Numerous Asymptomatic Facial Papules and Multiple Pulmonary Cysts: A Case of Birt-Hogg-Dubé Syndrome

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GOAL

To understand Birt-Hogg-Dubé syndrome (BHDS)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the cutaneous presentation of BHDS.
2. Describe systemic findings associated with BHDS.
3. Discuss the differential diagnoses for BHDS.

CME Test on page 110.

This article has been peer reviewed and approved by Victor B. Hatcher, PhD, Professor of Medicine and Biochemistry, Albert Einstein College of Medicine. Review date: July 2003.

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Birt-Hogg-Dubé syndrome (BHDS) is a rare genodermatosis with cutaneous and systemic findings. We report the case of a 47-year-old woman with BHDS who presented with numerous facial papules and the more recently associated finding of pulmonary cysts. We review recent genetic discoveries and the cutaneous and systemic findings associated with this rare syndrome.

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Case Report

A 47-year-old otherwise healthy white woman presented for evaluation of numerous asymptomatic facial papules that had gradually developed over the previous 2 years. Physical examination results revealed multiple white to flesh-colored, smooth,

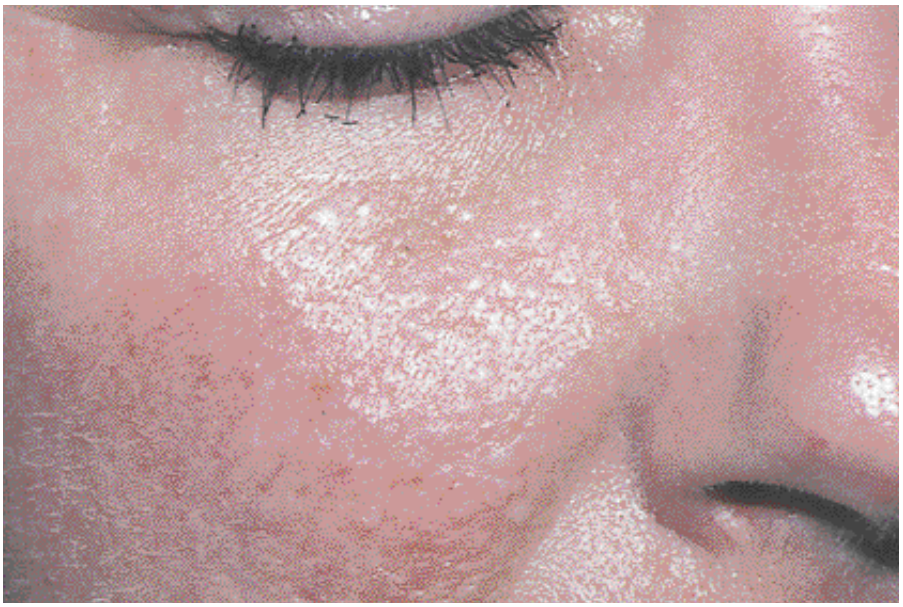

Figure 1. Numerous 1- to 3-mm, white to flesh-colored papules on the cheeks bilaterally.

