

Lymphangiomyomatosis

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Introduction

Lymphangiomyomatosis (LAM) is a rare, progressive, cystic lung disease that occurs almost exclusively in females, usually between menarche and menopause. The hallmarks of LAM are diffuse infiltration of the pulmonary parenchyma with atypical smooth muscle cells, airflow obstruction, pneumothorax and chylothorax, and progressive respiratory failure. LAM is often initially misdiagnosed as asthma or chronic obstructive pulmonary disease. Although patients are empirically treated with therapies that antagonize the effects of estrogen, there is no good evidence that these strategies are effective.

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Epidemiology

LAM was first reported in 1918 by Lutembacher^[1] in a patient with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous disorder. TSC occurs in about 1 of every 6000 births. It has no gender predilection and currently affects about 1.5 to 2.0 million people worldwide. This complex is a tumor-suppressor syndrome characterized by the formation of hamartomas and dysplasias in several organ systems. The most important manifestation of tuberous sclerosis in the lung is LAM, which until recently was believed to occur only 1% to 2.5% of female patients with TSC.

More recent studies have shown that 30% of female TSC patients have cystic lung changes consistent with LAM.^[2-4] Few of these patients undergo biopsy, so cystic lung conditions other than LAM may occur in TSC. This consideration is particularly important in TSC patients who smoke and in patients in whom diagnoses of emphysema and Langerhans' cell histiocytosis might also be considered. LAM occurs in males but is quite rare.^[5,6] Only 3 men with biopsy-proven LAM have appeared in the literature, and radiographic evidence of cystic pulmonary change in males has been reported in only a few series. It is estimated that worldwide, there are approximately 250,000 patients with TSC-LAM.

In 1937, von Stossel^[7] reported the occurrence of LAM in a patient without an obvious underlying genetic disease. Manifestation of this sporadic form of the disease (S-LAM) is limited to the lung, kidney (angiomyolipomas), and lymphatics and is much more prevalent among patients diagnosed with LAM than among those with TSC-LAM. Women with S-LAM currently represent more than 80% of the 1028 patients in the LAM Foundation Registry (as of early 2005) and the 237 patients in National Institutes of Health Registry.^[8] It is estimated that S-LAM affects 1 to 5 women per million. Thus, although the predicted prevalence of TSC-LAM is almost 10 times that of S-LAM, most patients who present for medical evaluation have S-LAM. This paradox remains unresolved, but possible explanations include that TSC-LAM may be less aggressive than S-LAM or that subclinical S-LAM is much more common than is currently appreciated.

Genetic Basis of LAM

Tumor-suppressor syndromes like TSC are caused by loss-of-function mutations in genes that control cell growth.^[9] Inactivating mutations in either of the tuberous sclerosis genes, TSC1 or TSC2, can result in TSC. In a TSC-affected individual, 1 copy of the TSC1 or TSC2 gene is inactivated by germ line mutations, which are present in all cells of the body, and tumors develop when "second hits," usually deletions, occur in somatic tissues.^[10] Thus, in patients with TSC-LAM, peripheral blood DNA analysis reveals a single mutation in either TSC1 or TSC2, and the LAM cells in the lung reveal a second hit (deletion), or loss of heterozygosity, for the normal allele^[11] (Table 1).

Patients with S-LAM do not have mutations in TSC genes in peripheral blood cells, normal lung, or normal kidney tissue.^[11] However, the tissue from the lung lesions, angiomyolipomas, and involved lymph nodes from patients with S-LAM exhibit "two-hit" in TSC2.^[12] The data suggest that S-LAM is most likely due to 2 somatic mutations in TSC genes -- that is, both "hits" occur in peripheral tissues.^[13] In essence, one can think of S-LAM as TSC isolated to the kidney, lung, and lymphatics.

