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Case Report

Birt-Hogg-Dubé Syndrome, Uncommon Germline Nonsense Mutation of FLCN Gene Detected: A Case Report

Anthony Boulos*, Maria Boulos and Amanda Roby

Department of Pulmonary/ Critical Care, Mercy Health, USA

***Corresponding Author**: Anthony Boulos, Department of Pulmonary/ Critical Care, Mercy Health, USA.

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Abstract

Birt–Hogg–Dube´ (BHD) syndrome is a rare autosomal dominant inherited syndrome that is characterized by the presence of fibrofolliculomas, trichodiscomas, pulmonary cysts, spontaneous pneumothorax, and renal tumors. Here we present a patient with recurrent spontaneous pneumothorax, fibrofolliculomas, trichodiscomas and strong family history of renal cell carcinoma. Blood samples were sent for deletion/duplication testing using exon-level oligo array data analysis and gene-specific filtering. The nonsense mutation identified in our case was at Q167X – an uncommon variant in European and African ancestry analysis. This nonsense mutation expands the mutation spectrum of FLCN associated with BHD syndrome. Recognition of physical features such as fibrofolliculomas and trichodiscomas as well as the association with spontaneous pneumothorax and congenital cystic lung disease aids in the identification of this uncommon syndrome.

Keywords: *Birt-Hogg-Dubé; Nonsense Mutation; FLCN Gene*

Abbreviations

BHD: Birt-Hogg-Dubé

Introduction

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant genodermatosis characterized by cutaneous skin tumors such as fibrofolliculomas (hamartomas of hair follicles), trichodiscomas (tumors of the hair disc), acrochordons of upper face, neck, trunk first described in 1977 [1]. The first case of reported renal cell carcinoma was defined in 1993 [2]; renal cell carcinoma later became an important manifestation of BHD syndrome [3]. The isolated germline mutation in the FLCN gene associated with BHD syndrome is mapped to chromosome 17p11.2 [4]. The FLCN gene encodes the folliculin protein which consists of 579 amino acids including 14 exons. Most BHD germline mutations are frameshift or nonsense mutations that truncate the BHD protein, folliculin [4]. In addition the association of BHD syndrome and tumors involving other organ systems has been previously described including colorectal, lung, and breast cancers [5]. We report a case of BHD syndrome in a single patient with recurrent spontaneous pneumothorax as well as fibrofolliculomas found to have an uncommon nonsense mutation on FLCN gene which lead to the identical mutation in 10 other family members.

Materials and Methods

The patient is a 55 y/o Caucasian male with past medical history significant for previous left-sided spontaneous pneumothorax with thoracotomy and pleurodesis in 1986 and tobacco use that presented with sudden onset shortness of breath and right-sided pleuritic chest pains. Upon chest radiography the patient had near complete collapse of the right lung (Figure 1); chest tube was placed. Computed tomography of the chest revealed diffuse cystic disease bilaterally with small right pleural effusion and no parenchymal anomalies involving lung tissue (Figure 3).

Upon further examination not only did the patient have decreased breath sounds in the right hemithorax with hyper-resonant percussion but there were numerous flesh-colored papules on the face as well as neck (Figure 2). At one point the patient was in discussion with his sister via telephone who also confirmed many others in the family had the fleshy lesions on their face and trunk that were thought to be cosmetic blemishes. Previous pulmonary function testing confirmed no obstructive ventilation defect.