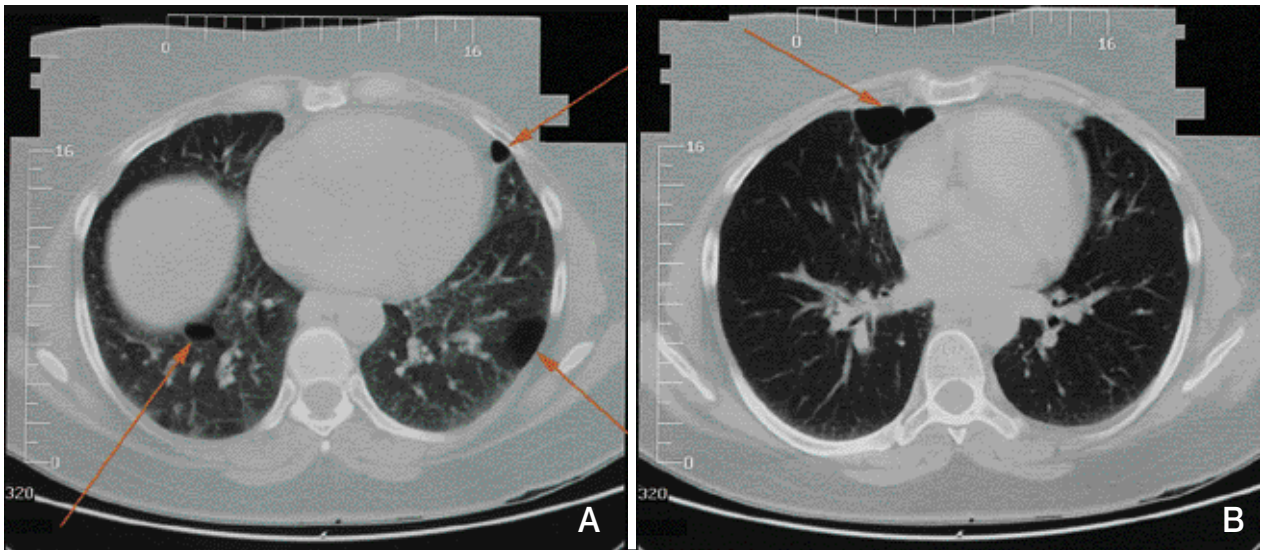

Figure 2. Noncontrast spiral computed tomography scan of the chest with lung windows and 5-mm slice thickness demonstrate multiple, 1.0- to 2.3-mm, primarily peripheral pulmonary cysts (A and B).

1- to 3-mm papules over the central face, most prominently on the cheeks (Figure 1), with no other mucocutaneous findings. The patient had a history of an eyelid acrochordon that had been removed.

Results of renal computed tomography scan with and without contrast were within reference range. Colonoscopy results revealed two 1- to 2-mm polyps located 10 cm from the anal verge that were normal on biopsy. A chest radiograph also showed normal results. A noncontrast spiral computed tomography scan of the chest with lung windows and 5-mm slice thickness demonstrated multiple, 1.0- to 2.3-mm, primarily peripheral, pulmonary bullae (Figure 2).

The patient reported that her parents had no facial lesions. Her father had a history of pulmonary adenocarcinoma, melanoma, and colonic polyposis. The patient's only 2 children had complete mucocutaneous examinations and renal ultrasounds performed. Her 16-year-old son was noted to have 2 axillary acrochordons that were confirmed histologically and large but otherwise normal kidneys. Her 15-year-old son's mucocutaneous examination had normal results; however, renal ultrasound revealed a congenital absence of the right kidney and a hypertrophic left kidney with mild left upper pole pelviectasis. There is no family

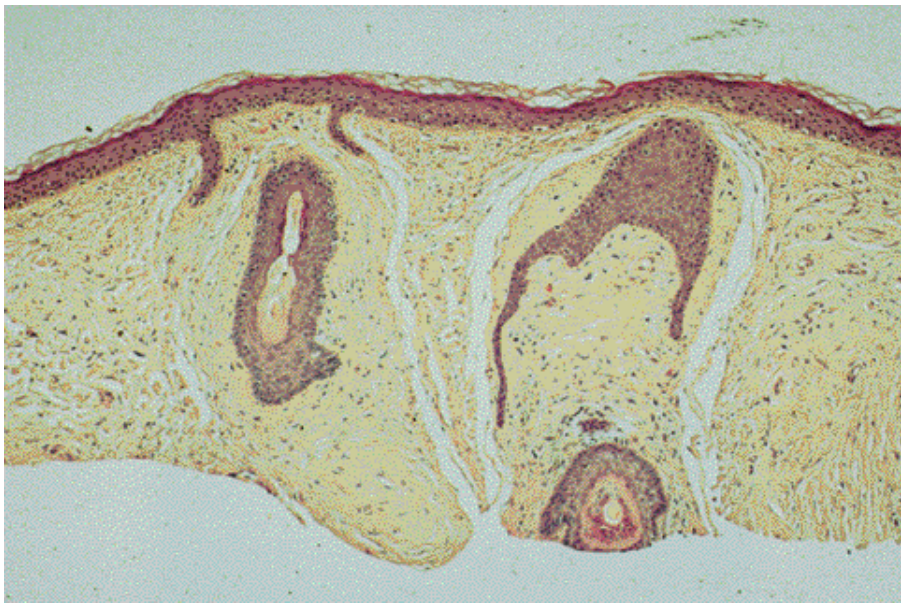

Figure 3. Biopsy of a right cheek papule demonstrates an adnexal structure with radiating epithelial strands and surrounding fibrous stroma consistent with a fibrofolliculoma (H&E, original magnification ×100).