To date, all cases of S-LAM have been due to TSC2 mutations. Karbowniczek and coworkers^[14] and Henske^[15] have raised the interesting and important possibility that LAM cells may arise in tissues outside the lung. This is based on genetic evidence that the TSC mutations found in the renal angiomyolipoma and the LAM lesion of individual patients are identical,^[13] suggesting a common source. In addition, recurrence of LAM in transplanted lungs has been reported in 2 cases, and in 1 case Karbowniczek and colleagues^[14] used genetic techniques to prove that the LAM lesions in the donor lung allograft comprised cells that originated from the recipient. The source of the metastatic cell is unknown.^[15]

Molecular Basis of LAM

TSC1 and TSC2 encode large proteins called hamartin and tuberin, which regulate signaling through the Akt pathway that controls cell size, growth, proliferation, and survival.^[16-18] Akt is activated by a variety of upstream signals, originating from both receptor tyrosine kinases, such as the insulin receptor (Figure 1) and G protein-coupled receptors. The tuberin/hamartin complex acts downstream of Akt by inhibiting the function of target of rapamycin (TOR). More specifically, binding of tuberin to hamartin activates the GTPase function of tuberin and maintains a small G protein called Rheb in the "off" state.^[19-21] Phosphorylation of tuberin, or loss of tuberin or hamartin function through genetic mutations, results in constitutive activation of Rheb and phosphorylation of signaling proteins downstream, including mTOR, and key proteins in protein translation, S6 and 4EBP1. The end result of deficiency or defective function of hamartin or tuberin is inappropriate stimulation of cell survival and proliferation. Brugarolas and colleagues^[22-24] have reported that TSC genes also regulate tumor formation through control of angiogenesis. Kumasaka and coworkers^[25] have reported that vascular endothelial growth factor (VEGF)-D, a lymphangiogenesis factor, is elevated in the serum of patients with LAM. Thus, tuberin and hamartin play several important roles in the control of cell growth and proliferation, lymphangiogenesis, and angiogenesis; loss of function of either protein results in hamartoma formation in TSC and LAM.

