Koenen's tumor and facial angiofibromas in a case of Birt-Hogg-Dubé syndrome: A cutaneous contribution to growing evidence of a relationship with tuberous sclerosis complex

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Birt-Hogg-Dubé syndrome (BHD) is an uncommon autosomal dominant genodermatosis characterized by fibrofolliculomas and trichodiscomas on the face and neck with acrochordons in flexural areas. These skin signs serve as markers for internal disease, most importantly spontaneous pneumothoraces and renal cancers. BHD is caused by a mutation in a tumor suppressor gene. This gene encodes the protein folliculin (FLCN), important for normal functioning of the mammalian target of rapamycin (mTOR) signaling pathway.[1]

Abbreviations used:

BHD:	Birt-Hogg-Dubé syndrome
FLCN:	folliculin
mTOR:	mammalian target of rapamycin
TS:	tuberous sclerosis complex

CASE REPORT

A 33-year-old man presented with multiple 1- to 3-mm firm, flesh-colored papules on the face (Fig 1, *A*); numerous, scattered 2- 3-mm white papules on the trunk; and a discrete, well-demarcated 6-mm periungual papule on the fourth digit of the right hand (Fig 1, *B*). The patient reported no history of trauma to the digit. Histology from one facial papule found an angiofibroma. Similar histology was noted from the periungual lesion (Fig 1, *C*). Analysis of 2 truncal papules showed fibrofolliculomas. A complete cutaneous examination found no shagreen patches, hypopigmented macules, or obvious tooth enamel pitting.

The patient also reported an extensive family history of facial papules in a pattern consistent with autosomal dominant inheritance. Two spontaneous pneumothoraces were reported in a paternal uncle and a single pneumothorax in that uncle's son (Fig 2). Gene sequence analysis of *FLCN* found a previously unreported deletion in the gene responsible for BHD in both our patient and his cousin. Subsequent genetic analysis of the proband found no mutations indicative of tuberous sclerosis complex (TS). No family history of renal tumors was reported.

DISCUSSION

This case and family history demonstrate the hereditary nature of BHD and its significant association with internal disease processes. Unique to this case is the presence of a Koenen's tumor (periungual angiofibroma). A PubMed search of the English-language literature failed to reveal a similar association.

Koenen's tumors are typically associated with TS. Whereas the typical facial papules of BHD consist of fibrofolliculomas and trichodiscomas, facial angiofibromas indistinguishable from those in TS have also been reported.[2,3] Likewise, there is a report of

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The case was previously presented in the resident session of the Fall 2014 Meeting of the Texas Dermatological Society Meeting by Dr James Allred, then a resident. That presentation was brief and did not go into the detail that we have described in this article.

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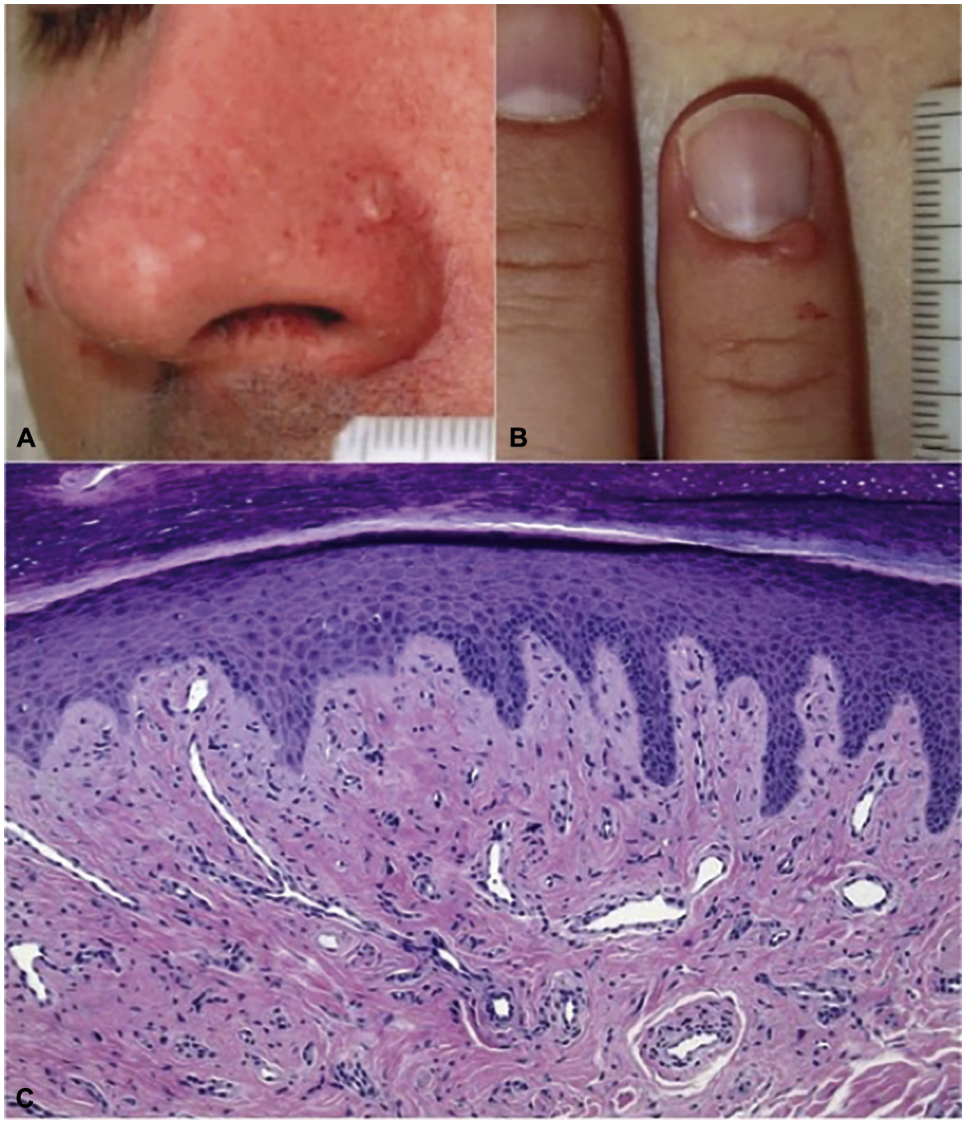

