Cystic Lung Disease in Genetic Syndromes with Deficient Tumor Suppressor Gene Function

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Keywords

Lymphangioleiomyomatosis · Angiomyolipoma · Tuberous sclerosis · Sirolimus · Vascular endothelial growth factor D · Birt-Hogg-Dubé syndrome · Tumor suppressor genes · FLCN protein, human · MTOR protein, human

Abstract

Cystic lung diseases constitute a distinct group of rare lung disorders, among which two result from monogenic defects affecting tumor suppressor genes: lymphangioleiomyomatosis, either sporadic or associated with tuberous sclerosis complex, and Birt-Hogg-Dubé syndrome. These disorders have similarities in their clinical expression, including occurrence in young adults, multiple pulmonary cysts, recurrent pneumothorax, skin hamartomas, and renal tumors. However, they markedly differ in their gender distribution, pathogenesis, disease course, and prognosis. Our knowledge on these two rare conditions is rapidly expanding. Management of lymphangioleiomyomatosis has substantially improved in the past decade with the understanding of its pathogenic mechanisms, the discovery of an effective therapy, and development of large cohorts and international guidelines. Birt-Hogg-Dubé syndrome has been described more recently and still awaits deeper understanding of its pathophysiology.

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Introduction

The increasing use of chest high-resolution computed tomography (HRCT) has led to better recognition of an imaging pattern characterized by multiple well-delimited hyperlucent zones of the lung parenchyma called pulmonary cysts. Cystic lung diseases now constitute a distinct group of rare lung disorders, with an expanding differential diagnosis. Among these disorders, two are characterized by genetic defects affecting tumor suppressor genes: lymphangioleiomyomatosis (LAM), either sporadic or associated with tuberous sclerosis complex (TSC), and Birt-Hogg-Dubé syndrome (BHD). This review aims at providing the clinician with the main characteristics of these two rare diseases, which share some similar features in their clinical expression, but markedly differ in many other aspects.

Previous articles in this series: 1. Lazor R, Nicod LP: The lung in rare systemic diseases. *Respiration* 2017;94:1. 2. Tran C, Barbey F, Lazor R, Bonafé L: Pulmonary involvement in adult patients with inborn errors of metabolism. *Respiration* 2017;94:2–13. 3. Borie R, Wislez M, Antoine M, Cadranet J: Lymphoproliferative disorders of the lung. *Respiration* 2017;94:157–175. 4. Dupuis-Girod S, Cottin V, Shovlin CL: The lung in hereditary hemorrhagic telangiectasia. *Respiration* 2017;94:315–330. 5. Uzunhan Y, Jeny F, Kambouchner M, Didier M, Bouvry D, Nunes H, Bernaudin J-F, Valeyre D: The lung in dys-regulated states of humoral immunity. *Respiration* 2017;94:389–404.

Fig. 1. **a** Macroscopic view of an explanted lung with lymphangioleiomyomatosis (LAM), showing multiple cysts diffusely distributed through the parenchyma. **b** Surgical lung biopsy image showing several clusters of LAM cells (arrows) located at the edge of a pulmonary cyst (asterisk). **c** Close view of a pulmonary LAM cell cluster (courtesy of Dr. I. Letovanec, Institute of Pathology, Lausanne University Hospital, Lausanne, Switzerland).

LAM and Tuberous Sclerosis

What Is LAM?

LAM is a rare multisystemic disease occurring almost exclusively in women of childbearing age, either sporadically (S-LAM) or in association with TSC (TSC-LAM). The prevalence of LAM ranges from 2.6 to 7.8 per million women, and the incidence from 0.2 to 0.4 per million women per year [1–3]. In the lungs, LAM is characterized by progressive lung tissue infiltration by atypical smooth muscle-like cells (LAM cells), leading to cystic destruction of the lung parenchyma (Fig. 1a), loss of respiratory function, increasing dyspnea, and recurrent pneumothorax. Extrathoracic manifestations include benign kidney tumors called angiomyolipomas (AML), pleural and peritoneal chylous effusions, thoracoabdominal lymphadenopathy, and chylous abdominal masses called lymphangiomas. Besides these manifestations, which occur in both S-LAM and TSC-LAM, patients with tuberous sclerosis present with additional involvement of various organs.

What Is Tuberous Sclerosis?

TSC is a genetic autosomal dominant disorder characterized by benign tumors in multiple organs including the skin, brain, retina, kidney, heart, and lung [4–6]. The prevalence of TSC is around 1/15,000. Although TSC is an autosomal dominant disease, most patients have de novo germline mutations and no family history of TSC. The clinical phenotype is highly variable: some patients develop severe neurologic conditions such as seizures or cognitive disability in early childhood, whereas others have only minimal morbidity, which may remain unnoticed until adulthood. Thus, adult patients with TSC-LAM may present with only subtle features of TSC which have been overlooked in childhood, or which appeared only in adulthood [7]. These patients are nevertheless at risk of severe manifestations of TSC, and may transmit the disease to their offspring [7].

Clinical Picture and Natural History of LAM

Most patients with LAM present with lung disease, manifesting mainly as progressive dyspnea and recurrent pneumothorax. A minority of patients present initially

with symptomatic AML or lymphangiomas, chylous ascites, or chylothorax. LAM may also be discovered incidentally on chest imaging performed for another reason [8].

Lung function in LAM at presentation is mainly characterized by a reduced carbon monoxide transfer factor (DLCO) and an obstructive ventilatory defect, found in up to 80 and 50% of cases at presentation, respectively [1, 9, 10]. Lung function declines at an accelerated rate in LAM as compared to normal subjects. The mean FEV₁ loss ranges from 70 to 120 mL/year [9, 11] but is highly variable and cannot be confidently predicted at diagnosis. Ten years after the onset of symptoms, half of patients have mMRC grade 3 dyspnea [12]. In one recent large study, the 10-year transplant-free survival rate was 86%, and the median transplant-free survival was 29 years from first symptoms and 23 years from diagnosis [13]. Pulmonary hypertension in LAM is rare and of mild severity, and likely results from loss of lung parenchyma and hypoxia rather than vascular disease [11, 14, 15].