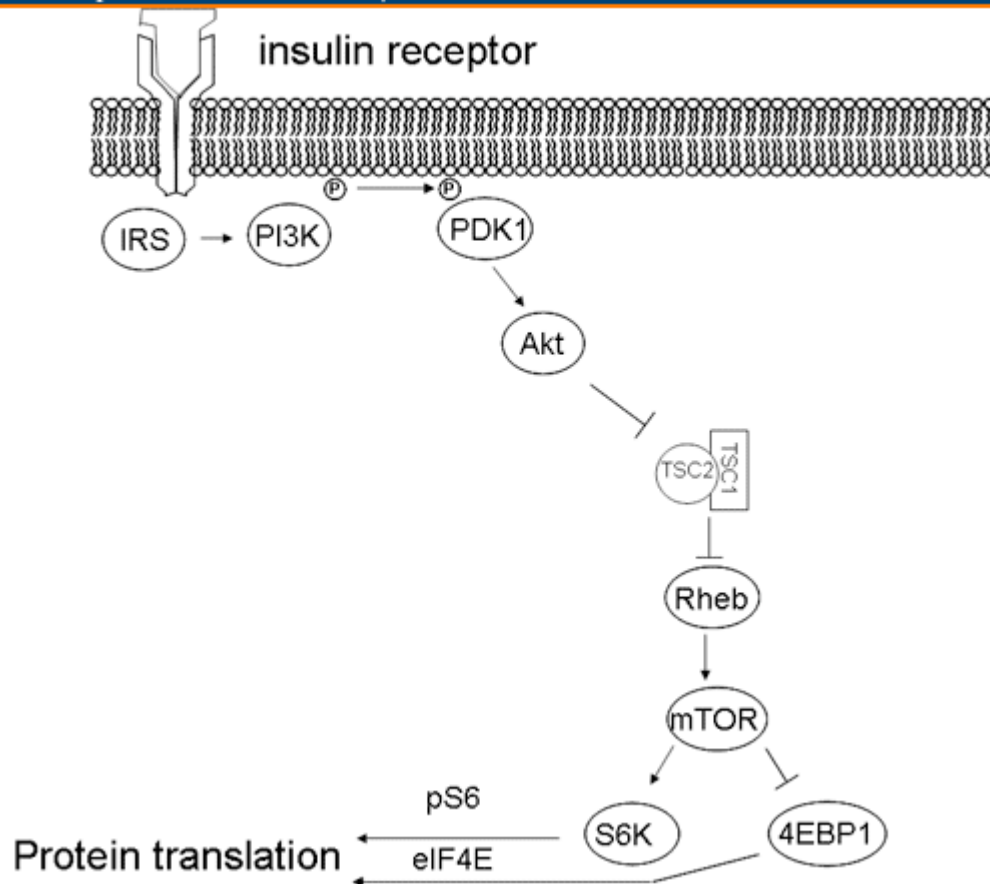


Figure 1.

Activation of the Akt pathway through binding of a ligand to a receptor, tyrosine kinase. Binding of insulin to the insulin-receptor results in a cascade of signaling events, which activate Akt and trigger protein synthesis and cell growth. Tuberin and hamartin form a complex that maintains the small G protein, Rheb, in the inactivated state. Phosphorylation of tuberin results in loss of its GTPase activating activity (GAP), allowing Rheb to activate mTOR and other downstream targets. Loss of tuberin or hamartin function through genetic mutations can result in constitutive activation of protein translation and cell growth, which is believed to play an important role in hamartoma formation in TSC and LAM. Signaling through mTOR can be inhibited by sirolimus or rapamycin, as well as other mTOR inhibitors.

Pulmonary Presentation

The most common presentations of LAM include progressive dyspnea on exertion, chylothorax, and pneumothorax in young and middle-aged women.^[26] The diagnosis of LAM can be delayed for 3 to 5 years after symptom onset because it is often confused with more common lung diseases, such as asthma or chronic obstructive pulmonary disease.^[27-29] Pneumothorax and chylothorax are often the sentinel events that trigger the ordering of computed tomography (CT) of the chest, resulting in the diagnosis of LAM. About 70% of women with LAM will have pneumothorax, and an equal percentage will have recurrent ipsilateral pneumothorax or contralateral pneumothorax. Patients with LAM have an average of 2 pneumothoraces before the diagnosis is made. About 20% to 30% of patients with LAM develop chylothorax, which is usually

unilateral.^[30] Other, less common presentations include chronic cough, atypical chest pain, chyloptysis, and hemoptysis. The mechanism of hemoptysis and chyloptysis are not entirely clear but almost certainly involve smooth muscle cell infiltration and obstruction of blood vessels in hemoptysis and lymphatic channels in chyloptysis. In patients with TSC, clinical manifestations of LAM tend to be milder, including an apparently lower frequency of chylothorax. However, screening of TSC patients often identifies LAM at an earlier stage (Table 2).

The most common pulmonary manifestation of TSC is not LAM, but multifocal micronodular pneumocyte hyperplasia.^[31] This disorder is a diffuse nodular proliferation of alveolar type II cells and has no gender predilection and no known prognostic or physiologic significance. Patients with TSC can also develop a rare neoplastic lesion called clear cell tumor of the lung (Table 3).

Extrapulmonary Presentation

Patients with LAM should be evaluated for physical evidence of TSC and abdominal LAM. The most common manifestations of TSC are a remote or current history of seizures, cortical tubers, subependymal nodules, or cognitive impairment in childhood. Facial angiofibromas, hypomelanotic macules (including the ash leaf lesion), subungual fibromas, and Shagreen patches of the skin are extremely common in TSC. Subtle autofluorescent manifestations of TSC should be looked for with a Wood's lamp. Less common findings include cardiac rhabdomyomas, which can be diagnosed by echocardiography, bone cysts, and gastrointestinal polyps.

Abdominal LAM can occur in patients who have TSC-LAM or S-LAM. Renal angiomyolipomas occur in approximately 70% to 80% of patients with TSC and in 30% to 50% of patients with S-LAM. Manifestation of lymphatic involvement in LAM can range from mild lymph node enlargement to massive, lymph-filled cysts that displace abdominal viscera, obstruct ureters, and increase abdominal girth. Chylous ascites occurs in about 15% of LAM patients; on rare occasions, chyle may appear in the gastrointestinal or genitourinary tracts through fistula formation.

