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Multiple Fibrofolliculomas Within a Fibrous Cephalic Plaque in a Patient With Tuberous Sclerosis

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Multiple fibrofolliculomas within a fibrous cephalic plaque in a patient with tuberous sclerosis

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Key words: angiofibroma; Birt-Hogg-Dube syndrome; fibrofolliculoma; fibrous cephalic plaque; mTOR; tuberous sclerosis.

INTRODUCTION

Fibrofolliculoma is a hamartomatous cutaneous lesion that usually occurs on the face and neck. Multiple fibrofolliculomas are characteristically found in Birt-Hogg-Dubé (BHD) Syndrome.[1] Less commonly, they can also present as isolated, solitary lesions. The presence of a fibrous cephalic plaque (FCP) or multiple angiofibromas (AF) is an important clinical finding for tuberous sclerosis complex (TSC).[1,2] Although BHD syndrome and TSC are clinically distinct diseases, with pathologic variants of the folliculin versus *TSC1/TSC2* genes, respectively; there are shared abnormalities including renal neoplasms, hamartomatous skin lesions, and bilateral pulmonary cysts.[3] This report describes a case of multiple fibrofolliculomas within a FCP in a patient with TSC.

Abbreviations used:

AF:	angiofibroma
BHD:	Birt-Hogg-Dube
FCCH:	folliculocystic and collagen hamartoma
FCP:	fibrous cephalic plaque
mTORC1:	mammalian target of rapamycin complex 1
TSC:	tuberous sclerosis complex

CASE REPORT

A 52-year-old African American man with a long-standing diagnosis of TSC presented to our clinic for evaluation of his facial lesions (referred by his neurologist who encouraged him to follow-up with specialists for establishment of care for his TSC). A physical exam revealed multiple firm brown dome-shaped papules on the cheeks, nose, and chin, as well as several skin-colored papules and plaques on the forehead and right cheek (Fig 1). The patient also had numerous hypopigmented macules on the thighs. The largest skin-colored nodule on the right cheek was removed by shave biopsy. Two brown dome-shaped papules on the nose and one small skin-colored papule from the central forehead were also removed by shave biopsy. Histopathology of the nodule (Fig 1, *B*) showed multiple foci of thin epithelial strands radiating from the upper part of the isthmus, surrounded by compact thin collagen fibers containing fibroblasts that stain for CD34 (cluster of differentiation 34), consistent with multiple fibrofolliculomas (Fig 2). An elastic stain revealed an absence of elastic fibers in the stroma surrounding the epithelial strands within the fibrofolliculomas (Fig 3, *A*). Within the stroma between the fibrofolliculomas, the elastic fibers were irregularly distributed with a decrease in amount in some areas (Fig 3,

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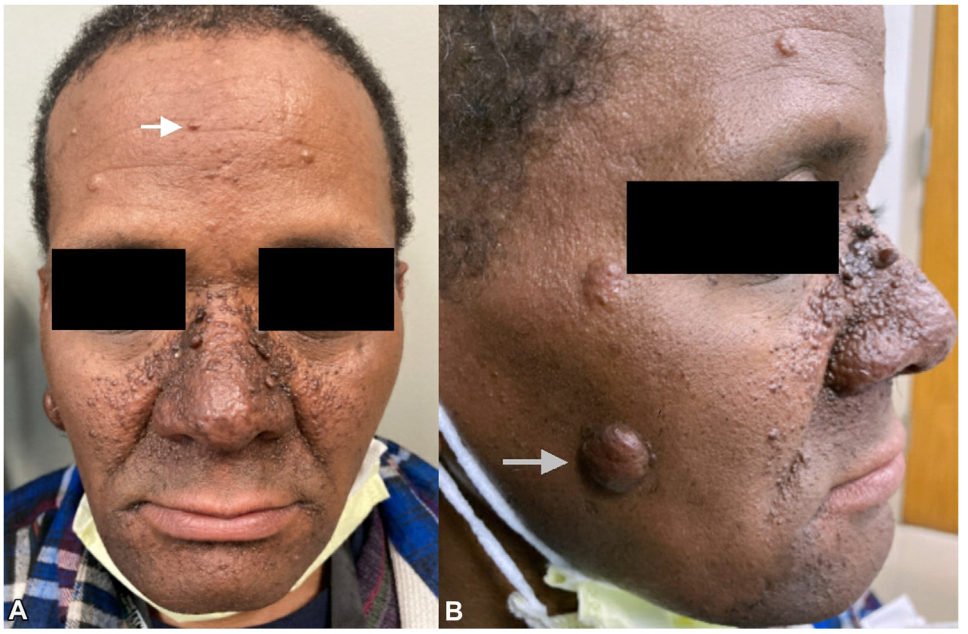

