



Key Facts About Lymphangiomyomatosis

Defining LAM

Lymphangiomyomatosis, or LAM, is an uncommon, progressive, cystic lung disease that predominantly affects young women. Pulmonary parenchymal changes consistent with LAM are found in about one third of women with tuberous sclerosis complex (TSC), an autosomal dominant tumor suppressor syndrome. LAM also occurs in a sporadic form that is not associated with germline mutations in TSC genes. Recent evidence that recurrent LAM after lung transplantation results from seeding of the graft from a remote source suggests a metastatic mechanism for the disease.

Characteristics of LAM

The most common presentation of LAM is progressive dyspnea on exertion, often in association with a history of pneumothorax or chylothorax. (Other symptoms of LAM include chest pain and coughing.) The histopathological hallmarks of the disease are dilated distal airspaces and diffuse infiltration of the pulmonary interstitium with atypical smooth muscle cells, including spaces surrounding airways, vessels, and lymphatics. The differential diagnosis of the thin walled cystic change that is characteristic of LAM also includes emphysema, Langerhan's cell histiocytosis, lymphocytic interstitial pneumonitis, Birt Hogg Dube syndrome, and Sjogren's syndrome. Rare syndromes of benign or malignant smooth muscle metastasis may also produce cystic change and closely mimic LAM, including benign metastasizing leiomyoma, endometrial stromal sarcomas, and low-grade leiomyosarcomas.

Renal Angiomyolipomas

Kidney tumors called angiomyolipomas, unusual hamartomas containing fat, smooth muscle and blood vessels, are present in about 70-80% of patients with TSC and 50% of sporadic LAM (Table 1). Hemorrhage into an angiomyolipoma can produce symptoms from chronic intermittent flank pain to acute abdomen with hypovolemic shock. Embolization or cauterization may be required to prevent bleeding, which may be more common in tumors that exceed 4 cm. in diameter (Table 2). Nephron-sparing partial resections may be required for very large tumors.

Understanding the Epidemiology of LAM

LAM occurs almost exclusively in women. Cystic radiographic changes in men with TSC have been described in some TSC series, but only two biopsy documented cases of TSC-LAM have been reported in men. Sporadic LAM (S-LAM) has never been reported in a man. All races are affected. In one LAM Foundation survey of 480 patients, Caucasians made up 90%, Asians 3.5%, African Americans 3%, and Hispanics, 2%. TSC does not differentially affect particular ethnic groups, and access to health care, education, and the internet likely play important roles in the skewed ethnic distribution for LAM reflected in The LAM Foundation database.

The prevalence of S-LAM is roughly estimated to be approximately 3-5 per million people (30,000-50,000 patients worldwide), based on organized attempts to identify LAM patients in England, the United States and France by saturation mailings to all pulmonary physicians identified in each country. The incidence of TSC-LAM can be calculated from population data (Table 1). TSC occurs in approximately 1/6000 births, and the estimated number of TSC patients on earth is about 1-2 million. The worldwide prevalence of TSC-LAM therefore most likely falls in the range of 180,000 to 240,000 people, given the equal gender distribution of TSC and recent findings that 30-40% of women with TSC have cystic changes consistent with LAM.

Although TSC-LAM appears to be roughly 6-8 times as common as S-LAM, patients with TSC-LAM represent only a small fraction of the LAM patients seen in pulmonary clinics. Approximately 13% of the 832 patients registered with The LAM Foundation (as of 9/2004) reported a history of TSC. Furthermore, LAM is a major clinical problem in only about 5% of TSC patients and is a primary health priority for only a few (<10) of the 300 patients in the Tuberous Sclerosis Clinic at the University of Cincinnati. There are several possible explanations for the low visibility of TSC-LAM patients in the LAM community, including that other TSC-related health priorities may overshadow pulmonary symptoms or that TSC-LAM behaves differently from S-LAM. Although screening of asymptomatic women with TSC will provide a mechanism to study the natural history of LAM, we must remain cognizant that TSC-LAM and S-LAM may not be exactly the same diseases.