Laboratory Evaluation

LAM most commonly presents with obstructive pulmonary physiology, including reduced FEV₁, reduced FEV₁/FVC ratio, gas trapping, and occasionally hyperinflation.^[32] Pressure volume analyses have indicated that airflow obstruction primarily results from airway narrowing rather than decreased elastic recoil forces.^[33] Airway narrowing in LAM is characterized by smooth muscle cell infiltration that results in both fixed and reversible components to airflow obstruction; up to 20% of LAM patients are bronchodilator-responsive. Some patients also have a restrictive component. Diffusing capacity for carbon monoxide is typically reduced, most likely through a combination of destruction of the pulmonary capillary bed and limitation of diffusion through expansion of the interstitium. Together with an elevated residual volume, reduced diffusing capacity of the lung for carbon monoxide (DLCO) is 1 of the earliest manifestations of LAM. Exercise capacity is limited by a combination of reduced ventilatory capacity due to airflow obstruction and increased dead-space ventilation.^[34] The chest radiograph is often uninformative in LAM, especially in the early stages. As the disease progresses, the chest radiograph may reveal hyperinflation, cystic changes, diffuse reticulonodular changes, hilar or mediastinal adenopathy, pleural effusions (typically chylous), and suspected or unsuspected pneumothorax (Figure 2). High-resolution CT of the chest reveals diffuse replacement of the pulmonary parenchyma with thin-walled cysts of widely varying sizes (Figure 3).^[35] Other CT features include linear densities, ground-glass opacities, nodular densities, effusions, hilar or mediastinal adenopathy, or dilatation of the thoracic duct. CT, magnetic resonance imaging (MRI), or ultrasonography of the kidney may reveal angiomyolipomas in over 70% of patients with TSC-LAM and 30% to 50% of patients with S-LAM^[36] (Figure 4). The presence of fat density in a renal mass is diagnostic for angiomyolipoma and generally obviates the need for biopsy. An increased

arterial alveolar gradient or frank hypoxemia may be found on blood gas analysis, but hypercarbia is rare except in late stages of the disease. No serum studies are helpful in LAM, but the recent discovery that the lymphangiogenesis marker, VEGF-D, is elevated in LAM may prove to be useful as a diagnostic tool or biomarker for the disease.





Figure 2.

Posterior-anterior chest radiograph of a patient with LAM showing cystic changes and right-sided chylothorax.