When screened by HRCT, the prevalence of pulmonary LAM in TSC appears to increase with age, from 27% in women under 21 years to 81% in women over 40 years [16–19]. At diagnosis of LAM, patients with TSC-LAM have better lung function than patients with S-LAM, although this probably results from earlier diagnosis [10, 20]. In one study, more than half of the patients with TSC-LAM became symptomatic during the disease course, and 13% died [17]. The average lung functional decline in TSC-LAM is similar to that in S-LAM [21]. Occurrence of LAM in men has exceptionally been reported [22, 23], although the presence of a small number of cysts at the lung bases has been described in 13–38% of men with TSC [24, 25].

Pneumothoraces occur in more than half of LAM patients during the disease course, and frequently recur. Chylothoraces occur in 10–20% of cases [1, 10]. AML occur in about 50% of patients with S-LAM, and in up to 80% of patients with TSC-LAM, and they are more frequently multiple and bilateral in TSC-LAM [10]. These tumors tend to grow slowly without symptoms but may undergo spontaneous rupture and cause life-threatening bleeding. The risk of bleeding increases up to 50% when the tumor size reaches more than 4 cm and/or if vascular aneurysms greater than 5 mm are present. AML are more likely to bleed in TSC-LAM than in S-LAM [20]. Meningiomas are found in up to 2% of patients with LAM, i.e., more often than in the general population [26, 27].

Histopathology of LAM

Despite its benign histological appearance, LAM is currently seen as a low-grade neoplasm classified among

perivascular epithelioid cell tumors, a group of mesenchymal tumors composed of epithelioid or spindle cells coexpressing smooth muscle and melanocytic markers typically arranged around vessels [28, 29]. In the lung, LAM cells proliferate around lymphatic vessels, veins, and bronchioles, and form small clusters located in the edge of pulmonary cysts (Fig. 1b, c). LAM lesions contain spindle cells located in the center of the nodular lesions, and epithelioid cells located on the periphery. Both cell types express the smooth muscle markers α -actin, vimentin, and desmin. Epithelioid cells also express the melanocytic marker gp100, which reacts with the human melanin black antibody HMB-45, and spindle cells express the proliferation cell nuclear antigen [30]. LAM cells also express estrogen and progesterone receptors [30], matrix metalloproteinases (MMP) [31], vascular endothelial growth factor receptor 3 [32–35], β -catenin and E-cadherin [36, 37], CD44v6, an adhesion molecule associated with metastatic behavior [38], and chemokines and chemokine receptors involved in homing of LAM cells to specific organs [39, 40]. LAM nodules contain cleft-like spaces lined by lymphatic endothelial cells, which express lymphangiogenic factors and their receptors [41].

AML are benign mixed mesenchymal tumors of the kidney consisting of smooth muscle-like spindle-shaped LAM cells, adipocytes, and dystrophic blood vessels. Lymphangiomas are dilated lymphatic vessels forming chyle-filled masses located in the pelvis, retroperitoneum, and posterior mediastinum. They are caused by obstruction to chyle flow due to LAM cell proliferation in the walls of lymphatic vessels.

Imaging of LAM

On chest HRCT, LAM is characterized by multiple thin-walled, round, well-defined air-filled cysts with preserved or increased lung volumes and no other significant pulmonary involvement. The cysts are usually small with very thin or no visible walls, and evenly distributed throughout all lung fields without any zonal predominance (Fig. 2). Although LAM features appear characteristic on imaging, several other diseases may present with multiple cysts on HRCT (Table 1) [42], including BHD [43–44], pulmonary Langerhans cell histiocytosis (PLCH) [45], and light chain deposition disease [46].

In men and women with TSC, with or without pulmonary LAM, multiple ground-glass nodules predominating in the upper lung zones may be visible. They represent hamartomatous changes called multifocal micronodular pneumocyte hyperplasia (Fig. 3a) [47]. Multifocal mi-

Fig. 2. **a** High-resolution computed tomography (HRCT) image of early pulmonary lymphangioleiomyomatosis (LAM): a few small, round, well-delimited cysts disseminated in an otherwise normal lung parenchyma. **b** HRCT image of more advanced LAM: diffuse parenchymal replacement by numerous cystic spaces. **c** HRCT image of severe LAM, associated with right chylothorax.

Table 1. Main differential diagnoses of cystic lung diseases

<i>Multiple cysts as the main feature</i>	
Lymphangioleiomyomatosis	~100%
Pulmonary Langerhans cell histiocytosis	~100%
Birt-Hogg-Dubé syndrome; familial pneumothorax	~80%
Non-amyloid immunoglobulin deposition disease	<5%
Metastases	rare
Other (e.g., Niemann-Pick disease, neurofibromatosis)	
<i>Multiple cysts in interstitial lung disease</i>	
Lymphocytic interstitial pneumonia	~60%
Hypersensitivity pneumonitis	~13%
Sjögren syndrome	~20%
Desquamative interstitial pneumonia	~40%

Percentages reflect the approximate frequency of multiple lung cysts in each disease, when available.

cronodular pneumocyte hyperplasia is not a feature of S-LAM.

AML present on imaging as heterogeneous lesions containing fat (Fig. 3b). Lymphangiomas appear as well-circumscribed, loculated masses of variable size with an outer wall and fluid-filled central parts [48, 49] (Fig. 3c). Their size tends to be smaller in the morning after fasting and to increase during the day after meals, which increase lymph flow from the digestive tract [50, 51].

Pathogenesis of LAM

Genetic Events

The genes responsible for TSC have been characterized in the 1990s [52, 53], and subsequent work has demonstrated the role of TSC mutations in the pathogenesis of S-LAM [34, 35]. LAM cells in patients with S-LAM and TSC-LAM bear mutations in the tuberous sclerosis genes *TSC1* and more frequently *TSC2*, respectively coding for the proteins hamartin and tuberin. Hamartin and tuberin form an intracellular dimer which inhibits the mechanistic target of rapamycin (mTOR), a kinase playing a central role in the regulation of cell growth and proliferation.