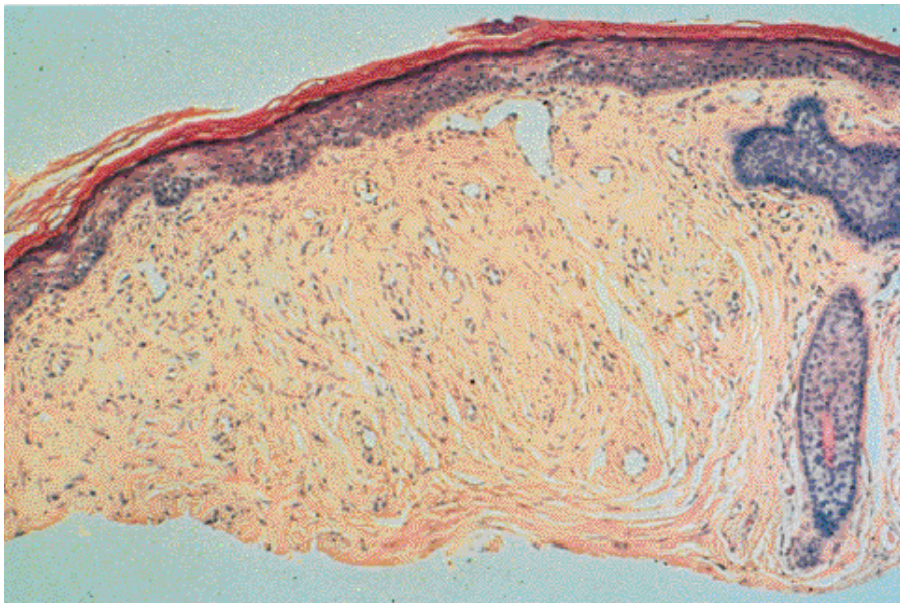

Figure 4. Biopsy of a left alar papule demonstrates a well-circumscribed proliferation of small blood vessels embedded in a fibrous stroma with a hair follicle located in the periphery consistent with a trichodiscoma (H&E, original magnification ×100).

history of renal neoplasia or pneumothorax. The patient had smoked one pack of cigarettes a day for the previous 30 years.

Shave biopsy results of a right cheek papule revealed an adnexal structure with radiating epithelial strands and surrounding fibrous stroma consistent with a fibrofolliculoma (Figure 3). Shave biopsy of a left alar papule demonstrated a well-circumscribed proliferation of small blood vessels embedded in a fibrous stroma with a hair follicle located in the periphery consistent with a trichodiscoma (Figure 4). A diagnosis of Birt-Hogg-Dubé syndrome (BHDS) was confirmed.

Comment

In 1977, Birt, Hogg, and Dubé[1] reported small, papular skin lesions in 15 members of 70 kindred studied. The asymptomatic lesions appeared in each patient after he or she reached 25 years of age and were distributed over the scalp, forehead, face, neck, and trunk. Histologically, these heritable lesions were confirmed to be fibrofolliculomas and trichodiscomas. Small, globoid acrochordons intermingled with these lesions but also were present on the upper eyelids, in the axillary folds, and on the antecubital fossae.[1] This triad of fibrofolliculomas, trichodiscomas, and acrochordons has become

known as BHDS. An autosomal-dominant pattern of transmission has been identified.[1] Schmidt et al[2] recently demonstrated that BHDS maps to chromosome 17p11.2. In a recent study of families with BHDS, Nickerson et al[3] used recombination mapping, which delineated the susceptibility locus to 700 kb on chromosome 17p11.2. They also discovered protein-truncating mutations in a novel candidate gene and a novel BHDS protein named *folliculin*.[3]

Ubogy-Rainey et al[4] reviewed the differential diagnosis of genetic disorders involving multiple firm papules of the face and categorized the diagnoses according to the histogenetic origin of the lesions. Lesions of epithelial origin include trichoepitheliomas and trichilemmomas. Mesodermal-originating lesions consist of trichodiscomas, perifollicular fibromas, and adenoma sebaceum. Fibrofolliculomas represent lesions of mixed epithelial and mesodermal origins.[4]

