INTERNAL MEDICINE

□ CASE REPORT □

Birt-Hogg-Dubé Syndrome and Familial Adenomatous Polyposis: An Association or a Coincidence?

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Abstract

An association between Birt-Hogg-Dubé syndrome (BHDS) and colon cancer remains conjectural, but herein we describe a case who may illustrate a significant link between them. The 60-year-old woman was diagnosed at 28 years of age with colon carcinoma and familial adenomatous polyposis (FAP). She also had repeated pneumothoraces, and was diagnosed with BHDS following the finding of pneumothorax in her son. We confirmed the presence of germline mutations in both her folliculin (*FLCN*) and adenomatous polyposis coli (*APC*) genes. The family pedigree suggested that a *de novo FLCN* mutation might have contributed to the development of colon carcinoma at a younger age than her family members.

Key words: Birt-Hogg-Dubé syndrome, colorectal neoplasm, *APC* gene, folliculin protein, pneumothorax

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Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare, autosomal dominant disease that was first described in 1977 (1). The cause of BHDS is currently attributed to a germline mutation in the folliculin (*FLCN*) gene, and the disease is characterized by skin fibrofolliculomas, multiple lung cysts, spontaneous pneumothorax, and renal neoplasms (2). Additionally, a range of tumors other than renal neoplasms have been reported in BHDS. Although an association between BHDS and colorectal neoplasms was suggested (3), no confirmation has been forthcoming as yet. We herein describe an individual who is one of several family members afflicted with familial adenomatous polyposis (FAP), a hereditary colorectal carcinomas caused by germline mutation of the adenomatous polyposis coli (*APC*) gene, and some have a *de novo* mutation in the *folliculin* (*FLCN*) gene. This is the first report of an individual who harbors germline *FLCN* and *APC* mutations along with the clinical manifestations of BHDS as well as FAP.

Case Report

A 60-year-old Japanese woman (index case) came to our attention in April 2009 because of a suspected familial pneumothorax. This condition was first noted a year earlier when her 32-year-old son was admitted to our hospital due to bilateral pneumothoraces. The mother's previous medical history showed recurrent pneumothoraces at 28, 41, 44, and 46 years of age, and she was finally treated surgically with video-assisted thoracoscopy. A thoracic CT she previously underwent in February 1992 (age 44) revealed multiple irregularly shaped pulmonary cysts with a bilateral, basal, and peripheral distribution (Fig. 1A). Her son was first diagnosed with pneumothorax in April 2008 (age 32), but it occurred simultaneously in both lungs. CT images of his chest depicted multiple pulmonary cysts with a shape and distribution similar to those of his mother (Fig. 1B).

In addition to the young age at which pneumothoraces developed in both mother and son, the other remarkable diagnosis in her past medical history was the emergence of colon carcinoma and multiple colon polyps when she was 28

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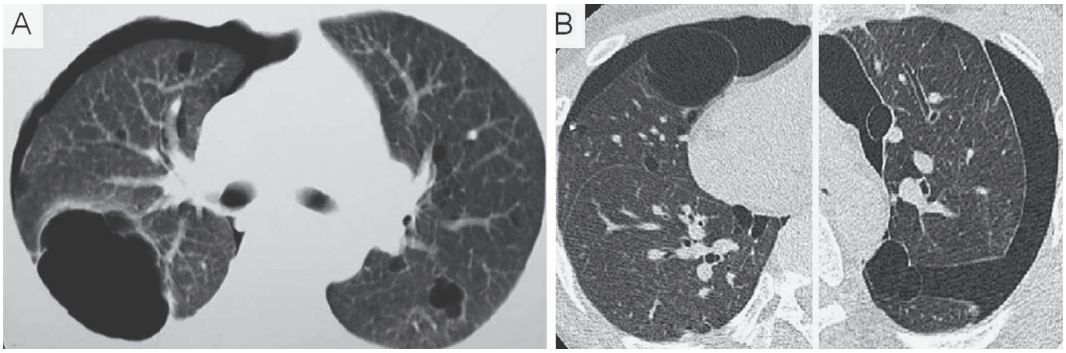

Figure 1. **Computed tomography depicts multiple irregularly shaped cysts with a bilateral, basal, and peripheral distribution in the patients' lungs. Scans from (A) the 44-year-old index case in February 1992 and (B) her 32-year-old son in April 2008.**