Fig 1. **A** and **B,** Multiple firm *brown* dome-shaped papules on the cheeks, nose, and chin, as well as several skin-colored papules and plaques on the forehead and right cheek. **B,** The *white arrow* denotes the biopsied nodule from the right cheek with histopathologic findings shown in Figs 2 and 3. **A,** The *white arrow* denotes the biopsied papule from the forehead with histopathologic findings shown in Fig 4.

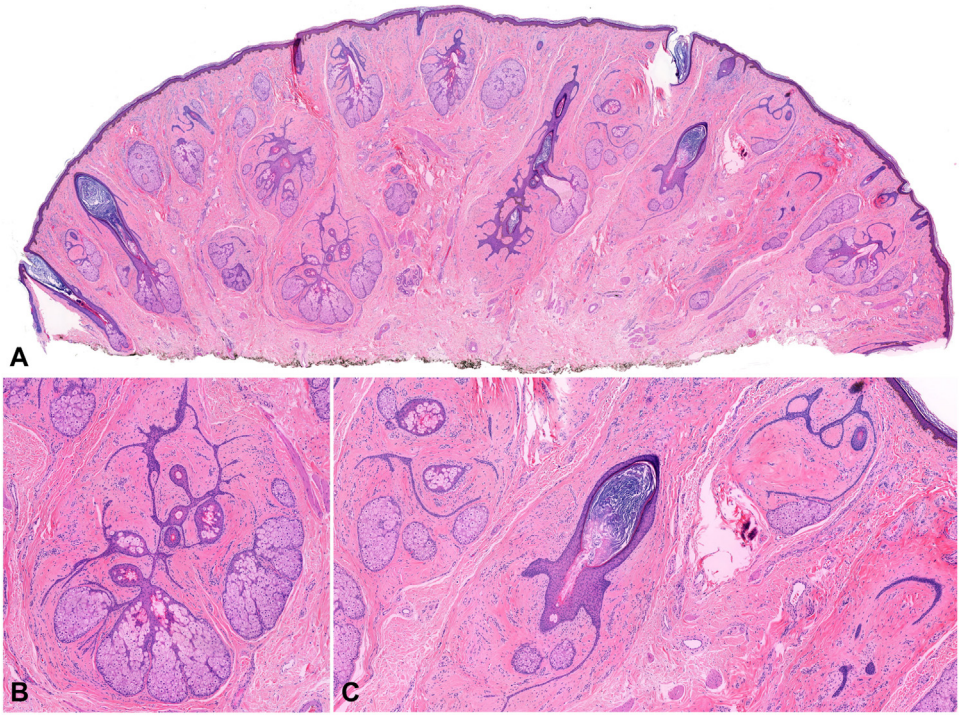

Fig 2. **A,** Multiple discrete foci of thin epithelial strands radiating from the *upper* part of the isthmus of the follicle. **B,** Mature sebaceous lobules associated with thin epithelial strands surrounded by well circumscribed compact thin collagen fibers containing increased fibroblasts. **C,** Several foci of fibrofolliculomas surrounded by compact and sclerotic stroma distinct from the surrounding normal dermis. (**A-C,** Hematoxylin-eosin stain; original magnifications: **A**, 20×; **B**, 100×; **C**, 100×).