S-LAM is caused by mutations in the *TSC2* gene [34, 35]. TSC is caused by mutations in the *TSC1* or *TSC2* gene, the latter usually resulting in a more severe clinical phenotype [54]. TSC mutations presumably occur through two consecutive genetic hits [55]. In patients with TSC-LAM, a germline mutation of a *TSC* gene is present in one allele, and a second sporadic mutation occurs after conception in the second allele of the same gene, resulting in loss of heterozygosity of the normal allele, and loss of the corresponding protein product hamartin or tuberin. In patients with S-LAM, no germline

Fig. 3. **a** Multifocal micronodular pneumocyte hyperplasia in tuberous sclerosis. Multiple, rounded, ground-glass opacities predominating in the right upper lobe (arrows). **b** Single angiomyolipoma of the right kidney: heterogeneous mass with a fatty component of low density (arrow). **c** Abdominal lymphangioma in tuberous sclerosis, presenting as loculated mass with a thin outer wall and low-density fluid-filled central part (arrows). **d** Dense sclerotic lesions of the pelvic bone in tuberous sclerosis (arrows).

mutation has been detected so far, and both genetic hits are thought to occur consecutively in somatic cells after conception [34, 35].

Cellular Events

The role of tuberin as a regulator of cell growth was first identified in the fly *Drosophila melanogaster* [56]. In the physiologic state, the hamartin-tuberin complex constitutes a critical regulatory point which integrates signals on cell nutritional and energetic status, amino acids, growth factors, and stress, and modulates the activity of mTOR through the GTPase Ras homolog enriched in brain. mTOR is constituted of two distinct complexes: mTORC1, which controls glucose uptake,

lipid metabolism, protein translation, and nucleotide synthesis and is sensitive to inhibition by rapamycin (sirolimus), and mTORC2, which regulates cell proliferation, assembly of the actin cytoskeleton, and cell survival, and is activated by insulin and insensitive to sirolimus. The loss of upstream negative regulation of mTOR due to a defective hamartin-tuberin complex induced by *TSC* gene mutations leads to constitutive overactivation of mTOR. Activation of mTOR leads to metabolic reprogramming, resulting in increased glucose uptake, de novo synthesis of proteins, lipids, and nucleotides, and uncontrolled cell growth, proliferation, motility, and survival [57, 58]. Interestingly, the amino acid-induced activation of mTOR is also regulated by the

tumor suppressor protein folliculin (FLCN), mutations of which cause BHD [59, 60].

Observations that LAM occurs almost exclusively in women of childbearing age, may worsen during pregnancy and estrogen therapy [59, 61], and stabilize after menopause [61, 62], as well as the presence of hormonal receptors on LAM cells, suggest that LAM is a hormone-sensitive disorder. Indeed, it has been shown that estrogens promote the growth of human AML cells [63], the invasiveness of human LAM cells in vitro [64], and pulmonary metastases of tuberin-null cells in a mice model of LAM [65].

Dissemination of LAM Cells

The source organ and the normal histological counterpart of LAM cells are currently unknown. One study suggested that LAM cells originate from uterine leiomyomas, as clusters of LAM cells were found in 90% of hysterectomy specimens from LAM patients but not in control subjects [66]. However, only 40% of patients with LAM have uterine leiomyomas [1]. Other putative sources of LAM cells are renal AML, axial lymphatics [67], and perivascular epithelioid cell tumors [66].

Several observations have led researchers to consider that the involvement of multiple organs in LAM is the result of metastatic spread of LAM cells. In rare cases of LAM recurrence after lung transplantation, LAM cells identified in the lung allograft were found to originate from the recipient [68, 69]. In over 90% of LAM patients, LAM cells can be identified in bronchoalveolar lavage fluid, blood, chylous effusions, or urine, usually consisting of one cell clone, although multiple clones have been found in up to 25% of cases [70–72]. These findings support the hypothesis of a metastatic mechanism of LAM cell dissemination. LAM cells are thought to circulate through lymphatics in clusters covered by a layer of endothelial cells, to enter the venous system, and to follow the bloodstream to reach the lung microvasculature [57].

Pulmonary Events

The mechanisms leading to cystic destruction of the lung parenchyma are incompletely understood. Development of cystic spaces is associated with proliferation of type II pneumocytes and destruction of elastic and collagen fibers in the walls of lung cysts. The latter has been attributed to the proteolytic action of MMP, which are overexpressed in LAM nodules [64, 73]. Cathepsin K, a collagenase and elastase regulated by mTOR, is also strongly expressed in LAM cells, and may contribute to the proteolytic environment leading to cystic lung de-

struction. Since LAM nodules contain lymphatic vessels and express lymphangiogenic factors and their receptors, it has also been suggested that lung cysts may represent a form of disorganized lymphangiogenesis [57].

Diagnosis of LAM

Imaging

Suspicion of LAM usually starts with the finding of multiple cysts on HRCT in a woman. However, even if the finding is typical, HRCT alone is insufficient to establish a firm diagnosis of LAM, and additional features are required. ERS guidelines have proposed a set of imaging and clinical criteria for diagnosing LAM [74] (Table 2).

Abdominopelvic CT may identify features of LAM or TSC, including AML, lymphadenopathy, lymphangio-mas, or chylous ascites. AML can usually be diagnosed by imaging only if the fatty component is well visible as a low-attenuation opacity associated with a heterogeneous mass (Fig. 3b). A study on thoracoabdominal CT in patients with S-LAM and TSC-LAM using bone window settings has shown that patients with TSC-LAM, in contrast to those with S-LAM, frequently present with multiple sclerotic bone lesions [75] (Fig. 3d). The presence of more than 4 of such lesions has been suggested to differentiate TSC-LAM from S-LAM with 89% sensitivity and 97% specificity [75].

Clinical Search for TSC Features

TSC should be carefully looked for in all patients with newly diagnosed LAM. The diagnosis of TSC is based on international criteria [5], and requires at least a detailed examination of the skin, eyes, and nervous system, as well as brain imaging.

