Chapter 8
Lymphangioleiomyomatosis

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Abstract Lymphangioleiomyomatosis (LAM) is a rare progressive cystic lung disease that affects women almost exclusively, occurring in a sporadic form and in association with Tuberous Sclerosis Complex. remendous progress has been made in understanding the pathogenesis of this disorder, leading to advances in noninvasive diagnostic approaches, and a targeted therapy has now been FDA-approved for treatment of LAM (rapamycin). In LAM, progressive decline in lung function occurs as dysregulated smooth muscle-like cells (LAM cells) of uncertain origin infiltrate the lung, disrupting lymphatics and leading to parenchymal destruction and cyst formation. LAM cells have constitutive activation of the mechanistic target of rapamycin (mTOR) due to sporadic or germline mutations in tuberous sclerosis genes (TSC1 or TSC2). Inhibition of mTOR by rapamycin suppresses disease progression as was demonstrated in the Multicenter International Lymphangioleimyomatosis Efficacy of Sirolimus (MILES) trial. In animal models of LAM and in vitro cellular studies, estrogen increases cell proliferation and migration. The reason for the marked gender discrepancy remains unknown, and at this time, hormone-modulating therapies remain largely unproven or insufficiently studied in patients with LAM.

Keywords Lymphangioleiomyomatosis • LAM • Tuberous sclerosis complex • TSC • mTOR • Sirolimus • Rapamycin • VEGF-D • Cystic lung disease

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Clinical Presentation

IntroductionLymphangioleiomyomatosis (LAM) is a rare cystic lung disease with prevalence estimated at 2-5 per million women (Harknett, E. C., et al. QJM. 104.11 (2011): 971-79; Johnson, S. R. and A. E. Tattersfield. Am.J.Respir.Crit Care Med. 160.2 (1999): 628-33). Definite or probable LAM causing pulmonary symptoms has been reported in only 4 men (Miyake, M., et al. Radiat.Med. 23.7 (2005): 525-27;Schiavina, M., et al. Am.J.Respir.Crit Care Med. 176.1 (2007): 96-98; Aubry, M. C., et al. Am.J.Respir.Crit Care Med. 162.2 Pt 1 (2000): 749-52. Kim, N. R., et al. Pathol.Int. 53.4 (2003): 231-35). Dysregulated smooth muscle-like cells (LAM cells) of uncertain origin infiltrate the lung causing lymphatic disruption and congestion, cyst formation, and parenchymal destruction. The neoplastic phenotype of LAM cells occurs as a consequence of constitutive activation of the mechanistic target of rapamycin (mTOR) due to loss of heterozygosity in the tuberous sclerosis genes (TSC1 or TSC2) (Henske, E. P. and F. X. McCormack. J.Clin.Invest 122.11 (2012): 3807-16. The natural history of LAM is variable but significant morbidity and mortality occurs (Johnson, S. R. Eur.Respir.J. 27.5 (2006): 1056-65; Ryu, J. H., et al. Am.J.Respir.Crit Care Med. 173.1 (2006): 105-11). The mTOR inhibitor sirolimus (i.e. rapamycin) is an effective suppressive therapy for LAM, though LAM cells persist and lung function decline resumes if sirolimus is discontinued McCormack, F. X., et al. N.Engl.J.Med. 364.17 (2011): 1595-606. LAM should be considered in women who present with spontaneous pneumothorax, chylous pleural effusions, unexplained dyspnea, refractory asthma-type symptoms, or incidental radiologic findings of multicystic lung disease. Other clinical manifestations can include hemoptysis, chyloptysis, chylous ascites, and chyluria. Among patients in The LAM Foundation registry, pneumothorax was reported by 66 % of respondents and 82 % had their first pneumothorax prior to diagnosis [1]. Angiomyolipoma (AMLs) may also be a presenting feature of LAM, coming to medical attention due to hematuria or retroperitoneal hemorrhage, or as an incidental radiologic finding. Several series report that delays in LAM diagnosis are common [1–3]. As discussed in more detail below, LAM is also a common pulmonary complication in women with Tuberous Sclerosis Complex (TSC), a heritable tumor suppressor syndrome.

