Comedonal and Cystic Fibrofolliculomas in Birt-Hogg-Dube Syndrome

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Birt-Hogg-Dube syndrome (BHD) is an uncommon autosomal dominant genodermatosis that is characterized by hair follicle hamartomas as well as increased risk of renal cell carcinoma (RCC), lung cysts, and spontaneous pneumothorax. It is caused by loss-of-function mutations in the BHD gene, FLCN (OMIM 607273), on chromosome 17p11.2. The syndrome was described in 1977 by Birt and colleagues2 as a triad of fibrofolliculomas, trichodiscomas, and acrochordons. However, 2 years earlier, Hornstein and Knickenberg had described a patient with perifollicular fibromas, skin tags, and colonic polyps that likely represented the same syndrome.3 Subsequently, multiple lung cysts, spontaneous pneumothorax, and RCC have been firmly established as systemic features of BHD.4

Two early case reports3,5 of BHD described individuals with papules that were clinically and histopathologically consistent with comedonal fibrofolliculoma; however, these findings, to our knowledge, have not been otherwise characterized in published articles. We describe 4 individuals with BHD and fibrofolliculomas with widespread open comedones and propose that BHD be included in the differential diagnosis of acquired and genetic conditions with extensive open comedones. Informed written consent was obtained from all patients. Protocol was approved by the National Cancer Institute Institutional Review Board.

**Report of Cases**

**Case 1**

A man in his 70s with multiple asymptomatic facial papules and a history of grade 3 clear cell RCC that was treated with right nephrectomy was referred to the National Institutes of Health for evaluation for possible BHD. He reported having a collection of black papules on the left lower abdomen that had possibly developed during puberty. The patient had known bullous emphysematous changes in the lungs but denied having a history of pneumothorax. His family history was significant for a nephew with a history of spontaneous pneumothorax and a confirmed diagnosis of BHD as well as 2 brothers with numerous facial papules, 1 of whom died of RCC.

Findings from the physical examination revealed hundreds of 1- to 4-mm firm skin-colored papules on the face, ears, chest, back, and flanks (Figure 1A). On the left side of the lower abdomen, there was a large collection of open comedones with thick keratin plugs overlying skin-colored papules that ranged from 2 to 6 mm (Figure 1B and C). Numerous acrochordons were also noted in the bilateral axilla.

Histopathologic findings from a skin-colored papule on the postauricular skin on the left side revealed a classic fibrofolliculoma with thin epithelial strands emanating from the epidermis.
from a hair follicle. Histopathologic findings from an open comedo overlying a skin-colored papule showed similar epithelial strands emanating from a cystic dilated follicle that were consistent with a cystic fibrofolliculoma.

Findings from a computed tomographic scan of the chest, abdomen, and pelvis showed scattered lung cysts and evidence of right nephrectomy. Findings from magnetic resonance imaging identified 2 small benign cysts in the left kidney. Results from further diagnostic evaluation revealed a heterozygous c.1285dupC mutation in the FLCN gene.

Case 2
A man in his 30s with a history of spontaneous pneumothorax and known FLCN mutation presented for evaluation of asymptomatic white papules on the face. The patient reported that his mother had numerous similar facial papules. He denied having a personal or family history of RCC but reported multiple episodes of “pleurisy” in his mother and grandmother. Findings from the physical examination revealed 2 single, 4-mm, white, flat-topped papules on the right cheek and the preauricular skin on the left side. Results from histopathologic examination of one of the facial papules revealed a dilated cystic follicle with thin epithelial strands emanating from the follicle that was consistent with comedonal fibrofolliculoma. Findings from a computed tomographic scan of the chest revealed thin-walled lung cysts and magnetic resonance imaging of the abdomen showed a 7-mm hyperintense focus in the right kidney, presumed to be a benign cyst.

