Sebaceous Gland Hyperplasia: An Atypical Presentation of Birt-Hogg-Dubé Syndrome

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ABSTRACT:

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Birt-Hogg-Dubé syndrome (BHD) is an inherited autosomal dominant hamartoma disorder, characterized by benign tumors of the hair follicle, lung cysts, and renal neoplasia. It is caused by germ-line mutations in the folliculin (*FLCN*) gene. Cutaneous manifestations are mainly presented with folliculoma or trichodiscoma. We report a case of a BHD patient with sebaceous gland hyperplasia on the face without other skin lesions. The diagnosis is confirmed by clinical symptoms and folliculin gene mutation. Ablative carbon dioxide laser is the effective treatment for sebaceous gland hyperplasia in our patient.

Key words: Birt-Hogg-Dubé syndrome, multiple sebaceous gland hyperplasia, folliculin gene

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Introduction

Birt-Hogg-Dubé syndrome is a rare inherited autosomal dominant disease, caused by the germline mutation of the folliculin (*FLCN*) gene, on chromosome 17p11.2. The characteristic skin lesions are asymptomatic fibrofolliculomas, trichodiscomas and acrochordons on the head, neck, chest, back and arms. In this study, we report the atypical presentation of Birt-Hogg-Dubé syndrome with sebaceous gland hyperplasia on the face.

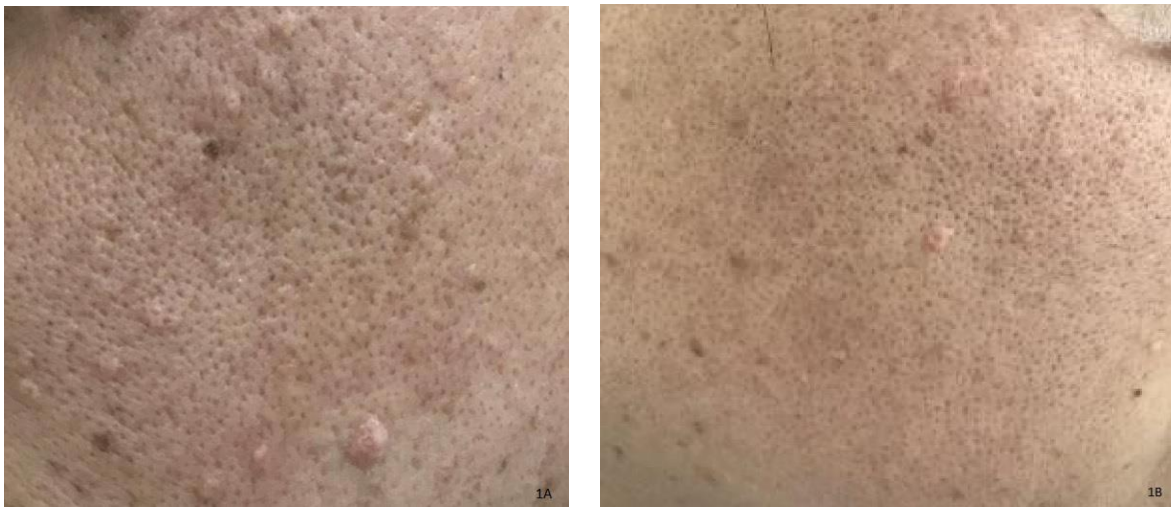

Figure 1 A, B Multiple symmetrical, ill-defined border, smooth-surface, skin-colored, dome-shaped papules on both cheeks

Our case

A 42-year-old Thai man presented with asymptomatic symmetrical skin-colored papules on his face for 8 years. (Figure 1 A, B)

Neither progression of their sizes nor other skin lesions were reported. He had a history of renal cell carcinoma, clear cell type, and received nephrectomy 2 months ago. His family members had history of various types of cancers in both genders (3 generations consecutively at age 30-50 years old). (Figure 2)

The dermatological examination showed multiple symmetrical, ill-defined border, smooth-surface, skin-colored, dome-shaped papules on both cheeks. The other manifestations were unremarkable. Skin biopsy was performed on his right cheek and revealed large lobulated mature sebaceous lobules opening to hair follicles, compatible with sebaceous gland hyperplasia (Figure3).