Approach to Diagnosis

Establishing a diagnosis of LAM can be achieved by a combination of clinical characteristics, thin section computed tomography (CT) imaging, serum vascular endothelial growth factor-D (VEGF-D) levels, and/or pathology (Fig. 8.1). An appropriate index of clinical suspicion is required, as pulmonary symptoms and physiology will overlap those of more common respiratory disorders. Pulmonary function tests may be normal initially, followed by a variable rate in decline in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and diffusion capacity of lung for

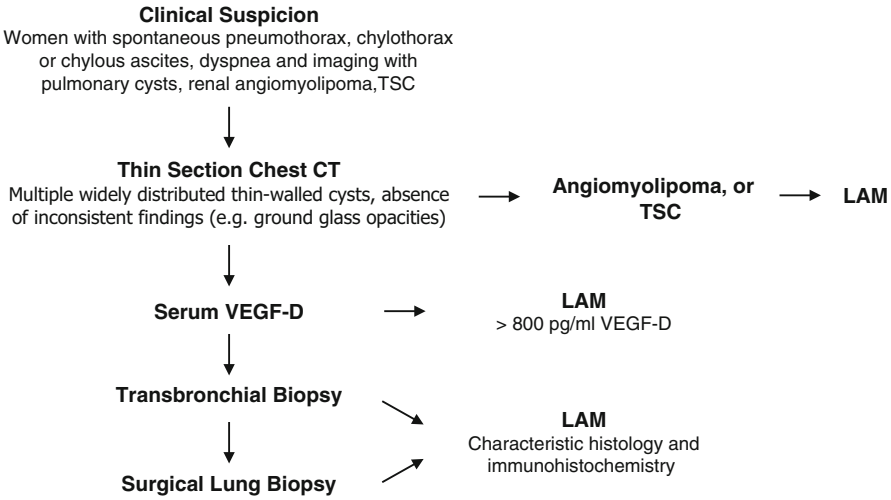

Fig. 8.1 LAM diagnostic algorithm. An approach to diagnosis for women in whom LAM is suspected is presented. Open lung biopsy is the historic gold standard, though it may not be necessary as outlined in the algorithm. Serum VEGF-D was approved as a clinical lab test and has been available since 2011

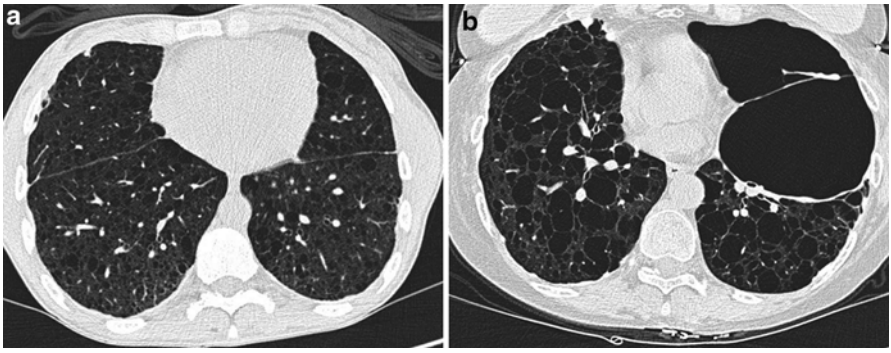

Fig. 8.2 Characteristic moderate and severe LAM CT. Numerous thin-walled cysts that are widely distributed are characteristic of LAM as seen in the CT images from LAM patients with moderate (**a**) and severe (**b**) disease

carbon monoxide (DLCO). Obstructive physiology with air-trapping may be present, or there may be a nonspecific or mixed ventilatory defect.

Chest imaging is a critical early step in the diagnostic evaluation. While chest radiographs may appear normal, multiple thin-walled cysts are seen on chest CT imaging and typically are widely distributed [4–6]. Representative CT images for moderate and severe LAM are presented in Fig. 8.2. LAM cysts vary in size from sub-cm to ~3 cm [6, 7]. An additional CT finding that aids in establishing a diagnosis is radiologic evidence for AMLs, often in the kidney [7]. Retroperitoneal or axial

lymphadenopathy may also be present, but this is a nonspecific finding. Ground glass opacities are not typical in the absence of pulmonary hemorrhage or significant lymphatic congestion, and the presence of other non-cystic radiologic features should raise suspicion for alternative or additional etiologies of lung disease.