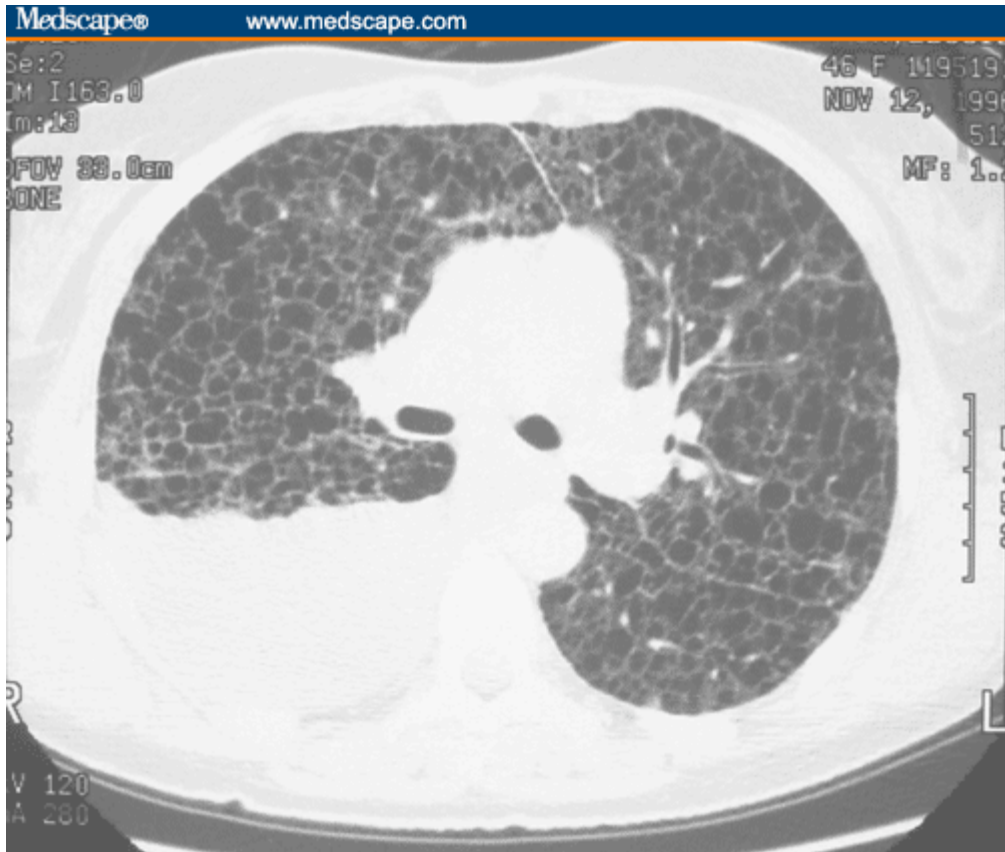


Figure 3.

High-resolution CT of the chest in a patient with LAM showing diffuse cystic changes in the lung and a large right chylothorax.

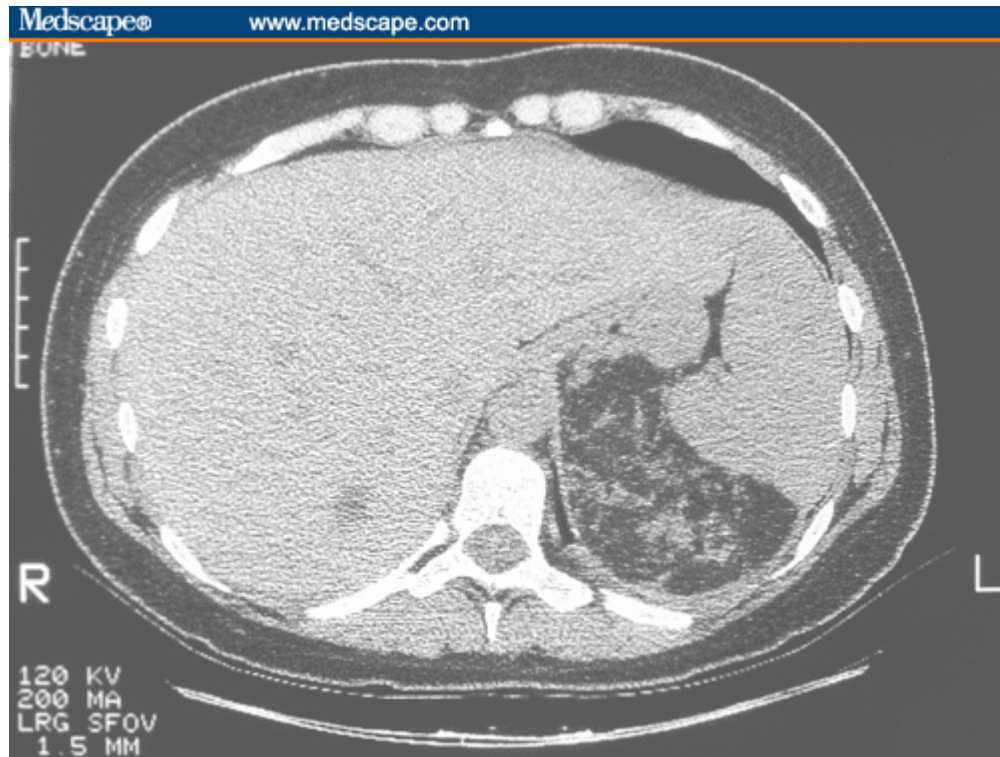


Figure 4.

