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REVIEW ARTICLE

# Birt–Hogg–Dubé Syndrome: A Review of Dermatological Manifestations and Other Symptoms

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**Abstract** Birt–Hogg–Dubé syndrome (BHD) is an autosomal dominant genodermatosis with malignant potential characterized by cutaneous and extracutaneous stigmata. Aberrations in the *folliculin* (*FLCN*) gene, which is located on chromosome 17, have been discovered in individuals with this condition. Over 150 unique mutations have been identified in BHD. The skin lesions associated with this condition include fibrofolliculomas, trichodiscomas, perifollicular fibromas, and acrochordons. Extracutaneous features of the syndrome typically include the lung (spontaneous pneumothorax and cysts) and the kidney (neoplasms). The only malignancies associated with BHD are renal cancers; however, other tumors have been observed in individuals with BHD. In this article, the skin lesions associated with this condition are reviewed, lung and renal manifestations associated with this syndrome are presented, and malignancies occurring in these patients are summarized.

**Key Points**

Birt–Hogg–Dubé syndrome (BHD) is an autosomal dominant condition with distinctive cutaneous skin lesions, extracutaneous features, and a predisposition for affected individuals to develop renal cancer.

The syndrome results from mutations in the *folliculin* (*FLCN*) gene.

Fibrofolliculomas, trichodiscomas, perifollicular fibromas, and acrochordons are syndrome-associated cutaneous lesions; evaluation of these skin lesions has introduced the possibility that all of the skin lesions may indeed be variants of the same lesion.

Pulmonary cyst, spontaneous pneumothorax, and kidney cancers are extracutaneous manifestations of BHD.

## 1 Introduction

Birt–Hogg–Dubé syndrome (BHD; Online Mendelian Inheritance in Man #135150), also known as Hornstein–Knickenberg syndrome and Hornstein–Birt–Hogg–Dubé, is a syndrome originally described as a triad of fibrofolliculomas, trichodiscomas, and acrochordons [1]. It is an autosomally dominant genodermatosis with extracutaneous features caused by mutations in the *folliculin* (*FLCN*) gene which code for the tumor suppressor folliculin. Folliculin is highly conserved across species and its homozygous deletion in animal models has proven lethal [2, 3]. The condition is characterized as a predisposition to develop numerous papules distributed mainly on the face, neck, and

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trunk, as well as extracutaneous conditions of multiple lung cysts, spontaneous pneumothoraces, and increased risk for renal neoplasia [4, 5]. Currently, renal cancers are the only malignancy associated with BHD but other tumors have been reported in individuals with BHD.

## 2 History

The first report of BHD may possibly be traced back to a 1925 article by Burnier and Rejsek [6, 7] in which they described a 56-year-old woman with skin-colored papules on the head and neck that were biopsied and reported as perifollicular fibromas. Birt, Hogg, and Dubé [1] gained recognition when they reported a triad of cutaneous findings in 15 family members consisting of fibrofolliculomas, trichodiscomas, and acrochordons. Although fibrofolliculomas are similar histopathologically to perifollicular fibromas seen by Burnier and Resjek [6, 7], Birt et al. [1] reported that the presence of hypoplastic sebaceous glands were not a feature of fibrofolliculomas. The family members reported by Birt et al. [1] developed medullary thyroid cancers, suggesting a systemic association. Re-evaluation, however, has since revealed the family also had a concurrent mutation in the *RET* proto-oncogene leading to multiple endocrine neoplasia type 2, which accounts for the medullary thyroid carcinomas seen [8].

Although the syndromic moniker is attributed to the report by Birt, Hogg, and Dube in 1977 [1], arguably, credit for the first systemic description of the syndrome can be ascribed to Hornstein and Knickenberg in 1975 [9]. Hornstein and Knickenberg [9] reported multiple papules identical in appearance, which were termed multiple perifollicular fibromas, myriad skin tags, and colonic polyps, which became known as Hornstein–Knickenberg Syndrome (HKS) [9]. A year later, Hornstein reported the autosomal dominant transmission as well an association with colon cancer [10]. Initially thought to be distinct separate entities, both BHD and HKS are now recognized to be the same syndrome [11, 12]. In 2002, the gene *FLCN* and protein folliculin were identified as the genetic mutation responsible for BHD.

## 3 Epidemiology

Over 430 families of BHD have been identified with 149 pathogenic variants described [13, 14]. The incidence of BHD is not known but is speculated to be underdiagnosed as there is variable penetrance of the known cutaneous and extracutaneous findings [15]. Of the individuals who fulfill diagnostic criteria, 7–9% don't have an identifiable *FLCN* mutation [16]. Disease severity can also vary within a family [16]. As many as 25% of BHD carriers do not have skin involvement at the time of diagnosis [15]. This is especially true in Asian BHD carriers, as more than half do not report having cutaneous lesions [17]. Up to 29–34% of people with BHD may develop renal neoplasia [18].

## 4 Clinical Presentation

### 4.1 Dermatologic Manifestation

Cutaneous manifestations of BHD include fibrofolliculomas, trichodiscomas, and acrochordons, as described by Birt et al. [1], and perifollicular fibromas in HKS. Fibrofolliculomas, trichodiscomas, and perifollicular fibromas are clinically indistinguishable as 2–4 mm flesh- and pale grayish–white-colored, smooth, dome-shaped papules that favor the face, neck, and trunk (Fig. 1) [19]. Several other genodermatoses may present similarly (Table 1) [20–29].

Many argue that fibrofolliculoma, trichodiscoma, and perifollicular fibroma are spectrums of the same disease or even the same lesion [2, 30, 31]. Cutaneous lesions typically appear in the third and fourth decade of life [2]. The lesions increase in size with age. Later presentation of cutaneous findings correlates with a milder skin phenotype. Men tend to have larger and more numerous lesions than women.

