# Multiple Facial Papules

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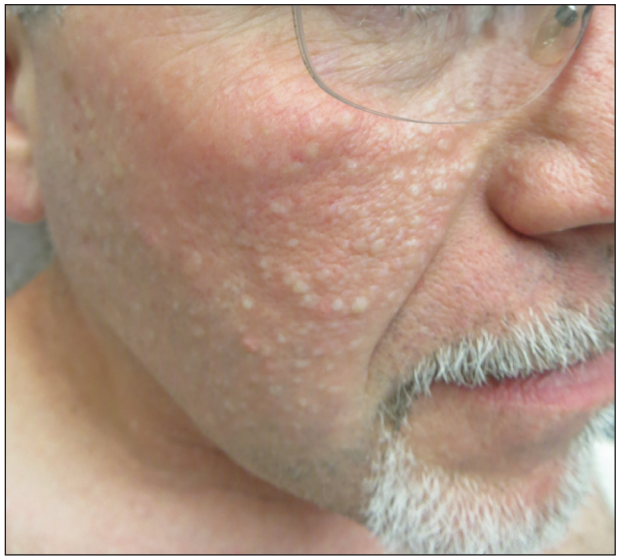

A 50-year-old man presented with facial papules on the cheeks that had appeared approximately 1.5 years prior and gradually spread over the face and neck. They were occasionally pruritic but otherwise were asymptomatic. His mother and brother reportedly had similar clinical findings. Family history was notable for a maternal uncle who had died in his 30s of an unknown type of renal cancer. Physical examination revealed innumerable white-gray papules that measured 1 to 5 mm and were scattered across the face and neck. Punch biopsies were obtained. Computed tomography of the chest showed multiple bibasilar pulmonary cysts. Magnetic resonance imaging was negative for renal tumors.

## WHAT'S THE **DIAGNOSIS?**

a. Birt-Hogg-Dubé syndrome
b. Brooke-Spiegler syndrome
c. Cowden syndrome
d. Muir-Torre syndrome
e. tuberous sclerosis

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The authors report no conflict of interest.
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# THE **DIAGNOSIS:** Birt-Hogg-Dubé Syndrome

Histopathologic examination revealed a collection of bland spindle cells with perifollicular fibrosis consistent with a fibrofolliculoma, confirming the diagnosis of Birt-Hogg-Dubé syndrome (Figure). Cosmetic treatment with ablative therapy was offered, but the patient declined.

Birt-Hogg-Dubé syndrome is an autosomal-dominant genodermatosis caused by a loss-of-function mutation in the folliculin gene, *FLCN*, on chromosome arm 17p11.2.[1] Cutaneous findings include benign follicular hamartomas, such as fibrofolliculomas and trichodiscomas. Angiofibromas, perifollicular fibromas, oral papillomas, and acrochordons also can be present.[1] Cutaneous lesions usually appear on the head and neck in the third decade of life.

Patients with Birt-Hogg-Dubé syndrome are at an increased risk for pneumothorax and renal cancer, specifically hybrid oncocytic-chromophobe renal cell carcinomas.[2] In a study of 89 patients with a *FLCN* mutation, 90% (80/89) of patients had cutaneous lesions, 84% (34/89) had pulmonary cysts, and 34% (30/89) had kidney tumors. Affected individuals were at a higher risk for pneumothorax and kidney tumors if there was a family history of these tumors.[2]

