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신장종양이 동반된 Birt-Hogg-Dubé Syndrome

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Birt-Hogg-Dubé Syndrome Associated with a Renal Tumor

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Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disorder characterized by the formation of hair follicle tumors, kidney tumors, and pulmonary cysts with recurrent spontaneous pneumothorax. A 44-year-old woman visited Wonkwang University Hospital with mild dyspnea. A chest X-ray on admission revealed pneumothorax in both lung fields. Chest computed tomography (CT) revealed both pneumothorax and multiple, irregularly shaped, variable-sized cysts in both lung fields. Upon physical examination, white dome-shaped papules were observed on the face. Histological examination of the skin lesion confirmed fibrofolliculoma, and genetic studies revealed a folliculin gene mutation. Abdominal CT revealed a 1-cm small solid renal mass at the lower pole of the right kidney. We surgically removed the renal tumor, and a histological diagnosis of oncocytoma was made. Here, we report a case of BHD that demonstrated all three clinical manifestations; this is the first case report of its kind in Korea. (Korean J Med 2019;94:379-382)

Keywords: Birt-Hogg-Dubé syndrome; Kidney neoplasms; Pneumothorax

INTRODUCTION

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disorder characterized by the formation of hair follicle tumors, kidney tumors, and pulmonary cysts with recurrent spontaneous pneumothorax. BHD is caused by inactivating mutations in the folliculin (FLCN) gene located on chromosome 17, which encodes a highly conserved tumor suppressor protein [1]. Patients with BHD do not always exhibit all three manifestations in the skin, kidneys, and lungs. Previous cases of BHD with pulmonary cysts along with skin lesions and spontaneous pneumothorax have been reported in Korea [2,3]. However, there have been no reports of cases exhibiting all clinical manifestations of BHD, including kidney tumors. Here, we report a case of BHD that manifested as fibrofolliculoma, multiple lung cysts with spontaneous pneumothorax, and a renal tumor. We confirmed the diagnosis in this patient as related to an FLCN gene mutation.

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CASE REPORT

A 44-year-old woman visited Wonkwang University Hospital with mild dyspnea that had persisted for more than 5 days. The patient had undergone chest X-ray imaging at another hospital and was diagnosed with bilateral pneumothorax. She had no history of smoking or alcohol use. She had a family history of pneumothorax, which had been responsible for her father's death. She had a history of operation for uterine leiomyoma at Wonkwang University Hospital 8 years ago.

She was alert, and the following findings were noted on a physical examination upon admission: blood pressure, 130/80 mmHg; pulse, 70 bpm; respiratory rate, 20 breaths per minute; and body temperature, 37.0℃. She seemed healthy in appearance. Breathing sounds were decreased in both lung fields and her heartbeat was regular without murmur upon auscultation. There were no abnormalities on abdominal or limb examinations. However, white dome-shaped papules several millimeters in size were observed on the face, particularly the cheek area (Fig. 1A). Punch biopsy of the skin lesions in cooperation with dermatologists revealed fibrofolliculoma (Fig. 1B). The results of laboratory examinations were as follows: hemoglobin, 13.6 g/dL, and hematocrit, 39.8% (both normal); white blood cell count, 8,390/μL (differential count: 54.1% neutrophils, 25.6% lymphocytes, 7.6% monocytes, and 12.2% eosinophils); platelet count, 214 × 10^9/L; C-reactive protein level, 1.23 mg/L (normal range 0-5 mg/L); serum rheumatoid factor level, 6.8 IU/mL (normal range 0-10 IU/mL); serum ANA negative; serum CA 125 level, 31.8 U/mL (normal range 0-35 U/mL); and serum α1-antitrypsin level, 113.98 mg/dL (normal range 90-200 mg/dL). The results of renal and liver function tests were normal. An arterial blood examination while breathing room air revealed a blood pH of 7.41, PaO_2 of 90.6 mmHg, $PaCO_2$ of 36.1 mmHg, and HCO_3 of 22.5 mM/L, with 96.6% oxygen saturation.

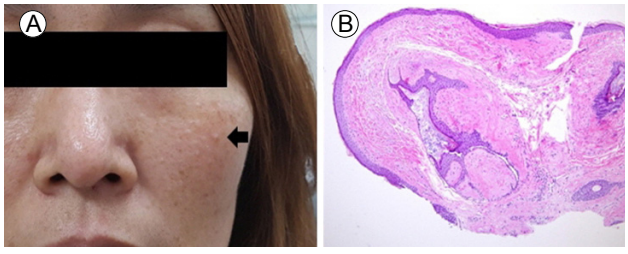

Figure 1. (A) Multiple, dome-shaped, whitish-colored papules present on the cheeks of a 44-year-old woman (black arrow). (B) The histological diagnosis of multiple skin papules was consistent with fibrofolliculoma. Microscopic findings showed thin epidermal strands originating from a central hair follicle and prominent connective tissue (hematoxylin and eosin [H&E staining, ×40]).