#### *4.1.1 Fibrofolliculoma*

Fibrofolliculomas are considered to be hamartomas of the hair follicle or benign tumors of the pilar apparatus [32]. The most prevalent cutaneous manifestation of BHD is that of fibrofolliculomas, which appear most often on the face or neck. Commonly appearing as small whitish papules, comedonal and cystic variants have been reported [19]. Furthermore, fibrofolliculomas may be subtle like comedonal papules, meaning patients may not seek medical care [8]. Patients may have as few as five scattered across several regions or several hundred papules that may coalesce into plaques [8].

Fibrofolliculomas develop in 75–90% of Caucasian BHD patients [4, 33], while as few as 30–48% of Asian BHD patients had skin papules [17, 34].

#### *4.1.2 Trichodiscoma*

Trichodiscomas were described by Birt et al. [1] as fibrofolliculomas. Like fibrofolliculomas, trichodiscomas are considered to be hamartomas or tumors of the pilar apparatus [32, 35]. Trichodiscomas are clinically indistinguishable from fibrofolliculomas and are likewise located predominantly on the head and neck.

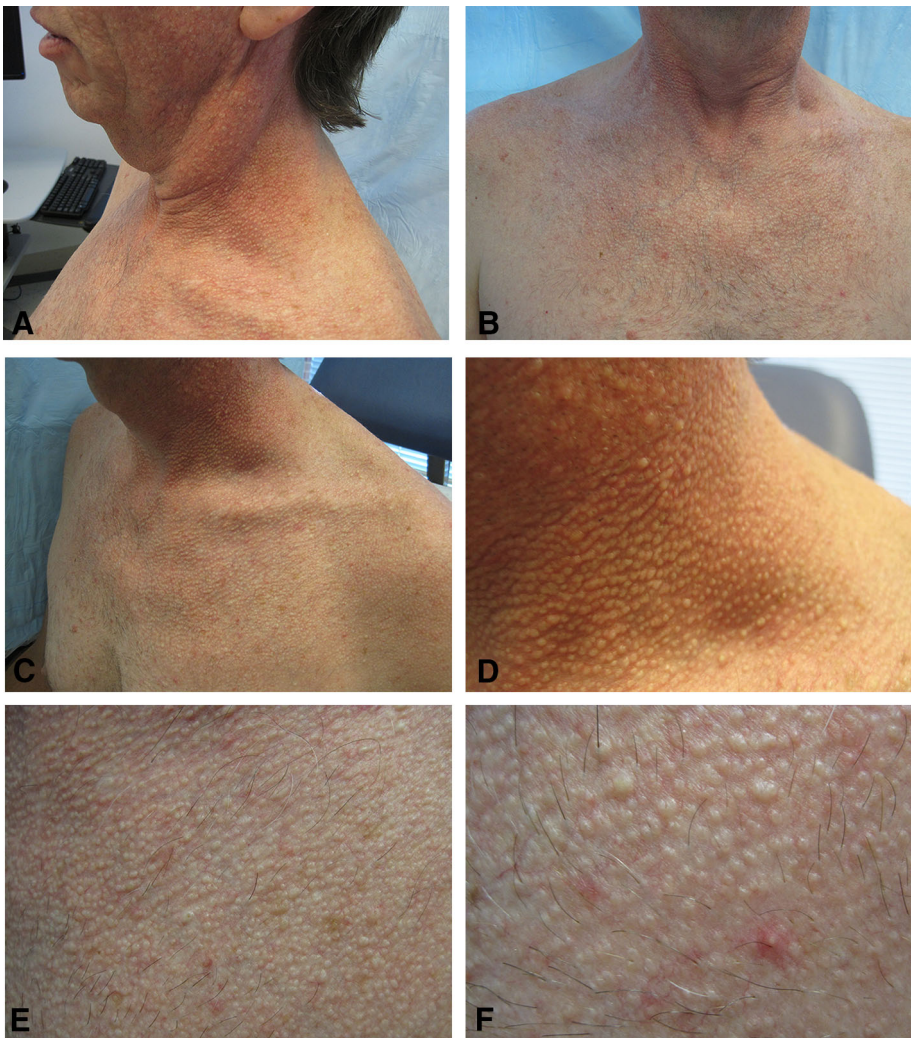


**Fig. 1** Distant (**a**–**c**) and closer (**d**–**f**) views of fibrofolliculomas in a man with Birt–Hogg–Dubé syndrome presenting as papules on the face (**a**), neck (**b**–**d**), chest (**a**–**c**), and supraclavicular fossa (**c**–**f**). A 48-year-old man presented for evaluation of numerous painless flesh-colored and white papules on his face, upper chest, and back. They had been present since his early twenties. Most recently, they have been increasing in number and size. He has a history of appendiceal carcinoma with metastasis to the peritoneum diagnosed 15 years ago. Prior cancer-directed treatment included surgery and adjuvant chemotherapy. He had no pulmonary cysts or renal tumors. His father had similar skin lesions without any history of malignancy. Cutaneous examination showed 2 mm skin-colored and hypopigmented flat-topped papules on the face (**a**), neck (**b**–**d**), chest (**a**–**c**), supraclavicular fossa (**c**, **d**–**f**), and upper back

#### *4.1.3 Perifollicular Fibromas*

Two years before Birt et al. [1] reported their findings in 1977, Hornstein and Knickenberg [9] described perifollicular fibromas in two siblings and allegedly similar lesions in their father. Perifollicular fibromas are hamartomas of the mesenchymal hair sheath [10]. They can appear as solitary lesions or multiple lesions. Most perifollicular fibromas are found on the face and neck like fibrofolliculomas and trichodiscomas [36]. Clinically, their appearance is indistinguishable from fibrofolliculomas and trichodiscomas. Indeed, many regard perifollicular fibromas and fibrofolliculomas as identical lesions [31].

