Birt-Hogg-Dubé Syndrome

A Novel Marker of Kidney Neoplasia

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Background: Birt-Hogg-Dubé syndrome (BHD) is a dominantly inherited predisposition for development of fibrofolliculomas, trichodiscomas, and acrochordons. Concurrent internal tumors, such as colonic polyps and renal carcinoma, have been described in patients with BHD.

Objective: To evaluate kindreds with familial renal tumors for cutaneous manifestations of BHD.

Design: One hundred fifty-two patients from 49 families underwent complete oral and skin examination. Skin lesions were identified by their clinical appearance, and the diagnosis was confirmed by results of histologic examination. Individuals underwent screening for familial renal neoplasms.

Setting: A tertiary referral research hospital.

Patients: Individuals with familial renal tumors and their asymptomatic at-risk relatives.

Main Outcome Measures: We determined whether any form of renal cancer is associated BHD.

Results: We identified 3 extended kindreds in whom renal neoplasms and BHD appeared to segregate together. Two kindreds had renal oncocytomas and a third had a variant of papillary renal cell carcinoma. Thirteen patients exhibited BHD. Seven individuals, including a set of identical twins, had renal neoplasms and BHD. An additional 4 patients (3 deceased and not examined) in these families had renal neoplasms but not BHD. Birt-Hogg-Dubé syndrome without renal neoplasms was present in 6 individuals. Thirteen patients with fibrofolliculomas and trichodiscomas presented clinically with multiple smooth skin-colored to grayish-white papules located on the face, auricles, neck, and upper trunk. Oral papules were present in 9 of 28 and acrochordons in 11 of 28 patients. Features of BHD not previously appreciated included deforming lipomas in 5, collagenomas in 4, and pulmonary cysts in 4 of 28 patients. Families with BHD did not display germline mutations in the von Hippel-Lindau gene or in the tyrosine kinase domain of the MET proto-oncogene.

Conclusions: Birt-Hogg-Dubé syndrome may be associated with familial renal tumors. Birt-Hogg-Dubé and renal tumors segregate together in an autosomal dominant fashion. Patients with BHD and their relatives are at risk for development of renal tumors. Therefore, patients with BHD and their relatives should undergo abdominal computed tomography and renal ultrasound screening for renal tumors.

Arch Dermatol. 1999;135:1195-1202

IN 1977, BIRT ET AL.1 described a kindred in which 15 of 70 members over 3 generations exhibited multiple, small, 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 (FFs), trichodiscomas (TDs), and acrochordons. This triad has become known as Birt-Hogg-Dubé syndrome (BHD).1 Typically, cutaneous lesions of BHD have their onset during the third or fourth decade of life. Since the initial report, several other cases have been described.2-12 The cutaneous manifestations of BHD have been associated with colonic polyps2,3 and a case of renal carcinoma.4 We herein describe 3 kindreds with familial renal tumors in which 13 individuals also had BHD.

Renal neoplasms can be familial or sporadic. Four types of familial renal neoplasms have been well described: (1) clear cell renal carcinoma associated with hemangioblastomas of the brain, spine, and eye resulting from mutations in the von Hippel-Lindau (VHL) gene5; (2) clear cell renal carcinoma associated with constitutional, balanced translocations involving the short arm of chromosome 36; (3) papillary renal cell carcinoma associated
with germline mutations in the tyrosine kinase domain of the \textit{MET} proto-oncogene, and (4) renal oncocytoma.\textsuperscript{18} Pure renal oncocytomas are considered to be benign tumors. Histologically, oncocytomas are composed of cells with an eosinophilic cytoplasm with bland round nuclei and abundant mitochondria as seen on electron microscopy.\textsuperscript{18} Papillary renal cell carcinomas have malignant potential, and biological aggressiveness varies with the type. Histologically, papillary renal cell carcinomas have fingerlike projections lined by cuboidal tumor cells with a basement membrane that contains a well-formed fibroconnective tissue stroma.\textsuperscript{19} During most of their growth, these renal neoplasms are asymptomatic and are often detected incidentally or through screening of at-risk family members. After noting multiple FFs in a pair of identical twins with bilateral renal oncocytomas, we performed complete skin and oral examinations to search for cutaneous manifestations of BHD in another 150 patients from 49 kindreds with familial renal tumors.

