

Andrew Blauvelt, MD *Feature Editor*

## Facial papules, spontaneous pneumothorax, and renal tumors

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### CASE SUMMARY

#### History

A 68-year-old woman was referred for evaluation of multiple white to skin-colored papules distributed over her face, neck, and upper trunk. She had a history of right-sided spontaneous pneumothorax that occurred in 1990 and recurrent spontaneous pneumothorax in 1991, at which time she underwent pleurodesis. In 1992, a computed tomographic (CT) scan of abdomen and pelvis revealed a 3- × 4-cm tumor on her left kidney. She underwent left partial nephrectomy and pathologic examination revealed an oncocytic neoplasm. Her family history was significant for multiple relatives with “skin bumps” (Fig 1).

#### Physical examination

The patient had more than 300 smooth, dome-shaped, white to skin-colored 2- to 4-mm papules distributed over her face, neck, and upper trunk (Fig 2). Skin tags were seen on her axillae and eyelids. In addition, smooth papules were present on her buccal mucosa and gingiva.

#### Histopathologic examination

Histologic examination of the facial papules showed multiple anastomosing strands of 2 to 4 epithelial cells originating from the central portion of hair follicles, consistent with the diagnosis of fibrofolliculoma (Fig 3).

#### Other significant diagnostic studies

High-resolution CT scanning of the chest revealed multiple air-filled lung cysts and a granuloma within the right lung. CT scanning of the abdomen and pelvis showed evidence of a previous partial left nephrectomy, a 2-cm tumor, and multiple bilateral renal lesions less than 1 cm in diameter. Some lesions demonstrated enhancement suggesting that they were solid masses.

#### DIAGNOSIS

- Birt-Hogg-Dube (BHD) syndrome

#### FOLLOW-UP

In May 2001, CT scans of the abdomen and pelvis revealed 3 tumors on her right kidney, which were treated with surgical enucleation. Gross examination of tumor tissue revealed 3 pink to tan-colored nodules: 1.2 × 1.0 cm, 1.0 × 0.9 cm, and 2.5 × 2.0 cm in size. Histologic examination showed oncocytic renal neoplasms.

After the proband was confirmed to have BHD syndrome, a field trip was carried out to evaluate her relatives. Dermatologic and oral examinations were performed and biopsies were performed on lesions suspected as being fibrofolliculomas. Seven individuals exhibited multiple fibrofolliculomas, of whom two had a history of spontaneous pneumothorax and/or lung cysts identified on subsequent high-resolution CT scans (Fig 1).

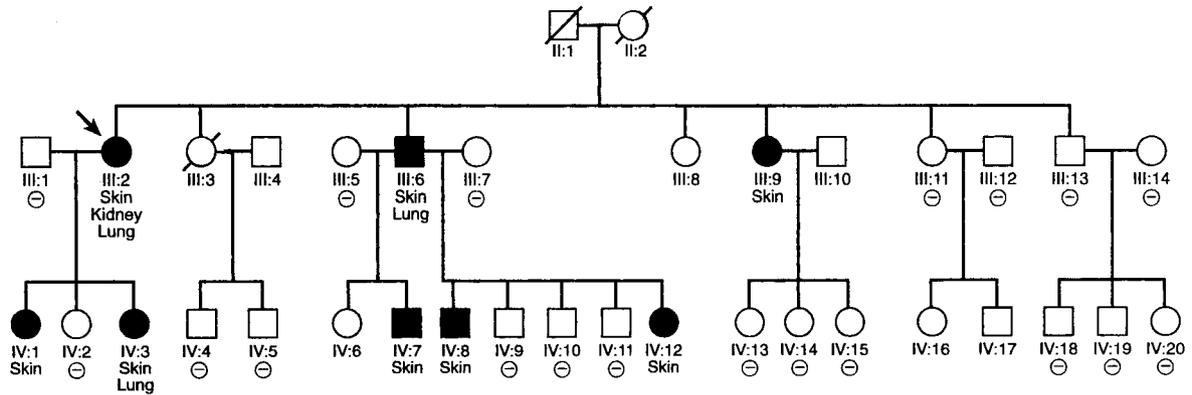
#### DISCUSSION

In 1977, Birt, Hogg, and Dube<sup>1</sup> described a kindred in which 15 of 70 members over 3 generations exhibited multiple small gray to skin-colored, dome-shaped papules distributed over the face, neck, and upper trunk inherited in an autosomal dominant pattern. Histologic examination of these lesions revealed fibrofolliculomas, trichodiscomas, and acrochordons. This triad of cutaneous lesions became known as the BHD syndrome. Since this initial report, many other cases have been described.<sup>2-10</sup> In