As discussed further below, radiologic findings of thin-walled lung cysts are considered sufficient for a diagnosis of LAM in women with an established diagnosis of TSC, as clinical experience from surgical biopsies and lung explants in TSC patients has revealed characteristic LAM histopathology. Additionally, in TSC, a few or many small pulmonary nodules may be present, which commonly represent multifocal micronodular pneumocyte hyperplasia (MMPH) [8, 9] and therefore are typically followed conservatively in low-risk nonsmoking individuals.

Serum VEGF-D level is a diagnostic advance that can facilitate noninvasive diagnosis of LAM. This diagnostic test became available in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory in 2011. VEGF-D is a logical pathobiologic marker in LAM, as LAM cells produce VEGF-D [10], and VEGF-D is well known to promote lymphangiogenesis, a prominent feature in LAM [11, 12]. Seyama et al. first reported serum VEGF-D levels that were threefold higher in LAM patients versus age-matched healthy volunteers [10]. This finding has been validated by other investigators worldwide. Serum VEGF-D levels are elevated in approximately 70 % of patients with LAM, but are not elevated in women with other cystic lung diseases including emphysema, pulmonary Langerhan's cell histiocytosis, lymphoid interstitial pneumonia, Birt–Hogg–Dube syndrome, and follicular bronchiolitis [13]. When evaluated as a diagnostic test for LAM, serum VEGF-D greater than 800 pg/ml had a sensitivity of 73 % and a specificity of 100 % [13]. Importantly, in the compatible clinical and radiologic context, if serum VEGF-D is elevated above 800 pg/mL, a diagnosis of LAM is considered definite, thereby obviating the need for biopsy.

If the serum VEGF-D level is in the normal range, cytologic or tissue diagnosis should be considered for diagnostic confirmation, particularly if sirolimus therapy is being considered. Prior to lung biopsy for tissue confirmation, it is worthwhile to consider that LAM diagnosis may occasionally be confirmed by cytology of pleural fluid, ascites, or fine-needle aspirates or biopsy of lymph nodes [7], with reported yield ranging from 15 to 39 % [2].

A lung biopsy for pathology can be obtained by bronchoscopy or by video-assisted thoracoscopic surgery (VATS). Transbronchial biopsy has a reported yield of 60 % [14]. Pathologic findings of LAM include foci of smooth muscle cell infiltration of the lung parenchyma and lymphatics, and adjacent thin-walled cysts. LAM cells stain positively for α-smooth muscle actin and the melanogenesis pathway enzyme HMB-45, which has high specificity for LAM in this context [15, 16]. Histologic review by a pathologist with LAM expertise should be considered when there is clinical suspicion for LAM, as the morphology of LAM cells is sometimes confused for fibroblasts and only a minority of cells in a lesion are typically HMB-45 positive. Additional immunohistochemical markers include desmin and vimentin [15], and expression of both estrogen and progesterone receptors has been reported [17–20].

Differential Diagnosis

There are a number of other causes of multicystic lung disease that should be considered in the differential. Tobacco-associated emphysema is vastly more prevalent and may occasionally include imaging findings of cysts, particularly when chronic bronchiolitis is present, often in an apical predominant distribution. Pulmonary Langerhans Cell Histiocytosis should also be considered when the patient is a smoker, and imaging has multiple sub-centimeter nodules, irregular thick-walled cysts, and costophrenic angle sparing of cystic changes [21]. Lymphocytic interstitial pneumonitis that is idiopathic or associated with immune dysfunction or connective tissue disease has varied radiographic appearance; a serologic clue can be a polyclonal gammopathy in adults [22]. Alpha-1-antitrypsin deficiency can be diagnosed by assessing genotype and serum protein levels. Suspicion for connective tissue diseases including rheumatoid arthritis, systemic lupus erythematosus, Sjogren's, and myositis can be ascertained by history of rheumatologic symptoms, physical exam findings, and serologies including rheumatoid antigen, anti-cyclic citrullinated peptide, anti-nuclear antibody, anti-Ro/SSA, anti-La/SSB, anti-Jo-1, and anti-synthetases. Birt–Hogg–Dube (BHD) syndrome is caused by mutations in the folliculin gene with autosomal-dominant inheritance. Features of BHD include multiple pulmonary cysts, pneumothorax, skin fibrofolliculomas, and renal cell carcinoma in about 30 % of patients [23, 24]. Multiple cystic changes can also occur following prior pulmonary infection and barotrauma, and have been reported in light chain deposition disease, hyperimmunoglobulin E syndrome, and recurrent papillomatosis [2].