A chest X-ray on admission revealed pneumothorax in both lung fields. Chest computed tomography (CT) revealed both pneumothorax and multiple, irregularly shaped, variable-sized cysts in both lung fields with a predominance in the lower medial lung zone. The pulmonary cysts were sharply demarcated with thin walls (Fig. 2A). We initially made a diagnosis of lymphangioleiomyomatosis (LAM) due to her history of uterine leiomyoma. However, the appearance of lung cysts observed on chest CT was more indicative of BHD than LAM.

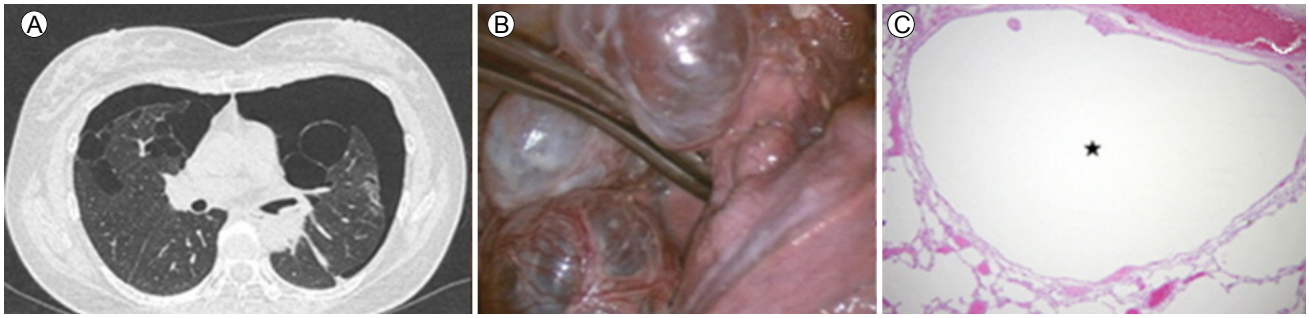

Figure 2. (A) Chest computed tomography showed multiple, variable-sized, thin-walled lung cysts in both lung fields, with spontaneous pneumothorax. (B) Thoracoscopy revealed multiple lung cysts. (C) Microscopic findings showed multiple cystic changes and bullae in the lung parenchyma (H&E staining, ×40).

We first performed chest intubation on both sides; thoracoscopic lung wedge resection was performed 4 days later, which revealed multiple lung cysts (Fig. 2B). The pathological diagnoses were multiple cysts and bullae only (Fig. 2C). Staining for smooth muscle actin was negative.

To confirm BHD, we performed an additional FLCN gene test. The results revealed a c.1285delC, p (His429Thrfs*39). heterozygous mutation (Fig. 3). Abdominal CT was performed to confirm the presence of renal tumors, and revealed a 1-cm solid renal mass at the lower pole of the right kidney (Fig. 4A). We confirmed a diagnosis of BHD based on the above three clinical features and genetic test results.

After the confirmation of BHD, we consulted with a urologist and performed laparoscopic partial nephrectomy on the renal tumor. The pathological diagnosis was oncocytoma (Fig. 4B). One week after surgery, she was discharged without any complications. Before discharge, she underwent a pulmonary function test, the results of which were within the normal range. We advised genetic testing of her family, but she refused.

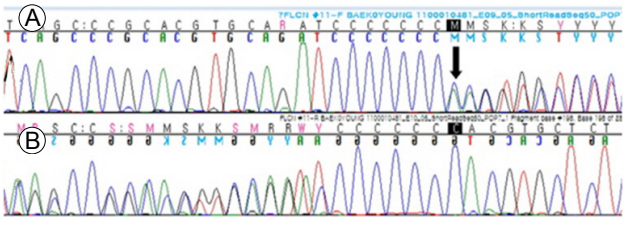

Figure 3. Sequence analysis of the folliculin gene revealed a deletion mutation (c.1285delC) in exon 11 (arrow) (A: patient, B: healthy control).

