Decoding the missing link in cystic lung disease: a unique case series of BHD syndrome

Mohd Imran Shamsi[1*], Papia Mondal[1], Amitabha Sengupta[2], Sudipta Pandit[3]

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ABSTRACT

Background: Birt-Hogg-Dubé syndrome (BHDS) is a very rare autosomal dominant inherited disease caused by mutations in the folliculin gene, characterized by a triad of clinical manifestations involving the skin, lungs, and kidneys.

Cases Presentation: We present a case series of four cases of BHDS with diverse phenotypic spectrum. Case 1 is a 48-year-old female who presented with right-sided hydropneumothorax and a typical triad of BHDS-cystic lung disease, fibrofolliculoma, and renal mass. Case 2 is a 31-year-old young male who presented with left-sided pneumothorax and cystic lung disease with no other systemic involvement. Case 3 is a 43-year-old female who presented with recurrent left-sided pneumothorax and cystic lung disease with no other systemic clinical manifestations. This particular case had a family history of pneumothorax. Case 4 is a 69-year-old female who presented with a chronic cough and right middle lobe pneumonia. She had typical nodular and papular skin lesions over the forehead and computed tomography-thorax showing bilateral cysts of varying size.

Conclusion: This case series highlights the diverse clinical spectrum of BHDS, emphasizing the importance of early recognition of this condition in patients with recurrent pneumothorax, genetic confirmation of the disease, and multidisciplinary management, including nephrology and pulmonology inputs to prevent complications such as recurrent pneumothorax and renal malignancies. Further research on genotype-phenotype correlation in BHDS is needed to optimize the diagnosis and treatment.

Keywords: Birt–Hogg–Dubé syndrome (BHDS), folliculin (FLCN) gene, renal cell carcinoma (RCC).

Type of Article: CASE SERIES **Speciality:** Pulmonary Medicine

Correspondence to: Mohd Imran Shamsi
*Senior Resident, Department of Pulmonary Medicine, Institute of Post Graduate Medical Education and Research (IPGME&R) 244, A.J.C. Bose Road, Kolkata 700 020, India.
Email: dr.shamsimran@gmail.com
Full list of author information is available at the end of the article.

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Background

Cystic lung diseases represent an umbrella term for a heterogenous group of disorders with shared radiographic features of multiple air-filled lucencies surrounded by discrete walls. Birt-Hogg-Dubé syndrome (BHDS) is an important part of the differential diagnosis of cystic lung diseases that include pulmonary Langerhans cell histiocytosis (PLCH), lymphangioleiomyomatosis (LAM), lymphocytic interstitial pneumonia, light chain deposition disease, amyloidosis, cystic metastatic disease, and neurofibromatosis type 1. It is a rare autosomal dominant monogenic disorder characterized by a triad of clinical manifestations involving the skin, lungs, and kidneys [1]. Click or tap here to enter text. Fewer than 1,000 families with BHDS have been described across all continents. Studies have reported prevalence estimates between 1 in 200,000 and 1 in 500,000 for BHD [2].Click or tap here to enter text. This syndrome is caused by mutations in the folliculin (*FLCN*) gene, which encodes the tumor suppressor protein FLCN [1,3,4].Click or tap here to enter text. The hallmark features of BHDS include cutaneous benign skin tumors known as fibrofolliculomas, typically appearing on the face, neck and upper trunks [5],Click or tap here to enter text. pulmonary cysts that increase the risk of spontaneous pneumothorax [1],Click or tap here to enter text. and an increased risk of renal tumors, particularly renal cell carcinoma (RCC) [1].Click or tap here to enter text. The type and location of lung cysts in BHDS are strikingly different from the apical location seen in PLCH or the diffuse distribution in LAM. LAM typically shows evenly distributed, round, thin-walled cysts throughout the lungs, while PLCH often presents with irregular, bizarre-shaped cysts concentrated in the upper lobes and sparing the costophrenic angles. Lung cysts in the context of BHDS are typically lower lobe predominant, para-mediastinal, in relation to the fissures, and often elliptically shaped [6].Click or tap here to enter text.

FLCN, a tumor suppressor gene, comprises 14 exons located at chromosome 17 (Chr.17p11.2). More than 200 different types of pathogenic variants have been identified, which result in BHDS. The majority of *FLCN* mutations translate into truncated protein, including frameshift (small deletions or insertions), nonsense or splice-site variants, which supposedly lead to a loss of function of FLCN [7].Click or tap here to enter text. Several pathogenic variants were identified in every coding exon of *FLCN*. However, the polycytosine tract of exon 11 is thought to represent a mutation hotspot, and almost half of affected individuals harbor either the c.1285delC or the c.1285dupC variant [5].Click or tap here to enter text. The function of *FLCN* is believed to be implicated in the regulation of cell growth, proliferation, and survival through interactions with the mechanistic target of rapamycin (mTOR) signaling pathway [8].Click or tap here to enter text.

