diagnosis is established through specific lung findings on high-resolution CT (HRCT) and a positive skin biopsy for fibrofolliculoma. Alternatively, it can be confirmed by compatible HRCT along with a documented family history of BHDS in a first- or second-degree family member. Additionally, tissue confirmation of renal chromophobe adenoma or oncocytoma, or positive genetic testing for BHDS can support the diagnosis.

Probable pulmonary BHDS: The classification requires HRCT findings that are characteristic of the condition, while excluding the possibility of Tuberous Sclerosis Complex (TSC) and Lymphangioleiomyomatosis (LAM). The presence of a personal or family history of pneumothorax can contribute to this classification. Alternatively, if compatible HRCT findings are observed, BHDS can be considered probable when excluding TSC and LAM and presenting any of the following: a family or personal history of renal tumors, skin angiofibroma, or renal angiomyolipoma.

Possible pulmonary BHDS: For this diagnosis HRCT should demonstrate compatible or characteristic features that align with the condition's typical manifestations.

Sasso and colleagues additionally also categorized lung HRCT findings into two distinct groups (13):

Characteristic lung HRCT findings: This category encompasses the presence of multiple thin-walled, round, elliptical, or lentiform well-defined air-filled cysts. These cysts demonstrate a predominant distribution in the basilar, medial, and subpleural regions, while maintaining preserved or increased lung volume. Notably, there is no evidence of internal structure or other significant pulmonary involvement, specifically no signs of interstitial lung disease.

Compatible HRCT findings: The compatible HRCT findings refer to the presence of thin-walled cysts. However, these cysts may deviate from the more typical elliptical shape or subpleural distribution observed in characteristic lung HRCT findings.

Asymptomatic cases are common, with symptoms arising during SP. Regarding the treatment of BHDS-related pneumothorax, a universally accepted consensus is still lacking. Nevertheless, the management of SP in BHDS remains consistent with the treatment for pneumothorax caused by other factors. Treatment approaches for BHDS-related pneumothorax vary, but chemical and surgical pleurodesis have shown potential. Thoracoscopic pleural covering technique is being explored for pneumothorax recurrence prevention (14). The recurrence rate for BHDS-related pneumothorax is 9.1% and 53.1% after surgery and conservative therapy, respectively, warranting further research on long-term therapeutic effects.

BHDS patients should be advised to avoid smoking, radiation, and activities like scuba diving with high atmospheric pressure. Timely diagnosis based on clinical symptoms and family history can offer significant health benefits for patients and their families (15).

Dermatological manifestations

The skin manifestations of BHDS, especially the fibrofolliculomas, can serve as important diagnostic indicators for BHDS. Thea are observed in approximately 58-90% of BHDS patients (1-2). Generally, these benign lesions typically do not require any treatment, except for cases of cosmetic purposes. The tumors usually appear during the third or fourth decade of life, rarely before 25 years of age (1-2).

Fibrofolliculomas are the most common dermatological lesions, along with trichodiscomas and acrochordons. Fibrofolliculomas are usually multiple, slightly elevated, pale yellow or white dome-shaped tumors, mostly found in the retroauricular area, face, neck, and upper torso. They closely resemble trichodiscomas, with both believed to be part of the same morphological spectrum. Acrochordons are also prevalent, found in 25% of the general population, and are associated with higher age and obesity. Diagnosing such benign skin tumors offers an opportunity to identify BHDS patients before lung cysts and/or renal tumors develop. While frequently observed in BHDS patients, the relationship may be coincidental due to their common occurrence (16).

While the skin manifestations are typically benign and non-life-threatening, their presence can prompt further investigation to identify potential underlying systemic manifestations and guide appropriate management strategies for affected individuals. Histological confirmation through skin biopsies verifies a diagnosis of fibrofolliculomas, and in children or patients with no family history, these benign skin tumors may be the initial symptom of BHDS, raising suspicion for the syndrome. Differential diagnoses include sebaceous hyperplasia and tumors like fibroadenoma, basal cell carcinoma, and other syndromes featuring multiple benign tumors (17).