Pathogenic folliculin gene mutation found positive in the next generation sequencing gene

test; this confirmed the diagnosis of Birt-Hogg-Dubé syndrome. The result in this case found *FLCN* c.1283 C>A and protein proline to histine (p.Pro428His). Our patient received carbon dioxide laser treatment to ablate the lesion. Surveillance lung cyst was done by computer tomography of the chest and the result showed normal. Genetic counseling with all his first-degree relatives and long-term surveillance of his internal malignancy had been completed by the genetic doctor.

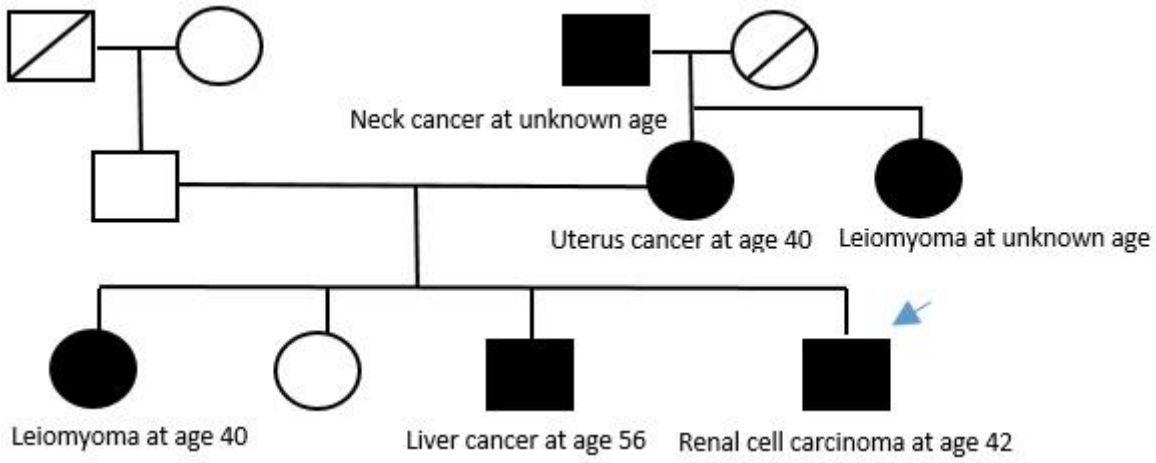

Figure 2 Family pedigree of cancer

Discussion

The folliculin gene is a tumor suppressor protein of the mammalian target of rapamycin (mTOR) pathway, encoding folliculin protein. It highly expresses within the lungs, skin and kidneys[1]. Thereafter, the clinical manifestations of Birt-Hogg-Dubé syndrome are mainly observed in these organs[1].

The diagnostic algorithm that needs to fulfill one major or two minor criteria for definite diagnosis has been proposed by Menko[2]. Major criteria consist of: 1) at least five fibrofolliculoma or trichodiscoma or at least histological confirmation of adult onset, 2) pathogenic folliculin germline mutation, could be detected by either single gene test or multigene panel. Most of the reported pathogenic *FLCN* mutations are frameshift or nonsense mutations that lead to protein truncation, and a small percentage are splice-site alterations[2,3].

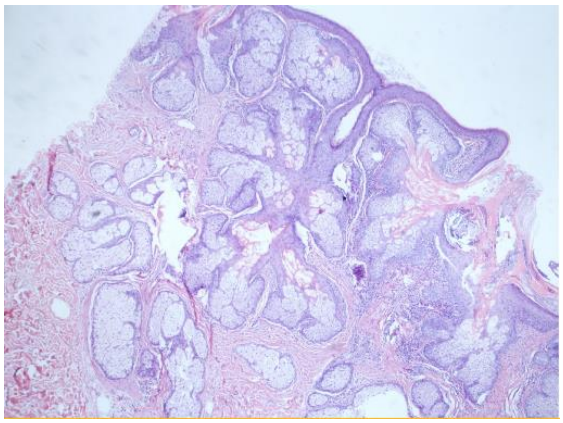

Figure 3 Large lobulated mature sebaceous lobules opening to hair follicles, H&E x100

Minor criteria are composed of: 1) multiple lung cysts with or without spontaneous pneumothorax, or 2) renal cancer which is early onset (less than 50-year-old age) or multifocal or bilateral renal cancer with hybrid chromophobe and oncocytic histology and lastly, 3) a first degree relative of Birt-Hogg-Dubé syndrome.

