INTERNAL MEDICINE

□ CASE REPORT □

Pneumothorax Developing for the First Time in a 73-year-old Woman Diagnosed with Birt-Hogg-Dubé Syndrome

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Abstract

Spontaneous pneumothorax in the elderly commonly occurs due to underlying pulmonary diseases, such as chronic obstructive pulmonary disease, interstitial lung disease, lung cancer, etc. A 73-year-old woman developed pneumothorax for the first time that was a clinical clue to a diagnosis of Birt-Hogg-Dubé syndrome (BHDS), an autosomal dominant condition characterized by fibrofolliculomas of the skin, renal tumors and multiple lung cysts predisposing to pneumothorax. Although BHDS patients frequently develop pneumothorax during their twenties to forties, the present case indicates that BHDS should be considered as an underlying cause of pneumothorax in the elderly with undisclosed BHDS.

Key words: pulmonary cysts, secondary pneumothorax, FLCN, fibrofolliculoma, cystic lung diseases

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Introduction

Birt-Hogg-Dubé syndrome (BHDS) is an inherited autosomal genodermatosis characterized by fibrofolliculomas of the skin, renal tumors and multiple lung cysts with or without spontaneous pneumothorax (1). Mutations in the *FLCN* gene, which is located on chromosome 17p11.2 and functions as a tumor suppressor gene, have been identified to be a cause of BHDS (2). Pulmonary cysts are the most common BHDS manifestation, with more than 80% of BHDS patients having multiple lung cysts (1). In addition, lung involvement is often the earliest of the three phenotypes of BHDS (skin, kidneys and lungs) to appear, and pneumothorax has even been reported in a 7-year-old BHDS patient (1). Zbar et al. reported that age is inversely associated with pneumothorax and that younger patients (<41 years) are approximately four times as likely as older patients (>40 years) to have pneumothorax (3). However, the present case report clearly indicates that BHDS can be the initial cause of pneumothorax in the elderly.

Case Report

A 73-year-old Japanese woman was referred for the treatment of asymptomatic left pneumothorax observed on a chest X-ray obtained during a health checkup. She did not require the insertion of a chest tube since her lung had already somewhat expanded. She was a never-smoker and had no previous episodes of pneumothorax. She did not have any triggering factors for pneumothorax before the health checkup. Computed tomography (CT) images of the chest were obtained to determine the underlying disease, which revealed multiple cysts of irregular shapes and various sizes located predominantly in the lower medial zones of both lungs (Fig. 1). The patient's sister and niece both had a history of repeated pneumothorax. Multiple papules around the patient's nose (Fig. 2) resembled those found on the nape of her sister's neck. The patient had noticed these papules since approximately 30 years of age.

Due to the family history of pneumothorax and papules and the characteristic radiologic findings on chest CT (4), we suspected a diagnosis of BHDS. A skin biopsy of the

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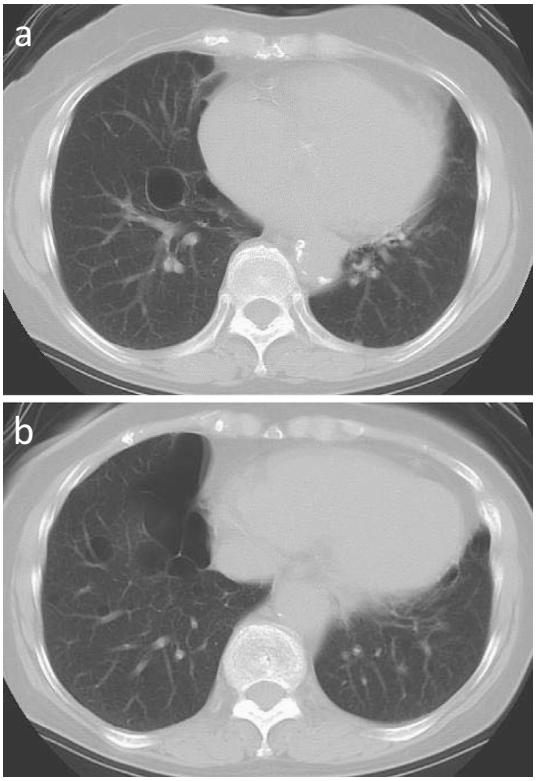

Figure 1. **CT of the chest (5-mm section thickness) revealed irregularly shaped lung cysts of varied sizes located predominantly in the bilateral lower medial zone. Images at the level of the right atrium (a) and inferior vena cava (b).**