CT of the abdomen showing a large angiomyolipoma with abundant fat density.

Pathology

Grossly, the lungs are enlarged and diffusely cystic.^[37,38] Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of lung parenchyma, airways, lymphatics, and blood vessels associated with areas of thin-walled cystic changes (Figure 5). Cystic spaces are uniformly lined with hyperplastic type II cells.^[39] Two actin-positive cell types are found in the lesion: small spindle-shaped cells and cuboidal epithelioid cells.^[40] The spindle-shaped cells are more proliferative, based on proliferating cell nuclear antigen staining. In addition, the cuboidal cells react with a monoclonal antibody called HMB-45, developed against the premelanosomal protein gp-100 (also known as Pmel17), an enzyme in the melanogenesis pathway.^[40] This immunohistochemical study is a useful diagnostic tool, since other smooth muscle-predominant lesions in the lung do not react with the antibody.^[41] Estrogen and progesterone receptors may also be present in LAM lesions,^[42,43] but their prognostic significance is uncertain.^[44] Diffuse nodular proliferation of type II cells indicative of multifocal pneumocyte hyperplasia may occur in patients with TSC regardless of whether LAM is present.^[31]

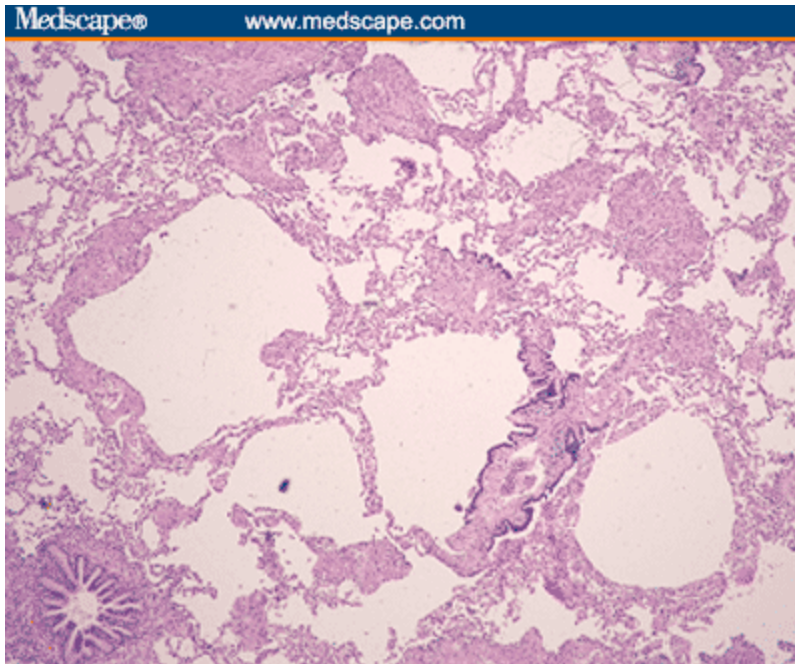


Figure 5.

Photomicrograph of LAM lung tissue showing cystic structures and infiltration of the pulmonary parenchyma, airways, blood vessels, and lymphatics with smooth muscle cells.

Diagnostic Approach and Management

The major diagnostic challenge in LAM is to consider the diagnosis in a young or middle-aged female who presents with pneumothorax, dyspnea, or obstructive lung disease. This message must reach a broader audience than the pulmonary community, since most of these patients are cared for by primary care physicians or internists. Young, nonsmoking women who present with unexplained pneumothorax should receive high-resolution CT of the chest. The differential diagnosis in this setting includes primary spontaneous pneumothorax, catamenial pneumothorax, and secondary pneumothorax related to asthma or interstitial lung disease. Chylothorax may also be the presenting manifestation of LAM in about 20% of patients. The differential diagnosis of chylothorax includes iatrogenic chylothorax due to surgery or line placement; yellow nail syndrome; trauma; and cancer, especially lymphoma.