LAM and TSC: Clinical Association

TSC is an autosomal-dominant disorder with germline mutation in tuberous sclerosis genes, TSC1 or TSC2, that result in constitutive activation of the mTOR signaling pathway. The phenotype of TSC is multi-organ hamartomas including involvement of brain, skin, kidneys, and lungs. A subset of individuals with TSC have seizures and developmental disability. The diagnosis of TSC is not always apparent in women presenting with an LAM diagnosis, and therefore careful evaluation for TSC and genetic counseling are recommended [25].

For women, LAM is recognized as a component of the genetic syndrome TSC, occurring in about 40–80 % of women with TSC [9, 26, 27]. In a large TSC clinic, the prevalence of lung cysts was 27 % in women under age 21 among 101 women with available CT scans [26]. There are some phenotypic differences between TSC1 and TSC2 mutations, and TSC2 may confer greater susceptibility to develop LAM [27, 28]. While the natural history of LAM in women with TSC is variable, with some individuals remaining asymptomatic, some young patients do progress rapidly from minimal to severe lung disease [29]. There are limited data to inform the

approach to screening from LAM in females with TSC. Currently, the European Respiratory Society guidelines recommend chest CT imaging in female TSC patients at 18 and again at 30 years of age [7]. A 2013 publication by Krueger et al. for the International Tuberous Sclerosis Consensus group recommended clinical assessment and initial CT at age 18 years, with follow-up screening imaging every 5–10 years in asymptomatic females [30].

Recent studies indicate that mild pulmonary cystic changes are seen in some men with TSC, though almost all of these cases are asymptomatic. Adriaensen et al. reviewed available chest and abdominal CT studies from 206 TSC patients and found that 42 % of females and 13 % of males had pulmonary cysts [28]. Cysts were larger in women, and extensive cystic changes were 10 times more common in women than men. In a series from the Mayo clinic, lung cysts were seen in 38 % of men with TSC, though the extent of findings was overall mild [31]. These data suggest that while TSC mutations are associated with cystic lung disease, there are marked gender differences in disease severity, with clinically significant lung disease restricted to females.

Mechanisms of mTOR Signaling and Dysregulation in TSC and LAM

Advances in the understanding of TSC biology have provided critical clues to LAM pathogenesis and treatment. Spontaneous or germline mutation of TSC is the major recognized underlying abnormality in the development of LAM. A landmark discovery was the identification of identical TSC2 mutations in DNA from LAM lesions in the lung and renal AMLs, but not in germline DNA in the blood of women with Sporadic LAM [32].

TSC1 and TSC2 proteins form a complex that inhibits signaling through the mTORC1 complex of the mTOR signaling pathway, via activation of the GTPase-activating protein Rheb. Disruption of the TSC1/TSC2 complex leads to dysregulated mTOR signaling, and specifically inappropriate increased signaling through mTORC1. Signaling through mTORC1 drives cell proliferation, and in fact, increased signaling through mTOR is a feature of several malignancies [33, 34]. Angiogenesis mediated by VEGF-A is regulated by TSC through mTOR signaling [35]. Sirolimus (rapamycin) is a mTOR inhibitor and in LAM it suppresses the aberrant increased signaling that results from TSC mutations.