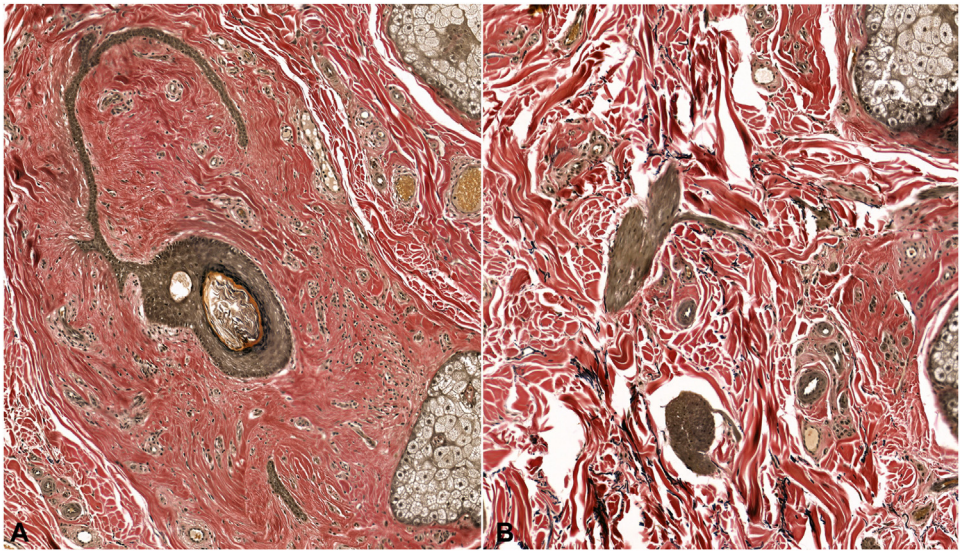

Fig 3. A, Elastic fibers were absent within the stroma associated with the fibrofolliculomas. **B,** Between the fibrofolliculomas, irregular distribution of elastic fibers was observed with a decrease in amount in some areas (**A** and **B**, Verhoeff-Van Gieson, **A**, 200×; **B**, 200×).

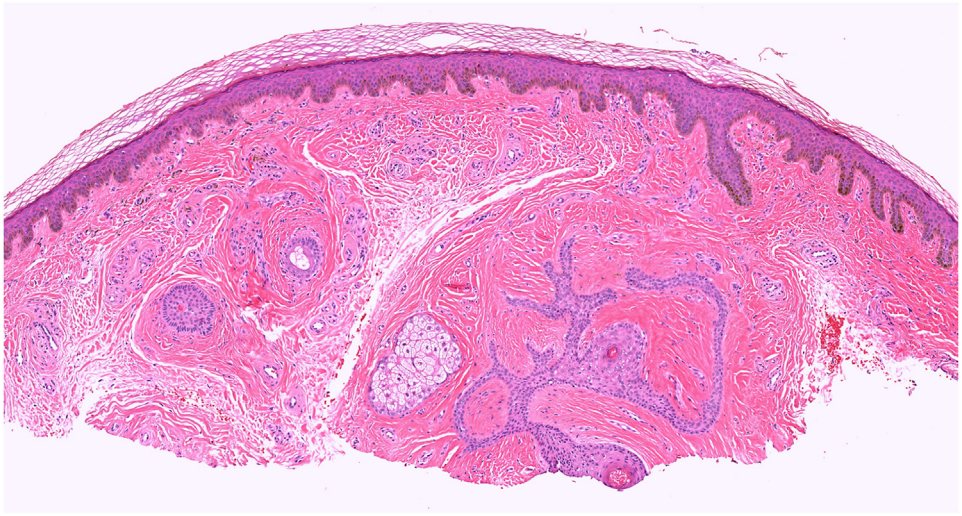

Fig 4. Thin epithelial strands emanating from the *upper* part of the isthmus surrounded by compacted thin collagen fibers (hematoxylin-eosin stain; original magnifications: 20×).

