Masquerading case of a lumpy bumpy face

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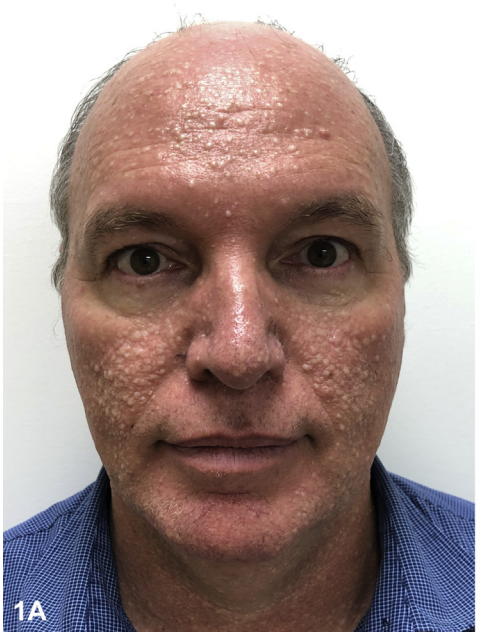
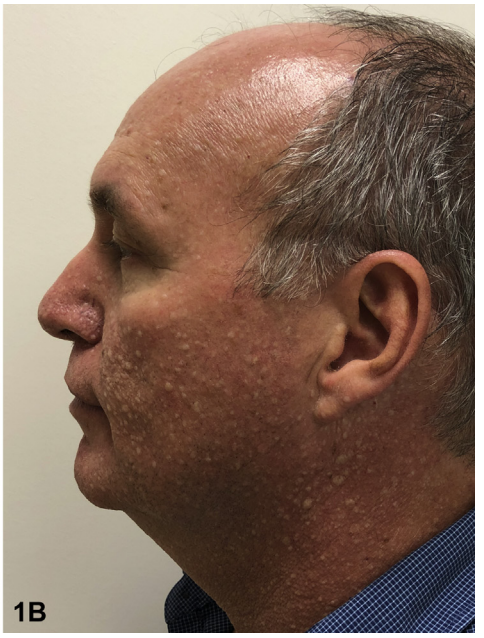
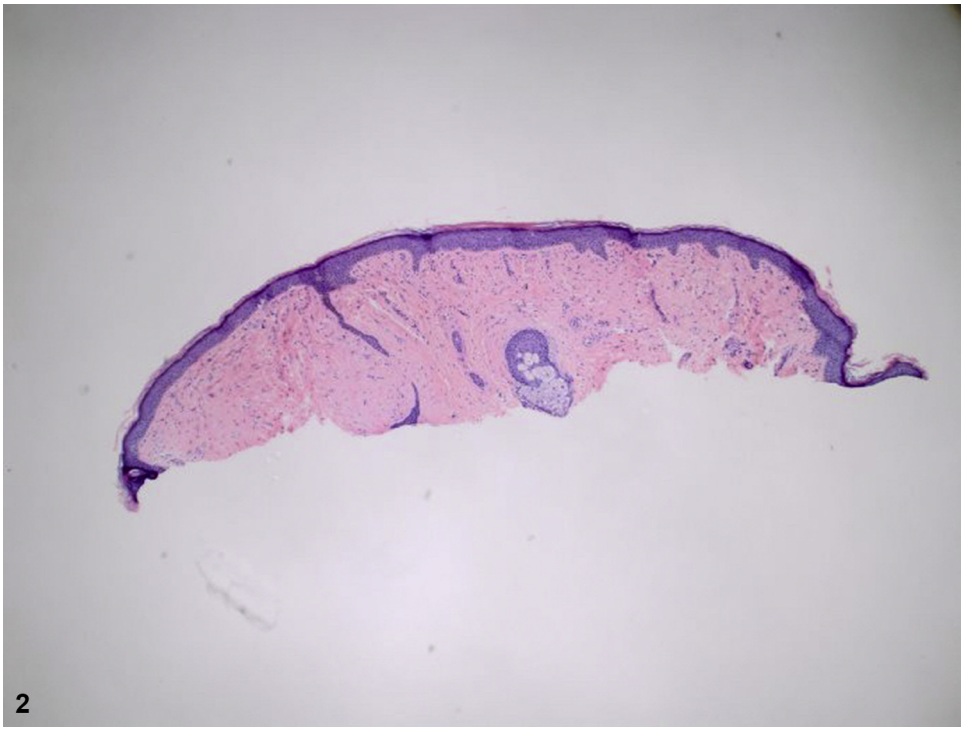
Key words: angiofibroma; Birt-Hogg-Dubé syndrome; fibrofolliculoma; renal cell carcinoma; trichodiscomas.







A 54-year-old man presented with multiple asymptomatic papules diffusely distributed on his face and neck, with the onset approximately 10 years ago. There was no significant family history. Physical examination demonstrated multiple white-to-skin colored papules distributed across his forehead and the middle of his face, with extension onto the neck and postauricular skin (Fig 1, *A* and *B*). Two shave biopsies favored a diagnosis of trichodiscomas (Fig 2). Computed tomography of the abdomen and pelvis demonstrated significant evidence of scattered pulmonary bullae. Abdominal magnetic resonance imaging revealed bilateral renal cysts. Genetic testing identified a pathogenic variant, c.1285dup (p.His429Profs*27), in the folliculin (*FLCN*) gene.

