

Melanoma in a patient with previously unrecognized Birt-Hogg-Dubé syndrome



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Key words: Birt-Hogg-Dubé syndrome; cancer; dermatology; fibroadenoma; melanoma; moles; papules.

INTRODUCTION

Birt-Hogg-Dubé syndrome (BHDS) is an uncommon genetic disorder affecting the skin, lungs, and kidneys. It is characterized by numerous benign skin tumors (fibrofolliculomas, trichodiscomas, and acrochordons), especially on the face, neck, and chest.¹ Although BHDS has a well-known link with malignancy, especially renal cancer, it is infrequently considered in dermatology patients with atypical nevi and melanoma.² However, increased melanoma risk, including choroidal melanoma, is associated with BHDS.³⁻⁹ Here, we report a patient with multiple primary cutaneous melanomas and atypical nevi that triggered evaluation for an underlying genetic cause. We bring this underreported clinical co-occurrence to the attention of dermatologists.

CASE REPORT

A 50-year-old woman with Fitzpatrick type 1-2 skin and a history of melanoma and atypical nevi presented for her recommended biannual dermatologic evaluation. Despite adherence to sun protection measures, prior dermatology examinations over 18 years had shown 15 biopsy-proven atypical nevi. Three were severely atypical, and 12 were moderately atypical. Just 4 months earlier, malignant melanoma, superficial spreading type (Breslow thickness of 0.7 mm and immunoreactive for melan A), was diagnosed from the anterior portion of her right forearm. Environmental risk factors included a limited, remote history of tanning bed use over 1 year and sunburns but no outdoor work or immunosuppression. She denied any history of lung or renal disease. On examination, tan-brown nevi of various

Abbreviations used:

AMPK:	adenosine monophosphate-activated protein kinase
BHDS:	Birt-Hogg-Dubé syndrome
FLCN:	folliculin

sizes in a widely scattered distribution and a slightly darker suspicious site on the right back-lateral aspect of the lower leg were noted. Biopsy showed superficial spreading melanoma, Breslow thickness of 0.28 mm, and positive melan A reactivity (Fig 1). This unexpected history of 2 new melanomas over a short period prompted more careful review. Genetics consultation with detailed family history showed paternal renal cysts requiring surgical removal and a brother and son each having dysplastic nevi and singular malignant melanoma at an unknown age and age 21 years, respectively. On skin examination, numerous firm, whitish, dome-shaped papules were noted on her face, chest, and back. Three subtle lesions were biopsied, and 1 histologically confirmed fibrofolliculoma was noted, which meets the criterion for dermatologic diagnosis of this syndrome (Fig 2 and Table I).¹ After pretest counseling with a genetics specialist, the patient was offered testing for an *FLCN* mutation. She declined because of cost and the potential for insurance discrimination.

DISCUSSION

BHDS is a rare autosomal dominant disorder affecting not only the skin but also the respiratory and renal systems. The clinical presentation varies

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Funding sources: None.

Conflicts of interest: None disclosed.

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JAAD Case Reports 2019;5:947-52.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2019.08.018>

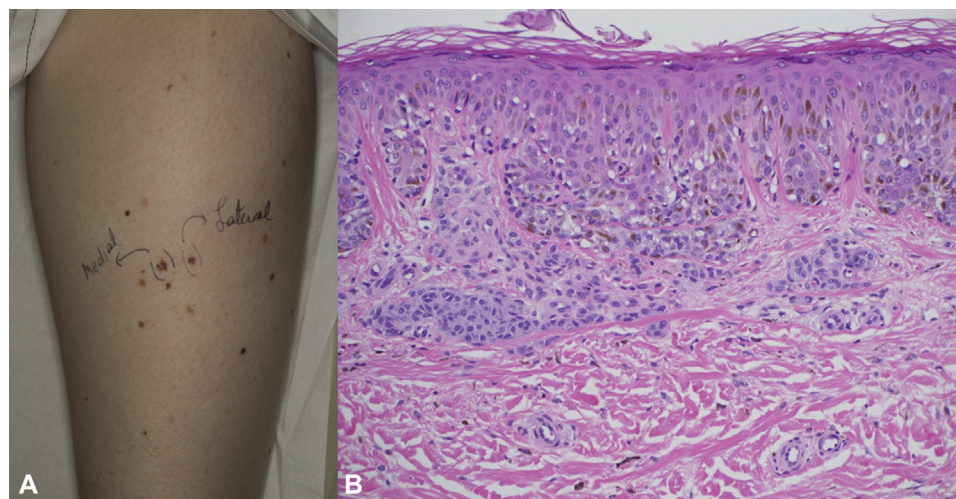


Fig 1. Melanoma. **A**, Lower part of the right leg, tibial region. Multiple atypical, pigmented nevi and biopsy-proven melanoma. **B**, Skin histopathology from right back-lateral leg, tibial area. Melanoma with superficial dermal invasion to 0.28 mm. (Hematoxylin-eosin; original magnification: $\times 40$.)