#### *4.1.4 Acrochordons*

One of the original triad with fibrofolliculomas and trichodiscomas, acrochordons are small, pedunculated outgrowths of epidermal and dermal tissue. These occur on the neck, eyelids, upper chest, and axillae [37]. There is evidence that some of the lesions clinically suggestive of acrochordons are actually fibrofolliculomas on histology [30].

### 4.2 Systemic Involvement

BHD is recognized as a genodermatosis with extracutaneous manifestations, including renal and pulmonary cysts, spontaneous pneumothorax, and renal cancers. The phenotype for patients with BHD is variable. Some individuals present without skin lesions and have only pulmonary involvement and/or renal tumors [16].

#### *4.2.1 Pulmonary Cyst*

Pulmonary cysts are the most common manifestation of BHD and are seen in over 80% of patients with BHD over the age of 50 years and, although usually seen after the fourth and fifth decades, they can appear from as early as the patient's teens to as late as the eighth decade [5, 33].

**Table 1** Characteristics of genodermatoses with multiple facial papules

| Genodermatosis | Gene mutation | Characteristic skin papule | Malignant potential | References |
|---|---|---|---|---|
| Basaloid follicular hamartoma syndrome | *PTCH* | Basaloid follicular hamartoma | Basal cell carcinoma | [20] |
| Birt–Hogg–Dubé syndrome | *FLCN* | Fibrofolliculoma, trichodiscoma, perifollicular fibroma | Renal cell carcinoma | |
| Brooke–Spiegler syndrome | *CYLD* | Trichoepithelioma, spiradenoma, cylindroma, spiradenocylindroma | Salivary and parotid tumors | [21] |
| Cowden syndrome | *PTEN* | Trichilemmoma | Breast, thyroid, endometrial cancers | [22] |
| Multiple endocrine neoplasia type 1 | *MEN1* | Angiofibroma | Pituitary, parathyroid, pancreas | [23] |
| Multiple endocrine neoplasia type 2 | *RET* | Mucocutaneous neuroma | Medullary thyroid carcinoma | [24] |
| Multiple familial trichodiscomas | Unknown | Trichodiscoma | None | [25] |
| Muir–Torre syndrome | *MLH1*, *MLH3*, *MSH2*, *MSH6* | Sebaceous neoplasms | Colorectal cancer | [26] |
| Neurofibromatosis type 1 | *NF1* | Neurofibroma | Malignancies in multiple organ systems including glial tumors | [27] |
| Rombo syndrome | Unknown | Trichoepithelioma | Basal cell carcinoma | [28] |
| Tuberous sclerosis complex | *TSC1*, *TSC2* | Angiofibromas | Malignancies in multiple organ systems | [29] |

Radiologists may distinguish BHD from other diffuse cystic lung diseases as pulmonary cysts in BHD typically predominate at the lung bases and periphery bilaterally [38]. Parenchyma surrounding the cysts are normal [39]. Though they vary in size, they are usually less than 1 cm and septated [5]. Imaging has shown no significant change in the size or number of pulmonary cysts with time for up to 66 months [40].

Initially, pulmonary cysts of BHD are histologically dissimilar pulmonary cysts that result from normal lungs or from diseases such as lung cancer and thymoma [41]. Pathological diagnosis may be difficult if the biopsied lesion has thickened secondarily to repeated ruptures. In actuality, BHD-associated cysts are neither bullae nor blebs, but are rather slow-growing hamartomatous cysts [41].

Pulmonary function tests show normal to minimally impaired function [42]. Haploinsufficiency with decreased number of normal-functioning folliculin may be enough for aberrant pulmonary cyst formation [41, 43]. Although unconfirmed in larger cohort studies, more severe cystic changes have been reported in smokers [5, 33]. While there are several reports of pulmonary malignancies, unlike renal carcinoma there is no clear association of BHD syndrome with pulmonary cancers [5, 44].

#### *4.2.2 Pneumothorax*

In a study involving 104 patients, 76% of BHD patients had at least one spontaneous pneumothorax during their lifetime [45]. As many as 70% of people with BHD presenting with a pneumothorax do not have a prior cutaneous or renal diagnosis [46, 47]. Generally asymptomatic and found incidentally, the manifestations of pulmonary cysts can be identified earlier than other BHD findings when a pneumothorax occurs spontaneously [43]. A family history of spontaneous pneumothorax should raise a strong suspicion for BHD, even without cutaneous findings present, among other genetic diseases associated with spontaneous pneumothorax such as α1 antitrypsin deficiency, Ehlers-Danlos syndrome, homocystinuria, and Marfan syndrome [48]. BHD patients have an age-adjusted 50-fold increased risk of developing a spontaneous pneumothorax [49]. Younger BHD patients (<41 years) are four times more likely to have a pneumothorax than older people with BHD [49]. Risk factors for developing a pneumothorax include the number and size of pulmonary cysts [5, 33].

## 5 Associated Conditions

### 5.1 Renal Cancer

Currently, renal cancers are the only malignancy to be widely recognized as being part of the BHD phenotype (Table 2) [50–53]. In several large cohorts, renal tumors developed in 29–34% of BHD-affected individuals [18, 54], but this may reflect ascertainment bias as another study found a frequency of only 12% [50]. Over half of BHD patients with renal cancer have neoplasms that are bilateral and multifocal [4]. The majority of renal tumors in

**Table 2** Established renal cancer types of Birt–Hogg–Dubé syndrome [50–53]

| Renal tumor | Benignity |
|---|---|
| Hybrid oncocytic tumor comprised of features of chromophobe RCC and renal oncocytoma (50%) | Malignant |
| Chromophobe (34%) | Malignant |
| Clear cell (9%) | Malignant |
| Oncocytoma (5%) | Benign |
| Papillary (2%) | Malignant |

*RCC* renal cell carcinoma

BHD are hybrid oncocytic tumors comprised of features of chromophobe renal cell carcinoma (RCC) and renal oncocytoma (50%) and chromophobe (34%) types which are usually indolent [14, 52]. Renal cancer is 6.9-fold more likely to occur in BHD than in the general population [49]. The mean age of diagnosis is approximately 50 years [52]. Renal tumor type and histology can differ within the same family [14, 52].