The mechanisms leading to the formation of lung cysts in BHDS are thought to be driven by dysregulated signaling pathways, including mTOR and 5′Adenosine Monophosphate-activated protein kinase, as a consequence of which there is deficient cell–cell adhesion. The "stretch hypothesis" proposes that cysts in BHD arise because of fundamental defects in cell–cell adhesion, leading to repeated respiration-induced stress and, over time, expansion of alveolar spaces particularly in regions of the lung with larger changes in alveolar volume and at weaker "anchor points" to the pleura [9].Click or tap here to enter text.

We present a case series of four patients of BHDS with variable clinical features.

Case 1

A 48-year-old, home-maker, non-smoker, female, known case of hypothyroidism on tablet thyroxine 25 micrograms, presented to us with a history of persistent dry cough for 1 year and exertional dyspnea [of Modified Medical Research Council (MMRC) grade II] for the last 6 months. She gave a history of sudden onset worsening of her breathlessness and right-sided chest pain for the last 3 days. Her chest x-ray was done on arrival to our facility, which showed hydro-pneumothorax on the right

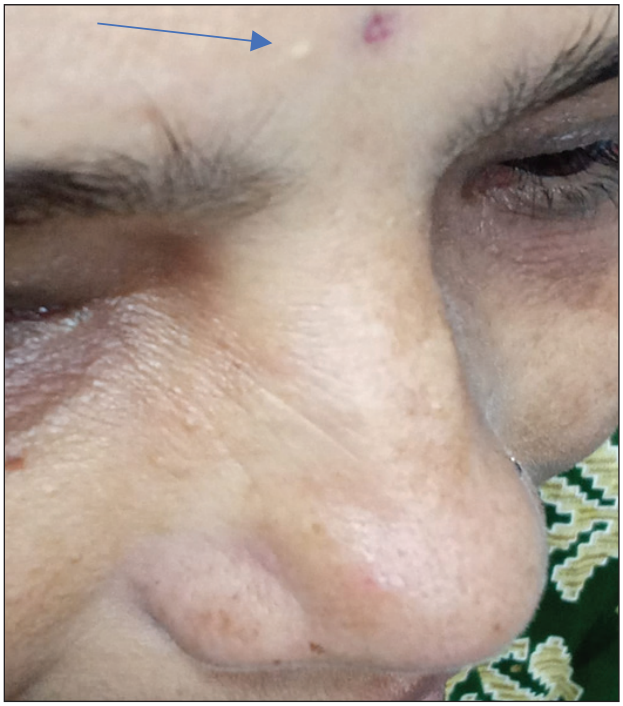

Figure 2. *White-coloured nodular skin lesions.*

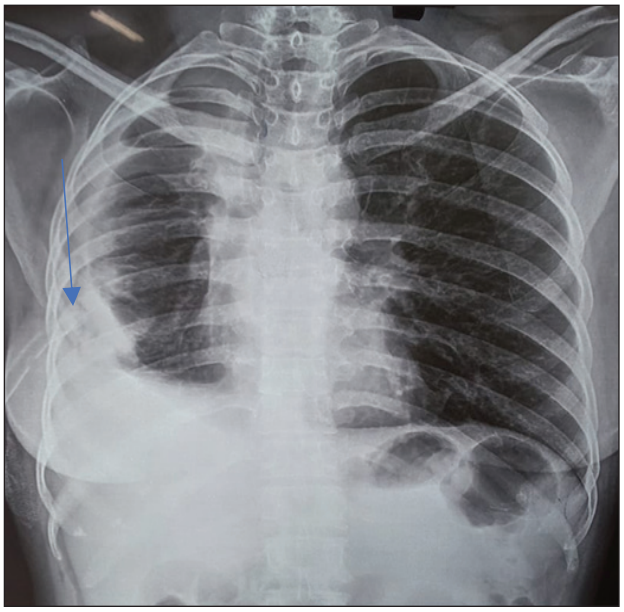

Figure 1. *Chest X ray hydro-pneumothorax on right side (ICD in situ).*

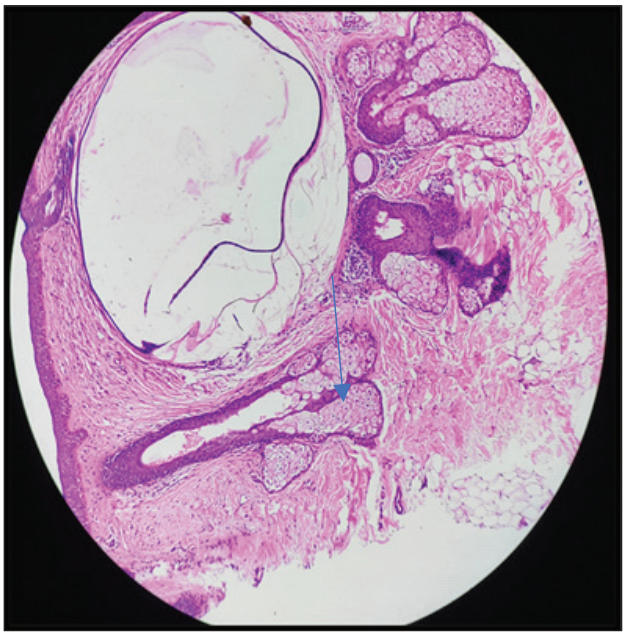

Figure 3. *Skin biopsy is suggestive of fibrofolliculoma.*

side (Figure 1). She was managed conservatively with intercostal tube drainage (ICD). About 500 ml of straw colored serous pleural fluid was drained, which relieved her symptoms drastically. There was no history of trauma, fever, hemoptysis, or weight loss. There was no significant family history. She denied any history of having connective tissue disease.

