Advances in Lymphangioleiomyomatosis

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Objectives

1. Define lymphangioleiomyomatosis (LAM).
2. Understand the genetic and cellular basis of LAM.
3. Understand the epidemiology of LAM.
4. Be familiar with the clinical presentation and diagnostic evaluation of patients with LAM.
5. Determine the proper therapeutic strategy for patients with LAM.

Abbreviations

4E-BP1 = 4E binding protein; GAP = GTPase activating protein; GTP = guanosine triphosphate; HRCT = high-resolution CT; LAM = lymphangioleiomyomatosis; LOH = loss of heterozygosity; mTOR = mammalian target of rapamycin; PI3K = phosphatidyl inositol 3-OH kinase; S-LAM = sporadic lymphangioleiomyomatosis; TSC = tuberous sclerosis complex

Lymphangioleiomyomatosis (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 (S-LAM) 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.

The most common presentation of LAM is progressive dyspnea on exertion, often in association with a history of pneumothorax or chylothorax. The histopathologic hallmark of the disease is 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, Langerhans" cell histiocytosis, lymphocytic interstitial pneumonitis, and Sjögren's syndrome. Rare syndromes of benign or malignant smooth-muscle metastasis, including benign metastasizing leiomyoma and low-grade leiomyosarcomas, may also produce cystic change and closely mimic LAM. Renal angiomyolipomas–unusual hamartomas containing fat, smooth muscle, and blood vessels–are present in about 70 to 80% of patients with TSC-associated LAM and 50% of S-LAM cases. Hemorrhage into an angiomyolipoma can produce a range of symptoms from chronic intermittent flank pain to acute abdomen with hypovolemic shock. When a history of chylothorax, angiomyolipomata, or known TSC is present, lung biopsy is usually not required for the diagnosis of LAM in nonsmoking female patients with typical thoracic radiographic changes. In the absence of these corroborating features, pathologic confirmation is usually prudent.

Patients with LAM should avoid exposure to tobacco smoke, discontinue estrogen-containing supplements, and become informed about the potential risks of pregnancy. Current therapies for LAM are targeted at antagonizing the action of estrogen, especially with progesterone or gonadotropin-releasing hormone agonists, but there is no convincing evidence that these empiric strategies are effective. Pneumothorax should be managed aggressively with pleural symphysis procedures because the likelihood of recurrence is >70%. Large angiomyolipomas should be evaluated for angiographic embolization. Lung transplantation is an important option for patients with end-stage LAM and outcomes are similar to those for other diseases, but the perioperative complication rate appears to be somewhat higher. Although LAM has recently been reviewed in the PCCU series, substantial progress in the molecular and cellular biology of the disease warrants another look.

The Molecular Pathophysiology of LAM

Great strides have been made in the understanding of the genetic and molecular basis of tuberous sclerosis and LAM in the past 5 years. The short version is that we now know a lot about the genetic basis of LAM and, through parallel work in Drosophila, about the disrupted molecular pathways that lead to abnormal LAM cell growth, movement, and function. Treatment trials based on molecular targets developed in the laboratory have begun.

TSC is an autosomal dominant disorder characterized by hamartomatous growths in multiple organs including the lungs, skin, eyes, kidneys, and CNS.[1] Although familial TSC results from inheritance of germline mutations, *de novo* mutations (which occur during embryogenesis) account for two thirds of TSC cases. LAM occurs in about 30 to 40% of patients with TSC (TSC-LAM).[2-4] Sporadic LAM (S-LAM) occurs in patients who do not have TSC (Table 1). Mother-daughter

transmission of TSC-LAM, but never of S-LAM, has been reported. The latter observation is consistent with the finding that TSC mutations are not found in the circulating blood cells of S-LAM patients.[5] TSC-LAM can result from mutations in either *TSC1* or *TSC2*,[6,7] but both TSC and TSC-LAM are most commonly due to mutations in *TSC2* .