\section*{Patients and Methods}

\subsection*{Patients}

All patients underwent evaluation at the National Institutes of Health Warren G. Magnuson Clinical Center, Bethesda, Md, and were enrolled in a protocol approved by the institutional review board. Informed consent was obtained from all participants. Two families were included in a previous publication of the renal findings of familial renal oncocytoma.\textsuperscript{18} One hundred fifty-two patients ranging in age from 17 to 79 years underwent evaluation from April 1, 1996, to December 31, 1998. All patients underwent complete skin and oral examinations and were photographed. Patients underwent pre- and postcontrast-enhanced computed tomography (CT) of the abdomen followed by renal ultrasound as previously described.\textsuperscript{19} Briefly, CT of the abdomen was performed on 1 of 2 units (9800 Quick or GE Hi Speed CT unit; General Electric, Milwaukee, Wis) with the intravenous injection of 120 to 135 mL of iopamidol (Isovue-300; Bracco Diagnostics Inc, Princeton, NJ) after a delay of 70 seconds. Slice thickness was 5 mm, and imaging was performed in a nonhelical mode. Available CT scans from other centers were also reviewed in 2 patients. In addition, each patient underwent renal ultrasound using 1 of 2 units (Acuson 128XT; Acuson Corporation, Mountain View, Calif, or Diasonic Spectra; Diasonic, San Jose, Calif). Scanning was performed using a 3- or 5-MHz transducer. Solid lesions seen on results of CT scan and ultrasound suggested the presence of renal tumors. Lesions were considered indeterminate if they were too small (2-5 mm) to be classified as cyst or solid. Individuals without renal tumors on CT findings were classified as not affected. Chest radiographs included posterior-anterior and lateral projections. Histologic criteria for the diagnosis of renal oncocytomas and papillary renal carcinoma were as described previously.\textsuperscript{19,18} In 3 patients, the diagnosis of renal carcinoma was made after review of death certificates, medical records, and pathology and autopsy reports.

\subsection*{Dermatologic Criteria}

Mucocutaneous lesions were diagnosed clinically. The diagnosis was confirmed by results of histologic examination of lesional skin biopsy specimens. We used the following clinical and histologic criteria. Fibrofoliculoculomas and TDs were multiple, 2- to 4-mm smooth-surfaced, white to skin-colored papules distributed over the face, neck, and upper trunk. Histologically, FFs were defined as multiple anastomosing strands of 2 to 4 epithelial cells extending from a central vesel follicle. A well-demarcated, loose, mucin-rich or thick connective tissue stroma encapsulated the epithelial component.\textsuperscript{1} Histologically, TDs consisted of a round to elliptical well-demarcated proliferation of a thick fibrous and vascular stroma in the reticulum dermis with a hair follicle at the periphery.\textsuperscript{21} Collagenomas were skin-colored to slightly hypopigmented, well-circumscribed indurated papules and plaques. Histologically, collagenomas consisted of a well-demarcated proliferation of thick collagen in the dermis.\textsuperscript{20} Acrochordons, or skin tags, were soft, pedunculated papules that histologically showed slightly acanthotic and occasionally mild papillomatous epidermis with a loose connective tissue stroma and dilated blood vessels.\textsuperscript{20} Papules of the oral mucosa were defined as multiple 1- to 2-mm dome-shaped papules involving the lip and buccal and gingival mucosae. Histologically, they were characterized by a collagenous stroma with few fibroblasts.\textsuperscript{18} The diagnosis of BHD was made in patients who had 5 or more facial or truncal papules, of which at least 1 papule was confirmed histologically as FF or TD.