Her general physical examination was normal, except the skin, which had white-colored nodular lesions over the nasolabial folds and the forehead (Figure 2). Skin biopsy of the lesions was suggestive of fibrofolliculoma (Figure 3). Routine laboratory investigations were within normal limits. computed tomography (CT) thorax was done after stabilization and lung expansion, which revealed lenticular elongated cysts in the para mediastinal areas (Figure 4). CT abdomen showed a renal mass at the upper pole of the left kidney (Figure 5). After multidisciplinary discussion, *FLCN* gene sequencing was done, which showed heterozygous frameshift mutation (c.1285 del), one base pair deletion in exon 11 of the *FLCN* gene that results in a frameshift and premature truncation of the protein 39 amino acids downstream to codon 429 (p. His429ThrfsTer39), which confirmed the diagnosis of BHDS. As pleurodesis reduces the recurrence rate of pneumothorax by approximately half compared with conservative management, the procedure was done by our team with sterile talc (chemical pleurodesis) after taking proper consent from the patient. Nephrology unit opinion was also taken for her left renal mass and was advised to undergo surgical intervention. Partial nephrectomy of the left-sided renal mass was done. Histopathology revealed a chromophobe type of RCC. The patient was discharged with advice of regular follow-up. Her follow-up chest X ray after 6 months did not reveal any recurrence of pneumothorax.

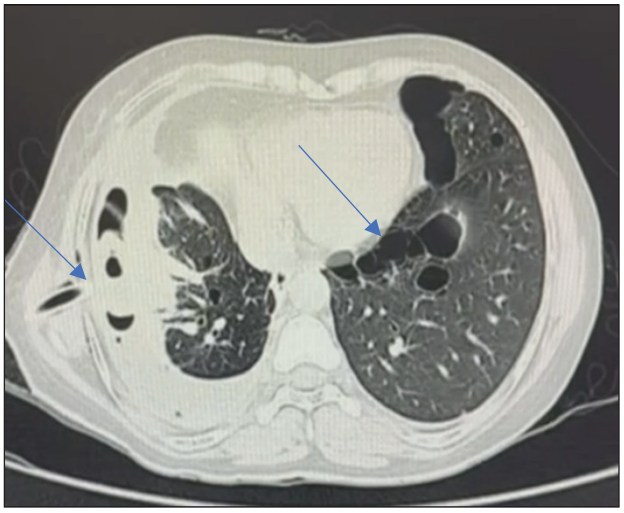

Figure 4. *CT-thorax showing right-sided hydropneumothorax and lenticular elongated cysts in the para mediastinal areas.*