Case 3
A man in his 50s presented for evaluation of possible familial RCC syndrome. Several family members, including the patient’s brother, had been diagnosed with RCC. He denied having a history of kidney disease or pneumothorax; however, he and several relatives exhibited facial papules. Findings from examination of the patient’s face, chest, back, and flanks revealed numerous dome-shaped white papules, some of which appeared to have dark central cores. On the right flank were groups of perifollicular dome-shaped papules coalescing into a plaque. Axillary acrochordons, verrucous papules of the lower mucosal lip, and 3 lipomas were also noted.

Histopathologic findings from multiple papules on the left side of the forehead, central chest, and right flank were consistent with fibrofolliculoma. In addition, results from biopsy of the lesion on the right flank showed a cystically dilated hair follicle surrounded by a zone of fibrosis with thin linear extensions of follicular shaft epithelium into the fibrous stroma that was consistent with cystic fibrofolliculoma.

Findings from a computed tomographic scan of the chest, abdomen, and pelvis did not show lung or kidney abnormalities, and a consistent germline FLCN mutation that segregated with the disease was not detected. Nevertheless, the patient fulfilled the clinical diagnostic criteria for BHD.

Case 4
A woman in her 60s with a family history of BHD presented to the National Institutes of Health for evaluation. She reported having progressive onset of cutaneous papules since her early 40s. Her mother had similar papules, as did her son, who had RCC and carried a diagnosis of BHD. Findings from the physical examination revealed hundreds of 1- to 5-mm dome-shaped papules that were skin-colored to white and diffusely covered the face, ears, shoulders, trunk, and extremities. Some of the lesions were larger and had central, keratin-filled puncta (Figure 2A). Multiple acrochordons were also noted on the patient’s neck and axillae. Histopathologic findings from 2 biopsy specimens of the supraclavicular skin revealed comedonal fibrofolliculoma (Figure 2B and C). Findings from a computed tomographic scan showed scattered pneumatoeyts in both lung fields and bilateral scattered renal lesions that were consistent with benign cysts. Genetic testing was not conducted; however, the patient fulfilled the clinical diagnostic criteria for BHD.
kidneys, lungs, and skin. Although the precise tumor-suppressor gene encodes the protein folliculin, which is expressed in the infundibular portion of the hair follicle. Thin epithelial strands emanate from the infundibular portion of the hair follicle, some of which reconnect to the follicular epithelium (hematoxylin-eosin, original magnification ×40). C. Higher magnification shows proliferation of the perifollicular fibrous sheath surrounding the infundibular portion of the cystically dilated hair follicle, with thin epithelial strands emanating from the infundibular portion of the hair follicle (hematoxylin-eosin, original magnification ×200).

Discussion

Currently, FLCN is the only gene known to cause BHD. This gene encodes the protein folliculin, which is expressed in the kidneys, lungs, and skin. Although the precise tumor-suppressor function of folliculin is still unclear, Baba and colleagues identified folliculin-interacting protein 1, which interacts with folliculin through its C terminus. Many of the reported pathogenic mutations in patients with BHD led to truncation of the C-terminal end of the protein, thereby preventing folliculin from binding to folliculin-interacting protein 1. The 5′ adenosine monophosphate (AMP)-activated protein kinase is believed to interact with folliculin-interacting protein 1 and to negatively regulate mammalian target of rapamycin activity. Interestingly, several other syndromes, including tuberous sclerosis complex and Peutz-Jeghers syndrome, also result from mutations in the 5′AMP-activated protein kinase and mammalian target of rapamycin pathways, emphasizing the importance of these pathways in hamartomatous cell growth.