\subsection*{Molecular Methods}

The DNA was extracted from peripheral blood leukocytes of patients. The presence of mutations in the \textit{VHL} gene was tested using Southern blotting and sequencing, as previously described.\textsuperscript{21} For screening of mutations of the \textit{MET} proto-oncogene, conformational, sensitive gel electrophoresis was performed, followed by sequencing of exons 16 through 19 of abnormally migrating bands, as described.\textsuperscript{21}

\section*{Results}

\subsection*{Molecular Studies}

Twenty individuals from 18 families with VHL had mutation in the \textit{VHL} gene, and 4 individuals from 5 families with hereditary papillary renal cell carcinoma displayed a mutation in the tyrosine kinase domain of the \textit{MET} proto-oncogene. No \textit{VHL} or tyrosine kinase domain \textit{MET} gene mutations were found in 13 patients from 9 families with renal oncocytomas. Families with BHD did not display mutations in the \textit{VHL} gene or the tyrosine kinase domain of the \textit{MET} proto-oncogene or karyotypic abnormalities. The results of mutation analysis in the families with BHD are summarized in the Table.

\subsection*{Renal Findings}

We examined 20 affected individuals from 18 families with VHL and 6 affected individuals from 5 families with...
hereditary papillary renal cell carcinoma. We also examined 6 affected individuals from 7 families with clear cell renal carcinoma, 14 affected individuals from 10 families with papillary renal cell carcinoma, and 15 affected individuals from 9 families with renal oncocytomas. No member from families with VHL, hereditary papillary renal cell carcinoma, or clear cell renal carcinoma exhibited cutaneous manifestations of BHD. Two kindreds with renal oncocytomas and a third with a variant of papillary renal cell carcinoma exhibited BHD.

The renal findings of families with BHD are summarized in the Table, and the pedigrees are shown in Figure 1. Families 166 and 168 (previously described) had affected members with multiple and bilateral renal oncocytomas. Family 166 has 3 individuals with renal neoplasms; III-2 and III-3, identical twins, exhibited bilateral multiple renal oncocytomas, and their father, II-2, had bilateral solid renal lesions on results of abdominal CT. Family 168 has 3 individuals across 2 generations with renal tumors; I-4 (not examined at the National Institutes of Health and, therefore, not included in the Table) and II-1 had multiple bilateral oncocytomas, and II-5 had oncocytomas on her left kidney. Five individuals in 3 generations from family 171 had renal neoplasms. Family 171 exhibits a variant of papillary renal cell carcinoma without mutations in the tyrosine kinase domain of the MET proto-oncogene. The renal histologic features varied among the affected family members and did not fit readily an existing classic diagnostic histologic category. Surgical pathologic specimens were available for microscopic examination in 2 of these 5 patients. Medical record review revealed that I-1 died when aged 68 years of unclassified renal cell carcinoma, and II-1 died when aged 70 years of bilateral renal tumors, some reported as papillary renal cell carcinoma, some as clear cell renal carcinoma, and some as renal oncocytomas. In the same family, II-4 had a left nephrectomy at age 71 years for a 2.5-cm tumor histologically consistent with a type papillary renal cell carcinoma; III-1 at age 34 years had a right nephrectomy for a 4.0-cm papillary renal cell carcinoma confined within the capsule; and III-7 at age 35 years had a 1-cm solid renal tumor on screening abdominal CT.
CUTANEOUS FEATURES

The cutaneous findings in patients from families with BHD are detailed in the Table. Nine men and 4 women ranging from 20 to 79 years of age (mean age, 38.6 years) from 3 kindreds exhibited multiple FF/TD (Figure 1). Clinically, FFs and TDs were indistinguishable; they presented in all patients as multiple, smooth skin-colored to grayish-white papules ranging from 1 to 5 mm in diameter (Figure 2, A and B). In addition, FF/TD presented as comedonal papules in 6 patients and as small cysts on 3 patients. Multiple FF/TD coalescing into a plaque were present on 3 individuals (Figure 2, C and D). All 13 patients had multiple papules on their faces, favoring the nose in 11 (85%), cheeks in 11 (85%), forehead in 8 (62%), and auricles in 4 (31%). Other involved areas included the neck in 10 (77%) and upper trunk in 11 (85%). The number of FFs and TDs ranged from 5 to more than 100. Although some individuals exhibited few papules localized to an area, others had extensive involvement with hundreds of lesions.