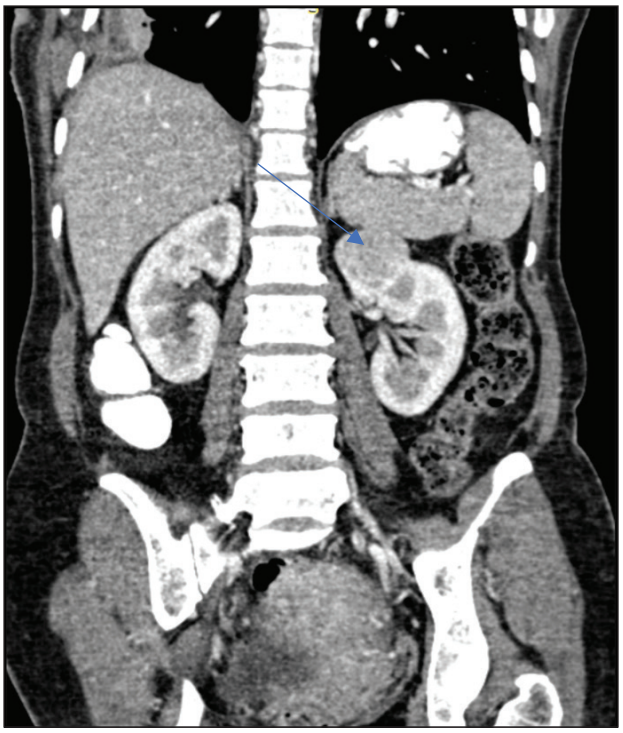

Figure 5. *CT abdomen showing renal mass at upper pole of left kidney.*

Case 2

A 34-year-old male, current smoker, school teacher by profession, presented to us with a history of dry cough for the last 2 years and exertional breathlessness (of MMRC grade II) for the last 1 year. Over the last 2 weeks, the patient developed left-sided pleuritic chest pain and worsened breathlessness to MMRC grade III. Chest x-ray on admission to our facility showed a pneumothorax on the left side (Figure 6) for which an ICD was inserted at the left fifth intercostal space in the triangle of safety. The patient felt symptomatically better after an ICD insertion.

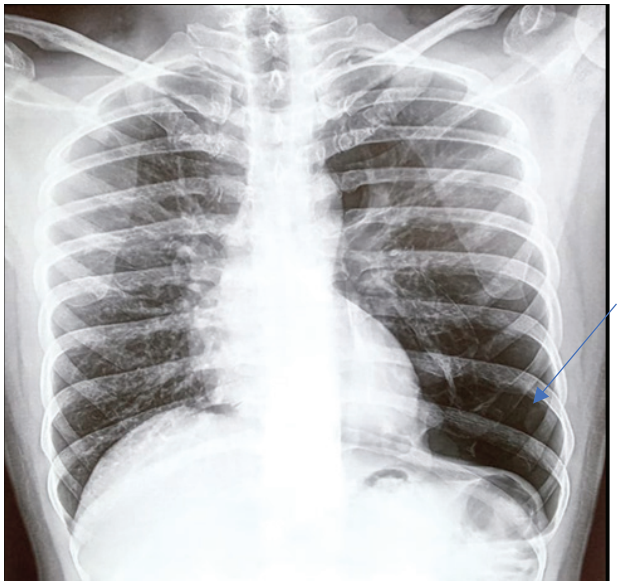

Figure 6. *Chest X-ray showing left-sided pneumothorax.*

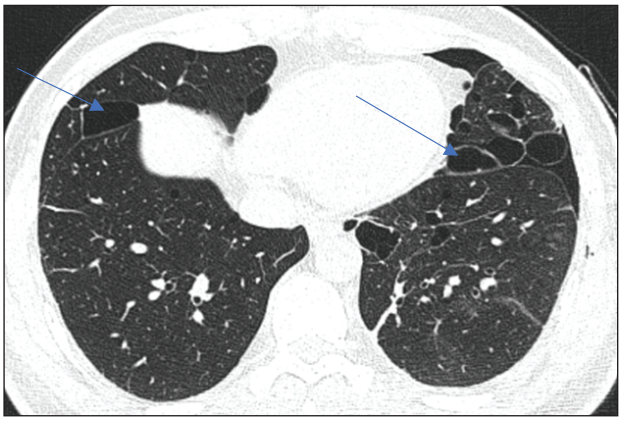

Figure 7. *CT thorax suggestive of cysts, predominantly at fissures and para mediastinum in both lungs.*

There was no history of trauma, fever, hemoptysis, or weight loss. There was no previous history of pulmonary tuberculosis. There was no significant family history. He denied any history of having connective tissue disease.

His routine laboratory investigations were within normal limit. His general physical examination was normal. CT thorax was done after resolution of pneumothorax, which revealed cysts, predominantly at fissures and para mediastinum in both lungs (Figure 7). His abdominal imaging did not reveal any abnormality. After the multidisciplinary discussion in our department, *FLCN* gene sequencing was done. A heterozygous nonsense variant in exon 11, c1215C>G was identified, which results into a stop codon, suggesting premature truncation of the protein at codon 405 (p. Tyr405Ter), which confirmed the diagnosis of BHDS. To avoid recurrence of pneumothorax, pleurodesis was done with sterile talc (chemical pleurodesis), and the patient was discharged with advice for regular follow-up. Till now patient is doing fine with no recurrence of pneumothorax.

Case 3

A 43-year-old home-maker, non-smoker, female was admitted to our facility with left-sided chest pain and progressive shortness of breath (from MMRC grade II to grade III) over the last 3 months, with significant worsening of her chest pain in the last 15 days prior to admission. She was diagnosed as a case of left-sided pneumothorax, and an ICD was given (Figure 8). There was a similar history of shortness of breath and chest pain 2 years back, for which she was treated at a local hospital conservatively. The patient also gave a family history of pneumothorax in her sister several years back. The old CT thorax of her sister also revealed multiple lung cysts.