### 5.2 Other Cancers

Numerous malignancies in addition to renal cancers have been described in people with BHD (Table 3) [4, 8, 15, 17, 18, 30, 31, 37, 42, 44, 47, 50, 52, 55–84]. Possibly incidental, they may also be a byproduct of mutated *FLCN* tumor suppressor and expand the spectrum of associated tumors in BHD. There is speculation by some authors that certain malignancies are also associated with mutations of *FLCN*, such as colon [9], lung [44], parotid [17], thyroid [1, 17], and parathyroid cancers [85]. Prior to merging with BHD, HKS was noted to have an association with colon polyps and colon cancer [86]. In a study involving 223 families with BHD, neither colon cancer nor colon polyps were found to be associated with BHD. As is discussed in Sect. 7, this difference may be secondary to differing germline mutations in *FLCN* which impart different phenotypic variations. While lower in incidence than renal cancers, further genetic and pathologic investigations may elucidate more tumor pathogenesis with BHD [17].

## 6 Pathology

Histologic findings of fibrofolliculoma, trichodiscomas, perifollicular fibromas, and acrochordons are highlighted in Sects. 6.1–6.3. Steffen and Ackerman [32] consider all four dermatologic conditions to be variations on a theme of the sebaceous neoplasm, mantleoma. Others agree and speculate the lesions are on a histologic spectrum [31].

### 6.1 Fibrofolliculoma

Although the cutaneous papules of BHD are clinically indistinguishable visually, on histology the most common finding is the fibrofolliculoma. Fibrofolliculomas are said to be folliculo-sebaceous hamartomas that arise from mesodermal and ectodermal components [12, 31]. On sectioning, they are easily identified by peculiar anastamosing strands of infundibular epithelial cells 2–4 layers thick extending from a normal (or dilated and distorted) central follicle down into the dermis, which sometimes terminate in sebaceous elements (Fig. 2) [12, 87]. The epithelial strands are encapsulated by a well-demarcated, loose mucin-rich or thick connective tissue stroma [8, 16].

While the prevailing theory of fibrofolliculoma is that of a hair follicle tumor or hamartoma, an alternative argument is that fibrofolliculomas are similar, if not, identical to mantleomas [88, 89]. Mantleomas are benign tumors originating from the infundibulum of the hair follicle, which is where the mantle—the sebaceous gland morphogenesis—resides [88]. Mantles consist of undifferentiated cells in cord structures encircling the follicle, which upon hormonal stimulation form sebaceous glands. Ciliary dysfunction, as mentioned in Sect. 7, is a byproduct of aberrant folliculin function that causes abnormal growth and differentiation of the mantle into fibrofolliculoma. Vernooij et al. [88] suggest this mantle theory can explain why fibrofolliculoma preferentially affects sebaceous gland-rich areas such as the nasal and perinasal area common in fibrofolliculoma.

### 6.2 Trichodiscoma

Trichodiscomas were termed first by Pinkus et al. [90], who described them as hamartomatous tumors of the haarscheibe (hair disc), which was defined as a slow-adapting touch receptor [90, 91]. More recent emphasis has been to designate trichodiscomas and fibrofolliculoma as follicular-sebaceous hamartomas [12, 92]. They are immunophenotypically similar and share similar epithelial and mesenchymal components [93, 94]. Trichodiscomas are predominantly derived from the pilosebaceous mesenchyme instead of having a larger epithelial prominence in fibrofolliculoma (Table 4) [2, 32].

Some believe fibrofolliculomas and trichodiscomas are variations of the same lesion [2, 30, 31, 95]. Characteristics of both fibrofolliculoma and trichodiscoma have been observed in the same lesion, albeit with different accentuation that suggests a single process, and are speculated to be temporal stages of the same lesion [4, 87, 89]. The fibrous stroma in the reticular dermis is the signature portion in trichodiscomas. In comparison to fibrofolliculoma, the overlying epithelial mantle-like cords are attenuated or

