BRIEF ARTICLES

Facial Papules in Birt-Hogg-Dubé Syndrome: A Growing Spectrum of Pathologic Findings

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ABSTRACT

Birt-Hogg-Dubé syndrome is a rare genodermatosis caused by a mutation in the folliculin gene. It is characterized by pulmonary cysts, renal tumors, and a variety of skin manifestations including trichodiscomas, fibrofolliculomas, less commonly reported angiofibromas, and perifollicular fibromas. These cutaneous lesions have overlapping histopathologic features. Here we report a case of a man presenting with facial papules and nonspecific histology found to have Birt-Hogg-Dubé syndrome and a novel mutation in the folliculin gene. Our aim is to raise awareness of the spectrum of associated cutaneous and pathologic findings in Birt-Hogg-Dubé syndrome, which are not all included in the diagnostic

INTRODUCTION

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant genodermatosis caused by a mutation in the folliculin (*FLCN*) gene on chromosome 17.[1] It is characterized by fibrofolliculomas, trichodiscomas, and acrochordons, in addition to pulmonary cysts and renal tumors.[1] Here we report a case of BHDS and discuss the spectrum of associated cutaneous and pathologic findings.

CASE PRESENTATION

A 46-year-old man presented to dermatology clinic with a six-year history of multiple asymptomatic facial papules and a history of two spontaneous right pneumothoraces at the ages of 38 and 39 years. Chest CT at the time of his second pneumothorax revealed a bleb in the anterior aspect of the right upper lobe of the lung and he subsequently underwent blebectomy and right mechanical pleurodesis.

Physical exam showed multiple 2-3 mm dome-shaped monomorphic whitish papules involving the neck, jaw, cheeks, forehead, and bilateral helices (Fig. 1a-b). The patient was otherwise healthy and denied family history of renal neoplasms, pneumothoraces, or genetic conditions.

Shave biopsies of two papules on the left neck and right jaw showed hair follicles with perifollicular fibrosis, dilated blood vessels surrounded by thickened concentric bundles of collagen, and increased stellate fibroblasts (Fig. 2a-b). Genetic testing on a peripheral blood sample revealed a variant in the *FLCN* gene, confirming the diagnosis of BHDS. Notably, this was a previously

unreported heterozygous pathogenic variant (NM_144997.5:c.808dup.). An abdominal MRI demonstrated an unchanged adrenal adenoma first diagnosed on CT eight years prior but no renal masses.

Figure 1. Clinical and pathologic features of a patient with Birt-Hogg-Dubé syndrome. Multiple 2-3 mm hypopigmented papules involve the (a) helix and (b) neck.

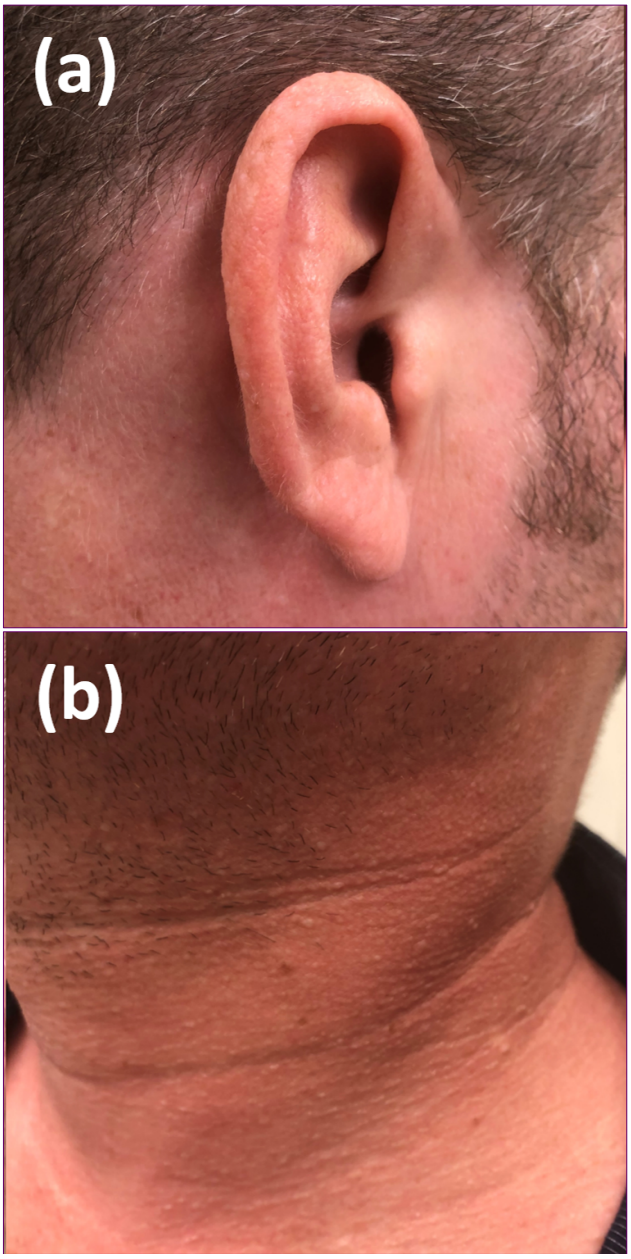
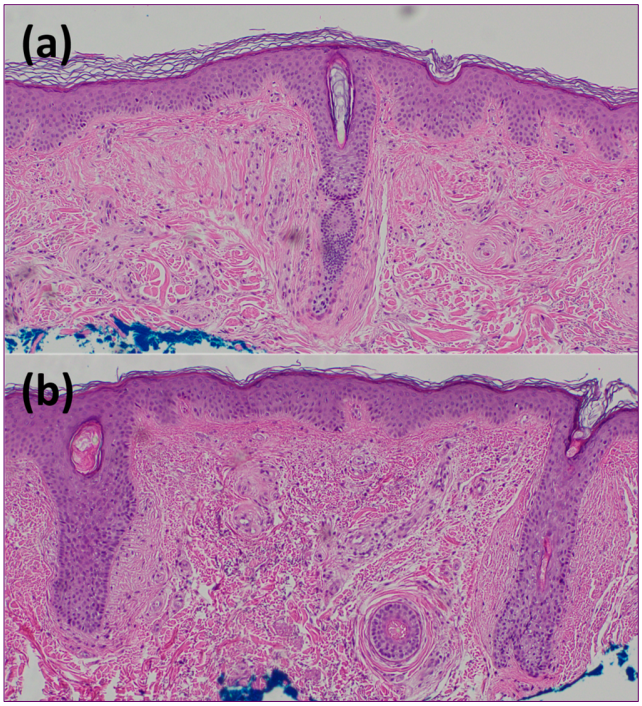