Chylothorax and recurrent pneumothorax usually precipitate referral to specialists. High-resolution CT typically leads to consideration of LAM among the lung diseases that produce cystic changes, including Langerhans' cell histiocytosis and emphysema. The diagnosis of LAM is based on a compatible, high-resolution CT appearance and either demonstration of HMB-45-positive smooth muscle infiltration of lymph nodes or lung tissue, or the presence of known TSC or angiomyolipoma confirmed pathologically or radiographically. Diagnosis of LAM by transbronchial biopsy has been reported in exceptional cases, but video-assisted thoracoscopic biopsy is the preferred method to obtain lung tissue.

I recommend the following diagnostic approach in a patient with a chest CT that is compatible with LAM. If the patient has known TSC or a renal lesion with fat density consistent with an angiomyolipoma, no biopsy is necessary and the diagnosis of LAM is certain. If not, the patient should have dedicated CT of the abdomen and dermatologic and ophthalmologic examinations

by physicians who are knowledgeable about TSC. CT or MRI of the head is also useful to rule out subclinical TSC. If the patient has any of the characteristic skin (angiofibroma, subungual fibroma, hypomelanotic macule, confetti lesions), renal (angiomyolipomas), or central nervous system manifestations (subependymal nodules or giant cell astrocytomas, cortical tubers) of TSC or LAM, the diagnosis is certain. Abdominal manifestations of dilated, lymph-filled cysts are very suggestive of LAM, but lymphangiomas and some low-grade uterine sarcomas and ovarian tumors can cause similar findings and should be considered. Thoracoscopic lung biopsy or abdominal lymph node biopsy is recommended in any patient who does not have either an abdominal angiomyolipoma or a convincing manifestation of TSC.

Treatment and Supportive Measures

There are no proven treatments for LAM, and it is not clear whether early treatment prevents disease progression. Asymptomatic patients are often managed without therapy. On average, patients with LAM lose about 100 mL in FEV₁ and about 60 mL of FVC per year. In patients who are progressing and interested in intervention, antagonism of the effect of estrogen with progestins is the most common therapy. Oral progestins at rational doses consistent with estrogen suppression (eg, Agestyn 5-10 mg per day) are preferred over suprapharmacologic intramuscular regimens (eg, *Depo-Provera* 400 mg IM per month) that have been used empirically in the past. Gonadotropin-releasing hormone agonists are occasionally used to suppress estrogen production, although they are quite expensive and unproven in LAM. No convincing evidence supports surgical removal of the ovaries in patients with LAM; thus, few LAM clinical experts currently recommend oophorectomy. Similarly, there is no proven role for ovarian irradiation, immunosuppression, or anti-inflammatory therapies in LAM. LAM patients are often frightened by the lack of familiarity of their local physicians with the disease and may benefit from a 1-time referral to a center or physician who has managed a larger number of patients.

Pneumothoraces in LAM frequently recur; the average number of lifetime pneumothoraces in a patient that has had a sentinel pneumothorax is 3.5. Although pleurodesis increases the risk for postoperative hemorrhage in patients who ultimately require lung transplantation, this complication is usually manageable and prior pleurodesis does not usually affect candidacy for transplantation at most US centers. Given the morbidity of multiple pneumothoraces, we recommend pleural fusion on the first event. Many centers prefer mechanical abrasion over talc or pleurectomy as the method of pleural symphysis for patients who may ultimately require transplantation.

Chylothoraces occur in about 30% of patients with LAM and can often be managed conservatively with observation or repeated taps. Chylothoraces rarely result in fibrosis or trapped lung, and asymptomatic patients do not necessarily require drainage or pleural fusion once the nature of the effusion has been defined through a diagnostic tap. Mechanical pleurodesis, with or without thoracic duct ligation, is the preferred method of pleurodesis for patients who are dyspneic or exercise-limited.