Fig 1. A, Angiofibroma on left nasal ala. **B**, Periungual angiofibroma on fourth digit of right hand. **C**, Photomicrograph from periungual lesion displays stellate capillary-sized blood vessels embedded within a fibrous stroma typical of angiofibromas.

fibrofolliculomas typical of BHD in a patient with confirmed TS.[4] Accordingly, significant cutaneous clinical overlap exists between BHD and TS.

Internal manifestations overlap as well. Both BHD and TS are associated with pulmonary cysts, renal cysts, and renal cancers. Recent case reports describe 2 BHD patients with seizures and a patient with a renal angiomyolipoma, both presentations typically associated with TS.[3,5]

The similarities between BHD and TS extend beyond clinical presentation. FLCN and the TS proteins, hamartin and tuberin, appear to have different yet important roles in the mTOR pathway.[1] BHD results in inhibition of the mTOR pathway. In contradistinction, TS results in mTOR activation. This finding suggests a new paradigm in which both inappropriately high and inappropriately low levels of mTOR activity can result in tumorigenesis.[6]

Multiple histologically different renal tumor types are associated with BHD. This finding suggests a 2-hit mechanism in which a second individual mutation, on the wild-type FLCN allele, is necessary for tumor promotion.[7] In contrast, cutaneous fibrofolliculomas[8] and lung cysts[9] show retention of the wild-type allele, suggesting that other genetic mechanisms, such as haplodeficiency, play a role as well.

This case adds to the constellation of cutaneous manifestations of BHD and illustrates the overlap between BHD and TS. If overlapping features of BHD and TS are present, genetic testing is important

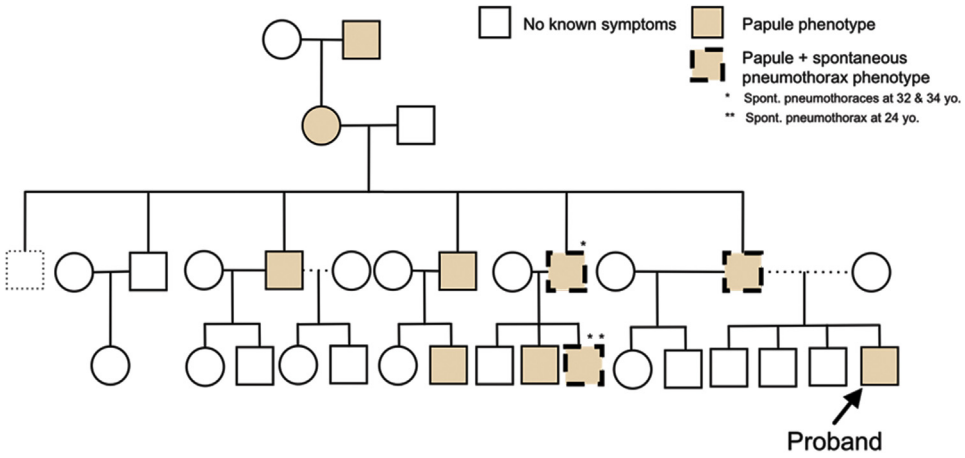

Fig 2. Patient pedigree consistent with autosomal dominant inheritance.

to establish the correct diagnosis. Once the diagnosis is established, genetic counseling should be provided to the patient and family members.

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