Routine laboratory investigations were normal. CT thorax was done after the resolution of pneumothorax showing sparse lung cysts predominantly at para-mediastinal and sub-pleural locations (Figure 9). The Ultrasonography (USG) abdomen was normal. *FLCN*

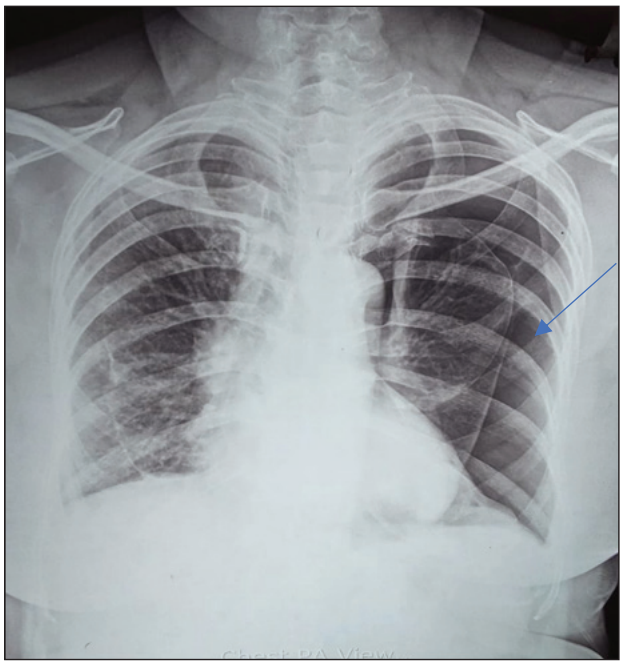

Figure 8. *Chest x-ray suggestive of left-sided pneumothorax.*

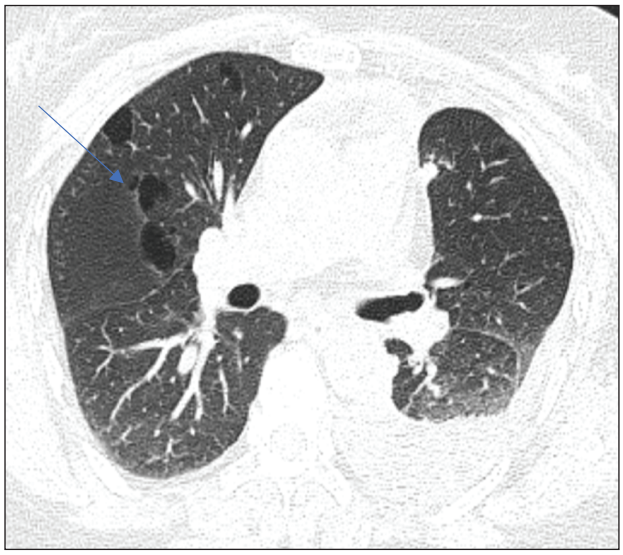

Figure 9. *High resolution computed tomography of thorax (HRCT) thorax showing non-uniform cysts of varying sizes, predominantly at subpleural and para mediastinal locations.*

gene sequencing was done, which revealed that a heterozygous nonsense pathogenic variant c.880G>T in exon 9 of the *FLCN* gene was detected, which confirmed the diagnosis of BHDS. In this case, chemical pleurodesis was done to avoid the recurrence of pneumothorax. Genetic testing was also done for her sister, the reports of which are awaited. Till now, both of these patients are doing fine and are under strict follow-up at our department.

Case 4

A 69-year-old home-maker, a non-smoking female, was presented to our out patient department with chronic

cough and expectoration for 1.5 months. Cough was intermittent with mucoid expectoration and was not associated with shortness of breath, chest pain, hemoptysis, or weight loss.

The patient gave a history of right-sided pneumothorax 1 year back, which was treated conservatively. There was no significant family history. She denied any history of symptoms related to connective tissue disease. The patient was addicted to chewing tobacco and betel nut for more than 30 years.

Her general physical examination was normal except the skin over the forehead, which showed numerous small nodular and papular lesions (Figure 10).

Routine laboratory investigations were within normal limits. Chest x-ray showed patchy opacity over the right lower zone (Figure 11). For further evaluation, CT thorax was done, which revealed multiple thin-walled cysts in all the lobes of both lung fields and patchy fibrosis and consolidation at the right middle lobe (Figure 12). The USG abdomen was normal. *FLCN* gene sequencing showed a heterozygous 1 base pair deletion in exon 11 of the *FLCN* gene that results in a frameshift and premature truncation of the protein 39 amino acids downstream of codon 429 (p. His429ThrfsTer39), which confirmed the diagnosis of BHDS. The presentation in this case, with chronic cough rather than pneumothorax, is unusual and differs from the usual typical presentations of BHDS. This could be because of underlying obstructive airway disease or recurrent lower respiratory tract infections. This case highlights the importance complete evaluation of a nonsmoker female patient who gives a history of just a chronic cough and no other systemic findings

