Birt-Hogg-Dubé syndrome. State-of-the-art review with emphasis on pulmonary involvement

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Summary
Background: Birt-Hogg-Dubé syndrome (BHDS) is a rare, inherited autosomal-dominant disorder characterized by the development of cutaneous lesions, renal tumors, pulmonary cysts, and spontaneous pneumothorax. The gene responsible for BHDS is located on the short arm of chromosome 17 (17p11.2) and codes for the protein folliculin, which is believed to be an

Abberivations: BHDS, Birt-Hogg-Dubé syndrome; CT, computed tomography; FLCN, folliculin; HIF-1α, hypoxia-inducible factor 1-alpha; LAM, lymphangioleiomyomatosis; LCH, Langerhans cell histiocytosis; mTOR, mammalian target of rapamycin; TSC, tuberous sclerosis complex.

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Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal-dominant disorder characterized by the development of cutaneous lesions, renal tumors, pulmonary cysts, causing spontaneous pneumothorax. In 1977, Birt, Hogg, and Dubé investigated members of the same family who presented with thyroid cancers. They found that some of them had fibrofollicular skin tumors that occurred in an inherited autosomal dominant pattern [1–3]. Although the familial disorder was later named BHDS, the German dermatologists Hornstein and Knickenberg had reported similar inherited skin tumors 2 years previously [4]. The genetic defect responsible for BHDS has been mapped to a gene on chromosome 17p11.2, which encodes the tumor suppressor protein folliculin (FLCN) [5–7].

Lung cysts have been described in most (77–89%) patients with BHDS, and the estimated incidence of pneumothorax in these patients is 33–38% [2,5–8]. No evidence of neoplasia, inflammation, or fibrosis has been found in association with these lung cysts [9]. Classically described skin findings consist of the triad of hamartomas of the hair follicles (fibrofolliculomas), tumors of the hair disk (trichodiscomas), and skin tags (acrochordons). Renal tumors when present are often multiple and bilateral [1,7,10,11].

BHDS is probably underdiagnosed because of the wide variability of its clinical presentation [12]. This review describes the main clinical, pathological, and imaging aspects of BHDS.

**Epidemiology and genetic aspects**

BHDS is a rare entity, although its precise prevalence is unknown [8,13,14]. Approximately 200 families with pathogenic FLCN mutations have been described in the literature [13]. Mutation-prone regions tend to differ between affected Japanese and Western families, which may partially explain geographic differences in phenotypic presentation [2,15].

The gene responsible for BHDS, located on the short arm of chromosome 17 (17p12q11.2), was first identified in 2001 based on a mapping analysis conducted in large families affected by BHDS. The FLCN gene sequence was identified and named in 2002. It contains 14 exons, 11 of which codify, transcript mRNA and encodes a 579 aminoacid protein (FLCN) [2,7,13,16,17]. FLCN is expressed in a wide variety of tissues, including skin, type-1 pneumocytes in the lungs, and distal nephron in the kidneys. The FLCN protein was found to be over expressed in proliferating epithelial fibrofolliculomas, but its expression was significantly lower in normal skin.
Pathogenesis

The energy-sensing mammalian target of rapamycin (mTOR) pathway has been implicated in the pathogenesis of several hereditary hamartoma syndromes, including BHDS [18]. FLCN is known to interact with the protein FIP1L1 and its homolog, FINP2, which in turn interact with 5’ adenosine monophosphate–activated protein kinase, a key molecule that negatively regulates mTOR activity. Inactivating mutations in this pathway result in dysregulated cell growth and protein synthesis, providing potential insight into the pathogenesis of BHDS [2].

BHDS mutations in exon 9 have been associated with more lung cysts than those in other exons [6]. In addition, the size and volume of the largest lung cyst have been found to be significantly greater in individuals with BHDS mutations in exons 9 and 12 than in those with mutations in other exons [6]. The potential relevance of exon 9 mutations for predisposition to cancer in BHDS has also been proposed [7,16].

Pathology

Although the pathology of renal and cutaneous manifestations of BHDS has been well described, few reports have described the histological characteristics of associated pulmonary cysts [2]. In contrast to the neoplastic process in the skin and kidney, no neoplastic changes have been reported in association with lung involvement [21,26].

By definition, cysts are well-circumscribed usually round spaces with epithelial or fibrous walls of variable thickness. Macroscopically, cysts in BHDS are often elongated and subpleural in distribution, with the total extent of lung involvement being less than 30% [27,28].

Microscopically, they are lined with pneumocytes and partially enveloped by septal and/or pleural interstitial tissue. Alveolar cells lining the inner surface of the cyst show positive immune-staining for epithelial markers and surfactant proteins. They may be attenuated or not easily visible; however, cuboidal cells resembling type II pneumocytes are often observed in the innermost layer [9,17].