Multiple skin tags distributed on the eyelids, periocular area, neck, axilla, and groin were present in 11 patients from these 3 families (Table). Eight of the 11 patients with skin tags had multiple FFs and TDs. Multiple small, discrete, soft papules involving the lips, buccal mucosa, and gingiva were present in 9 patients (Figure 3, A). Two types of collagenomas were present: atrophic papules and large plaques. Two patients exhibited atrophic papular lesions consisting of groups of white shiny papules less than 4 mm in diameter distributed on the upper or lower trunk. Two patients exhibited dermal plaques greater than 3 cm in diameter. Five patients exhibited multiple lipomas involving up to 30% of the body surface area. One patient showed fat infiltration into muscle on magnetic resonance imaging (Figure 3, B).

DERMATOPATHOLOGIC FEATURES

Sections from 55 skin biopsy specimens obtained from 19 patients were examined using light microscopy. Thirty-five FFs were identified in biopsy specimens (Figure 4). Nineteen biopsy specimens of FFs showed individual or small clusters of immature sebocytes and sebaceous ducts within the epithelial cords. Most (95%) of the biopsy specimens of FFs revealed an epidermis with aberrant follicular structures and thin columns of epithelial cells with and without sebocytes extending into the papillary dermis (Figure 4, B). The epithelial strands were surrounded by a well-demarcated, loose, mucin-rich stroma in 18 specimens (Figure 4, C) and a predominantly thick connective tissue stroma in 17. Sections stained with Alcian blue revealed the presence of mucin within the stroma in all 10 FF biopsy specimens (Figure 4, D). Sections from 4 biopsy specimens exhibited TDs. Five additional biopsy specimens exhibited features of TD and FF. Initial sections showed a thickened collagenous stroma with lamellar fibroplasia around blood vessels adjacent to a hair follicle. Deeper sections revealed a proliferation of cords of epithelial cells emanating from hair follicle characteristic of FF.

Biopsy specimens of lesions with the clinical appearance of collagenomas were obtained in 3 patients. Histologically, these lesions consisted of a well-demarcated proliferation of thick collagen bundles in the reticular dermis. Biopsy specimens of papules from the oral mucosa of 2 patients showed an acanthotic epidermis and dense collagenous stroma with few fibroblasts.

OTHER FINDINGS

Other systemic findings in patients with BHD and their at-risk relatives are summarized in the Table. Four patients had associated neoplasia other than renal, ie, malignant melanoma, prostate cancer, and basal cell carcinoma. In addition, 4 patients from 2 families exhibited pulmonary cysts and/or pneumothorax.

COMMENT

We identified 3 extended families in whom renal neoplasms and BHD appeared to be segregating together. Two families had renal oncocytes and the third had a type of papillary renal cell carcinoma with oncocytic fea-
tures. This type of papillary renal cell carcinoma was not associated with mutations in the tyrosine kinase domain of the MET proto-oncogene. Seven individuals, including a set of identical twins, had renal neoplasms and BHD. An additional 4 patients had renal neoplasms without BHD. Three deceased patients with renal neoplasms had not been examined for BHD. Six individuals had BHD without renal neoplasms. Since the onset of FF and TD is earlier than the onset of renal tumors, renal tumors may still develop in these 6 patients. Recently, Roth et al described a 61-year-old man with BHD and bilateral renal cell carcinoma. Histopathologic examination of renal tissue from this patient revealed an unusual chromophobe adenocarcinoma that consisted of a mixed population of clear and eosinophilic cells. These findings are very similar to those seen in some of our patients with BHD. This syndrome is associated with various types of renal tumors, and these tumors may constitute a spectrum from oncocytomas to chromophobe to a type of papillary renal carcinoma. The types of renal neoplasms associated with BHD need to be defined better in future studies. Families with BHD did not display mutations in the VHL gene or the tyrosine kinase domain of the MET proto-oncogene. Birt-Hogg-Dubé syndrome may be due to a single gene mutation leading to skin and renal tumors. It is also possible that different mutations lead to an increased or decreased risk for renal involvement. This may explain why some families have more individuals af-