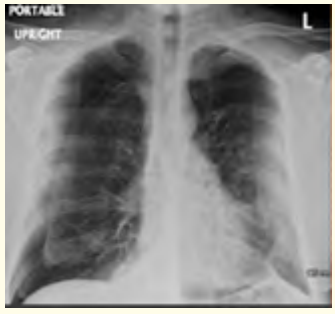

Figure 1: *Large right pneumothorax.*

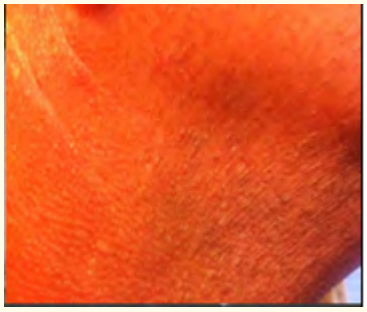

Figure 2: *Folliculomas of right face/neck.*

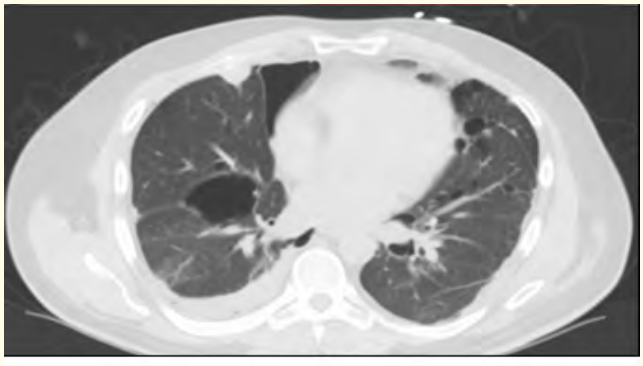

Figure 3: *Multiple bilateral pulmonary cysts, small right pleural effusion.*

Over the subsequent few days the patient had continuous air leak from his chest tube that necessitated cardiothoracic surgery evaluation for another pleurodesis. Video assisted thoracoscopic surgery with talc pleurodesis completed revealed multiple upper lobe blebs with cystic disease. Eventually air leak stopped, chest tubes were removed and patient was discharged home.

Serology from this patient was sent gene sequencing analysis. Sequencing was performed with analysis of exon-level oligo array CGH deletion/duplication of the FLCN using gene-specific filtering. Sequence and array of CGH alterations were reported according to the Human Genome Variation Society or International System for Human Cytogenic Nomenclature guidelines. Sequencing revealed an uncommon Q167X nonsense mutation variant confirming BHD syndrome (Table 1) [8].

Gene	cDNA	Variant	Zygosity	Classification
FLCN	c.499 C > T	p.Gln167Ter	Heterozygous	Disease Causing
		(Q167X)		Mutation

Table 1: *FLCN Gene Sequencing and Deletion/Duplication Analysis BHD.*

Discussion and Conclusions

BHD syndrome is characterized by lung pneumatocysts, spontaneous pneumothorax, non-obstructive pulmonary function testing, renal neoplasms, fibrofolliculomas and trichodiscomas but not all features are required to be present [6]. In 2002 defects in the FLCN gene were identified in families with BHD syndrome which aided in the detection of those afflicted with BHD syndrome [4]. According to the BHD Consortium (Table 2) [7], a patient with multiple lung cysts and early onset renal cancer (prior to age 50) could be found to be suffering from BHD syndrome if they had the FLCN germline gene mutation. In our patient BHD syndrome was suspected when recurrent spontaneous pneumothorax was evident in context of numerous lung cysts and the dermatologic features concerning for fibrofolliculomas, trichodiscomas.

Major Criteria:

(1) At least 5 fibrofolliculomas or trichodiscomas, as least 1 histologically confirmed, or adult onset

(2) Pathogenic FLCN germline mutation

Minor Criteria:

(1) Multiple lung cysts; bilateral basally located lung cysts with no other apparent cause, with of without spontaneous primary pneumothorax

(2) Renal cancer: early onset (< 50 y) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology

(3) A first-degree relative with BHD

Patients should fulfill 1 major or 2 minor criteria for diagnosis.

Table 2: *Diagnosis Criteria for BHD Syndrome Proposed by the European Birt-Hogg-Dube Consortium.*

Some studies reported that the risk of pneumothorax in patients with BHD syndrome was 50 times greater than in the normal population and up to 80% of BHD syndrome patients had lung cysts [6].

The diagnosis of BHDS is likely under diagnosed; actual incidence may not be accurately documented. It is imperative that physicians recognize physical manifestations of BHDS such as fibrofolliculomas or trichodiscomas in order to detect other underlying associated sequelae such as lung cysts, spontaneous pneumothorax, or renal neoplasms.

Bibliography

1. Birt AR., *et al*. "Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons". *Archives of Dermatology* 113.12 (1977): 1674-1677.

2. Roth JS., *et al*. "Bilateral renal cell carcinoma in the Birt-Hogg-Dube syndrome". *Journal of the American Academy* of *Dermatology* 29.6 (1993): 1055-1056.

3. Toro JR., *et al*. "Birt-Hogg-Dube syndrome: a novel marker of kidney neoplasia". *Archives of Dermatology* 135.10 (1999): 1195-1202.

4. Nickerson ML., *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.

5. Welsch MJ., *et al*. "Birt-Hogg-Dube syndrome". *International Journal of Dermatology* 44 (2005): 668-673.

6. Kunogi M., *et al*. "Clinical and genetic spectrum of Birt-Hogg-Dube syndrome patients in whom pneumothorax and/or multiple lung cysts are the resenting feature". *Journal of Medical Genetics* 47.4 (2010): 281-287.

7. Menko FH., *et al*. "Birt-Hogg-Dube syndrome: diagnosis and management". *Lancet Oncology* 10.12 (2009): 1199-1206.

8. Menko., *et al*. "Informing family members of individuals with Lynch syndrome: a guideline for clinical geneticists". *Familial Cancer* 12.2 (2013): 319-324.

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