Natural History and Prognosis

LAM progression is variable. A favorable prognosis is associated with older age at diagnosis and the presence of a renal AML, the latter for unclear reasons [36, 37]. Oprescu et al. reported an accelerated time to transplant or death among individuals presenting with dyspnea or cough, but no increased risk of death in association with

pneumothorax [37]. An obstructive pattern on pulmonary function tests and having a positive bronchodilator response portend of a worse prognosis [38, 39]. Morbidity includes recurrent pneumothorax, chylothorax, hemorrhage, hypoxemia, and pulmonary arterial hypertension. Recurrent pneumothorax is common [40, 41]. Renal AMLs occur in approximately 30 % of patients with spontaneous LAM and up to 75 % with TSC [26, 40]. Among women in the United States LAM registry, 31 % reported use of supplemental oxygen [37]. In this registry, the median age at death was 48 years and the most common cause of death was respiratory failure [37].

LAM Treatment

LAM treatment historically has focused on managing complications including pneumothorax and AMLs and providing symptomatic management and supportive therapy with bronchodilators and supplemental oxygen. Pneumothorax is frequently recurrent and therefore warrants secondary prevention. Pneumothorax recurrence occurred in 66 % of patients who had conservative management versus 27 % of 140 LAM patients treated with chemical pleurodesis, and 32 % treated with surgery [1]. Embolization is an approach to prevent hemorrhage from AMLs with prominent feeding vessels [42].

Management of LAM now includes focused pharmacologic therapy, as a disease-modifying therapy, sirolimus, was FDA approved for LAM in May 2015. The Multicenter International Lymphangioleimyomatosis Efficacy of Sirolimus (MILES) trial resulted in a momentous shift in management of LAM. This international, randomized, double-blind, placebo-controlled trial showed that sirolimus stabilized lung function and improved metrics of functional performance and quality of life in women with moderate to severe lung disease (Table 8.1) [43].

Table 8.1 MILES trial summary[a]

	Placebo $N=43$	Sirolimus $N=46$	p-value
Baseline:			
TSC Syndrome, N (%)	8 (9)	4 (9)	1.00
Age	45	46	0.74
FEV1, L (% predicted)	1.38 (48)	1.36 (49)	0.66
FVC, L (% predicted)	2.79 (80)	2.91 (81)	0.57
DLCO (% predicted)	10.4 (44)	10.1 (43)	0.52
Change at 12 months:			
Δ FEV1, ml	−134	+19	<0.001
Δ FVC, ml	−129	+97	0.001
DLCO	−0.62	−0.06	0.38
Δ VEGF-D (pg/ml)	−15	−1032	0.001

The Multicenter International Lymphangioleimyomatosis Efficacy of Sirolimus (MILES) trial demonstrated stabilization of lung function in women with LAM. Selected baseline participant characteristics and change in pulmonary function and VEGF-D at 12 months are presented

[a]Adapted from McCormack, et al. 2011, NEJM 364(17)

Serum VEGF-D levels decreased with sirolimus treatment, and patients with high baseline VEGF-D levels had incrementally greater change in pulmonary function in response to treatment [44]. Unfortunately, lung function decline resumes if patients discontinue sirolimus. While overall well tolerated, side effects of sirolimus include leukopenia, increased risk of infections, hypertension, hypercholesterolemia, diarrhea, peripheral edema, proteinuria, oral ulcers, acne, and rare others. Ongoing questions include when in the disease course to start sirolimus, and whether lower dose treatment could achieve similar efficacy with an improved safety profile. The LAM Foundation has organized a network of LAM clinics to provide improved multidisciplinary care for LAM patients and to collaborate in the development of data-driven practice guidelines.

Lung transplantation is an established option for women with severe pulmonary impairment due to LAM. Progressive decline in FEV1 and worsening dyspnea are reasons to consider an initial referral. Patients will need to maintain their functional status, i.e., walking, regardless of oxygen requirement to be eligible for transplant. The presence of a renal AML is not an exclusion factor. The risk of transplant morbidity and mortality must be weighed against risks of respiratory failure from LAM. Less than 10 % of women who receive transplants go on to have clinically significant LAM recurrence. Mortality after transplant at 5 and 10 years is 67 % and 47 %, respectively [45]. Sirolimus has typically been stopped prior to transplantation due to concern that it may impair healing at the implant anastomosis. Complications that can occur following transplant in LAM patients include chylous pleural effusions, renal AML hemorrhage, and LAM recurrence [45, 46]. Chronic immunosuppression regimens typically include sirolimus.