Question 1: What is the most likely diagnosis?

A. Tuberous sclerosis complex (TSC)

B. Birt-Hogg-Dubé syndrome (BHDS)

C. Muir-Torre syndrome

D. Cowden syndrome

E. Brook-Spiegler syndrome

Answers:

A. TSC—Incorrect. TSC is an autosomal dominant (AD) disorder caused by mutations in either *TSC1* or *TSC2*, which encode hamartin and tuberin, respectively. The notable cutaneous findings include angiofibromas, hypomelanotic macules, fibrous cephalic plaques, shagreen patches, periungual fibromas, and café-au-lait macules.[1]

B. BHDS—Correct. BHDS is a rare genodermatosis with an AD inactivating mutation of the *FLCN* gene. The key cutaneous features of this syndrome include benign tumors, including fibrofolliculomas, trichodiscomas, and acrochordons.[2]

C. Muir-Torre syndrome—Incorrect. Muir-Torre syndrome is a clinical variant of Lynch syndrome and is caused by an AD mutation in one of the DNA mismatch repair genes, including *MSH2*, *MLH1*, and *MSH6*. The cutaneous manifestations include sebaceous neoplasms and keratoacanthomas.[3]

D. Cowden syndrome—Incorrect. Cowden syndrome is a part of phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome and is caused by an AD mutation in the *PTEN* gene. The cutaneous features include tricholemmomas, sclerotic fibromas, punctate palmoplantar keratoses, and oral papillomas.[3]

E. Brook-Spiegler syndrome—Incorrect. Brooke-Spiegler syndrome is a rare genodermatosis inherited in an AD fashion and is caused by a mutation in the cylindromatosis gene. It is characterized by a triad of cutaneous tumors including cylindromas, spiradenomas, and trichoepitheliomas.[3]

Question 2: What malignancy is most commonly associated with this syndrome?

A. Renal

B. Colorectal

C. Breast

D. Salivary gland

E. Follicular thyroid

Answers:

A. Renal—Correct. BHDS is associated with a 7-fold increased risk of renal malignancy, which is predominantly a hybrid of renal oncocytoma and chromophobe renal cancer.[2] Depending on the size of the tumor, nephron-sparing surgery is recommended to maximally preserve renal function.[2]

B. Colorectal—Incorrect. While early case reports identified colon polyps and colorectal cancer in patients with BHDS, a risk assessment study did not find this association to be statistically significant.[2] Muir-Torre syndrome is primarily associated with

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colorectal cancer, but it is also associated with genitourinary malignancies.

C. Breast—Incorrect. Breast cancer is associated with Cowden syndrome and serves as a major criterion for PTEN hamartoma tumor syndrome.[4] BHDS is not associated with an increased risk of breast cancer.

D. Salivary gland—Incorrect. Neoplasms of the salivary glands are not associated with BHDS. Salivary gland and parotid tumors are associated with Brooke-Spiegler syndrome.

E. Follicular thyroid—Incorrect. There is no increased risk of thyroid cancer in patients with BHDS. Follicular thyroid cancer is commonly associated with Cowden syndrome and also serves as a major diagnostic criterion.[4]

Question 3: Histologically, how can the fibrofolliculomas associated with this condition be described?

A. Nodular proliferation of basaloid cells admixed with a varying proportion of sebocytes

B. A well-circumscribed hypocellular lesion with heavy collagen distributed in a storiform pattern

C. Multiple islands of basaloid cells outlined by an eosinophilic membrane in a jigsaw-puzzle pattern

D. Epithelial strands radiating from the pilosebaceous unit, forming a mitt-like structure encompassing a fibrous stroma

E. A dermal lesion with increased concentric periadnexal fibrosis, stellate fibroblasts, and dilated blood vessels

Answers:

A. Nodular proliferation of basaloid cells admixed with a varying proportion of sebocytes—Incorrect. This describes the histologic features of a sebaceoma, which is strongly associated with Muir-Torre syndrome.

B. A well-circumscribed hypocellular lesion with heavy collagen distributed in a storiform pattern—Incorrect. This describes a characteristic sclerotic fibroma associated with Cowden syndrome.

C. Multiple islands of basaloid cells outlined by an eosinophilic membrane in a jigsaw-puzzle pattern—Incorrect. This histologic description is consistent with that of cylindromas, a cutaneous feature of Brooke-Spiegler syndrome.

D. Epithelial strands radiating from the pilosebaceous unit, forming a mitt-like structure encompassing a fibrous stroma—Correct. This accurately describes a fibrofolliculoma associated with BHDS.

E. A dermal lesion with increased concentric periadnexal fibrosis, stellate fibroblasts, and dilated blood vessels—Incorrect. This histologic description defines an angiofibroma, which is a part of the major cutaneous criteria for TSC. Interestingly, multiple facial angiofibromas can also be seen in BHDS and multiple endocrine neoplasia type 1.[5]

Abbreviations used:

AD: autosomal dominant
BHDS: Birt-Hogg-Dubé syndrome
PTEN: phosphatase and tensin homolog
TSC: tuberous sclerosis complex

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