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

Characteristic	TSC-LAM	S-LAM
Estimated no. of patients worldwide	250,000	30,000–50,000
Germline TSC mutations	+	−
Both hits = somatic mutations	−	+
Inheritable	+	−
TSC1/TSC2 mutations reported	33% / 66%	0% / 100%
Angiomyolipomas	70–80% Often multiple/bilateral	40–50% Often single/unilateral
Micronodular pneumocyte hyperplasia	+	Very rare
CNS/skin/eye/cardiac lesions	+	−
Reported in male patients	+	−
Chylothorax	Less common	About 33%
Pneumothorax	Less common	66%

To fully appreciate the progress that has been made, it is important to understand a little about the genetics of tumor suppressor syndromes like TSC. Tumor suppressor proteins regulate orderly cell growth and differentiation by sensing the surrounding environment, transmitting signals to the nucleus, and directly affecting transcription, translation, or cell division. TSC is known to result from mutations in either of two tumor suppressor genes: the hamartin gene (*TSC1*) on chromosome 9 (9q34)[8] and the tuberin gene (*TSC2*) locus on chromosome 16 (16p13.3).[9] Hamartin has no informative homologies with other proteins in the National Center for Biotechnology Information database, while tuberin has a domain with GTPase activating protein (GAP) homology. In the classic tumor suppressor "two hit" paradigm,[10] a mutant copy of a TSC gene is inherited, and a tumor or dysplastic lesion develops when the second copy of the gene is inactivated through a random, somatic mutation. This second mutational event is often a large deletion, resulting in the loss of whole segments of chromosomes. A polymerase chain reaction technique can be used to detect the *loss of heterozygosity* (LOH) for the region containing the genetic locus. When both copies of the TSC gene contain critical mutations, the protein produced by the gene is defective or deficient, protein function is lost, and cell growth, survival, or function becomes dysregulated.

Nothing has focused attention on specific molecular pathways in LAM more than the demonstration that S-LAM also arises from TSC mutations. The first clue was the finding by Smolarek et al[11] that loss of heterozygosity (LOH) for *TSC2* was present in angiomyolipomas and lymph nodes from patients with S-LAM. Soon thereafter, Carsillo et al[12] demonstrated the presence of missense and protein-truncating *TSC2* mutations associated with LOH in the lesional lung and kidney tissue of patients with S-LAM. This finding was subsequently confirmed by Hino, and all S-LAM mutations described to date have been *TSC2* mutations.[12-14] It is important to note that in S-LAM patients, only the lesional tissue in the lung and the kidney, and not the normal tissue or circulating blood cells, contained mutations in TSC genes.[5] This pattern suggests that S-LAM is caused by two somatic mutations rather than an inherited germline mutation (for "hit" one) and a somatic mutation (for "hit" two). Furthermore, Henske's group (Carsillo et al[12]) found that the mutations present in the kidney and lung were identical, suggesting that both cells arose from a common origin. A model for LAM was proposed in which the lung infiltration and cystic destruction is a consequence of benign metastasis of LAM cells from the kidney tumor, axial lymph nodes, or a common progenitor cell. Reports of recurrence of LAM in the donor lung of LAM patients who had undergone lung transplantation are also consistent with the metastatic theory,[15-18] including two in which metastasis was proven by molecular techniques.[18-19] Other rare diseases that result from metastases of benign smooth muscle cells in women include leiomyomatosis peritonealis disseminata, intravenous leiomyomatosis, diffuse leiomyomatosis, and benign metastasizing leiomyomatosis. The metastatic theory of LAM, which is both novel and provocative, suggests new avenues for treatment based on early intervention.[20]

By the year 2000, it was clear that LAM was caused by the loss of tuberin (or hamartin) function, but it was not clear exactly how tuberin regulated orderly cell growth. Around that time, Ito and Rubin[21] first reported that the enlarged eye cells characteristic of the mutant fruit fly gene *gigas*, originally described in 1976 by Ferrus and Garcia-Bellido, could be induced by genetic inactivation in the fly homolog for tuberin.[21] The loss of tuberin resulted in a defect in cell cycle control, which caused the cells to repeat S phase without entering M phase. The mechanism of dysregulated growth inhibition in tuberous sclerosis was elucidated in 2001 by several laboratories that reported that tuberin and hamartin are key members of the phosphatidyl inositol 3-OH kinase (PI3K)/PKB (Akt)/S6K signaling pathway that regulates cellular size and proliferation.[22-

