ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Case Series

Birt-Hogg-Dubé Syndrome: How to Consider Diagnosis?

MA Makarova[1,2,3], GE Baimakanova[1,4]*, OA Denisenko[4] and EN Pirogova[4]

[1]Federal State Autonomous Educational Institution of Higher Education "NI Pirogov Russian National Research Medical University" of the Ministry of Health of the Russian Federation, Russia

[2]Federal State Budgetary Institution "Pulmonology Scientific Research Institute" Under Federal Medical and Biological Agency of Russian Federation, Russia

[3]State Budgetary Health Care Institution of the City of Moscow "City Clinical Hospital Named After SS Yudin of Moscow Department of Health", Russia

[4]State Budgetary Healthcare Institution of Moscow "Moscow Clinical Scientific and Practical Center Named After AS Loginov of the Moscow Department of Health, Russia

***Corresponding Author:** GE Baimakanova, State Budgetary Healthcare Institution "Moscow Clinical Scientific and Practical Center Named After A.S. Loginov" of the Moscow Healthcare Department, Moscow, Russia.

Received: September 15, 2025; **Published:** October 14, 2025

Abstract

There are 2 clinical cases of Birt-Hogg-Dubé syndrome. Patients had skin manifestations of the disease for many years, that were hereditary. Later, lung cysts were diagnosed on chest computed tomography (CT) due to an acute clinical situation. A rare diffuse cystic lung disease was suspected, which was definitively established as a result of a molecular genetic blood test of the folliculin gene and skin elements biopsy. Birt-Hogg-Dubé syndrome is the rare and complicated disorder. The lung biopsy in such patients does not lead to a definitive diagnosis. Thus it is essential to raise awareness among doctors of all specialties for early recognition and proper monitoring of these patients.

Keywords: *Lung Cysts; Pneumothorax; Folliculin Gene; Folliculin - FLCN; Fibrofolliculoma; Trichodiscoma; Birt-Hogg-Dubé Syndrome; Kidney Tumor*

Introduction

Birt-Hogg-Dubé syndrome is the rare autosomal dominant disorder associated with germline mutations in the folliculin gene (FOLLICULIN - FLCN) and a predisposition to benign of hair follicle tumors (fibrofolliculomas/trichodischomas), lung cysts, risk of spontaneous pneumothorax and kidney tumor [1,2].

The FLCN gene encodes the protein folliculin, a putative tumor suppressor gene whose function is still being studied. Birt-Hogg-Dubé syndrome is phenotypically very heterogeneous both within and between families. The syndrome prevalence is 1/200,000 population

[3], however, there are calculations that the disease occurs approximately 40 times more often [4]. In most cases, a patients have one of the parents with this syndrome, although there are also mutations of the FLCN gene de novo. Each affected parent can transmit the pathogenic gene to the child in 50% of cases. Prognostic testing of family members at risk after identification of the FLCN gene mutation and prenatal/preimplantation genetic testing to confirm or exclude this syndrome is possible [3].

The diagnosis of Birt-Hogg-Dubé syndrome can be established in the presence of one of two major criteria, namely, a pathogenic mutation in the FLCN gene or the presence of 5 or more fibrofollicles or trichodiscomas that arose in adults and are histologically confirmed. The diagnosis can also be verified in the presence of two of the following three minor criteria: 1. pulmonary involvement in the form of bilateral basal cysts with no other obvious cause; 2. early-onset (<50 years) multifocal or bilateral renal cell carcinoma or renal cell carcinoma with mixed chromophobe and oncocytic histology; 3. a family history of a first-degree relative with Birt-Hogg-Dubé syndrome.

Case Presentation

We present the first clinical case

A 43-year-old woman consulted a pulmonologist due to changes in her lungs on a chest X-ray.