Vascular Endothelial Growth Factor D

VEGF-D is a major angiogenic growth factor produced especially by malignant cells which promotes the formation of lymphatics and spread of tumor cells to lymph nodes. LAM cells express the lymphangiogenic factors VEGF-C and VEGF-D and their receptors VEGFR-2 and VEGFR-3 [67]. In TSC2-deficient cells in vitro, VEGF secretion is markedly elevated and this effect is only partly reverted by sirolimus, suggesting that tuberin regulates VEGF through both mTOR-dependent and mTOR-independent pathways [76]. Serum VEGF-D is increased in 70% of patients with LAM [32, 33], but not in patients with other cystic lung diseases, such as PLCH, emphysema, Sjögren syndrome, and BHD, as well as in healthy controls [77, 78]. A VEGF-D level above 800 pg/mL identified LAM among patients with various cystic

lung diseases with 73% sensitivity and 100% specificity [78]. In one retrospective study, the use of VEGF-D allowed reducing by 10% the need for surgical lung biopsy (SLB) to achieve a definite diagnosis of LAM [79]. Based on these data, ATS/JRS guidelines recommend using VEGF-D testing for the noninvasive diagnosis of LAM in patients with characteristic HRCT but no other extrathoracic features [19].

Biopsy

SLB with immunostaining for smooth muscle actin and HMB-45 had long been the standard method for LAM diagnosis, until its characteristic appearance on HRCT was recognized. Currently, the diagnosis of LAM can in most cases be confidently made according to clinical and imaging criteria [74] and VEGF-D testing [19], and SLB is less frequently needed. Recent data suggest that transbronchial biopsy can be safely performed in LAM with a diagnostic yield of 40–60% [80–82], and may thus constitute a less invasive alternative to SLB. The use of cryobiopsy has been reported in one case [83]. Tissue is sometimes obtained from other locations, such as abdominopelvic lesions.

Diagnostic Strategy

A stepwise approach is recommended to establish a confident diagnosis in the least invasive manner. A clinical search for TSC and thoracoabdominal imaging should be the initial steps, followed by VEGF-D testing. Transbronchial biopsy or SLB should be restricted to patients with LAM features on HRCT but with no extrathoracic findings supporting the diagnosis and serum VEGF-D below 800 pg/mL. In patients with typical HRCT findings, no symptoms, and near-normal lung function, a definite diagnosis may not be required immediately, and regular follow-up of lung function may initially be sufficient. However, if sirolimus treatment is considered, a definite diagnosis should be obtained.

Management

Initial Assessment and Follow-Up

Complete lung function testing should be performed at diagnosis. Follow-up is recommended every 3–6 months during the first year or if disease progression is observed, and every 6–12 months if the disease appears stable [74]. The follow-up of patients with TSC-LAM should be the same as for S-LAM.

Besides its diagnostic value, VEGF-D may provide additional prognostic information on disease severity, as higher serum VEGF-D levels were correlated with lower

Table 2. Diagnostic criteria for LAM according to the ERS international guidelines [74]

Definite LAM	1. Characteristic ^a or compatible ^a lung HRCT and lung biopsy fitting the pathological criteria for LAM OR 2. Characteristic ^a lung HRCT and any of the following: – angiomyolipoma (kidney) ^b – thoracic or abdominal chylous effusion ^c – lymphangioma ^d or lymph node involved by LAM ^d – definite or probable TSC ^e
Probable LAM	1. Characteristic ^a HRCT and compatible clinical history OR 2. Compatible ^a HRCT and any of the following: – angiomyolipoma (kidney) ^b – thoracic or abdominal chylous effusion ^c
Possible LAM	Characteristic ^a or compatible ^a HRCT

Comments: (1) LAM is considered to be associated with TSC when definite or probable TSC is present. Otherwise LAM is considered sporadic. (2) The diagnosis of LAM defined above is only for women. LAM is most exceptional in men without TSC and exceptional in men with TSC. In these, a diagnosis requires characteristic or compatible HRCT and typical pathological features. (3) The diagnosis of LAM requires the exclusion of other causes of cystic lung disease. A complete diagnostic workup for these alternative causes is necessary in patients with probable/possible LAM. LAM, lymphangioleiomyomatosis; HRCT, high-resolution computed tomography; TSC, tuberous sclerosis complex. ^a Characteristic HRCT: multiple thin-walled, round, well-defined air-filled cysts with a preserved or increased lung volume with no other significant pulmonary involvement (except multifocal micronodular pneumocyte hyperplasia in patients with TSC); compatible HRCT: the same as above, but with only few (2–10) cysts. ^b Diagnosed by CT features and/or histopathology. ^c Based on visual and/or biochemical characteristics. ^d Based on histopathology. ^e See Northrup and Krueger [5]. ^f Pneumothorax (multiple/bilateral) and/or altered lung function as in LAM.

FEV₁/FVC and DLCO/VA ratios [32], more severe disease at imaging [16], and faster lung functional decline [18, 84]. VEGF-D also appears more elevated in patients with lymphatic disease and chylous effusions than in those with only cystic lung disease or AML [16, 85].

General Measures and Patient Information

Nonspecific therapeutic measures include inhaled bronchodilators if airflow obstruction is present, smoking cessation, influenza and pneumococcal vaccination,

and pulmonary rehabilitation [74, 86]. About 25% of patients have a significant response to bronchodilators [11, 87]. Osteopenia is common in LAM [88], and periodic evaluation of bone mineral density and treatment of osteoporosis are recommended [74].

LAM patients should be informed of the high risk of pneumothorax, and advised to consult a physician if they develop sudden shortness of breath and/or chest pain [74]. A 2% incidence of flight-associated pneumothorax has been reported in LAM [89, 90]. Recommendations on this issue can be found elsewhere [74]. Avoidance of estrogens is recommended, including combined contraceptive pills and hormone replacement therapy. The preferred contraceptive methods include progesterone-based oral contraceptives or drug-eluting intrauterine devices. Retrospective series suggest that pregnancy may increase the incidence of pneumothorax and chylothorax, accelerate lung functional decline, and increase the risk of AML bleeding [1, 2, 91]. LAM patients with mild disease who want to become pregnant should be informed of the increased risk of complications [74], and it may be appropriate to discourage those with severe disease from becoming pregnant. Patients with TSC should receive genetic counselling prior to conception.