The mechanisms of cyst development under the condition of FLCN haploinsufficiency remain poorly understood. If accelerated mTOR signaling directly induces cystic remodeling, downstream molecules such as S6 kinase and hypoxia-inducible factor 1-alpha (HIF-1α), in human BHDS renal tumors. In the lung, cyst-lining cells have shown immunostaining positivity for phospho-mTOR and phospho-S6 ribosomal protein, suggesting that they are under activated conditions [2,13,15,23]. Neoplastic proliferation is absent in cyst-lining cells, the mTOR pathway may be less distinctively deviated in pulmonary cysts than in renal cell cancers [15].

The mechanisms of cyst development under the condition of FLCN haploinsufficiency remain poorly understood. If accelerated mTOR signaling directly induces cystic remodeling, downstream molecules such as S6 ribosomal protein may play a key role in pathogenesis. HIF-1α is a key molecule contributing to aberrant angiogenesis in many types of cancer. Proliferation of blood vessels was noted in the vicinity of pulmonary cysts [15]. Accelerated angiogenic signaling is due in part to increases in HIF-1α, which is known to contribute to aberrant angiogenesis in many types of cancer. The activation of angiogenic signaling contributes to the development of BHDS-associated pulmonary cysts [15].

The involvement of mTOR pathway in the pathogenesis of BHDS is also suggested by the phenotypic similarities of this syndrome to tuberous sclerosis complex (TSC), which is known to be caused by mTOR pathway dysregulation. However, this is not the only signaling pathway implicated in the tumor suppressing action of the FLCN gene [2,15,18,24].

In the past several years, lung cyst pathogenesis has been widely studied in pulmonary cystic diseases, such as lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), and cystic lung light chain deposition disease [25]. Metalloproteinases appear to have an important role in cyst formation [9,25]. These proteins belong to a family of proteolytic enzymes mostly responsible for maintaining extracellular matrix remodeling, but they also affect cell migration, angiogenesis, and pulmonary immunity. FLCN mutations may alter cytokines and proteases, which are important for extracellular matrix integrity. The pulmonary architecture depends on interactions between collagen and elastin fibers in the extracellular matrix, which maintain alveolar wall integrity. The overexpression of metalloproteinases leads to matrix breakdown, tissue destruction, and cystic lesions [9,25].
stasis. Other possible causes of edema include FLCN insufficiency, which may lead to matrix remodeling, and angiogenic factors leading to increased vascular permeability [17].

Pulmonary manifestations

Pulmonary cysts (Fig. 1) and repeated episodes of pneumothorax (Fig. 2) are clinical hallmarks of BHDS. Lung involvement is often the earliest phenotypical manifestation to appear, and pneumothorax may be the only manifestation of the syndrome in some patients [5,17,30]. However, most affected patients are asymptomatic. Older patients and those with more severe lung involvement are more likely to have symptoms, particularly dyspnea and cough [1,18,25].

Cystic lung lesions likely develop in early to mid-adulthood (30–40 years), but have been described in patients ranging in age from 20 to 85 years [2]. A 50-fold increase in risk of pneumothorax has been described in patients with BHDS [7], and correlates inversely with age [5,31]. Cyst size and volume correlate with increased risk of pneumothorax [6]. Although smoking is an important risk factor for primary spontaneous pneumothorax, no association between smoking history and the presence or frequency of pneumothorax has been found in patients with BHDS [7,18,32]. The severity of cutaneous involvement and the presence of kidney tumors do not correlate with the occurrence of pneumothorax [6].

Various other thoracic abnormalities, including pulmonary malignancy, and congenital chest malformation, have been observed in patients with BHDS. However, it remains unclear whether any of these abnormalities is causally related to the disease [2,17,18,33,34].

Cutaneous manifestations

Skin manifestations of BHDS usually appear in the third and fourth decades of life [35,36]. Birt and colleagues [3] described fibrofolliculomas (Fig. 3), trichodiscomas, and acrochordons as the triad of skin lesions characterizing BHDS. Currently, fibrofolliculomas and trichodiscomas are considered to be part of a morphological spectrum. In patients with BHDS, acrochordons may represent a phenotypic variant of fibrofolliculoma; however, they occur in the general population and cannot be used alone for the diagnosis of the syndrome [3,17–19,37].

Clinically, these lesions present as multiple, asymptomatic, firm, whitish papules with 2–4-mm diameters and a dome-shaped appearance, located mainly in the nose, forehead, and cheeks [5,8,10,12]. Other skin lesions less frequently seen in BHDS include lipomas, angiolipomas, mucous fibromas, melanoma, and collagenoma [16,19]. The presence of facial angiofibromas has occasionally been reported, although these lesions are more typically associated with TSC [6,18,35,38]. Specific dermatological manifestations may be helpful in distinguishing inheritable skin disorders which also include TSC, LCH, Marfan’s syndrome and Ehlers-Danlos syndrome [6].