It is known from the anamnesis that from the age of 27, skin elements began to appear on the face and neck, which increased over time. The young woman was examined and treated by a dermatologist for many years. Similar skin changes were also noted in the patient's mother. After 11 years, a biopsy of the skin elements of the neck was performed. Biopsy samples were fragments of the skin upper parts with epidermal atrophy, dermal fibrosis (probable trichodiscoma). A year later, due to the ambiguity of the morphological conclusion, a repeat biopsy of the skin formations was performed: epidermis was with slight acanthosis, perivascular lesions were in the upper parts of the dermis lymphohistoid infiltrates, erythrocyte extravasates; data for trichodiscoma, fibrofolliculoma were not received. At the same time, the dermatologist recommended examination by a geneticist. According to the results of molecular genetic blood testing, pathogenic and probable pathogenic variants in the FLCN gene were not detected. The diagnosis of Birt-Hogg-Dubé syndrome turned out to be unlikely. But given the family history, chest and kidneys CT and were recommended, which the patient refrained from. Two years later, left-sided spontaneous hydropneumothorax was diagnosed during routine chest radiography. For the first time, chest CT was performed, where intraparenchymal and subpleural cysts were detected in the lungs against the background of preserved pulmonary parenchyma. Left-sided videothoracoscopy was performed, atypical resection of the apex of the lung. The histological conclusion presented changes in the lungs as emphysema. Complex pulmonary test (PT) did not reveal any disturbances in ventilation or diffusion capacity of the lungs. An air cyst measuring up to 32 x 37 mm was detected in S8 of the right lung, similar cysts measuring up to 9x21 mm were detected in S5.9 of the left lung according chest CT (Figure 1). Ultrasound of the abdominal organs and kidneys did not reveal any pathology.

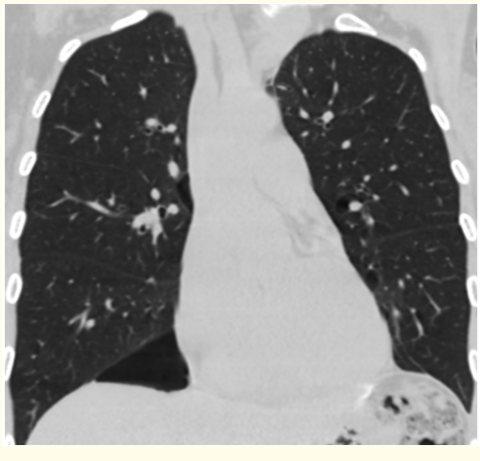

Figure 1: *Chest CT image of woman, Coronal plane.*

During the initial visit to our hospital, attention was drawn to the presence of multiple dome-shaped papules of flesh-colored and white color on the skin of the face, neck, and upper half of the body (Figure 2).

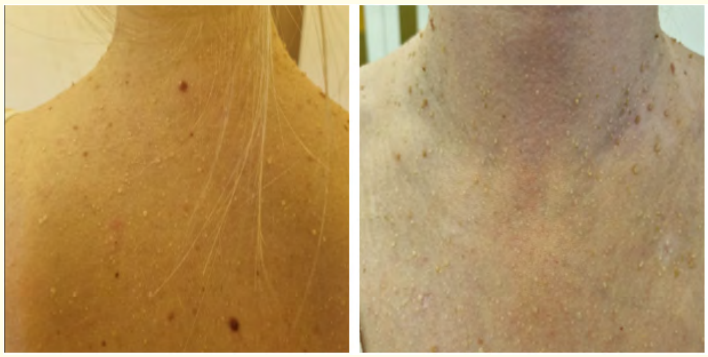

Figure 2: *Woman 's skin manifestations.*

SpO_2 at rest in air - 98%, without desaturation in the 6-minute walk test. Vesicular breathing, no wheezing.

Magnetic resonance imaging (MRI) of the abdominal organs did not reveal any evidence of pathological changes in the organs and retroperitoneal space.

Due to the high probability of Birt-Hogg-Dubé syndrome and the lack of criteria for establishing an accurate diagnosis, the patient underwent another skin biopsy, which revealed a fibrous papule (angiofibroma). The chest CT and PT series for 3 years were similar. Considering that fibrous papules may be observed in patients with Birt-Hogg-Dubé syndrome, the histological examination data did not contradict the presence of the syndrome. Repeated molecular genetic testing in the FLCN gene did not reveal pathogenic mutations. Sequencing of the complete coding sequence of the FLCN gene was performed: a pathogenic variant FLCN NM 144997.7 was detected in a heterozygous state. The patient's mother was with long-term skin changes from a young age underwent a chest CT for the first time in her life at the age of 68, where intraparenchymal and subpleural lung cysts were also detected (Figure 3).

