Birt-Hogg-Dubé Syndrome, a Rare Case in Korea Confirmed by Genetic Analysis

Won Woong Shin, Yoo Sang Baek, Tae Seok Oh, Young Soo Heo, Soo Bin Son, Chil Hwan Oh, Hae Jun Song

Department of Dermatology, College of Medicine, Korea University, Seoul, Korea

Simple benign tumors can present as part of a syndrome with substantial mortality. Fibrofolliculomas are benign skin tumors most often associated with the Birt-Hogg-Dubé syndrome (BHDS). The most life-threatening complication of this syndrome is renal cancer and other major features include multiple lung cysts and spontaneous pneumothorax. We present the case of a 54-year-old man with multiple flesh-colored papules on his face confirmed histologically as fibrofolliculomas. He had a history of recurrent pneumothorax and chest computed tomography showed multiple lung cysts. To confirm the diagnosis of BHDS, we conducted gene analysis that revealed a single nucleotide duplication in the folliculin (\textit{FLCN}) gene (Exon 11, C.1285dupC). BHDS confirmed by the \textit{FLCN} gene mutation is rarely reported in Korea. Appropriate investigation is recommended whenever a patient with benign skin tumors is encountered.


CASE REPORT

A 54-year old man with asymptomatic, tiny, multiple, flesh-colored papules on both cheeks (Fig. 1) was referred to us from the cardiothoracic surgery department, where he had been treated for recurrent pneumothorax of the left lung. He did not remember the onset of the lesions, but stated that the number was increasing. He had no special medical or family history. The papules were thought to be sebaceous hyperplasia or verruca plana and a punch biopsy was performed. The specimen showed an epithelial cord and fibrous stroma in the dermis and an anastomosing band from follicular epithelium (Fig. 2). A diagnosis of fibrofolliculoma was made, which is the major feature of BHDS.

There was no family history of the skin lesions, lung disease, and of benign or malignant tumors. Furthermore, multiple variable-sized lung cysts were found on his chest following computed tomographic scan and a right renal cyst 2 cm in diameter was found on abdominal sonography (Fig. 3). Molecular analysis of \textit{FLCN} was performed after informed consent from the patient. Sequencing revealed a single nucleotide frameshift duplication occurring within the polycytosine tract located in exon 11, c.1285dupC (p.H429Pfs*27), resulting in a change of the 429th amino acid from histidine to proline in the FLCN
gene product. Based on this, it is possible to accurately diagnose BHDS.

His pneumothorax was treated with thoracostomy and pleurodesis, and active treatment was not required for the skin lesions, lung cysts and renal cyst. He is on regular follow-up because renal and colorectal cancer can occur in this syndrome.

**DISCUSSION**

BHDS was first described in 1977 by three Canadian physicians who studied a family with several members affected by multiple skin fibrofolliculomas, trichodiscomas, and acrochordons. Fibrofolliculoma, histologically verified, is one of the major features of this syndrome and can be accompanied by multiple lung
Birt-Hogg-Dubé Syndrome, a Rare Case in Korea Confirmed by Genetic Analysis

Table. 1. Diagnostic criteria for Birt-Hogg-Dubé syndrome

| Panel: Diagnostic criteria for Birt-Hogg-Dubé syndrome (BHD; patients should fulfill one major or two minor criteria for diagnosis) |
|---|
| **Major criteria** |
| At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset* |
| Pathogenic FLCN germline mutation |
| **Minor criteria** |
| Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax |
| Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology |
| A first-degree relative with BHD |

*Fibrofolliculoma and trichodiscoma are two possible presentations of the same lesion?for the differential diagnosis, angiofibroma in tuberous sclerosis should be considered. Childhood-onset familial fibrofolliculoma or trichodiscoma without other syndromic features might be a distinct entity.

cysts, spontaneous pneumothorax and renal cancer. The disease is caused by a mutation of the FLCN gene, which is located in chromosome position 17p11.2 and encodes for the folliculin protein. The function of this protein is predicted to exhibit tumor-suppressor activity but this is largely unverifie.d2-3. Although the incidence is not yet established, about 200 families with BHDS containing pathogenic FLCN mutations have been reported worldwide2. Among these, an apparent difference in mutations were found, which include insertion, deletion, inactivating frameshift and nonsense mutations1,4. Because no genotype-phenotype correlation has been found to date and clinical expression is widely variable, BHDS is most likely under-diagnosed2,5.

