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CASE REPORT

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

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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 (*FLCN*) gene (Exon 11, C.1285dupC). BHDS confirmed by the *FLCN* gene mutation is rarely reported in Korea. Appropriate investigation is recommended whenever a patient with benign skin tumors is encountered. **(Ann Dermatol 23(S2) S193～S196, 2011)**

-Keywords-
Birt-Hogg-Dubé syndrome, Fibrofolliculoma, Folliculin

INTRODUCTION

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant condition characterized clinically by fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax and renal cancer. It is caused by germline mutations in the folliculin (*FLCN*) gene, detection of which confirm the diagnosis, but no correlation has been revealed between phenotypes and mutations. We report a 54-year-old male BHD patient with multiple, tiny, flesh-colored papules on both cheeks and multiple lung cysts with recurrent pneumothorax of the left lung.

CASE REPORT

A 54-year old man with asymptomtic, 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 *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

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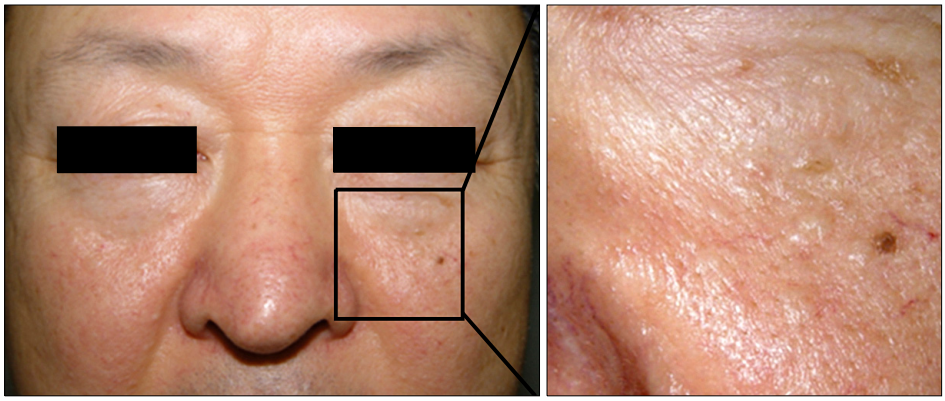

Fig. 1. Clinical features of fibrofolliculomas.

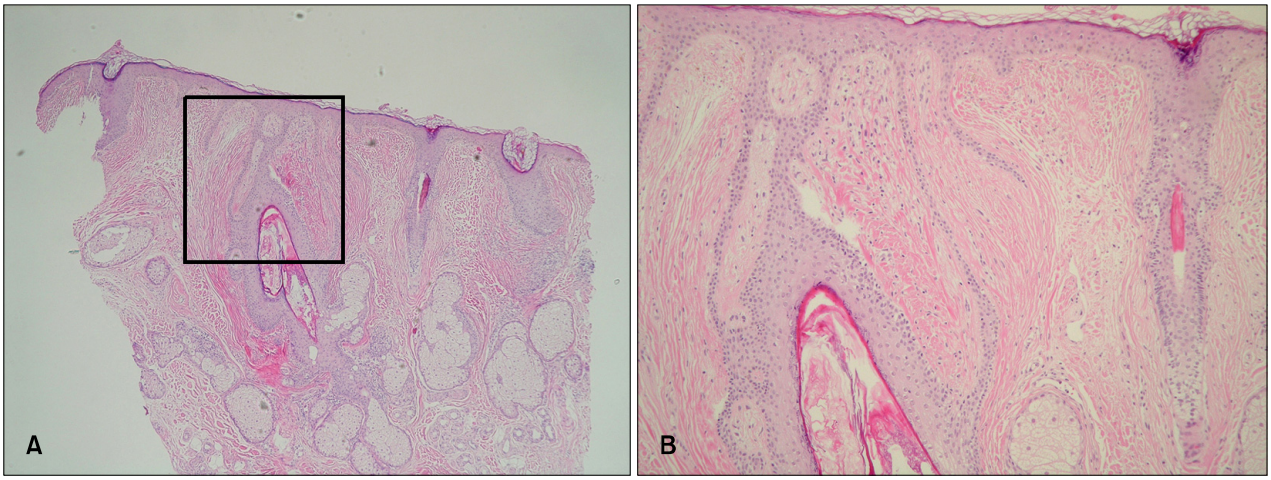

Fig. 2. Histopathology of fibrofolliculoma. (A) H&E stain, ×40. (B) H&E stain, ×100.

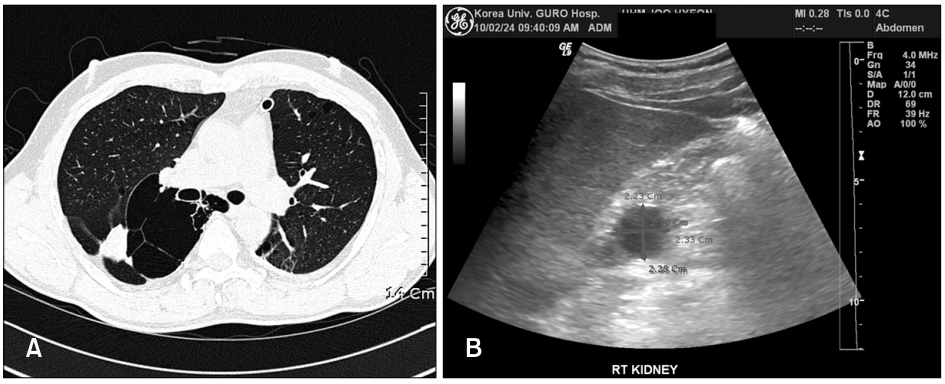

Fig. 3. Imaging studies. (A) Multiple lung cysts found on chest computed tomography. (B) A right renal cyst found on abdominal sonography.

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[1]. Fibrofolliculoma, histologically verified, is one of the major features of this syndrome and can be accompanied by multiple lung

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 diff erential diagnosis, angiofibroma in tuberous sclerosis should be considered. Childhood-onset familial fi brofolliculoma 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 unverified[2-4]. Although the incidence is not yet established, about 200 families with BHDS containing pathogenic *FLCN* mutations have been reported worldwide[2]. Among these, an apparent difference in mutations were found, which include insertion, deletion, inactivating frameshift and nonsense mutations[1,4]. Because no genotype-phenotype correlation has been found to date and clinical expression is widely variable, BHDS is most likely under-diagnosed[2,5].

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 previously[6]. 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 indicated[7]. 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 ultrasonography, 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 preventive[2]. Treatment for fibrofolliculomas using an erbium-YAG or fractional CO_2 laser provides temporary improvement[9-11]. 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 encourage.

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.

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