Pulmonary and cutaneous manifestations of Birt-Hogg-Dube Syndrome in a large clinical cohort

Brian D. Cortese, BS[1], Raju R. Chelluri, MD, MS[1,2]; David A. Ostrowski, BS[1]; Daniel S. Roberson, MD[1]; Phillip M. Pierorazio, MD[1]; Katherine L. Nathanson, MD[3]

[1]Division of Urology, Department of Surgery, University of Pennsylvania Health System, Philadelphia, PA; [2]Division of Urology and Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA; [3]Department of Medicine, Division of Translational Medicine and Genetics, University of Pennsylvania Health System, Philadelphia, PA, USA

INTRODUCTION

Birt-Hogg-Dube (BHD) Syndrome

- Autosomal dominant condition caused by *folliculin* (FLCN) gene mutation
- Characterized by fibrofolliculomas, pulmonary cysts, and renal masses
- Skin and lung features often act as catalyst for patient treatment

Importance

- Counsel about risk of renal masses in context of BHD phenotypes

Purpose

- Expand literature of BHD phenotypes and correlations with renal mass development
- Report on FLCN mutational status

MATERIALS and METHODS

Study Design:

- Retrospective single center study
- 81 patients with BHD syndrome

Patient Identification and Data:

- Clinical care or Penn Medicine Biobank (PMBB)
- Databases queried for *folliculin* gene mutations or classic BHD phenotypes

Statistics:

- STATA 15 (StataCorp LP), Student's t-test, $p < 0.05$ significance
- Quantitative data displayed with median and inter-quartile range (IQR)
- Germline mutations were obtained

RESULTS

Demographics

- Eighty-one BHD patients were identified, 67 (80.2%) through clinical care and 14 (19.8%) via PMBB. At diagnosis, patients were 38 (28-57) years old.

Cutaneous Findings

- Twenty-six (32.1%) patients had skin findings at diagnosis with fibrofolliculomas documented in 47 (58%) total patients at a median age of 46.5 (33-58) years.

Pulmonary Findings

- Twenty-eight (34.6%) patients had a pneumothorax history at diagnosis with pneumothorax affecting 34 (42%) total patients. The first episode occurred at median age of 36 (27-50) years with patients experiencing a median 2 (1-2) episodes in their lifetime. Of patients with pneumothorax, 10 (29%) had non-unique germline mutations with the remainder being unique or missing testing.

Correlation with Renal Masses

- Ten (12.3%) patients had a total of 15 renal masses. Notably, 9/47 (19.1%) patients with fibrofolliculomas and 4/34 (11.8%) patients with pneumothorax history had a renal mass. Four (40%) renal tumor patients had pneumothorax history.

Table 1. Demographic Characteristics and Skin Phenotypes of BHD Patients, Stratified by Method of Identification