In the United States, hypoxic patients with LAM receive supplemental oxygen to maintain saturations that exceed 85% with rest, exercise, and sleep. Bronchodilator therapy should be considered, since about 20% to 25% of patients with LAM have reversible airflow obstruction. Bone and cardiovascular health should be carefully monitored, especially in patients who are chemically, surgically, or naturally menopausal. Therapy with bisphosphonates is prescribed for patients with osteoporosis.

Several early studies reported that the 5-year survival in LAM is less than 10 years but these statistics tended to be based on patients who presented with advanced dyspnea. Patients who are diagnosed because of a pneumothorax or by screening TSC populations clearly have much longer survival.

Pulmonary transplantation remains the treatment of last resort for patients with LAM. Both single and double lung transplantations have been performed successfully. Although double lung transplantation has been found to have superior functional results in other obstructive lung diseases, it has not been shown to offer an advantage in LAM. There have been approximately 100 transplantations for patients with LAM in the United States, and long-term survival seems to be similar to that of patients with other lung diseases (ie, approximately 50% at 5 years).

Summary

LAM is a rare, progressive cystic lung disease that primarily affects women and can result in respiratory failure and the need for lung transplantation. Smooth muscle cell infiltration of the lung results in destruction of lung architecture; dilatation of distal airspaces; and obstruction of lymphatics, blood vessels, and airways. Recent evidence suggests that the molecular basis of abnormal cell growth and invasion in LAM is dysregulation of signaling through the Akt pathway. Pneumothorax and chylothorax occur frequently in LAM and tend to recur. Pulmonary function studies generally reveal an elevation in residual volume, reduction in DLCO, and variable degrees of airflow obstruction and restriction. There is no consensus on the optimal therapy for LAM, but research has revealed several promising molecular targets for therapy.

Experimental Trials and Patient Organizations

Based on this preclinical evidence, several trials of rapamycin or other mTOR inhibitors in patients with TSC or LAM are underway in Europe and the United States. Please contact the Tuberous Sclerosis Alliance (www.tsa.org) or the LAM Foundation (<http://lam.uc.edu>). Additional molecular targeted therapies that are being considered for LAM include tyrosine kinase inhibitors, angiogenesis inhibitors, and metalloproteinase inhibitors.

Much of the progress in LAM science has occurred because patients have had the foresight to organize themselves in a fashion that facilitates research. Additional information about LAM and support for LAM patients is available through the Tuberous Sclerosis Alliance and The LAM Foundation.

Table 1. Features of TSC-LAM and S-LAM

Variable	S-LAM	TSC-LAM
Prevalence per million	2-5	25
Heritable	-	+
Age at LAM diagnosis	35	35
Occurs in men	-	+
TSC1	Not reported	20%
TSC2	100%	80%
LAM Foundation Registry	85%	15%
National Heart, Lung, and Blood Institute Registry	85%	15%

Table 2. Clinical Manifestations in TSC-LAM and S-LAM

Organ	Manifestation	S-LAM	TSC-LAM
Lung manifestations	Dyspnea	++	±
	Pneumothorax	++	+
	Chylothorax	++	+
Renal-angiomyolipomas	Hemorrhage	+	++
	Size > 4 cm	+	++
	Bilateral	+	++
Lymphatics	Lymphadenopathy	++	+
	Extrapulmonary chylous fluid	++	+

Table 3. Organ Distribution of TSC-LAM and S-LAM

Organ	Manifestation	S-LAM	TSC-LAM
Lung	Smooth muscle infiltration	+	+
	Cysts	++	+
	Multifocal pneumocyte hyperplasia	-	+
Renal	Angiomyolipomas	+	++
	Cysts	+	+
Lymphatics	Infiltration	++	+
Skin	Angiofibromas	-	+
	Ash leaf macules	-	+
	Shagreen patch	-	+
	Subungual fibromas	-	+
Brain	Cortical tubers	-	+
	Subependymal nodules	-	+
	Giant cell astrocytomas	-	+
Bone	Bone cysts	-	+
	Bone islands	-	+
Eye	Retinal hamartomas	-	+
Heart	Rhabdomyoma	-	+

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