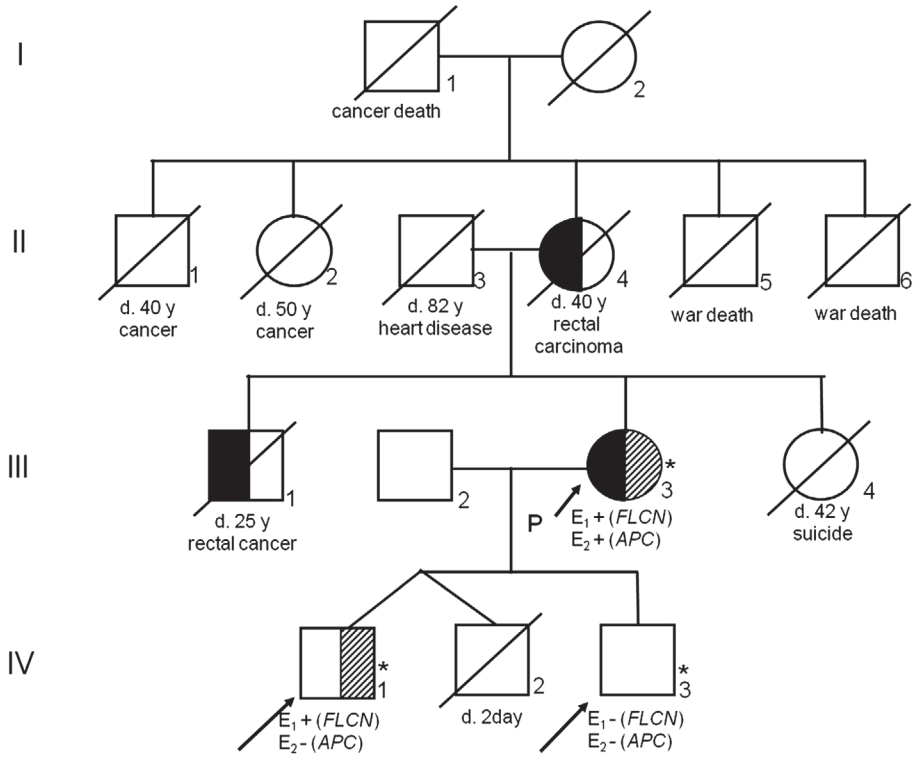

Figure 2. **This family tree reveals a marked prevalence of cancer- (unknown type) or rectal cancer-related death among first-, second-, and third-generation descendents and the occurrence of pneumothorax in the index case (III-3). Symbols used are: square, male; circle, female; solid symbols, affected by rectal cancer; shaded symbols, affected by spontaneous pneumothorax; oblique line, deceased. *Of individuals tested, E1 indicates examination of germline *FLCN* mutation and E2 examination of germline *APC* mutation. Results are shown as + (positive) or - (negative).**

years old. Her disease was attributed to possible FAP solely on the basis of documentation that her brother, mother, and other relatives had died of colorectal cancer at a young age (Fig. 2). Accordingly, she underwent a total colectomy to extirpate the colon carcinoma and to prevent further suffering from multiple colorectal neoplasia in the future.

Although this woman and her son had no sign of renal tumor, both exhibited small facial papules that, along with their family history of pneumothorax and the pulmonary cysts on CT images (irregular shape and relatively large size but small in number, and distributed predominantly in the lower-medial zone), were strongly suggestive of those of BHDS (4). Accordingly, we conducted genetic testing for BHDS as well as FAP with permission (signed informed consent) from her and her son. Our results confirmed the presence of germline mutations in both *FLCN* and *APC* genes of the mother, whereas her son (IV-1) had only the *FLCN* mutation (Fig. 3). No polyps were found in her son by colonoscopic examination. Her youngest son (IV-3) had no germline mutation in either the *FCLN* or *APC* gene.