Patients with AML should be instructed to recognize symptoms of bleeding such as abdominal or flank pain, hematuria, a palpable abdominal mass, or shock, and be advised to request urgent medical attention if such symptoms occur [74]. Patients should be informed about patient associations and support groups.

Management of Pneumothorax

Pneumothorax occurs in two-thirds of patients during the disease course and is highly recurrent. The relapse rate is reduced from 66% after conservative treatment to 27–32% after pleurodesis ($p < 0.01$) [92]. Pleurodesis should be performed after the first pneumothorax, preferably by pleural abrasion. A new technique of total pleural covering could further reduce the relapse rate [93].

Management of Parenchymal Lung Disease

The discovery of the role of mTOR activation in LAM pathogenesis – and the availability of sirolimus (rapamycin), an mTOR inhibitor used for renal transplantation – has allowed rapid therapeutic advances. The beneficial effect of sirolimus on lung function in LAM has been demonstrated in observational studies [85, 94–96] and a randomized controlled trial [97]. In the latter study, 89 patients were randomized to receive sirolimus or placebo during 12 months, followed by an observation period of

12 months without treatment. While a decline in FEV₁ was observed under placebo, sirolimus provided stabilization of FEV₁, with a statistically significant difference of 153 mL between groups [97]. During the 12-month follow-up after sirolimus discontinuation, FEV₁ declined at the same rate in both groups. The main adverse events were mouth ulcers, diarrhea, nausea, increased blood cholesterol levels, skin rash, and swelling of the extremities [97]. This study showed that sirolimus stabilizes lung function in LAM, but that continuous therapy is needed. Long-term observational studies showed that the efficacy of sirolimus is maintained over several years [85, 95, 98, 99]. One small series suggested that a low dose of sirolimus (1 mg/day) resulting in serum levels below 5 ng/mL may be sufficient to stabilize lung function [100]. Everolimus, an analog of sirolimus, also stabilized lung function in one observational study [101]. International guidelines now recommend that sirolimus be introduced in LAM patients if their lung function is abnormal (FEV₁ <70% predicted) or declining (an FEV₁ loss >90 mL/year over 6–18 months has been proposed as a threshold) [19].

Hormonal treatments (including oophorectomy, progesterone, antiestrogen, and gonadotropin-releasing hormone) have been largely used in LAM patients, but inconsistent results have been reported [62, 102], and no randomized trial is available. These therapies are no longer recommended [19]. Doxycycline, an inhibitor of MMP, was studied after a case report had suggested its efficacy in improving lung function [103], but no benefit was observed in one small randomized trial [104], and this treatment is not recommended [19]. Therapeutic strategies under investigation include autophagy inhibition by hydroxychloroquine [105] and reduction of estrogen synthesis by letrozole [106].

Lung transplantation is an effective therapy in advanced LAM [107–111]. The posttransplant survival with LAM is similar or even better than with other indications. Recurrence of LAM in the transplanted lung has been reported in 4–7% of cases, but this is usually an incidental finding which does not affect survival [107, 109–111]. Seventy to 90% of LAM transplant candidates have a history of previous pleurodesis, and this intervention is associated with an increased technical difficulty of transplantation and a higher risk of perioperative bleeding [107, 109–111]. However, previous pleurodesis does not constitute a contraindication to transplantation. As comorbidities occur in TSC, patients with TSC-LAM should have a careful multidisciplinary pretransplant evaluation, but TSC is not a contraindication to transplantation. Sirolimus is contraindicated immediately after transplan-

tation as it may induce dehiscence of bronchial sutures [112, 113], but it has been used at a later stage to manage LAM-specific complications [114–117]. Whether sirolimus should be stopped when patients are listed for transplantation to avoid being on therapy during the perioperative period is currently unclear.

Management of Chylous Effusions

Chylothorax of variable severity occurs in 10–20% of LAM patients, including postoperatively after transplantation. Observation or thoracentesis may be sufficient for small effusions, but large and recurrent effusions require therapy. Various strategies have been attempted, including pleurodesis, thoracic duct ligation or vaso-occlusion, pleuroperitoneal shunt, and fat-free diet. However, demonstration of the efficacy of sirolimus for chylous effusions has strongly modified the therapeutic approach [95, 100], and sirolimus is now considered the first-line therapy for chylous manifestations in LAM [19]. A response may, however, take several months to develop.

Management of AML

Screening for AML is recommended at diagnosis of LAM, and AML should be followed by imaging (preferably magnetic resonance imaging [MRI]) on a yearly basis. AML larger than 4 cm or with vascular aneurysms greater than 5 mm should be preventively treated to avoid hemorrhagic complications. Treatment of AML with mTOR inhibitors has been examined in open-label studies [94, 118, 119] and a randomized controlled trial [120]. Sirolimus or everolimus decreased the mean AML size by 26% to 53%, and about 40% of patients had a volume reduction greater than 50%. In a follow-up study, the benefit was maintained after 4 years, and no AML bleeding was observed [119]. Pharmacological treatment is thus recommended for asymptomatic AML larger than 3 cm [6], especially when multiple. Embolization is an alternative, especially for solitary AML. For an acutely bleeding AML, embolization is the first-line therapy [6]. Nephron-sparing surgery is an acceptable alternative.

Birt-Hogg-Dubé Syndrome

What Is BHD?

BHD is a rare inherited autosomal dominant disorder caused by germline mutations in the tumor suppressor gene *FLCN* encoding the protein folliculin. Its typical manifestations include cutaneous fibrofolliculomas, mul-

tle pulmonary cysts, recurrent spontaneous pneumothorax, and renal tumors of various histological types.