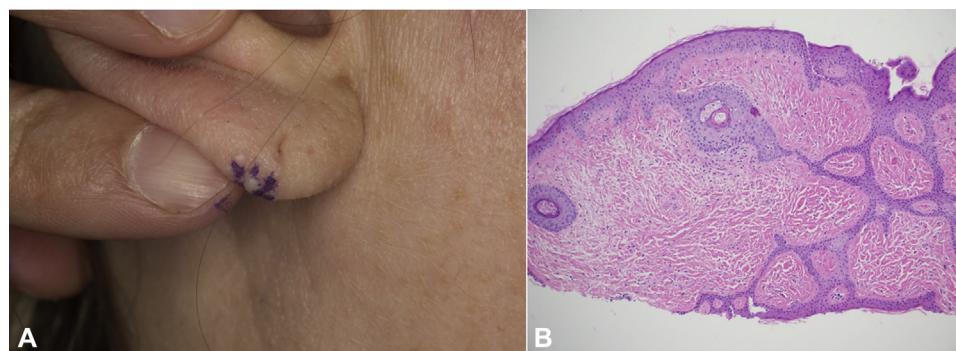


Fig 2. Fibrofolliculoma. **A**, Right ear lobe. Representative firm, white, dome-shaped papule. **B**, Skin histopathology from right ear lobe papule. (Hematoxylin-eosin; original magnification: $\times 40$.)

Table I. Criteria for diagnosis of Birt-Hogg-Dubé syndrome

Major criteria*

- Presence of >4 papules in the face or trunk and ≥ 1 fibrofolliculoma confirmed by histology
- Pathogenic germline mutation in *FLCN*

Minor criteria*

- Presence of multiple, basally located, bilateral lung cysts with no other apparent cause \pm spontaneous primary pneumothorax
- Diagnosis of renal cancer: early-onset (<50 years), multifocal, or bilateral renal cancer, or mixed chromophobe and oncocytic renal cancer
- Family history: first-degree relative with BHDS diagnosis

BHDS, Birt-Hogg-Dubé syndrome.

*Patients need to fulfill 1 major criterion or 2 minor criteria for diagnosis. Adapted from Toro.¹

greatly among affected individuals, even in the same family. Spontaneous pneumothorax due to lung cysts may be one of the earliest manifestations, and up to one third of individuals with BHDS have a lifetime likelihood of developing renal tumors. More than 90% of patients present with benign cutaneous manifestations, which are generally noted in a person's 20s or 30s, and these progressively increase in number and size over time.¹⁰ Despite progression, skin features are rarely cosmetically disfiguring and do not come to medical attention. Multiple melanomas and atypical nevi, however, are more likely to draw the attention of a dermatologist, especially when more than 1 melanoma is present in the same patient.

In general, skin cancer risk is considered to be multifactorial, that is, due to a combination of factors

Table II. Patient characteristics in reported cases of cutaneous melanoma diagnosed in BHDS patients

Study	Study description	Mutational analysis	Dermatologic assessment	Pulmonary involvement	Renal involvement	Others
Sattler et al ⁸	Multinational European study assessing the prevalence of dysplastic nevi and cutaneous melanoma in a cohort of BHDS families	<ul style="list-style-type: none"> • <i>FLCN</i> mutation present in 32 of 33 families • No mutations in genes known to predispose individuals to cutaneous melanoma identified 	<ul style="list-style-type: none"> • 10% diagnosed with cutaneous melanoma <ul style="list-style-type: none"> – Age, 52-90 years – >60% female – 62.5% invasive stage I-IV • 49% diagnosed with dysplastic nevi 	N/A	N/A	N/A
Jaster and Wachsmann ¹¹	Case report of a 64-year-old man with BHDS receiving immunosuppression therapy for renal transplantation	N/A	Malignant melanoma	Malignant mesothelioma, epithelial subtype	Polycystic kidney disease	N/A
Mota-Burgos et al ⁴	Case report of a 54-year-old man with BHDS	<i>FLCN</i> mutation present	<ul style="list-style-type: none"> • Cutaneous melanoma of epithelioid cell type, stage IIIb, ulcerated, and in a vertical growth phase • Multiple fibrofolliculomas and acrochordons around facial and cervical areas • Multiple lipomas on extremities • Cutaneous lesions appeared progressively in his 30s-40s 	None	None	Several colorectal tubulovillous adenomas