Figure 2. Histopathological exam of the biopsied papules showed (a) perifollicular fibrosis and (b) perivascular fibrosis (hematoxylin and eosin, 10x).



DISCUSSION

Proposed diagnostic criteria for BHDS include any one of: ≥5 facial or truncal papules with ≥1 histologically confirmed fibrofolliculoma; pulmonary cysts with or without history of spontaneous pneumothorax developing prior to age 40; multiple and bilateral chromophobe renal cell carcinoma or hybrid oncocytic tumors, which manifest on average between ages 46 and 52 years; a combination of cutaneous, pulmonary, or renal manifestations in a patient or family members; or germline mutation in *FLCN*.[1,10] The histologic features of our patient's lesions were insufficient to reach a diagnosis of fibrofolliculoma or trichodiscoma given the absence of epithelial strands and sebaceous lobules. The presence of perivascular fibrosis was suggestive, but not diagnostic of angiofibromas.

Fibrofolliculomas and trichodiscomas likely exist along a morphologic spectrum of a single entity comprised of a fibrocellular stroma with a prominence of folliculocentric epithelial strands in the former and clusters of sebaceous lobules in the latter. In comparison, angiofibromas classically exhibit an increased number of dilated, dermal vessels with perivascular fibrosis and a proliferation of fibroblast-like cells. Fibrofolliculomas/trichodiscomas and angiofibromas have been proposed to represent hamartomatous proliferations of follicular epithelial elements and perifollicular mesenchyme with overlapping histopathological and immunohistochemical features.[2] The term "perifollicular fibroma," emphasizing the prominence of concentrically oriented fibrous tissue around hair follicles, has been used in reference to all three diagnoses.[2,3] Furthermore, these lesions exhibit similar patterns of CD34, factor XIIIa, nestin, and CD117 expression within the stromal component and CK15 in the epithelial component.[2]

Although classically associated with tuberous sclerosis complex (TSC), angiofibromas as an initial presentation of BHDS have been described.[4-7] In one recent report, a patient with an initial diagnosis of TSC on the basis of multiple facial angiofibromas was later found to have a germline mutation in the *FLCN* gene.[8] Conversely, a case of fibrofolliculoma in a patient with TSC has been described.[9] These findings contribute to growing evidence for a pathophysiologic relationship between the two syndromes.[7] The causative genes of TSC and BHDS, *TSC1*/*TSC2* and *FLCN* respectively, are both involved in the mammalian target of rapamycin (mTOR) signaling pathway.[1] This role in cellular growth and signaling may account for the overlapping features of cutaneous lesions of TSC and BHDS.

While only fibrofolliculomas are part of the proposed diagnostic criteria for BHDS, the findings of perifollicular and perivascular fibrosis, regardless of final lesion diagnosis, should prompt the clinician to consider genetic testing for a mutation in *FLCN*.[10] The differential diagnosis for multiple angiofibromas should also include multiple endocrine neoplasia syndrome type 1 and TSC. Skin manifestations are benign, but laser ablation, dermabrasion, and superficial electrodessication are treatment options for those with multiple lesions.[10] A diagnosis of BHDS requires baseline and yearly abdominopelvic MRI given risk for renal tumors.[1] Referral to a urologist may be necessary for surgical management of renal tumors that are detected.[1,5] BHDS patients may be at increased risk for melanoma, warranting interval skin examinations by a dermatologist.[5] Our report highlights the importance of recognizing the spectrum of histologic features in cutaneous lesions of BHDS.

Conflict of Interest Disclosures: None

Funding: None

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