**Table 3** Additional tumors reported in patients with Birt–Hogg–Dubé syndrome

| Cancers | Benignity | References |
|---|---|---|
| **Cardiovascular** | | |
| Cardiac rhabdomyoma | Benign | [18] |
| **Endocrine** | | |
| Non-functional adrenal adenoma | Benign | [47] |
| Oncocytic adrenal tumor | Mostly benign | [55] |
| Pheochromocytoma | Malignant | [50] |
| **Dermatologic** | | |
| Angiomatous nodules | Benign | [15] |
| Basal cell carcinoma | Malignant | [56] |
| Collagenomas | Benign | [8] |
| Dermatofibrosarcoma protuberans (DFSP) | Malignant | [18] |
| Koenen's tumor (periungual angiofibroma) | Benign | [57] |
| Leiomyosarcoma (cutaneous) | Malignant | [4] |
| Leiomyoma (cutaneous) | Benign | [4] |
| Lipomas and angiolipomas | Benign | [58] |
| Melanoma | Malignant | [59] |
| Squamous cell carcinoma | Malignant | [60] |
| Trichoblastoma | Benign | [61] |
| **Gastrointestinal** | | |
| Colorectal | | |
| Appendiceal cancer | Malignant | Current report |
| Colon adenoma | Benign | [62] |
| Colon cancer | Malignant | [47] |
| Oncocytic colorectal carcinoma | Benign | [63] |
| Rectal cancer | Malignant | [64] |
| Other | | |
| Peritoneal mesothelioma | Malignant | [59] |
| Gastric adenocarcinoma | Malignant | [44] |
| Hepatic angiomas | Benign | [65] |
| **Gynecologic** | | |
| Breast cancer | Malignant | [66] |
| Breast sarcoma | Malignant | [67] |
| Endometrial carcinoma | Malignant | [64] |
| Fibroadenomatosis | Benign | [67] |
| Uterine cancer | Malignant | [18] |
| SCC of the cervix | Malignant | [18] |
| **Head and neck** | | |
| Salivary | | |
| Parotid oncocytoma | Benign | [68] |
| Pleomorphic adenoma | Benign | [37] |
| Submandibular oncocytoma | Benign | [69] |
| Thyroid and parathyroid | | |
| Hürthle cell carcinoma | Malignant | [17] |
| Thyroid adenoma | Benign | [30] |
| Thyroid cancer | Malignant | [47] |
| Thyroid clear cell carcinoma | Malignant | [70] |
| Medullary thyroid cancer | Malignant | [71] |
| Multinodular goiter | Benign | [4] |
| Papillary thyroid cancer | Malignant | [72] |
| Parathyroid adenoma | Benign | [58] |
| Other | | |
| SCC of head and neck | Malignant | [18] |
| Throat cancer | Malignant | [73] |
| Tonsillar SCC | Malignant | [67] |
| **Hematologic** | | |
| Hodgkin's lymphoma | Malignant | [18] |
| Lymphocytic leukemia | Malignant | [74] |
| Non-Hodgkin's lymphoma | Malignant | [56] |
| **Musculoskeletal** | | |
| Osteomas | Benign | [75] |
| Fibrosarcoma of the leg | Malignant | [56] |
| Myoma of the uterus | Benign | [47] |
| Rhabdomyoma in the neck | Benign | [76] |
| Sarcoma dorsi | Malignant | [67] |
| **Neurologic** | | |
| Astrocytoma | Malignant | [50] |
| Melanoma (choroidal) | Malignant | [77] |
| Meningioma | Benign | [31] |
| Neurilemmoma (schwannoma) | Benign | [78] |
| Neurothekeoma | Benign | [31] |
| Oncocytic pituitary adenoma | Benign | [50] |
| Schwannoma (vestibular) | Benign | [79] |
| **Pulmonary** | | |
| Bronchoalveolar carcinoma | Malignant | [80] |
| Clear cell sugar tumor (PEComa) | Benign | [81] |
| Lung adenocarcinoma | Malignant | [80] |
| Pulmonary histiocytoma | Malignant | [42] |
| **Urologic** | | |
| Kidney | | |
| Renal angiomyolipoma | Benign | [82] |
| Other | | |
| Bladder | Malignant | [73] |
| Neuroendocrine tumor of bladder or prostatic origin | Malignant | [83] |
| Prostatic carcinoma | Malignant | [84] |

*SCC* squamous cell carcinoma

seldom found in trichodiscomas [12, 94]. The follicular mantle is undifferentiated in fibrofolliculoma, whereas the mantles have effloresced to become sebaceous structures with ducts in trichodiscomas [96]. Vacuolated cells appear within the epithelial cords while simultaneously the

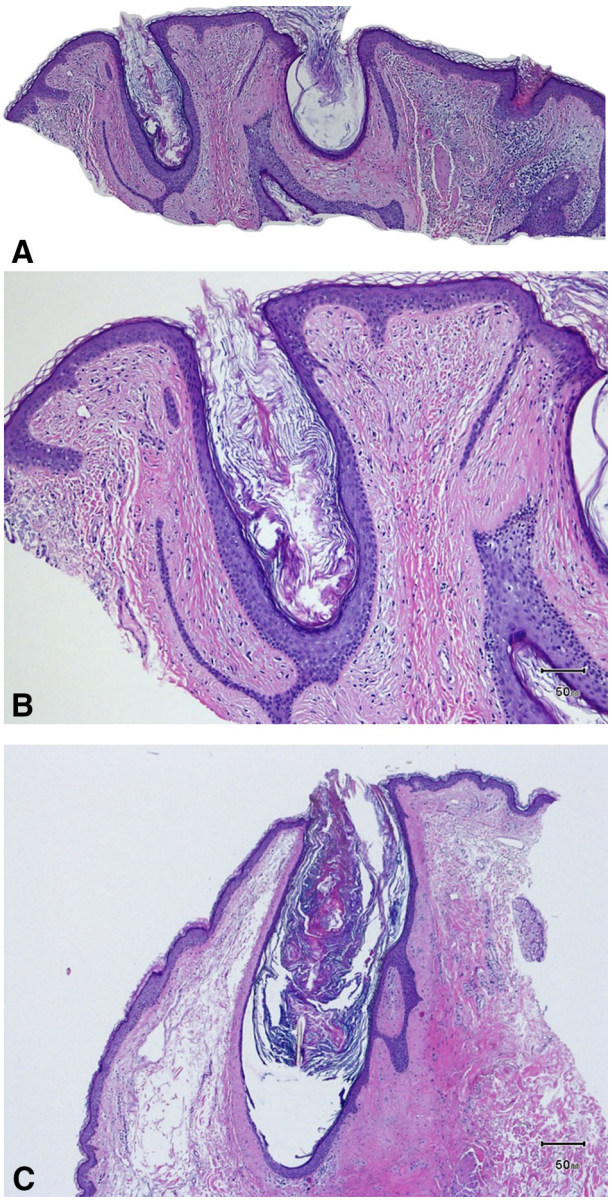


**Fig. 2** Histology: distant (**a**) and closer (**b**, **c**) views of the biopsied papules from the 48-year-old man with Birt–Hogg–Dubé syndrome (Fig. 1). Microscopic examination of the lesional skin biopsy from the left clavicle (**a**, **b**) and the right jawline (**c**) showed similar pathologic changes; there is a prominent dilated follicle connecting to anastomizing basaloid strands with a prominent mesenchymal component of fibroblasts wrapping around these anastomizing basaloid strands. These pathologic changes establish a diagnosis of fibrofolliculoma. Correlation of the patient personal and family history, numerous skin lesions, biopsy-proven fibrofolliculoma, and presence of visceral malignancy established a diagnosis of Birt–Hogg–Dubé syndrome. He developed recurrence of his metastatic appendiceal carcinoma and died prior to genetic testing (hematoxylin and eosin: **a** = ×4; **b** = ×20; **c** = ×20)

mantles form sebaceous lobules and ducts, which on histology is designated trichodiscoma [32]. The central follicle in fibrofolliculomas has been moved to the periphery in trichodiscomas [97]. The diagnosis of fibrofolliculoma or trichodiscoma may depend on the topographic location of the hair follicle within the biopsy specimen and/or stage of the lesion [8].