Figure 1 A 38-year-old woman with Birt-Hogg-Dubé syndrome. High-resolution computed tomography at the level of the lower lobes (A) and coronal reconstruction (B) show thin-walled, round and ovoid pulmonary cysts predominating in the lower-medial zones of both lungs.

Figure 2 A 54-year-old woman with Birt-Hogg-Dubé syndrome. Axial computed tomography with the lung window at the level of the lower lobes shows right pneumothorax. In addition, small round and ovoid cysts are visible in the pulmonary parenchyma.

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Renal manifestations

The most serious complication of BHDS is renal cancer (Fig. 4). The prevalence of renal tumors in these patients is 23–34%, with a sevenfold increased risk of malignancy when compared to the general population. Histological subtypes include chromophobe oncocytomas (50%), chromophobe carcinomas (34%), clear cell carcinomas (9%), oncocytomas (5%), and papillary renal cell cancers (2%) [1,5,7,8,14,26]. Most renal tumors are bilateral, multifocal, and slow growing [11,13,19,24]. Benign renal cysts have also been documented in patients with BHDS, but the exact prevalence in comparison to the general population is currently unknown [18,19,24]. Renal angiomyolipoma occasionally occurs in association with BHDS, but it is more frequent in patients with TSC [1,5,15,24].

Other clinical findings

Several other lesions have been reported in BHDS including benign entities such as multinodular goiter, parathyroid adenoma, parotid-gland adenoma and oncocytoma, colorectal polyp and adenoma, neural tissue tumor, tricho-blastoma, connective tissue nevus, focal cutaneous mucinosis and cutaneous leiomyoma [5,10,11,18]. Malignant tumors include breast cancer, colorectal cancer, sarcoma of the leg, tonsillar cancer, basal and squamous-cell skin cancer, dermatofibrosarcoma protuberans, and cutaneous leiomyosarcoma [5,7,10,11,18]. Other abnormalities observed in patients with BHDS include flocked choriot- etinopathy, bullous emphysema, and internal carotid artery aplasia [11,18]. However, their causal association with BHDS has not been clinically validated [16,18].

Pulmonary imaging findings

On computed tomography (CT), pulmonary cysts generally manifest as a rounded lesion with well-defined interface with normal lung parenchyma, usually containing air, or less commonly fluid. Cysts have variable wall thickness, usually <2 mm [28,39].

Certain CT imaging characteristics may suggest the diagnosis of BHDS-related cystic lung disease. In these patients, cyst location differs from the typical apical location of smoking-related emphysema and bullae/blebs seen in primary spontaneous pneumothorax [2]. In BHDS, cysts are typically located in the lower lung regions, distributed bilaterally, and intimately related to interlobular septa and/or visceral pleura, pulmonary arteries, and veins [8,18,29]. The number of cysts is quite variable [2,6,40] and their size range from a few millimeters to >2 cm although small (<1 cm) cysts are most commonly seen. The...
morphology of lung cysts varies within and amongst patients, ranging from round to oval, lentiform, and lobulated/multiseptated. Cyst walls tend to be perceptible, thin, and uniform [8]. Tobino et al. [40] reported that most pulmonary cysts in patients with BHDS were irregularly shaped and that their extent did not change over time. Cyst size, morphology, and distribution patterns seem to be inherited within affected families and differ among different family groups [41,42].

**Pulmonary function tests**

Despite the presence of multiple lung cysts, pulmonary function tests are usually normal or only mildly abnormal in patients with BHDS [5,6,18]. Nevertheless, diffusion capacity for carbon monoxide (adjusted for alveolar volume) was found to be mildly decreased, and absolute forced expiratory volume in 1 s was inversely correlated with cyst area measured by CT [2].

**Diagnosis**

The diagnosis of BHDS should be suspected in young patients presenting with spontaneous pneumothorax, especially those with personal or family history of pneumothorax, skin lesions, or renal tumors [2,5,20]. In the system proposed by Menko et al. [18], the diagnosis of BHDS should be based on fulfillment of one major criterion (at least five adult-onset fibrofolliculomas with histological confirmation of at least one; pathogenic FLCN germline mutation) or two minor criteria [multiple bilateral, basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax; early-onset (<50 years of age), multifocal, or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology; first-degree relative with BHDS]. However, BHDS should be considered even in patients who do not fulfill the diagnostic criteria but have an underlying FLCN mutation [2,17,18,28].