Sex Hormones and LAM

The gender disparity of LAM is striking as susceptibility to LAM is almost entirely limited to women. Decades of clinical observation and research findings implicate estrogen as having disease-modifying effects. LAM cells are known to express both estrogen and progesterone receptors. Higher estrogen states have been associated with progression of disease in some cases. However, definitive evidence is lacking regarding manipulating sex hormones as a therapeutic approach.

Reproductive hormones are suspected to affect LAM as clinical presentation occurs after puberty, accelerated progression is not infrequently observed during pregnancy, and menopause is associated with attenuated progression [36, 40, 47] The average age of symptom onset among LAM patients in the USA and the UK was 37 and 34 years of age, respectively, though this varies widely [36, 37, 40]. Decline in FEV1 was −170 ml/year versus −86 ml/year for premenopausal versus postmenopausal women, respectively [36]. During pregnancy, cases of pneumothorax, chylothorax, AML hemorrhage, and precipitous decline in pulmonary function have been observed [47–50]. Pregnancy risks also include an increased risk of

premature births [47]. Overall women with LAM have fewer children than women without LAM for various reasons including the decision not to become pregnant [47, 51]. Despite circumstantial and anecdotal clinical experiences, limited high-quality evidence exists to guide clinical recommendations on this controversial topic. Careful clinical assessments and counseling, in the context of individual patient preferences, are recommended.

A number of studies have evaluated the effect of hormonal therapies though small sample sizes and observational study designs have limitations. Eliasson et al. reviewed 30 reported cases and interpreted that 7 of 9 patients with oophorectomy +/− progesterone treatment and 4 of 8 patients on progesterone had "stabilization" of disease [52]. Oberstein et al. reported that women on oral contraceptive pills (OCPs) had an earlier onset of symptoms and were diagnosed at an earlier age (29 vs. 33, respectively; $p = 0.04$) [53]. A prospective observational study of 275 patients showed no difference in the decline of lung function (FEV1, DLCO) over 4 years among the 139 patients who received progesterone [54]. Case series report disease exacerbation including worsening symptoms, pneumothorax, and decline in FEV1 in conjunction with tamoxifen treatment [55, 56]. Women treated with the gonadotropin-releasing hormone (GnRH) analogue triptorelin ($n = 11$) experienced ongoing decline in FEV1 over a 3-year period that was similar or greater than declines reported in other observational studies [57]. A small trial of the aromatase inhibitor letrozole that suppresses estrogen synthesis peripherally was completed in 2015 and is expected to report soon (NCT01353209).

Histologic studies and in vitro studies of LAM cells provide evidence that these cells respond to estrogen. In explanted lung tissue from LAM patients undergoing transplant, 20 of 20 tissues had LAM cells that were positive for estrogen and progesterone receptors by immunohistochemistry [18]. The LAM cell staining was also notable for a high PR to ER ratio whereas ER expression dominates in other estrogen-mediated neoplasms. A primary culture of LAM cells from an angiomyolipoma with a proven TSC2 mutation had increased proliferation in response to estrogen and tamoxifen [58]. Estrogen influences interaction of LAM cells with the extracellular matrix. TSC2-deficient cells treated with estrogen have increased invasion in a collagen invasion chamber [17]. In TSC2-deficient cells, estradiol increases metallomatrix protein 2 (MMP2) which is predicted to influence predilection for metastasis [17].