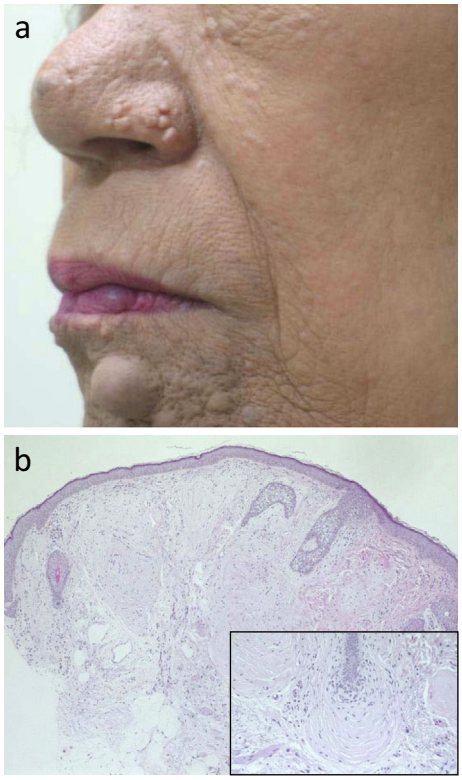

Figure 2. **Facial photograph showing multiple papules around the nose (a). Histology of the papules on the right cheek showed an increased fibromyxomatous area in the dermis (Hematoxylin and Eosin staining, ×5). (Inset: basaloid follicular epidermal hyperplasia surrounded by a fibromyxomatous area, ×20) (b).**

papules on the patient's right cheek revealed a trichodiscoma (Fig. 2). Trichodiscomas are hamartomas of the hair follicle and are considered to be the same as fibrofolliculomas (1). No renal tumors were observed on a subsequent ultrasonogram. Written informed consent was obtained for genetic testing of the *FLCN* gene, which revealed a germline *FLCN* mutation in intron 10 in the index case, sister and niece, i.e., c.1177-5_1177-3delCTC (a splice acceptor site mutation in intron 10 expected to produce exon 11 skipping and premature termination of protein synthesis).

Discussion

The present patient presented with the characteristics of skin lesions and pneumothorax; however, she did not have renal tumors. Growing evidence indicates that BHDS exhibits its diverse clinical heterogeneity and is not always associated with three characteristic phenotypes (involvement of the skin, kidneys and lungs) (1, 5). A study by Toro et al. found that 89% (177/198) of patients with BHDS had lung cysts on chest CT images, while 24% (48/198) had a history of pneumothorax, with a median age at first occurrence of 38 years (range: 22-71) (6). Pavlovich et al. reported that 34 of 124 individuals (27%) with BHDS had renal tumors (7). A risk assessment study of BHD patients identified a 50-fold increase in the risk of spontaneous pneumothorax and a seven-fold increase in the risk of renal cancer in individuals with BHD (3). Due to the increased risk of renal cancer, surveillance for renal tumors is indicated in BHDS patients. Annual renal MRI and/or ultrasonography have been reported to be the best available surveillance methods (1).

The age-related development of phenotypes has been reported in patients with BHDS (3). Skin papules are usually thought to develop after 30 years of age, since Birt et al. found that all patients with fibrofolliculomas were older than 25 years of age (8), while the incidence of renal tumors tends to increase after 40 years of age. On the other hand, pneumothorax frequently occurs in patients younger than 40 years of age. In one study, only 5.0% (6/119) of older patients (>40 years) had pneumothorax compared with 17.6% (18/102) of younger patients (<41 years) (3). The present patient is clinically of interest since she developed spontaneous pneumothorax for the first time at 73 years of age.

Various cystic lung diseases must be differentiated from BHDS. One of the most important diseases is lymphangioleiomyomatosis (LAM), especially in women. Tobino et al. reported that BHDS can be differentiated from LAM based on thin-section chest CT images. Multiple, the presence of irregularly shaped cysts of various sizes with lower medial lung zone predominance is a characteristic CT finding of BHDS. On the other hand, LAM presents with a more circular shape, smaller size and equal distribution of

cysts in all lung fields (9). In the present case, both the patient's sister and niece had a history of pneumothorax, and the typical cystic findings of BHDS were observed on their chest CT images.

In the elderly population, pneumothorax commonly occurs due to underlying pulmonary diseases. In a study conducted in Scotland, 80% of patients with pneumothorax over 50 years of age had a preexisting lung disease (10). In that study, chronic obstructive pulmonary disease was cited as the most common underlying cause; however, numerous conditions, including interstitial pneumonia, lung cancer, infectious diseases, such as *Pneumocystis* pneumonia, etc., can be involved (3). The diagnosis in the present patient, however, clearly indicates that BHDS can be a cause of pneumothorax in the elderly, even in patients diagnosed for the first time at an advanced age. Accordingly, evaluating skin lesions and chest CT findings and carefully interviewing the patient to record the family history is necessary in order to confirm the diagnosis and make decisions regarding follow-up.

The authors state that they have no Conflict of Interest (COI).

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