Table 1. Comparison of TSC-LAM and Sporadic LAM

	TSC-LAM	Sporadic LAM
Estimated # patients on earth	250,000	30,000-50,000
Reported in males	+	-
Reported in children	+	+
Ascertainment	mostly by screening	dyspnea and pneumothorax
Germ line TSC mutations	+	-
Both hits = somatic mutations	-	+
Inheritable	+	-
TSC1/TSC2 mutations reported	33%/66%	0%/100%
Angiomyolipomas	70-80% multiple/bilateral	40-50% single/unilateral
MMPH	+	very rare
CNS/skin/eye/cardiac lesions	+	-
Retroperitoneal, thoracic adenopathy	+	+
Dyspnea	less common	more common
Chylothorax	less common	33%
Pneumothorax	less common	66%
Respiratory failure	less common	more common

Abbreviations-CNS; central nervous system

MMPH; Multifocal micronodular pneumocyte hyperplasia

Table 2. Recommended interventions, studies and immunizations in patients with LAM

Stop smoking No estrogen containing meds	Pulmonary function testing	Head CT to r/o TSC
Yearly flu shot and pneumovax	Rest, sleep, exercise, oximetry	Wood's lamp skin exam
Counsel re: pneumothorax and pregnancy	HRCT chest	Transplant eval for FEV1 < 30%
Pleurodesis on first pneumothorax	α 1-antitrypsin level	Refer for embolization if AML > 4 cm
Baseline bone densitometry	Abdominal CT /USG	Oophorectomy rarely recommended

Clinical Presentation of LAM

The average age at diagnosis of S-LAM is about 35 years, after an average symptomatic period of 3-5 years. However, more recent reports include patients ranging from age 12-75 years. Most women registered with The LAM Foundation complained of dyspnea on exertion (51%). Symptoms of cough (6%), chest pain (5%), hemoptysis (5%), chylothorax and wheezing were all considerably less common. Pneumothorax occurs in 66% of registered LAM patients at some point in the course of their illness, with slightly more episodes on the right side than on the left. First recurrences after an initial pneumothorax occurred in more than 70% of patients, and contralateral pneumothoraces were almost as common. Thus, once a LAM patient has had a pneumothorax, a second event is more likely than not. Chylothorax occurs in about 33% of LAM patients at some point in the illness. Angiomyolipomas are present in most patients with LAM, including 70-80% of patients with TSC-LAM and 40-50% of patients with S-LAM. Rarely, LAM presents as retroperitoneal masses or adenopathy which mimic lymphoma, ovarian or renal cancer, or other malignancy. Large lymph filled abdominal lymphangiomyomas have also been described, and may vary in size with gravitational influences in supine and erect patients.

Chest HRCT screening of asymptomatic TSC patients identifies a population with fewer and less severe pulmonary manifestations, including lower incidence of associated manifestations of chylous pleural effusions, pneumothoraces, hemoptysis and chest x-ray and lung function abnormalities. Ascertainment bias almost certainly plays a dominant role in the differences in disease manifestations that have been described for TSC-LAM and S-LAM in the literature.

Laboratory Findings

There are no consistent laboratory findings that are helpful in the diagnosis or management of LAM. There have been isolated case reports of serum elevations in CA-125, which can lead to a misdirected search for ovarian carcinoma. Although TSC1 and TSC2 genotype analysis is commercially available through Athena Diagnostics, mutations are not present in peripheral blood cells from S-LAM patients and the clinical utility of genotyping TSC-LAM patients has not yet been established.

Pulmonary Physiology

Lung function may be normal in LAM, especially in TSC-LAM patients identified through screening. LAM commonly presents with reductions in FEV1 out of proportion to reduction in FVC, consistent with obstructive physiology. Reversible airflow obstruction is present in up to 20-25% of patients. Elevations in RV and the ratio of RV/TLC consistent with air trapping are frequently noted. Hyperinflation may also occur, which is unusual among the interstitial lung diseases. Mixed physiologic defects with superimposed restrictive changes are not uncommon, but it is unclear to what extent prior surgeries and pleural symphysis procedures may contribute to restrictive physiology. Impaired gas exchange and hypoxemia occur, but hypercapnea is rare even in end stage disease. Diffusion capacity for carbon monoxide (DLCO) is frequently reduced, and in some cases may be reduced out of proportion to the obstructive defect.