The fibrofolliculoma is a benign neoplasm that histologically consists of a characteristic well-formed hair follicle with a dilated infundibulum containing laminated keratin. Anastomosing epithelial strands 2 to 4 mm thick radiate from the epithelium of the hair follicle and are surrounded by a well-circumscribed mantle of loose connective tissue embedded in a mucoid, basophilic, hyaluronic acid–rich ground substance.[1,4] Trichodiscomas represent small hamartomatous tumors of the hair disk. A hair follicle is often noted at the periphery of the papule. Histologic features of trichodiscomas include a proliferation of only the fibrovascular component of the hair disk, small melanin granules containing cells in the substance of the tumor, and occasional myelinated nerves at the base of the lesion.[1,5,6] Thus, trichodiscomas and fibrofolliculomas differ histologically. However, a recent study demonstrated that they are immunophenotypically similar. The perifollicular stromal cells of both neoplasms stain $CD34^+$, $vimentin^+$, and factor XIII, indicating that they likely are derived from a similar histogenic precursor.[7] Acrochordons do not contain hair follicles, rather they consist of flattened, elastic epithelium and loose connective tissue, as well as dilated blood vessels.[1,8]

Schulz and Hartschuh[9] recently concluded that although BHDS and Hornstein-Knickenberg syndrome are characterized by multiple perifollicular fibromas, they are indeed the same syndrome. Both syndromes are transmitted in an autosomal-dominant pattern and are associated with colonic polyposis. The similar-appearing cutaneous lesions are distributed over the head, neck, and upper trunk in each syndrome. Histologic study of these lesions revealed that sectioning techniques may have skewed the interpretation of the lesions in the past. By using vertical and superficial and deeper horizontal sectioning planes and serial sections, Schulz and Hartschuh[9] showed that lesions appearing to be perifollicular fibromas with superficial horizontal sections proved to be fibrofolliculomas on deeper horizontal sections. Thus, the skin lesions in BHDS and Hornstein-Knickenberg syndrome most likely represent a similar pathological process.

Roth et al[10] described the first case of renal cell carcinoma in association with BHDS. The patient in their study had bilateral renal cell carcinoma with histopathologic findings demonstrating a chromophobe adenocarcinoma with a mixed population of clear and eosinophilic cells in one tumor and a hypernephroma in the other. Toro et al[11] identified 3 extended kindred in whom renal neoplasms (oncocytomas and a variant of papillary renal cell carcinoma) and BHDS appeared to segregate together. In a large study of BHDS-affected and nonaffected family members, Zbar et al[12] reported the age-adjusted odds ratio for renal tumor development in patients with BHDS was 6.9 times that of patients who did not have BHDS. Renal tumors in BHDS-affected patients were multiple, and in some patients they were bilateral. Median age for detection was 51 years. The most common type of renal cancer found in BHDS-affected patients was chromophobe renal carcinoma; but chromophobe-oncocytic tumor and clear cell renal carcinoma also were noted. Interestingly, 2 nonaffected family members had single clear cell renal carcinomas.[12]

Other features of BHDS noted by Toro et al[11] were deforming lipomas, collagenomas, and pulmonary cysts and/or pneumothorax. Zbar et al[12] also reported the age-adjusted odds ratio for pneumothorax in BHDS-affected individuals to be 50.3 times that of those not affected with BHDS. In addition, pulmonary cysts were present in 83% of BHDS-affected family members compared with 10% of unaffected control members of families with BHDS ($P=.0001$). These cysts were noted to be well circumscribed and separate from each other, and their location was either basilar, subpleural, or intraparenchymal.[12] Other reported associated manifestations of BHDS include: large connective tissue nevus[13]; oral mucosal papules on the lip, buccal area, and gingivae, which histologically demonstrate parakeratosis, acanthosis, prominent basal cell layer, and a few chronic inflammatory cells in the underlying connective tissue[8]; multiple spontaneous pneumothoraces, bullous emphysema, lipomas, angiolipomas, parathyroid adenoma, and prostate adenocarcinoma[14]; flecked chorioretinopathy[15];

parotid oncocytoma[16]; and colonic polyps, which are tubular adenomas with mild to marked epithelial dysplasia.[17] Colonic neoplasms and colonic polyps have not been found as an associated finding in a large cohort of patients with BHDS.[12] Although some of the above associations may be coincidental, screening for renal cancer and pulmonary cysts is recommended.

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