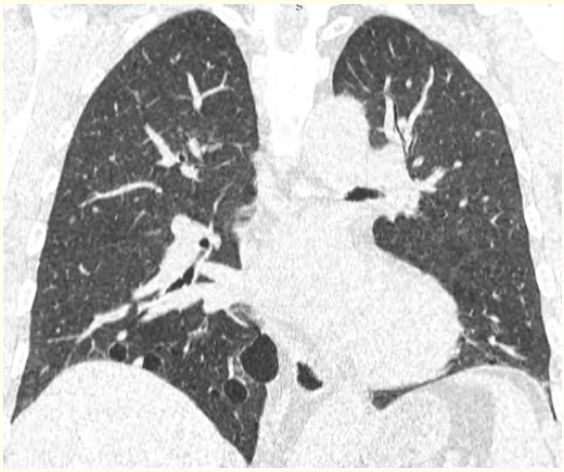

Figure 3: *Chest CT image of the woman's mother. Coronal plane.*

We present the second clinical case

A 53-year-old man consulted a therapeutist complaining of febrile body temperature, productive cough, and general weakness. A chest CT scan was performed, where pneumonia was diagnosed, and the patient was hospitalized in the pulmonology department.

From the anamnesis it is known that since the age of 14 skin lesions on the face and neck have been bothering, then appeared on the body and upper limbs, progressing over time. Repeatedly consulted a dermatologist, the clinical situation was assessed as papillomas, molluscum contagiosum. Repeated removal of lesions by cryodestruction was carried out, but without a lasting positive effect. Skin biopsy was not performed. At the age of 39, he suffered from spontaneous left-sided pneumothorax, resolved by drainage of the pleural cavity. Chest CT was not performed at that time. The patient was an ex-smoker, smoking index 37 packs/years. Similar multiple skin manifestations were observed in the patient's father and daughter; they had not been examined.

During the initial examination, attention was drawn to multiple lesions on the skin in the head, neck and upper torso, with a diameter of 0.5 to 10 mm (Figure 4). According to the chest CT, in addition to pneumonia, the protocol described uneven pneumatization due to areas of centrilobular, paraseptal (including paramediastinal) emphysema with the formation of large bullae in the middle sections of the lungs up to 62 mm in size. The identified changes prompted an in-depth examination by a dermatologist and geneticist.

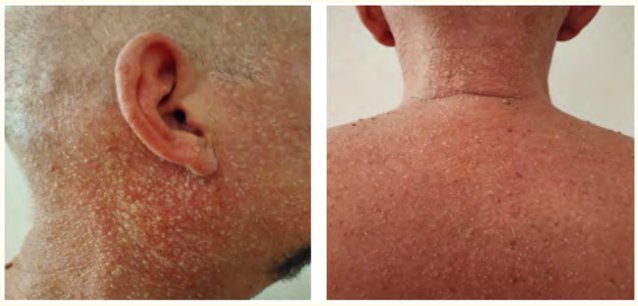

Figure 4: *Man's skin manifestations.*

The patient underwent a skin biopsy for the first time at age 53. Pathohistological description: a skin fragment with a single cystic-expanded structure from which thin epithelial strands and sebaceous glands extend; the perifocal stroma demonstrates fibromucoid changes and contains compact elongated fibrocytes; the revealed skin changes correspond to fibrofolliculoma (hamartomatous skin lesion with differentiation of the epithelium and mesenchyme of the hair follicle mantle) (Figure 5 A, B, C, D).

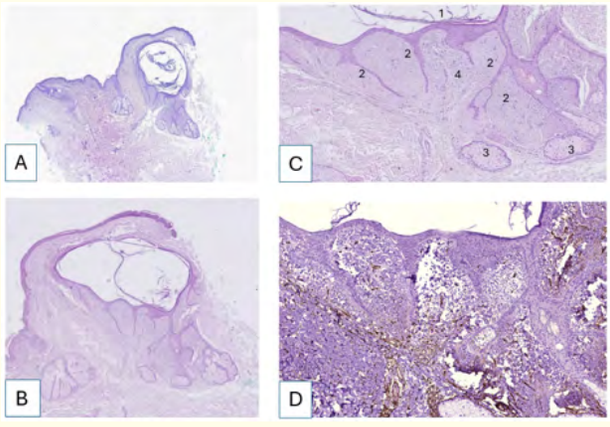

Figure 5: *Morphological examination of a man's skin biopsy, stained with hematoxylin and eosin: A, B - Fibrofolliculoma, C - 1. Central cystically expanded funnel-shaped structure 2. Epithelial cords 3. Sebaceous glands 4. Stroma with fibromucoid changes and compact fibrocytes, D - Immunohistochemical staining with antibodies to CD34 (marks vascular structures and fibrocytes located in the fibromucoid stroma).*