Figure 2. Clinical presentations of fibrofolliculomas. A, Multiple fibrofolliculomas (FFs) on the nose and paranasal area. B, Shiny small papules and papules with a central keratinous plug. C, Multiple FFs coalescing into a plaque. D, Higher magnification of C shows multiple papules with a central keratinous plug with a comedolike appearance.
Birt-Hogg-Dubé syndrome has been associated with tumors of various organ systems. In the original family, Birt et al described 1 branch (a sibship of 9) in which perifollicular fibromas (PFFs) were reported. Additionally, 2 cases of colon polyps have been associated with BHD. We identified 5 patients from 1 family who exhibited multiple lipomas involving up to 30% of the body surface area. One patient exhibited fat infiltration into muscle on magnetic resonance imaging. Lipomas had their onset during their third decade of life, similar to the onset of FF and TD. A solitary case of multiple lipomas associated with BHD has been reported. We found 2 types of collagenomas: atrophic papular and large plaque. To our knowledge, only 1 other case of BHD associated with collagenomas has been reported. We identified 5 patients from 1 family who exhibited multiple lipomas involving up to 30% of the body surface area. One patient exhibited fat infiltration into muscle on magnetic resonance imaging. Lipomas had their onset during their third decade of life, similar to the onset of FF and TD. A solitary case of multiple lipomas associated with BHD has been reported.

Since the original report, a variety of other cutaneous findings have been reported to be associated with BHD. We found 2 types of collagenomas: atrophic papular and large plaque. To our knowledge, only 1 other case of BHD associated with collagenomas has been reported. We identified 5 patients from 1 family who exhibited multiple lipomas involving up to 30% of the body surface area. One patient exhibited fat infiltration into muscle on magnetic resonance imaging. Lipomas had their onset during their third decade of life, similar to the onset of FF and TD. A solitary case of multiple lipomas associated with BHD has been reported.

In addition to BHD, there are several familial tumor syndromes in which the propensity for internal neoplasm is accompanied by the frequent occurrence of cutaneous tumors. These syndromes, such as tuberous sclerosis (TSC), neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 1 (MEN 1), and Cowden syndrome, are caused by the inheritance of mutations in tumor suppressor genes. These genes normally function to suppress cell proliferation and inhibit tumor growth. Tuberin and neurofibromin, the products of the TSC2 and NF1 genes, respectively, act in the ras signal transduction pathway to regulate cell proliferation and differentiation. Menin, the MEN1 gene product, interacts with the activator protein 1 (AP1) transcription factor JunD and represses JunD-activated transcription. The gene mutated in Cowden syndrome, PTEN, appears to modulate signaling pathways involving lipid second messengers by functioning as a phospholipid phosphatase.

None of our patients had a history of colon polyps. However, we did not examine our patients using sigmoidoscopy or colonoscopy. The association of BHD with colon polyps needs to be investigated in future studies. We found spontaneous pneumothorax in 1 individual and pulmonary cysts in 4 patients from 2 families (Table). Similar findings, including bullous emphysema and spontaneous pneumothorax, have been associated with BHD. The infrequent occurrence of these pulmonary findings suggests that they are manifestations of BHD rather than coincidental.
Figure 4. Microscopic features of fibrofolliculomas. A, Multiple anastomosing strands of 2 to 4 epithelial cells extend from the central follicle (original magnification, ×100). B, The underlying epidermis shows aberrant follicular structures with small sebocytes (original magnification, ×200). C, Small sebocytes are within the epithelial structures (original magnification, ×200). D, Alcian blue stain demonstrates the presence of mucin within the stroma (original magnification, ×200).
likely cause for cutaneous tumors in these patients. This involves a second somatic mutation, typically deleting the entire wild-type allele. In MEN 1, for example, angiofibromas, collagenomas, and lipomas develop.32 These cutaneous tumors, like the internal tumors in patients with MEN 1, show allelic deletion of the MEN1 gene.33 It is likely that the BHD gene functions in controlling cell growth as a tumor suppressor gene. Linkage studies are under way to identify the chromosomal localization for BHD as the first step toward identifying the BHD gene. Birt-Hogg-Dubé syndrome may represent another example in which inactivation of a tumor suppressor gene explains the association of cutaneous harmatomas and the internal neoplasia.

Accepted for publication May 18, 1999.


We appreciate the excellent photography of John T. Crawford, Rich Dreyfuss, Mary A. King, and Harry Schafer. We also thank Cia Manolatos, RN, and Inga Tokar, RN, for the excellent nursing care.

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