While no animal model recapitulates the cystic lung disease phenotype of LAM, preclinical models have been reliable in assessing the effects of mTOR inhibition on tumor development in TSC-deficient animals. Several models provide evidence that loss of tuberin, the protein product of TSC2, is associated with tumor development and that estrogen exposure promotes cell proliferation. One intriguing model is the Eker rat, which is heterozygous for a germline TSC2 mutation, and in addition to a predilection to develop renal tumors, the female animals develop uterine leiomyomas [59, 60]. TSC2 loss of heterozygosity (LOH) and/or loss of tuberin protein occurs in these tumors [59]. There is a hormonal dependence: ovariectomy at 4 months eliminates tumor development, and selective estrogen receptor modulators

(i.e., tamoxifen and raloxifene) decrease tumor growth. Further, using uterine leiomyoma cells from this tuberin-deficient rat model (ELT3 cells), Finlay et al. demonstrated that tuberin interacts with ERα and that re-expressing tuberin in ELT3 cells attenuated estrogen-induced proliferation [61].

Xenograft models have also been useful to study the role of estrogen on cell migration and invasion, tumor growth, and potential anti-tumor therapeutics. When ELT3 cells were injected into ovariectomized mice, estrogen treatment resulted in higher proliferative potential assessed by Ki-67 staining [62]. Additionally, mice treated with estrogen had a greater number of pulmonary metastases than the placebo control group. [62]. Estrogen upregulated signaling through the MEK/MAPK pathway and treatment with a MEK inhibitor completely eliminated the formation of pulmonary metastatic lesions while decreasing primary tumor size by a more modest 25 % [62]. Metabolomic profiling of ELT3 cells treated with estrogen identified increased glycolysis and pentose phosphate pathway intermediates [63]. In an ELT3 xenograft model, inhibition of the pentose phosphate pathway decreased estrogen-mediated colonization of ELT3 cells in the lung. Sun et al. also observed that in AML cells derived from LAM patients, estrogen increased glucose uptake in an AKT-dependent manner which was inhibited by Wortmannin and not the mTOR inhibitor rapamycin [63]. These preclinical studies have provided evidence of how estrogen may be important in LAM.

Additional Clinical Trials and Future Directions

There are many additional potential therapeutic targets in LAM. Strategies currently or recently under investigation include additional agents to inhibit mTOR, lymphangiogenesis inhibitors, drugs that affect metallomatrix proteins, and sex hormone modulating agents. Doxycycline, due to its activity as a metalloproteinase inhibitor, was evaluated in a 2-year double-blind placebo-controlled trial ($n = 23$) in which no effect was detected on pulmonary function tests (FVC, FEV1, DLCO), walk distance, or quality of life [64]. Sirolimus does not completely inhibit mTOR and therefore other inhibitors, including active site inhibitors, are being developed, as well as strategies to target both upstream and downstream of mTOR [65–67]. The mTOR inhibitor everolimus was evaluated for renal AML treatment in TSC or LAM patients in a double-blind, randomized, controlled trial ($n = 118$), and the progression-free rate for AML was 92 % at 12 months [68]; this trial was discontinued due to superiority of everolimus to placebo. A phase 2 trial of everolimus focused on pulmonary endpoints has recently been completed (NCT01059318).

Additional clinical trials for LAM currently listed at clinicaltrials.gov include simvastatin with rapamycin (NCT02061397), rapamycin with hydroxychloroquine, an autophagy inhibitor (NCT01687179), and Saracatinib (NCT02116712).

Summary

LAM is rare progressive lung disease that almost exclusively affects women, and women with TSC are a high-risk group that can benefit from screening for LAM. Diagnosis can be made without lung biopsy in many patients based on clinical features, characteristic chest CT patterns, and serum VEGF-D levels. The major known driver of disease is inappropriate activation of mTOR that leads to the proliferation and metastasis of LAM cells causing multisystem disease including cystic lung disease, lymphatic disruption, and renal AML. While the mechanisms of sex hormones on disease have been difficult to elucidate, estrogens likely contribute to LAM cell survival and migration. Clinics specifically organized for LAM patients provide centers of expertise for management of complications, treatment guidance, and infrastructure for conducting research. The MILES trial demonstrated that mTOR inhibition stabilized FEV1 and improved FVC in women with moderate to severe lung disease, but benefit persists only while sirolimus is continued. Additional efforts are needed to understand the gender disparity of LAM, improve the approach to screening in women with TSC, and develop strategies for disease prevention and treatment.

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