B). Histopathology of the specimens corresponding to the 2 brown papules from the nose showed increased capillary-sized vessels and fibrosis with stellate fibrocytes consistent with AF. The histopathology of the small skin-colored papule on the forehead showed a solitary fibrofolliculoma (Fig 4). Our patient met clinical criteria for TSC based on imaging studies demonstrating bilateral subependymal nodules, cortical tubers, a renal angiomyolipoma, multiple renal cysts, and the presence of multiple AF and confetti skin lesions.

DISCUSSION

TSC is characterized by mutations in either the *TSC1* or *TSC2* gene, resulting in a loss of function of either gene and subsequent increased activation of the mammalian target of rapamycin complex 1 (mTORC1).[1] Activation of mTOR results in aberrant cellular proliferation and differentiation.[3,4] This aberrant growth can result in the formation of hamartomas, characterized by benign structures with abnormal architecture, amount, or maturity.[4] The mutated folliculin protein of BHD syndrome

also is implicated in mTORC1 signaling, although its pathway is not as well elucidated. Recent studies demonstrate either increased or decreased mTOR activity depending on cell type.[3] TSC and BHD can be misdiagnosed for one another given the similar clinical presentations of renal lesions, bilateral pulmonary cysts, and similar cutaneous findings—suggesting a shared pathogenesis.[1,3]

The diagnosis of TSC can be based on genetic diagnostic criteria or a combination of major and minor clinical diagnostic criteria.[2] Skin findings include hypomelanotic macules, AF or FCPs, ungual fibromas, shagreen patches, confetti skin lesions, dental enamel pits, intraoral fibromas, and nonrenal hamartomas.[2] Of note, FCPs are defined as plaques on the scalp, forehead, face, or neck, and are reported to be variants of AF.[4] Previously described as forehead plaque and scalp fibroma, FCP usually occurs as a solitary 1- to 5-cm plaque on the face or scalp in 19% to 46% of patients in prior reports.[5] They may be present at birth and become more apparent in early childhood, sometimes being the first manifestation of TSC preceding other findings. Histopathology is characterized by thickened and disorganized collagen fibers, perifollicular fibrosis, and increased vascularity, similar to that of a typical angiofibroma observed in TSC, but larger. One study by Treichel et al[4] found fibrofolliculomatous changes in 9 of 21 FCPs. Notably, these changes were focal and subtle and not fully developed. In contrast, our patient had multiple fully developed fibrofolliculomas within the fibrous cephalic nodule, lacking prominent thickened disorganized collagen bundles or perivascular fibrosis, typically observed in FCPs.[2,4,5] The fibrous cephalic nodule also had no elastic fibers in the stroma surrounding the epithelial strands, which is often observed in fibrofolliculomas.[6] In the only other report of fibrofolliculoma in a patient with TSC, Misago and Narisawa observed a solitary fibrofolliculoma among the 10 lesions that were removed from the face that were thought to be AF.[7] In addition to the solitary fibrofolliculoma, our patient had a FCP in which fibrofolliculomas comprised the entire lesion. Multiple fibrofolliculomas occurring within a plaque (plaque-type fibrofolliculoma) have been reported in patients with BHD syndrome, but not in patients with TSC.[8,9] The incidence of these histopathologic findings within FCPs may be underestimated as most facial lesions of TSC patients are not biopsied or removed. FCPs can be considered as a clinical descriptive diagnosis with a spectrum of histopathologic features (angiofibroma and fibrofolliculoma).

Also included in the differential diagnosis is folliculocystic and collagen hamartoma, which is a newly described entity in patients with TSC.[10] Histopathology shows abundant and thickened collagen bundles throughout the dermis and into the subcutaneous fat, perifollicular fibrosis, comedo-like formation, and infundibular cysts.[10] Our patient's FCP lacked these characteristic comedo-like formations and cysts, and also lacked the pandermal thickened collagen bundles seen in this entity.

In conclusion, we report a rare finding of fibrofolliculomas presenting as a solitary papule and within a FCP in a patient with TSC. This supports a shared histopathogenesis between TSC and BHD via the mTOR signaling pathway.

Conflicts of interest

None disclosed.

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