Radiology

The chest radiograph in LAM can be surprisingly unremarkable, even in the presence of moderately advanced disease. Basilar reticulonodular changes are not uncommon, and lung volumes can be normal or increased. Cystic and bullous changes, pleural effusions (unilateral or bilateral), hilar and mediastinal adenopathy and pneumothoraces may be apparent. High resolution CT scanning of the chest is the most helpful radiologic modality in LAM, and usually demonstrates profuse thin walled cysts in all lung fields (Figure 1). Diffuse nodular changes consistent with micronodular pneumocyte hyperplasia may be present predominantly in patients with TSC LAM.

Abdominal CT scanning is positive in over 75% of patients, and may reveal fat containing renal or extrarenal angiomyolipomas, axial lymphadenopathy, cystic or noncystic lymphangiomyomas or chylous ascites (Figure 2). CT or MRI scanning of the brain is recommended at least once in the lifetime of all S-LAM patients to rule out findings of subclinical TSC such as cortical tubers, subependymal nodules or subependymal giant cell astrocytomas (Figure 3).

Figure 1

High resolution CT scan of the chest in a patient with LAM. Note the diffuse replacement of the pulmonary parenchyma with thin walled cysts.



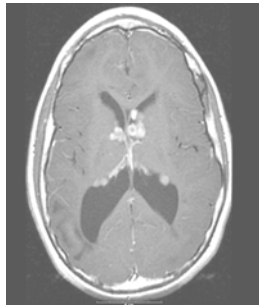
Figure 2

Abdominal CT scan in a LAM patient with an angiomyolipoma. Note the diffuse involvement of the right kidney with an angiomyolipoma. Observe solid and fat density which is characteristic of angiomyolipomas.

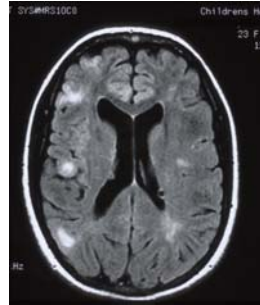


Figure 3

CT scan of the head in two patients with tuberous sclerosis. Subependymal nodules are present in panel a. Cortical tubers are present in panel b.



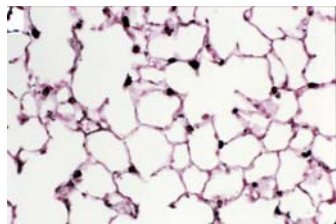
a.



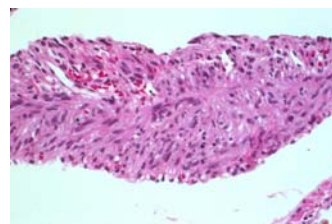
b.

Figure 4. Pathological features of LAM. Normal lung tissue with type II cells stained with antibody to surfactant protein A is shown. In panel b, an alveolar septal wall is expanded with spindle shaped and Epithelioid LAM cells. HMB 45 staining is shown in panel c. Cystic remodeling of the pulmonary parenchyma is shown in panel d.

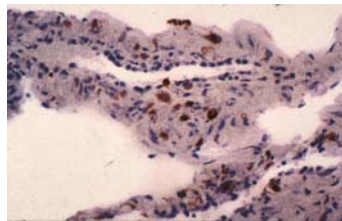
Figure 4



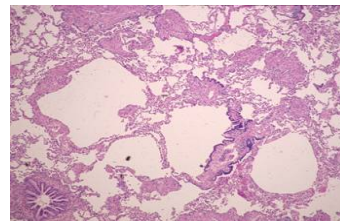
a.



b.



c.



d.