### 6.3 Perifollicular Fibroma

Early literature distinguished perifollicular fibromas from fibrofolliculomas and trichodiscomas. Birt et al. [1] thought that perifollicular fibromas and trichodiscomas are opposite ends of a spectrum with fibrofolliculoma in between. It has been argued, however, that the difference between perifollicular fibroma and fibrofolliculoma is artificial as they share similar histology and may even possibly be identical on correct sectioning [12, 90]. Much of this is in part due to reports that perifollicular fibromas represent transversely cut fibrofolliculomas [12, 30, 31, 98].

Perifollicular fibromas are rare cutaneous hamartomas thought to arise from the connective sheath of the hair follicle [98]. Histologically, the prominent stroma in perifollicular fibroma is rich in fibrocytes and separated from the surrounding dermis by clefts without sebaceous lobules. While trichodiscomas and fibrofolliculomas rarely have a hair follicle with an enclosed hair shaft, in perifollicular fibroma hair follicles possess unaltered epithelium or dilated infundibula surrounded by a dense concentric fibrous sheath in an onion-like array [12, 30, 31, 90]. Whereas fibrofolliculomas have multiple epithelial protrusions from the hair follicle, which can anastomose, perifollicular fibromas are devoid of these protrusions [12]. It was noted, however, by Schulz and Hartschuh [12], among others, that many previous publications reporting perifollicular fibromas actually exhibited follicles with small epithelial struts suggestive of fibrofolliculoma.

Originally, perifollicular fibroma, the principal cutaneous lesion in HKS, and its syndrome was incorporated into BHD. Some consider perifollicular fibroma to be distinct or part of the fibrofolliculoma/trichodiscoma spectrum [8, 99, 100]. However, most reported literature of diagnosed perifollicular fibroma related to horizontal sectioning [12]. Similar horizontal sectioning by Schulz and Hartschuh [12] produced a similar outcome, whereas vertical sectioning revealed the typical architecture of fibrofolliculoma (protruding epithelium from the infundibula, sebaceous glands, lack of accompanying hair canal with the enclosed hair). Sebaceous lobules were not seen by horizontal sectioning until deeper levels are obtained. The two differing results are of the one same lesion, fibrofolliculoma, where the epithelial cords are oriented vertically. Therefore, the epithelial cords and sebaceous lobules will hardly ever appear in their entirety in superficial horizontal sections [12].

**Table 4** Pathologic features of Birt–Hogg–Dubé syndrome-associated lesions

| Lesion | Cystic pattern | Epithelialization | Infundibulum | Orientation | Stroma | References |
|---|---|---|---|---|---|---|
| Fibrofolliculoma | ++ | +++ | Central | Vertically | +++ | [138] |
| Perifollicular fibroma | + | ++ | Central | Vertically | +++ | [12, 98, 99, 138] |
| Trihodiscoma | +/– | + | Peripheral | Horizontally | +++ | [138] |

+/– may be present, + present—low, ++ present—medium; +++ present—high

### 6.4 Acrochordons

Along with fibrofolliculomas and trichodiscomas, acrochordons are part of the three cutaneous conditions first described by Birt et al. [1]. In addition to the usual fibroepithelial polyps typical of acrochordons, fibrofolliculoma pedunculated lesions that are acrochordon-like have also been reported on histology [101]. With arguments that trichodiscomas and fibrofolliculomas are spectrums of a single lesion, the inclusion of acrochordon-like lesions as fibrofolliculoma makes the previous triad of BHD into a single pathological process [30, 67].

## 7 Pathogenesis

The pathogenesis of BHD has been identified to 17p11.2, the *FLCN* gene locus, which codes for folliculin, a 579 amino-acid protein [3, 4]. Folliculin is a tumor suppressor gene as all germine mutations observed to date in renal tumors are frameshift and nonsense mutations that result in a truncated folliculin protein [102]. As a tumor suppressor, genetic mutations result in loss of a functional folliculin protein, resulting in unchecked tumor growth. Approximately 150 different folliculin loss-of-function mutations have been identified [14]. The most common region for a mutation is a hypermutable polycytosine (C8) tract in exon 11 [3, 14].

Haploinsufficiency of folliculin (where the germline-mutated gene leaves only one wild-type functional allele that is insufficient for a normal phenotype) is seen in cutaneous lesions and in the lung cyst-lining epithelial cells [41, 103]. This is in contrast to 70% of renal tumors which show a somatic second hit mutation or loss of heterozygosity via a second hit to the remaining somatic wild-type copy rendering no functional alleles [102]. There appears to be differences in mechanisms that lead to BHD manifestations as renal tumors have a decreased number of normal folliculin messenger RNA (mRNA) expressed; however, there is no loss of folliculin mRNA, but actually strong expression of folliculin in fibrofolliculomas [104].

There is speculation as to whether BHD pulmonary cysts and renal cysts may be secondary to ciliary dysfunction, much like von Hippel Lindau and tuberous sclerosis [82, 105]. Folliculin is detected in a unique microtubule protrusion from the cell surface called the primary cilium, which is involved critically in energy sensing and homeostasis by acting on the mammalian target of rapamycin (mTOR) signaling pathway, but not in FLCN-deficient renal tumor cells [106].