Fibrofolliculomas and trichodiscomas in BHD typically develop in the third to fourth decades of life. Both are hair follicle hamartomas that are clinically indistinguishable, appearing as small, dome-shaped, white papules on the face, neck, and upper trunk. Fibrofolliculomas and trichodiscomas also have overlapping histological features and punch skin biopsy, rather than shave biopsy, is preferred to examine the overall architecture of the skin lesions. A fibrofolliculoma appears as a proliferation of the perifollicular fibrous sheath surrounding the infundibular portion of the hair follicle, with thin epithelial strands emanating from this infundibulum into a dense collagenous stroma. A trichodiscoma, which also emanates from a hair follicle, is a fibrous tumor composed of thin-walled blood vessels and often has peripherally located sebaceous lobules. Acrochordons, the third cutaneous sign of BHD, are common in the general population and therefore lack diagnostic utility. Furthermore, acrochordon-like lesions may be a phenotypic variant of fibrofolliculoma. Other cutaneous lesions that are reported to occur in patients with BHD include facial angiofibromas, lipomas, angiolipomas, and oral mucosal fibromas.

Patients with BHD have a 7-fold increased risk of developing renal tumors compared with unaffected siblings. The tumors are often multifocal or bilateral and are diagnosed at a mean age of 50 years. In a study of 130 renal tumors in 30 patients with BHD, a chromophobe/oncocytic hybrid was most common (50%), followed by chromophobe RCC (34%), clear cell RCC (9%), oncocytoma (5%), and papillary RCC (2%). More than 80% of adult patients with BHD have multiple lung cysts, often in the basal lung regions, and affected individuals have a 50-fold increased risk of spontaneous pneumothorax compared with their unaffected siblings. Other tumors reported in patients with BHD include colorectal polyps, colorectal cancer, melanoma, parotid gland tumors, and breast cancer. A causal relationship between these tumors and BHD has not yet been established.

Menko and colleagues proposed criteria for the diagnosis of BHD. Suggested major criteria include 5 or more adult-onset fibrofolliculomas or trichodiscomas (at least 1 must be histologically confirmed) or a pathogenic FLCN germline mutation. Minor criteria are multiple lung cysts that are bilateral and basally located, with no other apparent cause (with or without spontaneous pneumothorax); RCC that is either (1) early onset (age, <50 years), multifocal, or bilateral or (2) of mixed chromophobe and oncocytic histologic features; or a first-degree relative with BHD. Individuals who fulfill 1 major or 2 minor criteria are given a clinical diagnosis of BHD.

Patients with BHD may manifest a variety of skin lesions ranging from classic-appearing, white, 1- to 2-mm fibrofollicu-
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Conclusions

We describe comedonal or cystic fibrofolliculomas in 4 patients with BHD. Birt-Hogg-Dube syndrome should be included in the differential diagnosis of conditions with extensive open comedones to assist in the early detection and diagnosis of BHD. Because BHD is a condition with variable clinical presentation, broader characterization of the phenotypic variations of this syndrome will allow for further clues to diagnose the condition and thus screen for the associated life-threatening systemic complications.

Table 1. Syndromes Associated With Multiple Comedones

<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance/Gene</th>
<th>Age at Onset of Comedones</th>
<th>Clinical Findings</th>
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</thead>
<tbody>
<tr>
<td>Birt-Hogg-Dube syndrome</td>
<td>AD/FLCN</td>
<td>Third or fourth decade of life</td>
<td>Dome-shaped white papules with or without central keratin plug</td>
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<tr>
<td>Generalized basaloid follicular hamartoma syndrome&lt;sup&gt;1, 1&lt;/sup&gt;</td>
<td>AD/PTCH</td>
<td>Birth to early childhood&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Open comedones, milia, small skin-colored to hyperpigmented papules; palmoplantar pitting, hypohidrosis, hypotrichosis; increased risk of BCC, may be associated with multiple sclerosis</td>
</tr>
<tr>
<td>Bazex syndrome&lt;sup&gt;1, 2&lt;/sup&gt;</td>
<td>XLD/unknown</td>
<td>Birth to early childhood&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Open comedones, milia; multiple BCCs (usually on face); hypotrichosis, hypohidrosis, follicular atrophoderma</td>
</tr>
<tr>
<td>Dowling-Degos disease</td>
<td>AD/KRT5</td>
<td>Late adolescence to early 20s</td>
<td>Comedolike hyperkeratotic follicular papules, reticulated pigmentation of flexures, pitted perioral scars</td>
</tr>
<tr>
<td>Familial dyskeratotic comedones&lt;sup&gt;3, 4&lt;/sup&gt;</td>
<td>AD/unknown</td>
<td>Childhood or adolescence</td>
<td>Generalized comedones (spare face, scalp, palms, soles)</td>
</tr>
<tr>
<td>Comedonal Darier disease&lt;sup&gt;14&lt;/sup&gt;</td>
<td>AD/ATP2A2</td>
<td>Variable (adolescence to seventh decade of life)</td>
<td>Large open and closed comedones on face and scalp, classic Darier lesions also present</td>
</tr>
<tr>
<td>Tuberous sclerosis complex&lt;sup&gt;4, 5&lt;/sup&gt;</td>
<td>AD/TSC1, TSC2</td>
<td>Childhood</td>
<td>Folliculocystic and collagen hamartomas with multiple comedolike openings and keratin-filled infundibular cysts; angiofibromas, ungual fibromas, Shagreen patch, hypomelanotic macules&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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Abbreviations: AD, autosomal dominant; BCC, basal cell carcinoma; XLD, X-linked dominant.