Continued

Table II. Cont'd

Study	Study description	Mutational analysis	Dermatologic assessment	Pulmonary involvement	Renal involvement	Others
Kasi and Dearmond ⁵	Case report of a 70-year-old man with BHDS	N/A	<ul style="list-style-type: none"> • Multiple acrochordons • Melanoma • Lipoma • Actinic keratosis • Squamous cell carcinoma 	Multiple pulmonary cysts	Clear cell renal cell carcinoma and bilateral renal cysts	Colorectal tubulovillous adenoma
Cocciolone et al ⁹	Case report of a 58-year-old man with BHDS	<i>FLCN</i> mutation present	<ul style="list-style-type: none"> • 2 desmoplastic melanomas on right cheek and left shoulder • Multiple facial fibrofolliculomas 	History of spontaneous pneumothorax	None	Salivary gland oncocytoma
Welsch et al ³	Case report of a 52-year-old man with BHDS	N/A	<ul style="list-style-type: none"> • Cutaneous lesions appeared progressively in his late 30s • Malignant cutaneous melanoma on the trunk • Multiple fibrofolliculomas on face, nose, ears • Multiple acrochordons in axillae and lateral aspect of the chest wall 	Solitary bullae in right lung and history of pneumothorax	Chromophobe-type renal cell carcinoma	Multinodular goiter
Toro et al ¹²	Case series assessing renal findings in 28 BHDS patients	<i>FLCN</i> mutation present in 1 of 2 patients	<ul style="list-style-type: none"> • Melanocytic nevi in a 61-year-old woman • Malignant melanoma in a 64-year-old man <p>– Oral papules – Fibrofolliculomas and/or trichodiscomas</p>	N/A	Renal oncocytoma and bilateral solid lesions	N/A

Khoo et al¹³

Case series assessing genetic and clinical findings in 32 BHDS patients	FLCN mutation present	<ul style="list-style-type: none"> • A 52-year-old patient with superficial malignant cutaneous melanoma • Multiple cutaneous lesions present in the majority of patients 	Pneumothorax and lung cancer in some patients	Renal cysts and renal cell carcinoma present in some patients	The following findings were observed in some patients: <ul style="list-style-type: none"> • Colorectal polyps • Pleurisy • Gastrointestinal cancer • Nodular cutaneous elastoidosis • Retrobulbar neuropathy • Cutaneous and parotid masses • Breast carcinoma • Meningioma • Vulvar epithelioma • Finger histiocytofibroma • Hashimoto thyroiditis
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N/A, Not available.

such as genetics, environment, and random chance. This patient endorsed some environmental risk factors for melanoma but not others. Her striking history of multiple melanomas despite sun protection suggested a genetic cause and prompted more careful review. Genetic consultation included closer review of family history and physical examination for signs of a genetic cancer syndrome to improve the accuracy of genetic testing or make a diagnosis. This review found multiple, previously unrecognized facial papules suspicious for BHDS.

A literature review for association of BHDS and melanoma showed a case series reporting 8 patients with cutaneous melanoma diagnoses in a cohort of 83 individuals with BHDS. Similar to our case, 1 patient had multiple primary diagnoses of melanoma.⁸ Interestingly, the rate of melanoma increased from 2.1% in the general population to 10% for patients with BHDS. Table II¹¹⁻¹³ summarizes all reports of cutaneous melanoma in patients with BHDS to date. Further studies are warranted to determine the lifetime risk of melanoma in patients with BHDS and how environmental factors and skin type influence this risk.

BHDS is caused by mutations in the tumor suppressor folliculin (*FLCN*), which is expressed in and is important for the development of skin, lungs, and kidneys.¹⁴ Loss of FLCN constitutively activates adenosine monophosphate-activated protein kinase (AMPK), a key enzyme that regulates energy metabolism and melanogenesis.¹⁵⁻¹⁷ Constitutive activation of AMPK leads to autophagy and resistance to many stressors that would normally kill atypical cells. This eventually leads to cellular transformation and, possibly, tumor formation. Autophagy has been strongly linked to the formation of melanoma.¹⁸⁻²² This is likely the same process responsible for melanoma in patients with BHDS, but further work is warranted in this area.

Because of the subtle presentation of the BHDS lesions, we recommend obtaining a thorough family history in patients with multiple primary melanomas and a careful examination for subtle facial and upper body follicular papules due to the increased possibility of BHDS. In addition, the reverse applies as well. Patients with suspected BHDS should be examined for abnormal or dysplastic moles and potentially melanoma.

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