Pathology

Grossly, the lungs are enlarged and diffusely cystic, with dilated airspaces as large as 2.0 cm in diameter. Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of the parenchyma, airways, lymphatics, and blood vessels associated with areas of thin-walled cystic change (Figure 4). There are two major cell morphologies in the LAM foci, small spindle shaped cells in the center, and more cuboidal epithelioid cells in the periphery. LAM cells stain positively for smooth muscle actin and desmin. The lesions also react with a monoclonal antibody, HMB-45, developed against the premelanosomal protein gp-100. This immunohistochemical study is very useful diagnostically, since other smooth muscle predominant lesions in the lung do not react with the antibody. Unlike the dilated airspaces in emphysema, the cystic spaces are uniformly lined with hyperplastic type II cells. Diffuse nodular proliferation of type II cells called micronodular pneumocyte hyperplasia (MNPH) may occur in patients with TSC, in the presence or absence of LAM.

Diagnosis

Diagnostic dilemmas in LAM fall into two major categories; 1) How to identify LAM with progressive dyspnea and/or pneumothorax, 2) How to make the diagnosis of LAM in a woman with diffuse cystic changes on a CT scan of the chest with or without other corroborating evidence of LAM or TSC. The first scenario presents major challenges; how do we identify a rare, life threatening disease in a sea of common, less morbid obstructive diseases such as asthma and COPD. LAM is not usually part of the differential diagnosis for emergency and primary care physicians faced with a dyspneic patient, nor is it realistic to think that it will become so in the foreseeable future. Physical examination of the thorax and the chest radiograph can be surprisingly devoid of clues. Even severe cystic disease can be radiographically invisible on a chest radiograph. We submit that high resolution CT scanning should be obtained on all young nonsmoking women who present with dyspnea and a history of pneumothorax. While it is true that primary spontaneous pneumothorax (PSP) is a more common cause of pneumothorax in young females than LAM, PSP is almost always associated with tobacco use.

Although pneumothorax can also occur in the setting of asthma, these patients have significant bronchial hyperreactivity and characteristic relapsing/remitting bronchospasm.

The diagnosis of LAM occurs to most pulmonary physicians when pneumothoraces recur, occur in patients with TSC, or occur in a patient with chylothorax. High resolution CT scanning of the chest is routinely performed once the diagnosis is considered. Interpretation of the HRCT by expert radiologists leads to the correct diagnosis of LAM about 80% of the time. Diagnostic accuracy of 80% is not adequate in the setting of a life threatening lung disease, however, when deciding whether to perform a lung biopsy, the physician must determine if the clinical context is sufficiently compelling to make a clinical diagnosis without a biopsy. A full history including smoking, use of birth control pills, seizure history and family history of TSC should be obtained. Physical evidence of tuberous sclerosis should be sought, including acne-like angiofibromas-like lesions on the face, subungual fibromas, Shagreen's patches, ash leaf lesions, and other hypomelanotic lesions that fluoresce under the Wood's lamp such as confetti lesions. An abdominal CT or ultrasound to identify renal or extrarenal angiomyolipomas should be obtained if the abdominal cuts of the chest CT are inadequate. CT or MRI of the head should be considered for cortical tubers or other clinically occult manifestations of TSC. An α 1 antitrypsin level should be sent to screen for hereditary forms of emphysema, and serologies for Sjogren's syndrome considered if xerostomia and xerophthalmia are present.

In the setting of a compatible HRCT and specific corroborating clinical features, such as chylothorax, known TSC, or the presence of an angiomyolipoma in the kidney, the diagnosis of LAM can be made with certainty and lung biopsy is often not necessary. Lung biopsy should be considered when pulmonary cystic change is present without other clues, unless lung transplantation is imminent, in which case knowing the precise cause of the end stage lung disease is not usually critical. Video assisted thoracoscopic lung biopsy is the preferred method if pathologic confirmation is indicated. Transbronchial biopsies have occasionally been reported to be diagnostic in LAM when HMB-45 staining is positive.