<sup>a</sup> Hypotrichosis and hypohidrosis present at birth.

<sup>b</sup> Not a complete list.

Table 2. Acquired Causes of Multiple Comedones

<table>
<thead>
<tr>
<th>Condition</th>
<th>Causative Agent</th>
<th>Clinical Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Acne vulgaris</td>
<td>Sebum production due to hormonal stimulation, cornocyte adhesion/proliferation, and Propionibacterium acne; medications</td>
<td>Papules; pustules; open comedones</td>
</tr>
<tr>
<td>Acne from radiation treatment</td>
<td>Previous exposure to therapeutic ionizing radiation</td>
<td>Open comedones at site of previous irradiation</td>
</tr>
<tr>
<td>Pseudoacne of the transverse nasal crease</td>
<td>Unknown</td>
<td>Linear arrangement of comedones along the lower third of the nose</td>
</tr>
<tr>
<td>Favre-Racouchot syndrome</td>
<td>Actinic damage</td>
<td>Numerous periorbital open comedones</td>
</tr>
<tr>
<td>Nevus comedonicus</td>
<td>Unknown</td>
<td>Clusters of dilated follicular openings containing keratin plugs, often distributed linearly</td>
</tr>
<tr>
<td>Occupational/environmental acne</td>
<td></td>
<td>Open and closed comedones; straw-colored cysts in malar region, posterior auricular region, axillae, scrotum</td>
</tr>
<tr>
<td>Chloracne</td>
<td>Halogenated aromatic compounds</td>
<td>Comedones and inflammatory papules on dorsal hands and extensor surfaces of arms</td>
</tr>
<tr>
<td>Oil acne</td>
<td>Cutting oils containing large amounts of mineral oil (often seen in mechanics and those operating machine tools)</td>
<td>Numerous open comedones on malar region</td>
</tr>
<tr>
<td>Pitch- or coal-tar acne</td>
<td>Pitch or coal tar (often seen in roofers and road paving-crew members)</td>
<td>Comedolike lesions containing vellus hairs and keratin on face and trunk</td>
</tr>
<tr>
<td>Childhood flexural comedones</td>
<td>Unknown</td>
<td>Double-orifice comedones in flexures, often axillae or groin, of prepubescent children</td>
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Lomas to larger comedonal or cystic fibrofolliculomas. Clinically, comedonal folliculomas consist of open comedones centered in skin-colored to white papules or cysts. Histologically, cystically dilated hair follicles that contain keratinous debris are present along with the classic features of fibrofolliculoma. Comedonal fibrofolliculomas are a variant of fibrofolliculomas that are not previously well characterized in patients with BHD. However, multiple open comedones are a feature of several genodermatoses (Table 1) and acquired conditions (Table 2). We propose that BHD be included in the differential diagnosis of multiple comedonal papules to facilitate early diagnosis of the syndrome.
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REFERENCES