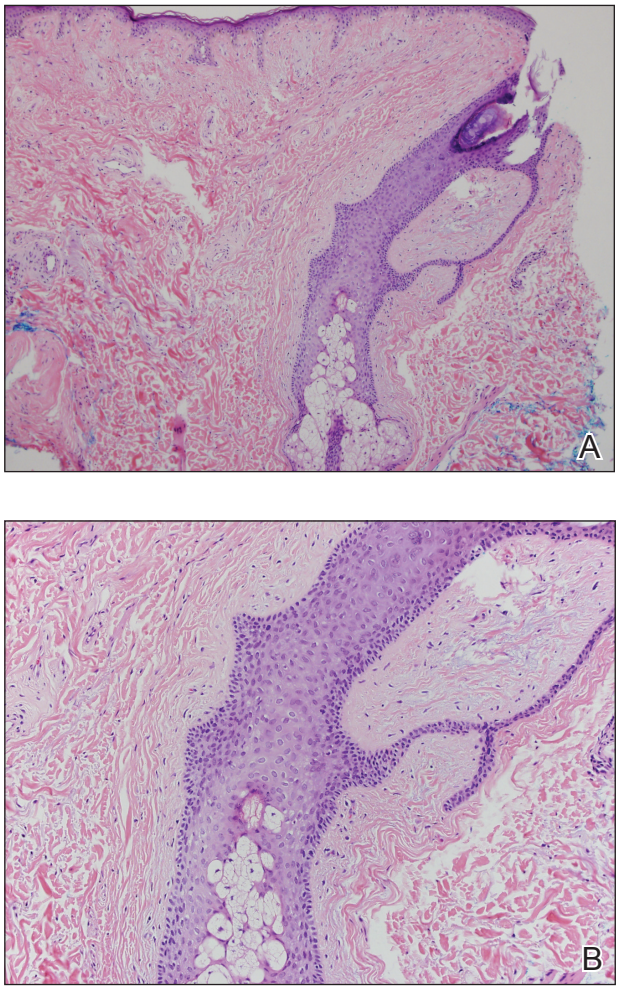
Proposed diagnostic criteria include any 1 of the following: 2 or more skin lesions clinically consistent with fibrofolliculomas and 1 histologically confirmed fibrofolliculoma; multiple bilateral pulmonary cysts in the basilar lung with or without pneumothorax before 40 years of age; bilateral multifocal chromophobe renal carcinomas or hybrid oncocytic tumors; combination of cutaneous, pulmonary, or renal manifestation in the patient and family; or a *FLCN* mutation.[3]

Current recommendations for the workup of a patient with Birt-Hogg-Dubé syndrome include referral to genetic counseling for the patient and family, a baseline computed tomography of the chest to evaluate for pulmonary cysts, and gadolinium-enhanced abdominal magnetic resonance imaging starting at 20 years of age and repeated every 3 to 4 years to screen for renal tumors.[1] Pulmonary function tests can be considered if the patient is symptomatic or has a high cyst burden. Patients should be advised against smoking and scuba diving.

The differential diagnosis of multiple facial papules includes Cowden syndrome, tuberous sclerosis, Brooke-Spiegler syndrome, and Muir-Torre syndrome. Cowden syndrome is caused by a mutation in the protein tyrosine phosphatase gene, *PTEN*.[4] The characteristic cutaneous findings on the face are trichilemmomas, which appear as flesh-colored papules that may have a verrucous surface.

Tuberous sclerosis is caused by mutations in hamartin *(TSC1)* or tuberin *(TSC2)*. Angiofibromas are most commonly found on the face and appear as flesh-colored to red-brown papules. Fibrous plaques, periungual fibromas, gingival fibromas, hypopigmented macules, and connective tissue nevi also are found in tuberous sclerosis.[5]

Brooke-Spiegler syndrome is caused by a mutation in the CYLD lysine 63 deubiquitinase gene, *CYLD*. Trichoepitheliomas, cylindromas, and spiradenomas are caused by the *CYLD* mutation and appear on the head and neck. Trichoepitheliomas are flesh-colored to pink papules found on the face, often concentrated in the nasolabial folds.[6] Cylindromas and spiradenomas are flesh-colored to pink papules or nodules most commonly found on the scalp.[6]




Birt-Hogg-Dubé syndrome. A and B, Histopathology revealed a collection of bland spindle cells with perifollicular fibrosis consistent with a fibrofolliculoma (H&E, original magnifications ×100 and ×200).



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Muir-Torre syndrome is caused by a mutation in DNA mismatch repair genes *MSH2* and/or *MLH1*.[7] Sebaceous neoplasms, including sebaceous adenomas, sebaceomas, and less frequently sebaceous carcinomas, are characteristic cutaneous findings and appear as pink to yellow papules commonly found on the head and neck.

Careful history taking, physical examination, and histopathologic analysis are important in recognizing the features of Birt-Hogg-Dubé syndrome. Accurate and timely diagnosis is essential for the appropriate care of patients and their families, given the syndrome's systemic implications.

## REFERENCES


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