New diagnostic criteria based mainly on chest CT characteristics of pulmonary cysts have been recently proposed [2] (Table 1).

**Imaging criteria for differential diagnosis**

The main differential diagnosis of BHDS include cystic lung diseases, particularly LAM, lymphocytic interstitial pneumonia (LIP), LCH and *Pneumocystis jiroveci* pneumonia [1,2,8]. The distribution of cysts along with ancillary findings on imaging studies may be helpful in distinguishing these entities [6,27]. Diseases such as Marfan syndrome, homocystinuria, Ehler-Danlos syndrome, and alpha-one antitrypsin deficiency can present with familial histories of spontaneous pneumothorax and should also be considered in the differential diagnosis of BHDS [2,6,8,21].

The presence of cysts in the setting of an autoimmune disease, particularly Sjögren syndrome, is very suggestive of LIP, which presents on CT as ground-glass opacities, poorly defined centrilobular nodules, and thin-walled cysts with a basal predominance. Although cysts may vary in size, they are often <30 mm in diameter and sparse. Additional CT findings reported in LIP include peribronchovascular thickening, interlobular septal thickening, subpleural nodules, lymphadenopathy, and areas of consolidation [27,43]. Pulmonary LCH is a smoking-related lung disease that includes bronchiolocentric stellate interstitial nodules. The nodules may subsequently cavitate and form thick- and thin-walled cysts. Frequently, nodules and cysts are seen simultaneously. The cysts are often irregular, bilobed or bizarrely shaped. *P. jiroveci* pneumonia is seen in patients with immunosuppression with acute or subacute respiratory symptoms and typically presents on imaging studies with bilateral ground-glass opacities, occasionally with consolidation and nodules. Cystic lesions, or pneumatoceles, occur in approximately 30% of the cases, are typically transient and have upper zone predominance. Spontaneous pneumothorax can also occur [8,27].

Amongst the cystic lung diseases, LAM is the most difficult to differentiate from BHDS, especially when associated with TSC with renal and cutaneous involvement [1,2]. Similar to BHDS, TSC has a wide clinical spectrum. Patients with TSC usually show angiomylipomas (70–90%), angiofibromas, hypopigmented macules, shagreen patch, and/or periungual fibromas [6]. Pulmonary LAM is a rare progressive disease that predominantly affects women of childbearing age. Men may be affected in the setting of underlying TSC. Globally, LAM associated with TSC is 5- to 10-fold more common than sporadic LAM. Clinical manifestations include shortness of breath, cough, chest pain, chylous pleural effusions, hemoptysis, and occasionally respiratory failure although

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### Table 1 Proposed diagnostic criteria for BHD [2].

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<thead>
<tr>
<th>Definite pulmonary BHD</th>
<th>Compatible or characteristic HRTC.</th>
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<tr>
<td>1. Characteristic or compatible lung HRCT and skin biopsy positive for fibrofolliculoma or trichodiscoma</td>
<td>a. Family or personal history of renal tumors</td>
</tr>
<tr>
<td>2. Characteristic or compatible lung HRCT and confirmed family history of BHD in first or second degree family member</td>
<td>b. Skin angiofibroma</td>
</tr>
<tr>
<td>3. Characteristic or compatible HRCT and tissue confirmation of renal chromophobe adenoma or oncocyotma</td>
<td>c. Renal angiomylipoma</td>
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</table>

**Probable pulmonary BHD**

1. Characteristic HRCT, exclusion of TSC and LAM, and personal or family history of pneumothorax
2. Compatible HRCT, exclusion of TSC and LAM, and any of the following:
   - a. Family or personal history of renal tumors
   - b. Skin angiofibroma
   - c. Renal angiomylipoma

**Possible pulmonary BHD**

Compatible or characteristic HRCT.

a. Characteristic lung HRCT findings: Multiple thin-walled round, elliptical or lentiform well-defined air-filled cysts, without internal structure, in a basilar, medial and subpleural predominant distribution, with preserved or increased lung volume, and no other significant pulmonary involvement (specifically no interstitial lung disease).

b. Compatible HRCT findings: Thin walled cysts without the more typical elliptical shape or subpleural distribution.
asymptomatic cases may occur. Spontaneous or recurrent pneumothorax may be the presenting finding in up to 50% of patients with LAM [44]. It has been suggested that LAM associated with TSC most closely mimics BHDS on radiological exams. Cysts in BHDS and LAM are thin walled, but those associated with LAM are smaller and more circular, homogeneous, and equally distributed. The intervening lung parenchyma is typically normal in LAM although small centrilobular nodules, septal thickening, and focal ground-glass opacities have been reported [2,8,24,27].

**Conflict of interest statement**

The authors have no conflict of interest.

**References**