Menko et al.2 suggested diagnostic criteria for BHDS (Table 1). Our patient had more than 10 fibrofolliculomas on the face, which were confirmed histologically, as well as multiple lung cysts with recurrent spontaneous pneumothorax. In addition, molecular analysis showed a mutation in the folliculin gene, c.1285dupC (p.H429Pfs*27), which had been reported previously6. Therefore, he fulfilled two major criteria and one minor criteria for BHDS diagnosis.

Because of a 7-fold increased risk of developing renal tumors in BHDS-affected individuals, surveillance for renal cancer is indicated7. However, there are no established guidelines on what the optimum age is to start surveillance, the methods of examination, and the interval between examinations. Possible methods include ultrasoundography, computed tomography, and magnetic resonance imaging. Our patient was advised to be screened every 6 to 12 months for renal cancer including consultation with a nephrologist.

Also, differential diagnosis is important, as firm, dome-shaped papules that appear predominantly in the head and neck region can be seen in several tumor-related syndromes. These include angiofibromas in tuberous sclerosis, trichilemmomas in Cowden disease, and trichoepitheliomas in Brooke-Spiegler syndrome, etc.8. Histologic examination of the lesions and thorough evaluation for concomitant systemic disease can differentiate BHDS from other disorders.

Management strategies currently are symptomatic and preventive2. Treatment for fibrofolliculomas using an erbium-YAG or fractional CO2 laser provides temporary improvement9-11. Individuals exposed to large ambient pressure differences such as piloting and deep-sea diving should be assessed by a pulmonary physician. Smoking, which is an important risk factor for both spontaneous pneumothorax and renal cancer, should be strongly discouraged. Further investigations such as the molecular analysis of the FLCN gene for patients suspected of BHDS and their 1st degree families should be strongly encouraged.

In this study, we experienced a case of BHDS confirmed by genetic analysis, which has rarely been reported in Korea. Based on this case, it is important that physicians recognize facial papules that can be developed concurrently with systemic disease and conduct adequate studies to detect other features of the disease.

REFERENCES

1. Leter EM, Koopmans AK, Gille JJ, van Os TA, Vittoz GG, David EF, et al. Birt-Hogg-Dubé syndrome: clinical and genetic studies of 20 families. J Invest Dermatol 2008;128:45-49.

2. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al; European BHD Consortium. Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet Oncol 2009;10:1199-1206.

3. Kim EH, Jeong SY, Kim HI, Kim YC. A case of Birt-Hogg-Dubé syndrome. J Korean Med Sci 2008;23:332-335.
4. Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. Am J Hum Genet 2005;76:1023-1033.

5. Kunogi M, Kurihara M, Ikegami  TS, Kobayashi T, Shindo N, Kumasaka T, et al. Clinical and genetic spectrum of Birt-Hogg-Dube syndrome patients in whom pneumothorax and/or multiple lung cysts are the presenting feature. J Med Genet 2010;47:281-287.

6. Maffé A, Toschi B, Circo G, Giachino D, Giglio S, Rizzo A, et al. Constitutional FLCN mutations in patients with suspected Birt-Hogg-Dubé syndrome ascertained for non-cutaneous manifestations. Clin Genet 2011;79:345-354.

7. Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. Cancer Epidemiol Biomarkers Prev 2002;11:393-400.

8. Vincent A, Farley M, Chan E, James WD. Birt-Hogg-Dubé syndrome: a review of the literature and the differential diagnosis of firm facial papules. J Am Acad Dermatol 2003;49:698-705.

9. Kahle B, Hellwig S, Schulz T. Multiple mantleomas in Birt-Hogg-Dubé syndrome: successful therapy with CO2 laser. Hautarzt 2001;52:43-46.

10. Jacob CI, Dover JS. Birt-Hogg-Dube syndrome: treatment of cutaneous manifestations with laser skin resurfacing. Arch Dermatol 2001;137:98-99.

11. Gambichler T, Wolter M, Altmeyer P, Hoffman K. Treatment of Birt-Hogg-Dubé syndrome with erbium:YAG laser. J Am Acad Dermatol 2000;43:856-858.