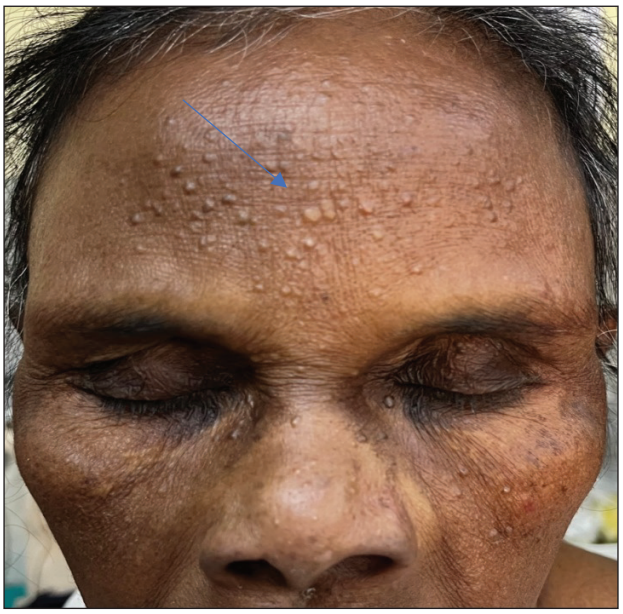

Figure 10. *Numerous small papular and nodular lesions were noted all over forehead and upper part of nose.*

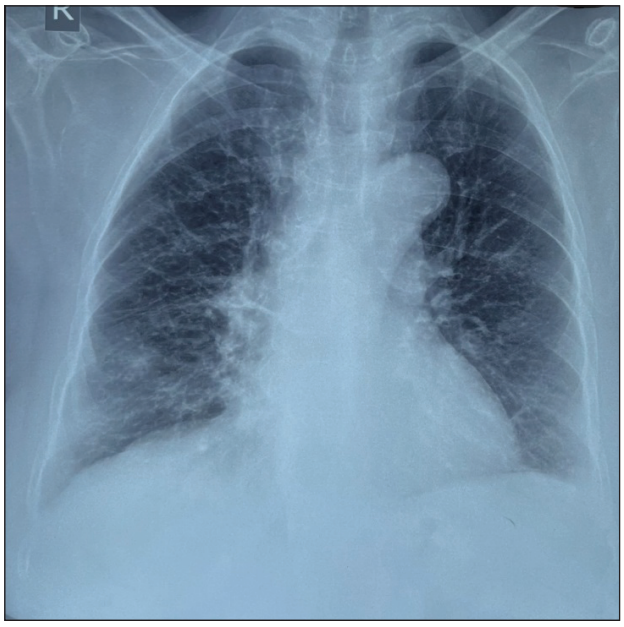

Figure 11. *Chest x-ray showing patchy opacities over the right lower zone.*

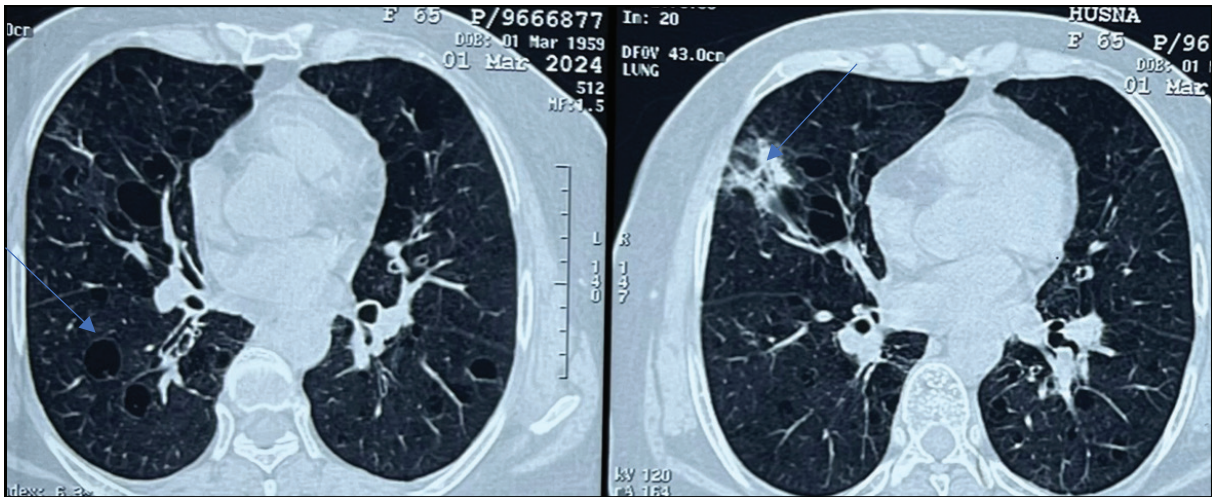

Figure 12. *HRCT thorax revealed multiple thin-walled cysts in all the lobes of both lung fields and patchy fibrosis and consolidations at the right middle lobe.*

as because in Asian countries like India, physicians can miss out such a diagnosis if early CT thorax and genetic testing are not done.