Most attention, however, is focused on its interaction with AMPK (5′AMP-activated protein kinase) in the mTOR pathway via FLCN-interacting protein 1 and 2 (FNIP1 and FNIP2) [44, 107, 108]. *FLCN* may prevent tumorigenesis by preventing AMPK-dependent hypoxia-inducible factor activation [109]. There is conflicting evidence whether it is stimulation or inhibition of the mTOR pathway that leads to BHD-associated renal tumors [110–113]. This suggests that regulation of mTOR pathway may depend on cell type or context [14]. In vitro cell lines with *FLCN* mutations and a xenograft mouse model developed with FLCN-deficient renal tumor cells from a BHD patient, and rat model of BHD with germline *Flcn* mutation develop RCC, which are subsequently suppressed with *Flcn* rescue [5, 114, 115].

### 7.1 Laboratory Studies

Approximately 150 pathogenic *FLCN* mutation variants have been described [14]. There is no widely regarded phenotypic–genotypic association in BHD, although certain mutations have been reported to impart a higher risk of certain manifestations. When compared to BHD patients with a c.610_611delGCinsTA frameshift mutation, those with a c.1285dupC mutation had a higher colorectal cancer risk [116]. BHD patients with a c.1285delC variant been reported to have a five-fold lower risk of developing renal cancers than c.1285dupC carriers [16, 54].

## 8 Clinical Evaluation

### 8.1 Cutaneous

Given the potential for severe extracutaneous manifestations, including renal cancer and pneumothoraces, timely diagnosis of BHD is vital in ensuring prompt treatment

with minimal delay and unnecessary or costly diagnostic testing. Since at least 75–80% of people with BHD develop fibrofolliculoma, the cutaneous manifestations may be the initial sign or clue to help diagnose BHD [4]. As seen in Table 1, other cutaneous mimickers include trichoepitheliomas, which tend to be flesh-colored rather than the whitish lesions of fibrofolliculoma, and clustered around nasolabial folds [31]. In addition, fibrofolliculomas have more fibrous appearance than the basaloid hamartomas (Table 4).

Angiofibromas of tuberous sclerosis are smaller than fibrofolliculomas and have telangiectasias. However, angiofibromas have been the predominant lesion in a patient with BHD [2]. Toro [16] contends that angiofibromas are clinically and histologically indistinguishable from fibrofolliculomas; therefore, it has been suggested that tuberous sclerosis should be excluded before diagnosing BHD [5, 16].

### 8.2 Pulmonary

Potentially as many as 25% of patients older than 20 years of age may not have skin lesions [4]. Many BHD patients may only present with an extracutaneous event such as spontaneous pneumothorax or the symptoms that arise with RCC [4]. The presence of lung cysts, which generally affect patients in their twenties to thirties, and/or pneumothoraces (along with the requisite skin findings) should prompt a search for BHD due to its predisposition for renal cancers, which typically appear decades later [41]. BHD may manifest initially as spontaneous pneumothoraces, especially in younger patients, which can occur as young as 14 years of age, much younger than the usual third- or fourth-decade appearance of fibrofolliculoma [2, 117]. Lung cysts are generally asymptomatic, although they can present as dyspnea or chest pain due to a pneumothorax. The differential diagnosis and evaluation of patients with lung cysts has been reviewed elsewhere [118–120]. Other diffuse cystic lung diseases such as lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis can present with lung cysts and spontaneous pneumothoraces. High-resolution computed tomography (CT) can differentiate those conditions from BHD-associated lung cysts. In addition, high-resolution CT can not only help with the correct management but also be a cost-effective screening tool for patients presenting with seemingly primary spontaneous pneumothorax [121].

### 8.3 Renal

Patients with a presentation of renal tumors prior to age 50 years, bilateral renal cysts or cancers, and family history of renal cancers should raise suspicion for BHD [5, 14, 122]. Diagnostic consideration should include von Hippel-Lindau, which also features renal cysts and tumors. von Hippel-Lindau renal tumors, however, usually have cystic components rather than the solid renal cancers of BHD [5]. Renal tumors are also present in lymphangioleiomyomatosis in addition to the shared cystic lung disease with BHD. Imaging can detect the characteristic fat that is present in angiomyolipomas of lymphangioleiomyomatosis, although angiomyolipomas have also been reported in patients with BHD [5, 82, 123].

### 8.4 Diagnosis

The most commonly cited diagnostic criteria for BHD creates major and minor criteria (Table 5) [4]. The most prominent criteria includes the identification of the *FLCN* gene in BHD patients. A new proposed diagnostic criteria stratifies likelihood of BHD and classifies definitive diagnosis of BHD with a positive genetic test while other supportive findings are major and minor criteria (Table 6) [14, 124]. Gene panel testing for multiple genes first is now commonplace. If the manifestations strongly suggest BHD, genetic testing of the entire *FLCN* coding region should be performed, followed by analysis for deletions/duplications of *FLCN* [16]. Seven to 9% of individuals don't have an identifiable *FLCN* mutation, but can and do fulfill diagnostic criteria by having other major criteria (adult-onset, biopsy-proven fibrofolliculoma or trichodiscoma) or any three of the minor criteria including a first-degree relative with BHD, renal cancer, or history of spontaneous pneumothoraces [16]. Fibrofolliculomas are rare and specific for BHD syndrome and can be confirmed by punch biopsy.

### 8.5 *FLCN* Genetic Testing for the Patient and Family

Family members of positive probands should have diagnostic genetic screening to evaluate for the family-specific *FLCN* mutation. This is the definitive genetic test that should occur as it will identify at-risk family members, improve diagnostic certainty, and minimize unnecessary testing on non-affected family members [16]. The American Society of Clinical Oncology recommends delaying genetic testing for at-risk individuals until age 18 years when they can make an informed decision for themselves.