Two months after clinical and laboratory recovery from pneumonia, a PT and chest CT were performed. The PT revealed an obstructive type of pulmonary ventilation disorder (FEV_1/VC - 65%, z-criterion - 1.67, FEV_1 - 2.71 L, 78% pred.). The diffusion capacity of the lungs was not impaired. The salbutamol test was positive. Chest CT showed resolution of infiltrative changes in the lungs and lung multiple cysts (Figure 6). DNA analysis was performed, using next-generation sequencing technology using the paired-end reading method. A heterozygous variant of the nucleotide sequence chr 17:17216394TG> (c.1285delC;pHis429fs) was identified in the FLCN gene.

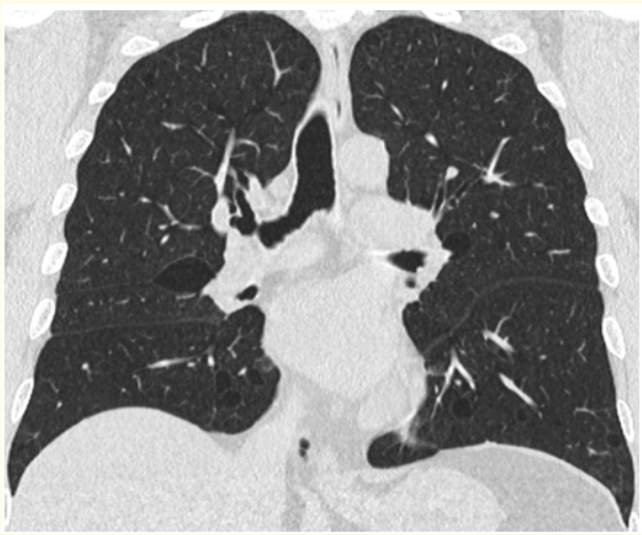

Figure 6: *Chest CT image of man, coronal plane.*

Discussion

The diagnostic pathway for establishing a diagnosis of a rare cystic lung disease is demonstrated using two clinical cases.

The most common diseases with the development of multiple cysts in the lungs and involvement of the skin in the general pathological process include Langerhans cell histiocytosis, tuberous sclerosis, and Birt-Hogg-Dubé syndrome. Hereditary genesis of cysts is visible only in the last two cases.

In the presented cases, the nature of the cysts in the lungs according to chest CT was typical for the Birt-Hogg-Dubé syndrome. These are a few bilateral oval, round, lenticular or irregular cysts with a predominance in the lower and medial parts of the lungs. Subpleural and fissure cysts are very typical, as well as the coexistence of small cysts (< 1 cm) with large air cavities (>2 cm) [5].

In addition, both cases had a hereditary skin lesion. However, the patients' relatives were not examined for this reason. And if we return to the history of the discovery of the disease, it was the hereditary skin manifestations that initiated the entry of this new disease into clinical practice. In 1977, Burt, Hogg and Dubé reported a study of 70 people of three generations, 15 of whom were found to have multiple dome-shaped skin-colored or grayish-white lesions distributed over the face, neck and upper torso. Histological analysis revealed fibrofolliculomas, trichodiscomas and acrochordons [6]. The triad of lesions, inherited as an autosomal dominant trait, was called the "Burt-Hogg-Dubé syndrome".

Quite often, skin manifestations, especially in young patients, can become the primary reason for visiting a doctor, which makes knowledge of this disease by dermatologists relevant. In the first clinical history, it was the doctor of this specialty who motivated further

examination of the patient, and in the second case, the dermatologist, on the contrary, was far from this suspicion. The uninformativeness of a triple skin biopsy in a young woman can be explained by the fact that diagnostic trichodiscomas/fibrophylrulomas in this syndrome are localized mainly on the skin of the face, and the patient's changes on the body were examined three times, which was associated with the patient's desire to exclude post-traumatic changes on the skin of the face. And in a man, fibrofolliculomas were diagnosed already during the first histological examination of the skin with immunohistochemistry. Fibrofolliculomas, papules, the number of which varies from several to several hundred, are a distinctive feature of the syndrome [7,8]. They are asymptomatic and develop during the third or fourth decade of life, increasing in number and size as patients age, which was also observed in our patients. There is evidence that all patients have cutaneous fibrofolliculomas, but trichodiscomas and acrochordons are less common [7-9].