Determining the Proper Therapeutic Strategy

Although LAM patients with LAM have been managed empirically with antiestrogen therapies, there is no proof that these strategies are effective. Many clinicians do not treat asymptomatic LAM patients. Therapies that are currently discussed with patients who suffer progressive decline in lung function include progestins (both oral and intramuscular) and GnRH agonists. Doses of oral progestins that are sufficient to suppress serum estrogen production (e.g., Agestyn 10 mg po qd to bid) are suggested rather than the suprapharmacologic intramuscular progesterone doses that have been propagated in the literature (e.g., Depoprovera 400 m IM q month). Progestins can cause fluid retention and mood swings. Gonadotropin releasing hormone agonists (e.g.-Lupron) have been used in LAM patients with LAM, but benefits are unproven and induction of early menopause is distressing and morbid in young women. There is no proven role for corticosteroids, immunomodulatory cytotoxic agents or ovarian irradiation in the treatment of LAM. Oophorectomy is no longer recommended because the benefits are unknown and the risk of bone and heart disease is increased. In the face of therapeutic uncertainty, the patient and physician should make treatment decisions jointly, after thorough discussion of the risks and limited available data.

Estrogen containing medications should be discontinued (Table 2). Patients should be advised that pregnancy has been reported to result in exacerbations of LAM and pneumothorax. However, the risk of pregnancy in LAM has not been rigorously studied. The physician and patient should discuss the risks of pregnancy carefully and decisions should be made on an individual basis.

Patients with LAM should avoid exposure to tobacco smoke. A trial of bronchodilators should be considered. Based on extrapolation from the COPD populations, the use of oxygen may prolong life in hypoxic patients with LAM. Oxygen should be administered to maintain oxyhemoglobin saturations of greater than 90% with rest, exercise and sleep. Bone densitometry should be considered in all patients who are immobilized and/or on antiestrogen therapies (Table 2). Calcium and bisphosphonate therapy should be considered in osteoporotic patients. Proper attention should be paid to cardiovascular health in patients who are rendered menopausal by therapy.

Pulmonary rehabilitation seems to be particularly rewarding in this young, motivated population, but studies that document improvements in exercise tolerance have not been done. Many patients with LAM avoid air travel. Of 400 patients who responded to the LAM Foundation enrollment questionnaire, eight reported an episode of pneumothorax during air travel. In four cases, there was some evidence that the pneumothorax was present at the time the patient boarded the plane. Of over two hundred LAM patients who have been flying to and from the NIH clinical study for LAM, there have been no adverse events during air travel. It is wise to obtain a CXR prior to boarding a plane if pleuritic chest pain or unexplained persistent shortness of breath is present.

Pleural disease should be aggressively managed. Over 65% of patients with LAM develop pneumothorax and the average number of pneumothoraces per LAM patient is 3.5 (Table 1). The use of a pleural symphysis procedure is recommended on the first pneumothorax, given the >70% chance of recurrence. Chemical pleurodesis (preferably with talc), mechanical abrasion, talc poudrage and pleurectomy have all been effective in patients with LAM. Chyle does not cause pleural inflammation or fibrosis, and small chylous effusions most often require no intervention once the diagnosis is made. Shortness of breath may mandate drainage, however; and in some cases repeatedly. Pleural effusion may be required to prevent nutritional and lymphocyte deficiencies that can result from repeated taps or persistent drainage. Chemical pleurodesis is an effective alternative for chylothorax from other etiologies.

Referral for lung transplantation should be considered as FEV1 approaches 30% of predicted (Table 2). Some patients qualify based on other factors that profoundly affect quality of life, such as disabling dyspnea or problems maintaining oxygen saturation with lesser degrees of airflow obstruction, however. Bilateral lung transplantation produces slightly better functional outcomes in other obstructive lung diseases, but is not always feasible due to the limited availability of organs and urgency of the need for transplant. LAM patients should avoid exposure to tobacco smoke, discontinue estrogen-containing supplements, and become informed about the potential risks of pregnancy (Table 1).

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Other Support Organizations

Tuberous Sclerosis Alliance: www.tsalliance.org

JLAM (Japan): j-lam.org

FLAM (France): www.orpha.net/nestasso/FLAM

LAM Action (England): www.lamaction.org

ALAMBRA (Brazil): www.alambra.org.br

LAM Trust (New Zealand): www.lam.org.nz

A.I.LAM (Italy): www.ailam.it

AELAM (Spain): personal.telefonica.terra.es/web/aelam

LAM Selbsthilfe (Germany): lam-info.de

LAM Australia: www.LAM.org.au

Tante Mela Foundation (Netherlands): benien@hollandfestival.nl

LAM Canada: www.lamcanada.org