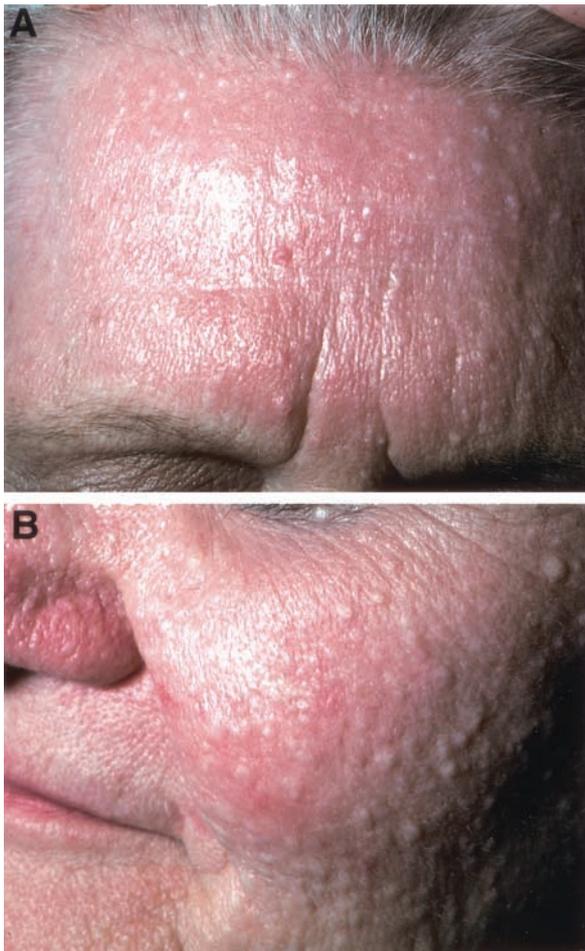
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**Fig 1.** Pedigree of family affected with BHD syndrome. *Squares*, Males; *circles*, females; *slashes*, deceased; *filled symbols*, affected with BHD; *open symbols*, not affected with BHD.



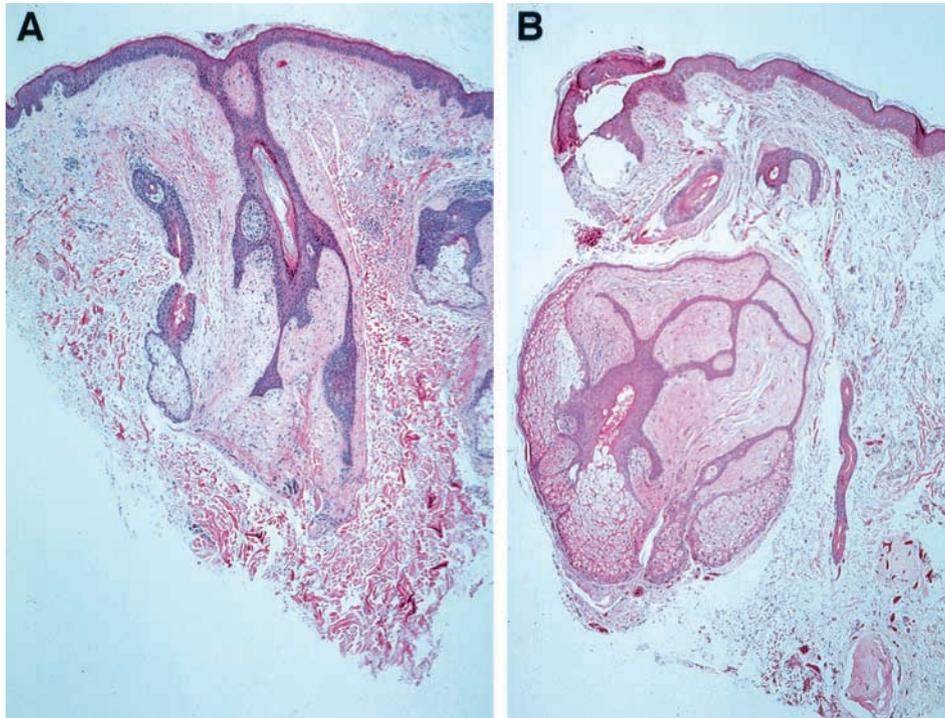
**Fig 2. A and B.** Multiple fibrofolliculomas on the nose and paranasal areas.

