

The Birt-Hogg-Dubé Syndrome: A Clinical Diagnostic Challenge

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Received: June 04, 2021; **Published:** June 29, 2021

Abstract

We report our experience about two patients with spontaneous pneumothorax, surgically treated by wedge resections and characterized by postoperative (case 1) and preoperative (case 2) appearance of skin folliculomas extending mainly to the face. Anatomopathological study on the surgical finding and subsequent genetic investigations confirm the diagnosis of Birt-Hogg-Dubé Syndrome.

Keywords: *Birt-Hogg-Dubé Syndrome; Folliculomas; Spontaneous Pneumothorax; Genetic Disease*

Introduction

The Birt-Hogg-Dubé syndrome is a rare hereditary disorder characterized by the association of parenchymal pulmonary cysts, renal disease (often neoplastic) and benign cutaneous lesions. The clinical presentation is characterized at first by spontaneous pneumothorax or renal disorders. Few cases are reported in literature linked to the finding over time of pleural, renal and cutaneous symptoms. The peculiarity of our case depends on the unusual kidney problem. In fact, it was an anatomical defect on a genetic basis that determined a single painful episode positively treated pharmacologically.

Case Reports

Case 1

A thirty-three-year-old male patient, transferred to our Thoracic Unit from another hospital for persistent air leaks (12 days) after insertion of the pleural drainage carried out for a right spontaneous pneumothorax. Patient reported many previous hospitalizations for not identified urinary tract problems without organ impairment, treated with anti-inflammatory drugs. Preoperative computed tomography (CT) scan of the thorax and abdomen showed various bilateral cystic parenchymal areas ranging from 1 mm to 25 mm in the lung and, in the kidneys, a left calico-pyelic dilatation without an obvious cause also confirmed by a subsequent CT urography. Patient underwent uniportal right video-assisted thoracoscopic surgery (VATS) wedge resections (12 in total), associated with subtotal parietal pleurectomy. We did not notice any postoperative surgical complications and the pleural drainage was removed on the third day. However, on the second day, the skin-like cutaneous lesions located on the forehead and in the upper part of the face appeared (Figure 1), positively treated with cortisone and antihistamine drugs for three days. The clinical pulmonary, renal and cutaneous evidence, supported by the histological

evaluation of lung resections that confirmed the bullous and cystic nature of the lesions, suggested a genetic disorder such as the Birt-Hogg-Dubé Syndrome (BHDS). Patient underwent molecular analysis of FLCN mutated gene research on DNA extracted from peripheral blood. Genetic evaluation revealed the presence of the variant “c.1285_1286insC” in exon 11 of the FLCN gene, confirming the diagnosis of BHDS. The genetic analysis was immediately extended to relatives, with negative findings. The annual follow-up consists in: 1) the Chest X-ray, with the recommendation to eliminate all lung risk factors (in particular smoke and pressure variations/pressurized environments); 2) the dermatological check of the skin (lesions are at low risk of neoplastic degeneration); 3) the magnetic resonance imaging of the kidneys, due to the high risk of the renal cell carcinoma. After two years, there are no signs of disease progression or recurrence.



Figure 1: The folliculomas extended to the forehead of patient.

Case 2

Fifty-four year old man, with a second episode of left spontaneous pneumothorax (2 months after the first). In the medical history we found only a major facial folliculitis (Figure 2) which has never been thoroughly investigated. Computed tomography (CT) of the chest and abdomen revealed, in addition to the left pneumothorax, multiple bilateral cystic areas of the lung, kidney and liver. Patient underwent wedge resections (7 total) of the lung by right uniportal VATS, associated with subtotal parietal pleurectomy. No postoperative complications were recorded and the pleural drainage was removed on the third day. The histological diagnosis of BHDS on resected lung lesions was supported by genetic testing, showing the variation “c.1285_1286insC” of exon 11 of the FLCN gene.



Figure 2: The folliculomas extended to the face of patient.

Discussion

The Birt-Hogg-Dubé Syndrome, first described in 1977, is a rare hereditary disease with autosomal dominant incomplete penetrance, caused by mutations in the FLCN gene on chromosome 17 (locus 17p11.2) that codes for folliculin. The focal point appears to be an insertion/deletion mutation in a 8 cytosines segment of exon 11 of the FLCN (c.1285dupC or c.1285delC) [1]. The function of the gene is not known yet; it is expressed by the skin, nephrons and pneumocytes of types 1 and could have the role of tumor suppressor [2]. The mutation that determines the syndrome can arise de novo or transmitted by one of the parents on average to 50% of children. The demographic percentage rate is unknown; in fact, very few cases are described in literature. The BHDS often starts with a spontaneous pneumothorax, with the risk is 50 times higher compared to healthy subjects [3,4]. The pulmonary cysts, found in about 89% of the carriers of the mutation and determining spontaneous pneumothorax, may depend on cell-cell adhesion defects according to the "Stretch Hypothesis". This concept explains that the repeated mechanical stress due to breathing, mostly during physical activity, would lead to a gradual expansion of the alveolar spaces, especially in the peripheral parenchymal regions at the anchorage points with the pleura. About the kidney, in one patient the renal symptoms cannot be traced back to a manifest etiology so much so as to be underestimated in the previous hospitalizations. Frequently, the pathology can manifest itself unilaterally or bilaterally as a kidney cancer but the possibility of other manifestations starting from simple benign cystic formations should be considered. In BHDS patients, the risk of developing a various neoplasm histotypes as oncocytomas, clear cell tumors, chromophobe or hybrid cells is between 6.5% and 34% [5-7]. In the skin, lesions are mainly located on the face (as in our two patients), neck and trunk and are found in about 90% of affected patients as folliculomas, trichodysomes, acrocordones and all benign tumors of the annexed pilosebaceous [7]. In order to suspect BHDS, one of these conditions should be present [1,8]: 1) five or more fibrofolliculomas of the face or trunk; 2) facial papules (angiofibromas) in patients who do not meet the clinical criteria of the tuberous sclerosis complex (TSC) or type 1 multiple endocrine neoplasia (MEN1); 3) single or multiple and bilateral chromophobe, oncocytic and/or hybrid renal tumors and a family history of renal cancer; 4) a family history of autosomal dominant primary spontaneous pneumothorax without a history of smoking or COPD. The test list to confirm the diagnosis involves: 1) sequence analysis of exon 11, as a majority of affected patients with one of two pathogenic variants found in exon 11; 2) sequencing the entire coding region of FLCN, if targeted sequence analysis of exon 11 does not identify a pathogenic variant; 3) deletion-duplication analysis of FLCN, if full gene sequence evaluation does not identify a pathogenic variant. The BHDS may also present other less common manifestations such as thyroid nodules, parotid oncocytomas, colonic polyposis, angioliomas, parathyroid adenoma, maculata chorioretinopathy, neurothekeoma, meningioma, breast cancer, tonsillar tumor, colorectal cancer, sarcoma, lung carcinoma, melanoma, basal cell carcinoma and squamous cell carcinoma [2]. This explains how the clinical and diagnostic suspicion of the pathology can be difficult to interpret.

Conclusion

In conclusion, the BHDS exposes patients to greater risks to develop severe respiratory problems and serious neoplasia than the normal population. The genetic test, extended to the family members for the specific mutation analysis, provides a very useful tool for the early diagnosis.

Conflict of Interest

None reported.

Funding Support

None reported.

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Volume 10 Issue 7 July 2021

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