The syndrome is named after the physicians who described the cutaneous phenotype of the disease and its autosomal dominant inheritance in 1977 [121]. The association with renal tumors, pulmonary cysts, and spontaneous pneumothorax, suggested in prior case reports [122–125], was more extensively described in 1999 [126]. The gene locus responsible for BHD was located on the short arm of chromosome 17 in 2001 [127, 128], and the *FLCN* gene was eventually identified in 2002 [129]. By February 2016, 183 different *FLCN* mutations had been identified in 616 BHD families (BHD Foundation; <https://www.BHDsyndrome.org>). It has recently been suggested that BHD be renamed as “*FLCN* (folliculin) gene-associated syndrome” or “*FLCN* syndrome” based on the present state of knowledge on the disease [130].

Pathogenesis

The majority of mutations identified in the *FLCN* gene result in loss of function of the protein folliculin [131]. It was therefore suggested that *FLCN* acts as a tumor suppressor gene [132, 133]. Folliculin is expressed in most tissues, including the lung, skin, and kidneys [134, 135]. Its exact function is unknown, but it is thought to be involved in the regulation of cell growth, proliferation, and survival through interactions with the mTOR signaling pathway [59, 136].

The mechanism by which loss of folliculin function results in the formation of pulmonary cysts remains unclear. Dysregulation of different signaling pathways has been described, including mTOR and 5' AMP-activated protein kinase [137, 138], as well as impaired cell-cell adhesion [139] and imbalance of extracellular matrix homeostasis through alterations in MMP [140]. It was recently hypothesized that pulmonary cysts could result from defects in cell-cell adhesion, leading to repeated stretch-induced stress caused by breathing and, in the long term, to expansion of alveolar spaces, primarily in regions subject to larger changes in alveolar volume during the breathing cycle. This theory could explain the predominantly basal and subpleural distribution of lung cysts in BHD [141].

Clinical Picture

The condition displays great phenotypic heterogeneity. Individuals with *FLCN* mutations may be asymptomatic or present with any combination of skin, pulmonary, or renal manifestations. The typical clinical picture shows cutaneous lesions and spontaneous recurrent pneumo-

thorax due to pulmonary cysts. However, some patients present with pulmonary cysts and/or relapsing pneumothorax without any skin or renal involvement [142–147]. The disease has no gender predilection [148], and it typically manifests in the 3rd or 4th decade of life but can affect individuals at any age [149]. Asian patients seem to have a lower incidence of cutaneous and renal manifestations but a higher recurrence rate of pneumothorax than Caucasians [146, 147, 150–152].

Pulmonary Manifestations

Multiple bilateral pulmonary cysts are found in more than 80% of patients with BHD [43, 132, 153]. The cysts tend to develop in the 4th to 5th decade of life [144, 147] but can be seen in younger adults [154]. The cysts are prone to rupture and predispose to spontaneous pneumothorax at a high recurrence rate. The risk of pneumothorax is estimated to be 50-fold higher than in the general population [153]. However, the prevalence rates of spontaneous pneumothorax vary considerably depending on the cohorts analyzed [155], ranging from 23–38% in renal/dermatologic cohorts [43, 132, 153, 156, 157] to 42–76% in pulmonary cohorts [151, 158, 159]. In three large cohorts, the mean age at occurrence of the first pneumothorax was between 36 and 38 years [43, 156, 159]. The rate of recurrence is 75–82%, with an average number of 3.6 episodes [43, 159]. When pleurodesis is performed, the recurrence rate is halved from more than 60% with conservative management to approximately 30% [159].

Risk factors for the occurrence of pneumothorax in BHD include the presence of pulmonary cysts; the number, size, and total volume of the cysts; and a family history of pneumothorax [43, 157]. There is no gender predilection for pulmonary cysts and/or pneumothorax, nor any association with smoking or the presence and/or severity of cutaneous and renal involvement [43, 153]. The risk of pneumothorax is thought to be increased during and following air travel or diving due to atmospheric pressure changes causing cyst expansion and favoring their rupture. The flight-related pneumothorax rate with BHD was estimated to range from 0.12 to 0.63% per flight [158–160]. While the vast majority of BHD patients experiencing pneumothorax have pulmonary cysts [157], there have been reported cases of pneumothorax without obvious cysts on HRCT [161, 162].

Apart from episodes of pneumothorax, the cystic lung disease in BHD is usually asymptomatic, or only causes mild exertional dyspnea and/or cough, even when lung involvement is extensive. The data on lung function in

BHD are limited to case reports or small series [154, 163, 164]. In 14 patients with baseline data only, the pulmonary function test results were essentially normal with mean spirometric values within the normal range and minimally reduced DLCO [165]. Whether pulmonary function declines over time is currently unknown. It seems, however, that the lung involvement in BHD does not usually result in respiratory failure.

Although some studies have reported the occurrence of lung adenocarcinoma, atypical adenomatous hyperplasia, or micronodular pneumocyte hyperplasia-like lesions in patients with BHD [144, 151, 163, 166], no association with pulmonary neoplasms has been formally established so far.

Cutaneous Manifestations

Skin involvement is common in BHD, and may be the first symptom of the disease [43, 132, 156, 161, 167]). Typical manifestations include fibrofolliculomas, trichodiscomas, and acrochordons. [135, 149]. They usually appear in the 3rd to 4th decade, and are only exceptionally seen before the age of 25 years [132, 161]. The most frequent and characteristic lesions are fibrofolliculomas, which are macroscopically undistinguishable from trichodiscomas [161]. They both represent benign hamartomas of the hair follicles and likely belong to the same morphological spectrum [164, 168–170]. They present as multiple characteristic, whitish, dome-shaped, smooth papules with a diameter of 2–4 mm occurring primarily on the nose and cheeks, in the retroauricular area, and on the neck and upper chest (Fig. 4a) [171]. Acrochordons, also known as skin tags, are small, soft, skin-colored benign tumors with thin necks mainly distributed on the eyelids, neck, and axilla. They are often seen in BHD, but are also very common in the general population [172]. The identification of fibrofolliculomas should raise suspicion of BHD and lead to further investigations to confirm the diagnosis and screen for renal tumors and pulmonary cysts.