Once skin lesions have developed, they are permanent, and curative treatments remain unavailable. Treatments for cosmetic reasons involve surgical removal or CO_2 laser procedures, but these measures offer only temporary relief, with the lesions often recurring over time. Topical use of mTOR inhibitor rapamycin on fibrofolliculoma in BHDS patients has shown no significant effect (18).

Renal manifestations

Renal manifestations are a key feature of BHDS. Literature data show that BHDS patients face higher renal tumor risk. Individuals with BHDS may develop multiple renal tumors, including renal cell carcinomas (RCC) and oncocytomas. Approximately 30% develop renal tumors, representing seven-fold increased risk. Age plays a significant role and patients>70-year-olds have 16% relative RCC risk. RCC commonly emerges around the age of 50, but BHDS's earliest onset was at 20. BHDS renal tumors differ histologically from sporadic RCCs. Typical RCCs are 85% clear cell carcinomas (ccRCC), 5–10% papillary (pRCC), 5–10% chromophobe (chRCC), and 3–5% benign oncocytomas (19). BHDS presents 50% hybrid chRCC/oncocytoma, 33% chRCC (both low malignancy), 9% aggressive ccRCC, and 5% benign oncocytomas. 56% have bilateral tumors and 65–77% multiple tumors.

RCC symptoms unfortunately often appear late. The main manifestations includehematuria, flank pain, fatigue, and palpabletumors, and in some advanced cases bone pain,anemia and weight loss (20). All diagnosed BHDS patients are advised to undergo abdominal screening and followfurther regular screening even if no tumors are initially detected. Screeening may include ultrasonography, CT, or MR imaging. If necessary invasive diagnostic and fine needle biopsy may be considered to confirm diagnosis (20). BHDS patients without renal tumors should undergo abdominal MR imaging screening every 1–5 years based on their risk profile. Those with renal tumors require closer monitoring, with patients having tumors< 1 cm offered annual MRI and those with tumors> 1 cm evaluated more frequently, considering size, location, and growth rate. Small renal tumors in BHDS are generally slow-growing. Prognosis varies, depending on histological subtype, tumor size, and metastatic disease. Around 80–85% of BHDS kidney cancers exhibit slow growth with low metastatic potential and a favorable prognosis. Conversely, ccRCCs are more aggressive and prone to metastasis.

Surgical treatment is the gold standard therapeutic approach when renal tumors are diagnosed. For sporadic renal cancer without metastases, depending on tumor size,laparoscopic nephrectomy or partial nephrectomy is indicated. Small renal tumors (<4 cm) may alternatively be treated with radiofrequency ablation (RFA) or cryoablation. In cases of metastatic ccRCC, chemotherapy is ineffective, and treatment is purely palliative, relying on targeted and immune

agents (20). Nephron-sparing surgical techniques are recommended to preserve kidney function. Radical nephrectomy should be reserved for cases where partial nephrectomy would lead to an inferior outcome or non-functioning kidney remnant, considering BHDS patients' risk of multiple and bilateral renal tumors. Surgery should thus be postponed until the largest solid tumor reaches 3 cm in diameter (20).

It is essential for clinicians to be vigilant about renal manifestations in BHDS patients, as early detection and intervention can lead to better outcomes and management of the condition. Regular renal imaging and close follow-up are crucial to identify any changes in tumor size or potential development of new lesions, thus ensuring timely and appropriate medical interventions to preserve renal function and overall health.

5. CONCLUSION

We report an unusual case of spontaneous pneumothorax recurrence in a patient with Birt-Hogg-Dube syndrome, emphasizing the importance of vigilant long-term follow-up in such patients. Understanding the characteristic imaging findings and employing a multidisciplinary approach are crucial for accurate diagnosis and appropriate management of pulmonary complications in Birt-Hogg-Dube syndrome. Further studies are warranted to enhance our understanding of this rare syndrome and its associated pulmonary manifestations.

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- **Conflicts of interest:** There are no conflicts of interest.
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