Discussion

Birt-Hogg-Dubé Syndrome (BHDS) is a rare autosomal dominant genodermatosis caused by mutations in the *FLCN* gene, located on chromosome 17p11.2. The *FLCN* gene encodes FLCN, a protein implicated in cell growth, proliferation, and survival, potentially through the mTOR signaling pathway. Loss of FLCN function is hypothesized to contribute to BHDS pathogenesis, leading to cutaneous, pulmonary, and renal manifestations [1,3,4].Click or tap here to enter text.

The diagnosis of BHDS, according to the European Birt-Hogg-Dubé consortium guidelines, is based on one major or two minor criteria. Major criteria include: (1) five or more fibrofolliculomas with at least one confirmed histologically, and (2) identification of a heterozygous pathogenic variant in *FLCN*. Minor criteria include: (1) multiple pulmonary cysts (bilateral basal predominance) with no other apparent cause, with or without spontaneous pneumothorax, (2) early-onset renal cancer (age < 50 years), (3) multifocal or bilateral renal cancer, (4) renal cancer of mixed chromophobe and oncocyte histology, and (4) first-degree relative with BHDS [1].Click or tap here to enter text.

While the classic triad of cutaneous, pulmonary, and renal involvement is diagnostic of BHDS, it is not universally present, and isolated pulmonary or renal features may predominate in an individual patient. Likewise, our only two cases that is case 1 and case 4, had characteristic skin lesions (fibrofolliculomas) while only case 1 had a renal mass (chromophobe variety of RCC). Notably, pulmonary cysts and recurrent pneumothorax can be the sole presenting features in some patients [10].Click or tap here to enter text. All of our cases had a presenting clinical feature of pneumothorax, except case number four, which presented to us with a chronic cough with expectoration, which was the atypical presentation.

Multiple bilateral pulmonary cysts are present in more than 80% of BHD patients [5,11,12].Click or tap here to enter text. Although occasionally reported in young adults (as seen here in case 2) [13],Click or tap here to enter text. cysts are typically more common in the 4th or 5th decades of life [1,14].Click or tap here to enter text. Patients with BHD are thought to be 50 times more likely than the general population to experience a pneumothorax [11].Click or tap here to enter text. The "stretch hypothesis" suggests that deficient cell adhesion and repetitive stretch-induced stress during respiration contribute to cyst formation [1]. Click or tap here to enter text. A family history of pneumothorax is present in 35% of patients with BHD [3].

Renal tumors, seen in approximately 15%-30% of patients, are predominantly chromophobe RCC (50%), although nonhybrid chromophobe RCC and oncocytomas can also be found in 34% and 5% of Birt-Hogg-Dubé syndrome patients [5].Click or tap here to enter text. Clear cell RCC is found in as many as 9% and papillary RCC in as many as 2% of patients with Birt-Hogg-Dubé syndrome [1].Click or tap here to enter text. These tumors exhibit low malignant potential compared to sporadic RCC, but their multifocality and bilateral nature necessitate regular surveillance. Specific *FLCN* mutations, such as c.1285dupC or c.1285delC, are associated with an increased risk of colorectal cancer [1,3,4,15].Click or tap here to enter text. The majority of patients with renal mass associated with BHDS will need only partial nephrectomy in their lifetime [1].Click or tap here to enter text. Despite being described, metastatic disease is uncommon [16].Click or tap here to enter text. There is a report that patients with the cytosine deletion mutation in the hypermutable hotspot of the *FLCN* gene have a significantly lower risk of developing renal tumors (6%) than patients with the cytosine insertion mutation in this hotspot (33%) [15,17,18].Click or tap here to enter text. A few studies, however, have suggested some possible genotype–phenotype associations. In particular, Toro et al. [17], reported an increased number of pulmonary cysts in individuals harboring mutations in exon 9, as well as more pneumothoraxes in individuals carrying variants located in exons 9 and 12. Another study found a significantly increased risk of pneumothorax for carriers of mutations c.1300G>C (59%) or c.250-2A>G (77%), as compared to those with the hotspot mutation c.1285dupC. The occurrence of lung adenocarcinoma, atypical adenomatous hyperplasia, or micronodular pneumocyte hyperplasia-like lesions has been reported in patients with BHDS [14].Click or tap here to enter text.