Renal Manifestations

Renal cancer represents the most threatening manifestation of BHD. The prevalence of renal tumors is approximately 30% [132, 151, 153, 157, 173], with a 7-fold increased risk of developing renal cancer compared to unaffected family members [153]. The mean age at presentation is 50 years (range 31–74) [173], but it has been reported in a 20-year-old patient [167]. In more than half of the cases, the tumors are bilateral and/or multifocal [153, 173, 174]. Renal tumors encountered in BHD may have

different and sometimes mixed histologies with varying potential for malignancy, ranging from benign oncocytomas, observed in 5% of cases, to malignant clear cell renal carcinomas, accounting for 9% of BHD-associated renal tumors [173–175]. Chromophobe renal cell carcinoma and a mixed pattern of chromophobe renal cell carcinoma and oncocytoma, both associated with a low malignant potential, account for more than 70–80% of BHD-associated renal tumors, which differs from the large predominance of the clear cell histologic subtype observed in sporadic renal tumors [167, 173, 175]. AML are rare in BHD [165]. Renal cysts have frequently been reported in BHD patients, but they are also common in the general population, and it is not known whether an association between BHD and renal cysts exists [126, 161].

Other Clinical Manifestations

Other benign or malignant tumors have occasionally been reported in BHD, such as parotid oncocytomas [176], parathyroid adenomas [125, 177], lipomas [125, 126], breast cancer, melanoma, and others [149, 178], although no formal causal relationship to *FLCN* gene mutations has been established so far. An association between BHD and colorectal polyps or carcinoma has been suspected [122], but it was not confirmed by colonoscopic screening of 45 BHD patients [153]. However, a recent study found a significantly higher risk of colorectal neoplasia in a subset of patients with BHD, suggesting a genotype-phenotype correlation [179].

Imaging

HRCT is the recommended imaging modality for the assessment of lung involvement in BHD. The typical HRCT feature is the presence of multiple bilateral pulmonary cysts with a normal surrounding parenchyma [44]. However, the mere presence of characteristic pulmonary cysts is not sufficient to establish the diagnosis with certainty [165]. The cysts can vary widely in size, shape, and number, but they are typically thin-walled and predominantly distributed in the basal, subpleural, or paramediastinal regions of the lung (Fig. 4b, c) [44, 180]. They can be round, oval, lentiform, or irregularly shaped, and they

Fig. 4. Birt-Hogg-Dubé syndrome. **a** Multiple fibrofolliculomas of the nose. **b** Chest computed tomography: a few pulmonary cysts of uneven distribution, size, and shape in the lung bases (arrows). **c** Chest computed tomography with frontal plane reconstruction: multiple cysts adjacent to blood vessels, fissures, and visceral pleura, with predominantly basal and paramediastinal locations (arrows).

are generally surrounded by perceptible thin, uniform walls. Large cysts usually have a lobulated, multiseptate appearance [180]. The size of the cysts can range from a few millimeters to 2 cm or more, but the majority is below 1 cm in diameter [140]. They range in number from a few to more than 400 [43, 44, 165], with fewer than 20 cysts in the majority of cases [180] and less than 30% of the lung volume involved [44]. A larger cyst size and a basal localization of the cysts are associated with an increased risk of spontaneous pneumothorax [43, 154, 164].

The morphological aspects and distribution of the lung cysts helps in differentiating BHD from emphysema and other diffuse cystic lung diseases such as LAM. Large irregular cysts with a lobulated or multiseptate appearance, particularly if located in the subpleural lower lung fields, as well as cysts abutting or including the proximal portion of the lower pulmonary veins or arteries, are suggestive of BHD [165]. The basal and medial predominance of BHD-associated cysts contrasts with the apex-predominant distribution of dilated airspaces and blebs observed in smoking-related emphysema and primary spontaneous pneumothorax [148]. In comparison to LAM, pulmonary cysts in BHD are of larger size, lower number, and less circular shape and have a more predominant distribution at the lung bases and in paramediastinal locations [165]. Unlike in LAM, the number and size of lung cysts in BHD do not seem to increase significantly over time [44, 181]; however, the available data are scarce.

Histopathology

Based on the examination of ruptured cystic lesions of resected lung specimens following a spontaneous pneumothorax, the histological features of pulmonary cysts in BHD have been described as nonspecific and indistinguishable from those of emphysema, except for the predominantly basal location of the lesions [182]. However, the analysis of unruptured cysts provided some clues for the histological diagnosis of BHD. The inner surface of the cysts is lined by epithelial cells, without evidence of associated aberrant proliferation, atypical morphology, inflammation, or fibrosis [137, 183]. The cysts are located near the interlobular septa and/or visceral pleura, and each cyst is merged in part with the interstitial stroma of the interlobular septum and/or pleura, and in part with the normal alveolar structures.

More recently, an analysis of 229 cysts from 50 patients with BHD confirmed the predominantly basal distribution of the cysts, and that they were surrounded by normal lung parenchyma without any evidence of neoplastic cell proliferation or inflammation [184]. The cysts were

frequently intraparenchymal with no apparent communication with the airways, most often abutting the interlobular septa, and sometimes containing intracystic structures composed of interlobular septa. Together with the abnormal location of the cysts, these findings suggest that cystic lesions in BHD are clearly distinct from the apical centrilobular-predominant pattern of emphysema and subpleural blebs.

Diagnosis

BHD is a rare condition and is therefore likely to be underdiagnosed or misdiagnosed as primary spontaneous pneumothorax, emphysema, or another cystic lung disease such as LAM. Moreover, given its highly variable clinical expression, the diagnosis is often delayed by years [159]. Nevertheless, an early diagnosis is crucial to offer patients and their affected relatives regular screening for renal cancer.

Spontaneous pneumothorax is the most frequent manifestation leading to the diagnosis of BHD, although usually only after the second episode [159]. BHD is likely to be responsible for 5–10% of cases of apparent primary spontaneous pneumothorax [146, 185]. HRCT screening for BHD or another underlying diffuse cystic lung disease such as LAM or PLCH appeared cost-effective for patients presenting with apparent primary spontaneous pneumothorax, and should therefore be considered [159].