Variables	Method of Identifications			P Values
	100% [N=81/81]	80.2% [N=67/81]	19.8% [N=14/81]	Clinical Care vs. BioBank
Age [Median [IQR]				
First Presentation	38 [28-57]	37 [27-54]	.	.
Diagnosis of BHD	46 [34-57]	46 [34-57]	.	.
Fibrofolliculoma First Noted	46.5 [33-58]	46.5 [33-58]	.	.
Fibrofolliculoma Biopsy	47 [40-60]	47 [40-60]	.	.
Sex [N, [%]]				
Male	44 [54.3%]	34 [50.7%]	10 [71.4%]	0.154
Race [N, [%]]				
Caucasian	69 [85.2%]	58 [86.6%]	11 [78.6%]	0.519
African American	4 [4.9%]	2 [3.0%]	2 [14.3%]	0.274
Asian	3 [3.7%]	3 [4.5%]	0 [0.0%]	0.083
Other	5 [6.2%]	4 [6.0%]	1 [7.1%]	0.881
BMI [Median, [IQR]]	27.3 [24.8-30.9]	27.2 [24.4-30.8]	28.4 [26.3-36.0]	0.135
Reason for Coming to Medical Attention				
Clinical Presentation of BHD	45 [55.6%]	45 [67.2%]	.	.
Family History of BHD	21 [25.9%]	21 [31.3%]	.	.
Unknown	1 [1.2%]	1 [1.5%]	.	.
First Phenotype of Presentation [N, [%]]				
Skin	26 [32.1%]	26 [38.8%]	.	.
Renal Tumors	5 [6.2%]	4 [6.0%]	1 [7.1%]	0.881
Lung Cysts	8 [9.9%]	7 [9.9%]	1 [7.1%]	0.687
Pneumothorax	28 [34.6%]	26 [34.6%]	2 [14.3%]	**0.042**
None	16 [19.8%]	6 [19.8%]	10 [71.4%]	**<0.001**
Other	1 [1.2%]	1 [1.2%]	.	.
Method of Fibrofolliculoma Diagnosis [N,				
Skin Exam by Dermatologist	8 [9.9%]	8 [11.9%]	.	.
Skin Exam by Medical Geneticist	15 [18.5%]	15 [22.4%]	.	.
Confirmed with Biopsy	17 [21.0%]	17 [25.4%]	.	.
Unknown	7 [8.6%]	7 [10.4%]	.	.
Fibrofolliculoma Findings by Age [N, [%]]				
0-9	.	.	.	
10-19	1 [1.2%]	1 [1.5%]	.	.
20-29	7 [8.6%]	7 [10.4%]	.	.
30-39	20 [24.7%]	20 [29.9%]	.	.
40-49	16 [19.8%]	16 [19.8%]	.	.
50-59	19 [23.5%]	19 [28.4%]	.	.
60-69	19 [23.5%]	19 [28.4%]	.	.
70-79	8 [9.9%]	8 [11.9%]	.	.
80+	.	.	.	.

Table 2. Lung Pathology and Treatment Characteristics of BHD Patients

Variables	BHD Cohort [n = 81]
History of Pathology [N [%]]	
Lung Cysts	51 [63.0%]
Pneumothorax	34 [42.0%]
Abnormal PFTs	14 [17.5%]
Age [Median, [IQR]]	
Lung Cysts	45 [35-59]
Abnormal PFTs	49 [39-53]
First Pneumothorax	36 [27-50]
Second Pneumothorax	40 [28-50]
Third Pneumothorax	34 [28-45]
Fourth Pneumothorax	28.5 [22-34.5]
Pneumothorax History [Median [IQR]]	
Number of Pneumothorax Events	2 [1-2]
Range of Pneumothorax Events	1-8
Age at First Pneumothorax (years)	36 [27-50]
Age at Second Pneumothorax	40 [28-50]
Age at Third Pneumothorax	34 [28-45]
Age at Fourth Pneumothorax	28.5 [22-34.5]
Treatments for Pneumothorax Patients [N [%]]	
Oxygen	4 [12%]
Chest Tube	22 [65%]
Blebectomy	12 [35%]
Pleurodesis	23 [68%]
Germline Mutations in Patients with Pneumothorax History [N]	
c.1285delC	4
c.1117C>T	2
c.1285dupC	2
c.1021delC	2
Partial Deletion including exons 11-14	1
c.1036_1043del	1
c.1177-3_-5delCTC	1
Del. Exon 1	1
c.499C>T	1
c.49dupC	1
Partial Deletion (Exons 13-14)	1
c.1062+2T>G	1
c.1219delA	1
c.927_954dup28	1
c.1062+T>C	1
5'UTRdel	1
c.1528delG	1
c.381dupG	1
No Germline Testing	10

CONCLUSIONS

- Over two-thirds of BHD cohort presented with skin or lung findings first.
- 19% patients with fibrofolliculomas and 12% of patients with pneumothorax history developed a renal mass.
- Of those with a renal mass, 40% had experienced a pneumothorax in their lifetime.
- Potentially suggest BHD screening in select patients may elucidate increased BHD incidence in the population.
- Correlations between non-renal BHD phenotypes and renal mass development may guide urologists in risk counseling for BHD patients.

LIMITATIONS

- Limitations include sample size, limited follow up time, and retrospective nature of the cohort.

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