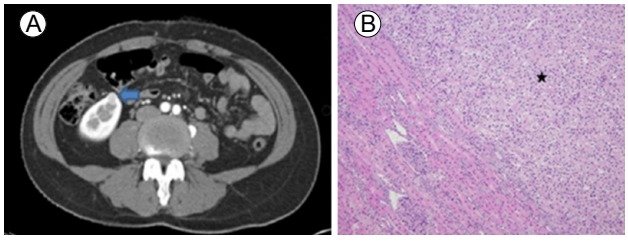

Figure 4. (A) Abdominal computed tomography revealed a 1-cm solid renal mass at the lower pole of the right kidney (arrow). (B) The pathological diagnosis of the renal mass was oncocytoma. The tumor cells (asterisk) were arranged in nests, had uniform small nuclei, and had a more eosinophilic cytoplasm than normal kidney cells (left of image; H&E staining, ×40).

One month after discharge, she was admitted again for bilateral spontaneous pneumothorax. She underwent additional chest intubation and thoracoscopic lung wedge resection and was discharged. She is currently undergoing follow-up observation without any changes in an outpatient setting.

DISCUSSION

BHD is a rare autosomal dominant monogenic disorder caused by constitutional mutations in the FLCN gene, which is located at 17p11.2 and encodes folliculin, a protein widely expressed in the skin, kidneys, lungs, and other organs. The normal protein functions as a tumor suppressor protein involved in regulation of the mammalian target of rapamycin signaling pathway. The exon 11 c.1285delC mutation observed in this case is the most common mutation with c.1285dupC. A mononucleotide tract of eight cytosines within exon 11 has been identified as a hypermutable hotspot. To date, various FLCN germline mutations have been identified. They are characterized by skin folliculoma, renal tumors, and multiple lung cysts with or without spontaneous pneumothorax [1,4].

Skin fibrofolliculoma is a benign hamartoma of the hair follicle; this is the hallmark of the cutaneous manifestation of BHD. Fibrofolliculomas typically appear after 20 years of age and present as multiple, dome-shaped, whitish papules that are most commonly observed on the face, neck, and upper torso [5].

Pulmonary involvement manifests as pulmonary cysts and the development of recurrent pneumothorax. Multiple and bilateral pulmonary cysts are observed in > 80% of patients with BHD. Pulmonary cysts have been reported in patients of widely varying age, but are more common in patients aged 40-50 years. The characteristic chest CT findings of patients with BHD can be summarized as multiple, irregularly shaped, thin-walled pulmonary cysts of various sizes, distributed predominantly in the lower medial and subpleural regions of the lungs. Patients with BHD have a 50-fold increased risk of developing spontaneous pneumothorax after adjusting for age, with a median age of 38 years at pneumothorax occurrence. However, the parenchyma surrounding the pulmonary cysts in BHD is normal. Therefore, the limited data on pulmonary function testing in BHD have demon-

strated preserved or minimally impaired lung function [6].

One of the most important clinical features of BHD is the development of renal tumors. Patients with BHD are at increased risk of developing bilateral, multifocal, renal cell cancers; a 7-fold increased risk of renal cell cancer has been reported in patients with BHD. Chromophobe renal cell carcinoma is the most common subtype, followed by oncocytic and clear cell tumors. Most renal cancers associated with BHD tend to follow an indolent course, and only a few cases of metastatic spread have been reported. As renal cancer is the most life-threatening complication of BHD, regular screening is essential in the long-term management of these patients. However, the optimal mode, timing, and duration of surveillance remain unclear [7].

Patients with BHD do not always exhibit all three manifestations, including skin, kidney, and lung manifestations. Toro et al. [8] reported that skin fibrofolliculomas, pulmonary cysts, and renal tumors were found in 98%, 89%, and 23% of 198 patients, respectively. Furthermore, Houweling et al. [9] analyzed 115 FLCN mutation carriers from 35 BHD families to evaluate renal cancer and pneumothorax risk in BHD. The results indicated the estimated penetrance of renal cancer and pneumothorax to be 16% and 29% at 70 years of age, respectively.

There have been several reports of cases of BHD in Korea. However, no cases of BHD with all three typical clinical manifestations, particularly renal tumors, have been reported [2,3,10]. In this case, the patient had skin lesions typical of BHD, accompanied by spontaneous pneumothorax and multiple lung cysts. After confirming the FLCN gene mutation and diagnosis of BHD, the possibility of a renal tumor was realized and abdominal CT was performed for diagnosis and surgical tumor removal. Although BHD is a relatively rare disease, clinicians should be aware that renal tumors may be present when multiple lung cysts are found. We reported a case of BHD that manifested with all three clinical features, including fibrofolliculoma, multiple lung cysts with spontaneous pneumothorax, and a renal tumor. We confirmed the diagnosis by FLCN gene mutation analysis. This is the first case report of its kind in Korea.

중심 단어: Birt-Hogg-Dubé 증후군; 신장종양; 기흉

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