addition to cutaneous lesions, which typically begin during the third or fourth decade of life, BHD syndrome was also shown to be associated with renal neoplasms<sup>2-4</sup> and spontaneous pneumothorax.<sup>2,9,10</sup>

Colonic polyps were also believed to be associated with BHD syndrome,<sup>5,6</sup> but this has not been definitively proven.

Recently, we have documented that the BHD syndrome confers an increased risk for the development of renal tumors and lung cysts/spontaneous pneumothorax, but not for the development of colonic polyps.<sup>10</sup> Herein we have identified 3 additional individuals who had multiple fibrofolliculomas and a history of spontaneous pneumothorax (Fig 1). In addition, the proband of this family had BHD syndrome with multiple bilateral oncocyctic renal neoplasms. Previously, renal neoplasms have been reported in BHD families as multiple, bilateral, and with a spectrum of histologic types including renal oncocyctomas, oncocyctic-chromophobe (hybrid tumors), chromophobe, and clear-cell renal cell carcinoma.<sup>2-4,10</sup> The spectrum of renal tumors associated with BHD syndrome suggests that the BHD susceptibility gene plays an important role in renal development during embryogenesis.

In 1999, we excluded *VHL* and the tyrosine kinase domain of the *MET* proto-oncogene as candidate genes in two BHD families with renal oncocyctomas. In addition, Toro et al<sup>4</sup> have excluded *PTCH*, *PTEN*, and *CTNGB1* as candidate genes for BHD syndrome. These particular genes were studied because mutations in each of these genes have been linked to disorders with overlapping clinical features with BHD syndrome. Recently, we performed a genome wide scan in one large family with BHD syndrome and found linkage to chromosome 17p11.2 with a LOD score of 4.98 at D17S740.<sup>9</sup> Linkage to chromosome 17p11.2 was then confirmed in 8 additional BHD families. Critical recombinants narrow the BHD region to an interval less than 4-cM between markers *D17S1857* and *D17S805*. This region of



**Fig 3.** Photomicrograph of fibrofolliculoma shown in Fig 2. There are multiple anastomosing strands of 2 to 4 epithelial cells emanating from a central hair follicle.

chromosome 17p is rich in genes, with more than 40 known genes and many known expressed sequence tags (short DNA sequences that are useful in mapping genetic polymorphisms and defects). Screening of candidate genes from the region of BHD linkage is now in progress. Identification of the gene locus responsible for BHD syndrome may reveal a gene with a novel role in kidney, lung, and hair follicle development.

#### KEY TEACHING POINTS

- Cutaneous lesions of BHD syndrome consist of the triad of fibrofolliculomas, trichodiscomas, and acrochordons.
- BHD syndrome is associated with an increased risk for the development of renal neoplasms and air-filled lung cyst/spontaneous pneumothorax.
- All patients with BHD syndrome and their relatives should undergo abdominal CT scans and ultrasound screening for renal tumors. Renal ultrasound alone is not sufficient for screening for renal tumors.
- BHD syndrome is transmitted in an autosomal dominant manner and the susceptibility gene has been linked to chromosome 17p.

*Editor's note:* Dr Toro and colleagues at the NIH make up a team that consists of dermatologists, pathologists, urologic oncologists, and geneticists. Working together,

they have greatly advanced our understanding of all aspects of BHD syndrome, a life-threatening inherited condition that can be recognized early by dermatologic examination. Since the submission of this article, the *BHD* gene has been identified (see Nickerson M, Warren M, Toro J, Matrosova V, Glenn G, Turner M, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. *Cancer Cell* 2002;2:157 for details).

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