The first clinical observation demonstrates a slow (6 years) "invasive" path to diagnosis. Three biopsy studies of the formations on the skin of the body and two molecular genetic studies of the blood were performed, and videothoracoscopy with lung biopsy was also performed. The videothoracoscopy with biopsy apparently pursued the goal of morphological verification of the diagnosis. However, with this syndrome, it is not informative. Unfortunately, access to the pleural cavity against the background of spontaneous pneumothorax did not initiate pleurodesis, which would reduce the risk of subsequent pneumothoraces.

The diagnosis of the disease in a man turned out to be even more long-term. Skin manifestations from the age of 14 and spontaneous pneumothorax at 39 in a young man did not prompt a chest CT. Only an acute situation in the form of pneumonia at 53 years initiated a chest CT and already during the initial examination, a pulmonologist suspected Birt-Hogg-Dubé syndrome. The diagnostic thought was aimed at immediately identifying two main criteria for making a diagnosis.

In both patients, despite lung cysts, there are no disturbances in the diffusion capacity of the lungs with complex PT. The obstructive changes in spirometry in the man may be related to hyperreactivity of the respiratory tract or associated with long-term smoking, requiring dynamic monitoring.

In the diagnosis of rare diseases, a multidisciplinary approach to patient management is always relevant, however, the main role belongs to a clinical doctor who has experience in managing orphan pathology.

Treatment of established Birt-Hogg-Dubé syndrome is aimed at preventing pneumothorax and early detection and treatment of kidney tumor. Lifelong renal surveillance is necessary, with renal imaging by renal MRI every 36 months for patients without tumors at initial presentation. Clinical evaluation, pedigree analysis, and FLCN gene mutation analysis are recommended for all patients with a family history of lung cysts and/or pneumothoraces and/or renal malignancies or any combination of spontaneous pneumothorax and renal cancer in an individual or family [10].

Conclusion

Skin lesions in Birt-Hogg-Dubé syndrome are benign and cause only aesthetic problems, cystic lung lesions are few in number and do not lead to functional disorders of the lungs and respiratory failure. However, there is a high probability of the occurrence of benign and malignant kidney tumors, which makes the diagnosis of this syndrome important for the prognosis of patients.

Disclosure of Interest

The authors declare that they have no competing interests.

Authors' Contribution

The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Funding Source

'The authors declare that there is no external funding for the exploration and analysis work.

Compliance with the Principles of Ethics

The study protocol was approved by the local ethics committee. Approval and protocol procedure was obtained according to the principles of the Declaration of Helsinki. The provision of medical care was carried out on the basis of current recommendations. Informed consent was obtained for medical procedures, interventions, genetic research, processing of personal data and publication.

Consent for Publication

Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

Bibliography

1. "Respiratory medicine: a manual: in 5 volumes". Edited by AG Chuchalin. 3rd edition, additional and revised - Moscow: Pulmomedia 2 (2024): 734.
2. Michael L Nickerson., *et al*. "Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome". *Cancer Cell* 2.2 (2002): 157-164.
3. Marianne Geilswijk., *et al*. "ERN GENTURIS clinical practice guidelines for the diagnosis, survey and management of people with Birt-Hogg-Dubé syndrome". *European Journal of Human Genetics* 32.12 (2024): 1542-1550.
4. Savatt JM., *et al*. "Frequency of truncating FLCN variants and Birt-Hogg-Dube-associated phenotypes in a health care system population". *Genetics in Medicine* 24.9 (2022): 1857-1866.
5. Jung Eun Lee., *et al*. "Birt-Hogg-Dubé syndrome: characteristic CT findings differentiating it from other diffuse cystic lung diseases". *Diagnostic and Interventional Radiology* 23.5 (2017): 354-359.
6. Birt AR., *et al*. "Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons". *Archives of Dermatology* 113.12 (1977): 1674-1677.
7. Schmidt LS., *et al*. "Birt-Hogg-Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2". *American Journal of Human Genetics* 69.4 (2001): 876-882.
8. Toro JR., *et al*. "Birt-Hogg-Dubé syndrome: a novel marker of kidney neoplasia". *Archives of Dermatology* 135.10 (1999): 1195-1202.
9. Choyke PL., *et al*. "Hereditary renal cancers". *Radiology* 226.1 (2003): 33-46.
10. Menko FH., *et al*. "Birt-Hogg-Dubé syndrome: diagnosis and management". *Lancet Oncology* 10.12 (2009): 1199-1206.

Volume 14 Issue 11 November 2025