This syndrome has no sex predilection and tends to manifest in the third or fourth decade of life. The phenotype for patients with BHD syndrome is variable. The cutaneous lesions are mostly present with fibrofolliculoma, trichodiscoma, and achrocondon[4]. Fibrofolliculomas are 2-4 mm yellowish white, smooth, dome-shaped papules and usually are multiple lesions. They predominantly locate at upper body, especially the area of dense sebaceous follicle concentration (e.g., face), and appear at over 20 years of age[5]. Trichodiscomas are clinically distinguishable by fibrofolliculoma[6]. Other cutaneous lesions reported occurring in patients with BHD syndrome include facial angiofibromas, lipomas, angiolipomas, and oral mucosal fibromas. Some reports show that sebaceous gland hyperplasia could be found in BHD syndrome patients, particularly 2/51 families (sebaceous gland hyperplasia with fibrofolliculoma)[7] and 2/31 japanese patients (isolated sebaceous gland hyperplasia without other skin lesions) [8].

Lung cysts on imaging are the earliest extra-cutaneous findings in BHD patients. These cysts typically have lentiform shape and are predominant at the periphery of bilateral lung bases with surrounding normal parenchyma[9,10,11]. Nevertheless, the most common symptom that prompts the patients to seek medical care is spontaneous pneumothorax. The BHD patients with a family history of pneumothorax are found in 35% of the cases, with the individuals having a 50-fold increased lifetime risk of pneumothorax[9].

The most classic renal tumors are renal cancer carcinoma, preferentially called FLCN-associated RCC[12,13]. This is because of their folliculin gene mutation and distinct histological appearance (mainly chromophobe and mixed oncocytic/chromophobe tumors)[14]. Multifocal and bilateral tumors usually present at an average age of 50 years. The risk of getting renal-

tumor increases seven-fold; such tumors can be either benign or malignant[14].

Moreover, other cancers were also increasingly reported nowadays in this syndrome, for example medullary thyroid cancer, and uterine carcinoma[15]. The investigation includes baseline abdominal CT scan with contrast or gadolinium-MRI, a useful test for screening of renal tumor, and chest CT for lung cyst surveillance. Genetic consultation and long-term follow-up are also indicated.

The *FLCN* gene mutation in this case found the c.1283 C>A (p.Pro428His) by the next generation sequencing gene test. This identified missense heterozygous single nucleotide variant, located in coding exon 8 of the FLCN gene, results from a C to A substitution at nucleotide position 1283. The proline at codon 428 is replaced by histidine, an amino acid with similar properties. This mutation could potentially lead to non-functional protein, however the supporting evidence is limited at this time, the clinical significance of this alteration remains unclear. This variant of unknown significance still needs to study further in the future for its potential virulence. To date, no clear correlation between type of mutation or location within the *FLCN* gene and any of the phenotypic manifestations has been identified. In this regard, the clinician should be aware of the genotype-phenotype correlation in each suspected case before making diagnosis. Furthermore, the future functional study could be benefit to confirm pathogenicity of this variant.

Benign skin lesions require no treatment due to benign course. However, destructive therapy, such as Erbium-YAG or fractional CO2 laser ablation, can be treated for cosmetic purposes, but recurrence of skin lesions can occur[16]. Patients with pneumothorax are recommended to perform pleurodesis at the first time of symptoms[17]. The renal tumor can be observed if it is smaller than 3.0 cm in size, but requires partial nephrectomy when its size is greater than 3.0 cm and/or rapidly growing. The continuing surveillance for renal tumor has been suggested to be done every 2 years[18].

In conclusion, isolated sebaceous gland hyperplasia shows essential aspects in one of the Birt-Hogg-Dubé syndrome manifestations. We believe that the isolated sebaceous gland hyperplasia with history of renal tumor or lung cyst could represent a clinical variant of Birt-Hogg-Dubé syndrome.

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