Skin lesions are often the presenting sign and reported in approximately 80%-90% of Caucasian patients with BHDS [1,3-5,12,17],Click or tap here to enter text. but this prevalence may be lower and less typical in Asian populations (around 30%) due to underreporting or genetic differences [1,3,19].Click or tap here to enter text. The most common skin lesions associated with BHDS include fibrofolliculomas, which are flesh-colored to whitish, painless, small, dome-shaped papules that typically measure 2-3 mm in diameter. They often appear during the 3rd to 4th decade of life and are commonly found on the scalp, face, neck, chest, and back. Trichodiscomas, which are considered to be different evolutionary stages of the same lesion as fibrofolliculomas and acrochordons (skin tags), are soft, small growths that hang off the skin, often found on the eyelids, neck, and axillae [4,19].Click or tap here to enter text. While common in the general population, they can also occur in individuals with BHDS [19].Click or tap here to enter text. Comparison of all four cases included in this case series is given in Table 1. Management of mainly consists of early pleurodesis in the case of pneumothorax,

Table 1. Comparison of the cases of BHD syndrome.

CASE NO.	AGE	SEX	CLINICAL PRESENTATION	FAMILY HISTORY OF PTX	SKIN	PULMONARY CYSTS (LOCATION)	ABDOMEN	FAMILY RELATIVES SCREENING	GENETIC VARIANT	OUTCOME/FOLLOW UP
1.	48	F	Hydropneumothorax	-	Fibrofolliculoma	Para mediastinal	Left renal mass	-	c.1285del	Partial nephrectomy done. No recurrence of pneumothorax after 6 months of pleurodesis.
2.	31	M	Pneumothorax	-	-	Fissure	-	Positive	c.1215C>G	Pleurodesis was done with no recurrence of pneumothorax
3.	43	F	Recurrent pneumothorax	Present	-	Subpleural and para mediastinal	-	Positive	c.880G>T	Failure of pleurodesis. Recurrent left sided pneumothorax
4.	69	F	Chronic cough Past H/O pneumothorax	-	Fibrofolliculoma	Para mediastinal	-	-	c.1285del	Follow up after 6 months- no development of pneumothorax

C = cytosine base; del = deletion; F = female; G = guanine base; H/O = history of; M = male; PTX = pneumothorax; T = thymine base.

periodic renal imaging for tumor detection, and diagnostic work-up in search of BHDS in relatives of the index patient [20].Click or tap here to enter text. It should be mentioned that renal malignancies are often asymptomatic before metastasizing. Therefore, follow-up with regular kidney surveillance is essential to detect renal neoplasms in an early stage. Moreover, detection before tumors reach a size of 2-3 cm enables nephron-sparing surgery and could improve patients' prognosis.

Preventative measures, including smoking cessation and pneumococcal and influenza vaccinations, are recommended for optimal pulmonary health. The first three cases had undergone a successful pleurodesis procedure without any recurrence of pneumothorax till now. Case 1 had undergone partial left-sided nephrectomy under nephrology care unit, and she is doing fine. Case 2, who was a young male smoker, was enrolled under smoking cessation program.

BHDS may be underreported because it is a rare disorder and not many clinicians are aware of the syndrome. Even when they are, they may not recognise it due to the heterogeneity of clinical manifestations between families, between patients within one family, and between patients of different ethnicities.

Conclusion

This case series highlights the diverse clinical spectrum of BHDS emphasizing the importance of early recognition of this condition in patients with recurrent pneumothorax, genetic confirmation of the disease, and multidisciplinary management, including nephrology and pulmonology inputs, to prevent complications such as recurrent pneumothorax and renal malignancies. Extensive research on genotype-phenotype correlation in BHDS is needed to further optimize the diagnosis and treatment.

What is new?

This case series presents the clinical heterogeneity of BHDS. While the classic triad of cutaneous, pulmonary, and renal involvement is diagnostic, it is not universally present, and isolated pulmonary or renal features may predominate. Different genotypic variants may have different phenotypic presentations & the possible genotype–phenotype association is an area of further research interest in BHDS.

List of Abbreviations

BHDS	Birt–Hogg–Dubé syndrome
FLCN	folliculin
RCC	renal cell carcinoma
PLCH	pulmonary langerhans cell histiocytosis
LAM	lymphangioleiomyomatosis
mTOR	mechanistic target of rapamycin
ICD	intercostal tube drainage

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding
None.

Consent for publication
Due permission was obtained from the patient/guardians of the patient to publish the case and the accompanying images.

Ethical approval
Ethical approval is not required at our institution to publish a case report/case series .

Author details
Mohd Imran Shamsi[1], Papia Mondal[1], Amitabha Sengupta[2], Sudipta Pandit[3]

1. Senior Resident, Department of Pulmonary Medicine, Institute of Post Graduate Medical Education and Research (IPGME&R) 244, A.J.C. Bose Road, Kolkata 700 020, India
2. Professor & Head of Department, Department of Pulmonary Medicine, Institute of Post Graduate Medical Education and Research (IPGME&R) 244, A.J.C. Bose Road, Kolkata 700 020, India
3. Professor, Department of Pulmonary Medicine, Institute of Post Graduate Medical Education and Research (IPGME&R) 244, A.J.C. Bose Road, Kolkata 700 020, India

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