When BHD is suspected, a detailed personal and family history of skin lesions, pneumothorax, lung cysts, and renal tumors can provide important diagnostic clues. If present, they support the suspicion of the disease and should prompt further investigations. The patient should undergo a skin examination with punch biopsy if skin lesions are present, an abdominal CT or MRI as screening for renal tumors, a chest HRCT with review of the cysts' morphology and distribution by an expert radiologist, and pulmonary function testing [148]. Genetic counseling with testing for *FLCN* gene mutations should be offered to confirm the diagnosis and facilitate the screening of family members.

Confirmation of a BHD diagnosis relies on different combinations of clinical features and/or the identification of a *FLCN* germline mutation. Two diagnostic algorithms have been proposed, but they still await multidisciplinary validation (Table 3) [148, 149]. It is worth noting that a negative *FLCN* gene test result does not exclude the diagnosis. Regarding renal involvement, multifocal or bilateral renal cancer is very specific to BHD, and a mixed chromophobe and oncocytic histology is almost pathognomonic of the syndrome.

Management and Prognosis

Management of BHD should focus on early diagnosis of the disease, identification of affected family members, early detection and treatment of renal tumors, and prevention of pneumothorax. Given the high prevalence of pulmonary cysts and renal tumors in BHD, screening for lung and kidney involvement is recommended in asymptomatic individuals with genetically confirmed disease.

There are currently no therapeutic options for BHD-associated cystic lung disease. Whether inhibition of the mTOR pathway could play a role in preventing cyst formation is unknown. Consequently, management of BHD primarily aims at preventing and treating pneumothorax [148]. Patients with BHD must be informed about the risk and symptoms of pneumothorax and encouraged to seek medical care in case of new or worsening dyspnea or chest pain. It seems wise to discourage patients from diving, but unreasonable to advise against air travel, regardless of the slightly increased risk of pneumothorax observed during and after a flight [158]. However, patients with an ongoing or recently treated pneumothorax should not travel by air. Given the high recurrence rate of pneumothorax, pleurodesis should be considered after the first episode of spontaneous pneumothorax [148]. As pulmonary function test results are usually normal and cystic involvement is unlikely to significantly impact lung function, regular follow-up with pulmonary function tests and chest HRCT is not recommended for most patients. In case of profusion of pulmonary cysts along with impaired lung function, periodic pulmonary function testing should be considered [148]. Although there is no evidence of a causal association between tobacco and the development of pulmonary cysts, pneumothorax, or lung functional decline, smoking should be discouraged. Pneumococcal vaccination and annual influenza vaccination are recommended.

All patients with BHD should be offered screening for renal tumors at the time of diagnosis or from 20 years of age [186]. If no tumor is detected on initial screening, life-long surveillance is recommended with follow-up imaging every 3–4 years in order to identify tumors at an early stage. As renal ultrasound is not sensitive enough to detect small tumors [187] and the cumulative radiation exposure from repeated CT is prohibitive, MRI is the recommended imaging modality [186, 188]. The majority of BHD-associated renal tumors have a low malignant potential, and the prognosis is usually favorable. As patients can develop several renal tumors during their lifetime, a delayed nephron-sparing strategy is favored to prevent metastatic spread in time but also to preserve as much

Table 3. Diagnostic criteria for BHD

Diagnostic criteria proposed by Menko et al. [149]

The patient should fulfill 1 major or 2 minor criteria for the diagnosis

Major criteria	<ul style="list-style-type: none"> • At least 5 fibrofolliculomas or trichodiscomas, at least 1 histologically confirmed, of adult onset • Pathogenic <i>FLCN</i> germline mutation
Minor criteria	<ul style="list-style-type: none"> • 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 1st-degree relative with BHD

Diagnostic criteria proposed by Gupta et al. [148]

Definite pulmonary BHD	<ul style="list-style-type: none"> • Characteristic or compatible lung HRCT and skin biopsy positive for fibrofolliculoma or trichodiscoma • Characteristic or compatible lung HRCT and confirmed family history of BHD in 1st- or 2nd-degree family member • Characteristic or compatible lung HRCT, and tissue confirmation or renal chromophobe adenoma or oncocytoma • Characteristic or compatible lung HRCT, and tissue confirmation of genetic testing positive for BHD
Probable pulmonary BHD	<ul style="list-style-type: none"> • Characteristic HRCT, exclusion of TSC and LAM, and personal or family history of pneumothorax • Compatible HRCT, exclusion of TSC and LAM, and any of the following: <ul style="list-style-type: none"> – family or personal history of renal tumors – skin angiofibroma – renal angiomyolipoma
Possible pulmonary BHD	<ul style="list-style-type: none"> • Compatible or characteristic HRCT

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). Compatible HRCT findings: thin-walled cysts without the more typical elliptical shape or subpleural distribution. BHD, Birt-Hogg-Dubé syndrome; HRCT, high-resolution computed tomography; TSC, tuberous sclerosis complex; LAM, lymphangioleiomyomatosis.

kidney function as possible [186, 188]. In addition, prior surgical procedures can complicate subsequent resections and interfere with imaging interpretation. Therefore, once one or more tumors are detected, it is recommended to postpone surgery until the largest mass reaches 3 cm in diameter, with subsequent imaging intervals depending on the type, size, and growth rate of the lesions [173, 186, 188]. Cryotherapy and radiofrequency ablation are alternative nephron-sparing techniques if surgery is contraindicated. One Japanese patient with BHD and metastatic renal cancer was treated with everolimus, which, reportedly, exhibited a relatively long-term effect [189]. Further studies are needed to assess the efficacy of agents targeting the mTOR pathway in BHD-associated renal cancer.

Cutaneous manifestations of BHD are benign, and no treatment or follow-up is needed. The skin lesions can be removed surgically – or with laser therapy or curettage for cosmetic reasons, but they tend to recur [190–193]. A recent trial of topical sirolimus has shown no improvement with regard to the number and size of fibrofolliculomas in patients with BHD [194].

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