## 9 Treatment

While benign, the cutaneous lesions of BHD can be troubling given their number and propensity to occur on the face. Good outcomes without recurrence up to 2 years later have been reported with hyfrecation with or without

**Table 5** Diagnostic criteria for Birt–Hogg–Dubé syndrome (from the European BHD consortium [4])

| | | |
|---|---|---|
| One major or two minor criteria are necessary | | |
| Major | ≥5 fibrofolliculomas/trichodiscomas | One must be confirmed histologically |
| | Pathogenic *FLCN* germline mutation | |
| Minor | Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax | |
| | Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology | |
| | A first-degree relative with BHD | |

*BHD* Birt–Hogg–Dubé syndrome

**Table 6** Proposed new diagnostic criteria for Birt–Hogg–Dubé syndrome (from Schmidt and Linehan [14, 124])

| Definitive diagnosis | Positive genetic test for a germline *FLCN* mutation | |
|---|---|---|
| Major criteria (high likelihood of BHD) | ≥2 cutaneous papules clinically compatible with fibrofolliculoma/trichodiscoma with at least one biopsy-proven/histologically confirmed fibrofolliculoma | Adult onset |
| Minor criteria (suspicious for BHD) | Multiple bilateral basilar lung cysts ± spontaneous pneumothorax (<40 years of age) | Family history of these pulmonary manifestations |
| | Bilateral multifocal chromophobe or hybrid oncocytic renal tumors | Family history of these histologic subtypes |
| | Any combination of cutaneous, lung, or renal manifestations known to be associated with BHD in an individual or his family | |

*BHD* Birt–Hogg–Dubé syndrome

curettage [125, 126]. Laser resurfacing with Erbium-YAG (yttrium aluminium garnet) and fractional $CO_2$ have generally been effective without scarring, hypopigmentation, or hyperpigmentation [89, 127]; however, some cases relapse [16, 128]. Unfortunately, a topical double-blind randomized clinical trial failed to show benefit using rapamycin to inhibit the mTOR pathway [129].

For the extracutaneous stigmata, pleurodesis or partial pleural covering is recommended after the first episode of pneumothorax [130]. Nephron-sparing surgery is recommended for renal masses over 3 cm [124, 131]. Cryoablation and radioablation are not generally recommended in patients able to withstand surgery as BHD-associated renal tumors are usually multifocal [122]. mTOR inhibitor treatment for BHD-associated RCC have been attempted in case reports and in mice, which suggests a possible role for mTOR inhibitors. A phase II clinical trial evaluating the mTOR inhibitor everolimus in BHD-associated renal cancer is currently ongoing [5, 113, 132].

### 9.1 Observation

Guidelines for tumor surveillance in BHD patients vary widely, including the imaging modality, frequency, and age for initiating kidney screening. Additionally, what malignancies beside renal cancer should be monitored has been a topic of debate. Some authors have offered their patients yearly abdominal ultrasounds [103, 133]. However, ultrasound may be unreliable because of the similar echogenicity of hybrid oncocytic and chromophobe tumors to the surrounding renal parenchyma [122] while CT scans can lead to excessive radiation accumulation, leaving magnetic resonance imaging (MRI) the preferred surveillance modality for renal cancers [120]. The Urologic Oncology Branch of the US National Institutes of Health (NIH) recommends MRI of the abdomen with or without contrast every 2–3 years [134]. While the frequency may be dictated by the imaging chosen, the literature suggests that lifelong surveillance be annual if tumors are detected; for BHD patients without an identified renal lesion, there is little consensus as some recommend annual surveillance or even as infrequent as every 4–5 years [16, 48, 122, 133].

While renal tumors typically develop in the fifth decade [52, 103], they have occurred at less than 25 years of age, and it is suggested that screening begin with annual renal MRIs from age 18 years onwards [16]. Danish recommendations suggests renal screening 10 years before the onset age of the first affected family member [133]. Furuya et al. [17] suggest that RCC screening start at age 35 years.

Screening for other malignancies has been broached, including melanoma and colon cancer. Depending on the level of concern for melanoma, regular skin checks may be considered [16]. With the uncertain association of BHD with colon cancer, the question of colon cancer screenings at a greater frequency than in the general population is also undecided [48, 116].

Smoking should be highly discouraged as it has strong association with RCC and more severe cystic lung disease [16, 40]. To prevent pneumothoraces, patients should be counseled to avoid scuba diving and smoking [135]. Prior to surgeries, including those for renal cancer, patients should have a pulmonary assessment and avoid excessive intraoperative positive pressure ventilation [54]. Routine lung imaging is not recommended after initial screening [122].

## 10 Prognosis

Following diagnosis of BHD, the cutaneous and extracutaneous manifestations can usually be managed and have a favorable prognosis. Although displeasing, the cutaneous papules of BHD are benign and cosmetic procedures have produced excellent results [125]. Lung cysts may arise in many people with BHD and may be risk factors for spontaneous pneumothoraces but are otherwise not significant on pulmonary function [136]. Good outcomes have been reported for even recurrent, intractable pneumothoraces [137]. BHD-associated tumors are often slow growing [16, 120, 122]. Other renal tumor varieties also have a good prognosis when surgery is performed for tumors of 3 cm or smaller [122, 124].

## 11 Conclusion

BHD is an inherited autosomal-dominant germline mutation in the *FLCN* gene with variable phenotypic dermatologic stigmata as well as lung cysts, spontaneous pneumothorax, and increased risk for renal neoplasia. Dermatologically, BHD presents with a spectrum of distinctive histologically similar harmless papules, of which fibrofolliculomas and trichodiscomas are the most specific and well-reported. The systemic ramifications of having a *FLCN* mutation include renal cancer and pneumothoraces. Focus should be on early diagnosis of BHD to allow prompt management for probands and affected family members.

**Compliance with Ethical Standards**

**Conflict of interest** Yun Tong, Jeremy A. Schneider, Alvin B. Coda, Tissa R. Hata, and Philip R. Cohen have no relevant disclosures or conflicts of interest to report relating to the content of this manuscript.

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