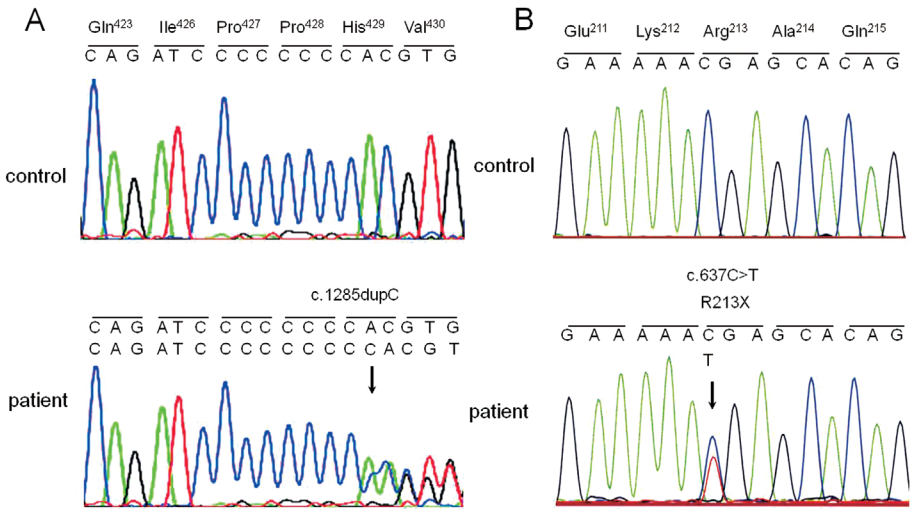

Figure 3. **Identification of a germline *FLCN* mutation and an *APC* mutation in the index case. This patient harbors a c.1285dupC (a C insertion in the exon 11 causing a frameshift) in the *FLCN* gene (A) and c.637C>T (C to T substitution causing a nonsense mutation at codon 213) in the *APC* gene (B).**

Discussion

In the female patient described here, BHDS and FAP co-existed, representing the extraordinary emergence of two tumor suppressor gene syndromes. Historically, BHDS was first identified in a family who developed hereditary medullary carcinoma of the thyroid, a disease now recognized as a tumor suppressor gene syndrome caused by a germline *RET* mutation (1). This kindred consisting of 70 members initially inherited medullary carcinoma of the thyroid from a male antecedent of French Canadian origin and an accompanying fibrofolliculoma, a cardinal skin manifestation of BHDS, from his wife of English descent. In contrast, our female patient appeared to be the only bearer of a *de novo* *FLCN* mutation that occurred in a family with a pre-existing FAP and passed it to only one of her sons, according to a review of her family tree. In the line of descent preceding the index case presented here, no clinical feature suggestive of BHDS was apparent; however, marked variability in the phenotypic manifestations in BHDS has recently been reported (2).

The exact frequency of *de novo* *FLCN* mutations in patients with BHDS remains unknown. The germline *FLCN* mutation identified in the present patient was c.1285dupC, a C insertion that occurred in a mutational hotspot of the mononucleotide tract of eight cytosines (poly C8 tract) (5) in exon 11. This mutation most commonly occurs in Caucasians (6) and a reported 53% of families with the *FLCN* mutation had a cytosine insertion or deletion in the poly C8 tract (7). Mononucleotide tracts are thought to be hypermutable due to slippage of the DNA polymerase during replication (8). Furthermore, they are a potential target sequence of microsatellite instability (MSI). Some studies performed on sporadic colorectal cancer showed that the poly C8 tract of the *FLCN* gene was indeed an effective target of MSI, at a frequency comparable with that of other target genes (9, 10).

We cannot exclude the possibility that BHDS and FAP coexisted in our index patient's forebears or that one of her parents harbored the mosaicism of a germline *FLCN* mutation superimposed on the preexisting germline *APC* mutation, since they underwent no such genetic testing or interviewing. In fact, their medical histories were available only from information supplied by the index case. In terms of this family's clinical features, the colon cancer and multiple colon polyps might have stemmed from germline mutations of both *FLCN* and *APC*. The index case and her brother developed colon cancer before the age of 30 years, possibly when they were even younger than her mother's generation had been at the cancer onset. Nahorski et al. suggested that somatic mutations of the *FLCN* gene in patients with colorectal cancer are "passengers" rather than "driver mutations" (10). If so, the existence of a germline *FLCN* mutation could have accelerated the malignant transformation of colorectal epithelial cells driven by the "driver," a germline *APC* mutation of both the index case and her brother. Thanks to the clinical decision that led to her total colectomy, based on the occurrence of her colon carcinoma and multiple colon polyps at a young age, her brother's death from colorectal carcinoma when he was only 25 years old, and a marked family history of cancer death, she had survived to the age of 60. This longevity then provided an opportunity for the development and diagnosis of BHDS, which might have also arisen in her brother if he had lived long enough.

The possibility of a pathogenic association between BHDS and colon cancer still remains conjectural, but recent epidemiological reports disputing any relationship between BHDS and colon cancer (11, 12) are certainly open to ques-

tion. That is, some groups reported that patients with BHDS and a *FLCN* mutation in the poly C8 tract were predisposed to colorectal neoplasia with MSI (9, 10). Compared with hereditary colon cancer induced by tumor suppressor gene mutations (e.g., FAP or HNPCC), which tends to develop at an early age at multiple sites, BHDS appears to be associated with later-onset colon cancer, which does not manifest until an average age of 57.4 years (10). This may be one of the reasons why it is difficult to determine whether the development of colorectal carcinoma in patients with BHDS is an associated event or merely a coincidence. Now, the clinical insight provided here into the role of a *FLCN* mutation as a possible facilitator of colon cancer may suggest that a significant link exists between BHDS and colon cancer and that further study is obviously needed.

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

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