[24] The positioning of tuberin in the Akt/S6K pathway was accomplished by elegant epistatic genetic analyses and one model of these rapidly developing data is shown in Figure 1. These and other studies have demonstrated that tuberin and hamartin associate into a complex that functions as a master regulator for the kinase mammalian target of rapamycin (mTOR), through an intermediate G protein called Rheb.[25,26] The intact tuberin/hamartin complex acts as a GAP for Rheb, and maintains Rheb in an inactivated, nonphosphorylated state (Rheb-guanosine diphosphate). Phosphorylation of tuberin by Akt inactivates the GAP activity of the tuberin/hamartin complex, increases the abundance of Rheb- guanosine triphosphate (GTP), and permits activation of downstream targets through mTOR to S6 and the initiation factor 4E binding protein (4E-BP1). The end result is stimulation of protein synthesis, cell motility, and cell growth.[27] Genetic mutations that result in the absence or dysfunction of tuberin or hamartin, as occur in patients with tuberous sclerosis and LAM, cause constitutive activation of S6K and 4E-BP1. Goncharova et al[28] demonstrated abundant S6 phosphorylation and unregulated cell growth in LAM cells isolated from patients who had undergone lung transplantation. They further demonstrated that rapamcyin, which binds and inactivates mTOR, a downstream target in the Akt pathway, could block inappropriate signaling, mimic the function of the tuberin/hamartin complex, and restore orderly cell growth. These studies form the basis for the trial of rapamycin in patients with tuberous sclerosis and LAM that is currently underway in the United States and Europe.

Fig 1.

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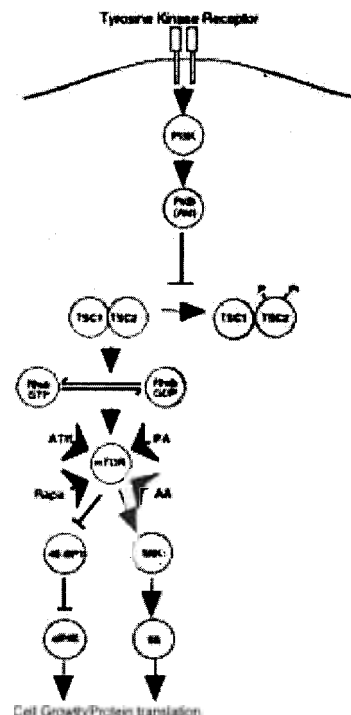
Figure 1. Tuberous sclerosis proteins regulated signaling through the Akt growth and protein translation pathway. A phosphorylated growth factor receptor activates PI3K followed by Akt. Activated pAkt phosphorylates *TSC2*, which blocks its GAP activity. When not phosphorylated, *TSC2* complexed with *TSC1* functions as a GAP for Rheb, maintaining Rheb in an inactivated Rheb-guanosine diphosphate state. Activated Rheb (Rheb-GTP) is therefore abundant when *TSC1* or *TSC2* is missing or when *TSC2* is phosphorylated. Rheb-GTP activates mTOR in a manner that is potentiated by the availability of amino acids, phosphatidic acid, and ATP, and blocked by the absence of these substrates or the presence of rapamycin. Activated mTOR phosphorylates downstream targets S6K and 4E-BP1. pS6K phosphorylates S6 and 4E-BP1 releases eIF4E, which together activate the translational machinery and promote cell growth.

Many questions remain unanswered. What is the molecular basis of the extensive cystic remodeling of the lung in LAM? Similar cystic changes occur in patients with metastatic endometrial stromal sarcoma, benign metastasizing leiomyoma, and mesenchymal cystic hamartoma of the lung, implicating an inherent capability of ectopic smooth muscle cells to result in cystic remodeling in the lungs. LAM lesions have been shown to be associated with protease imbalances, including up-regulation of matrix metalloproteinase -2 and matrix metalloproteinase-9,[29,30] and down-regulation of tissue inhibitor of metalloproteinase-3.[31] Why is LAM restricted to women? Presumably, estrogen plays a role in LAM cell migration, infiltration, or proliferation, or in secretion of destructive proteases.[27,32] There are anecdotal reports of pneumothorax

associated with menses and very early in pregnancy, which suggests that sex hormones may modulate LAM cell function in a time frame that is more consistent with an alteration in proliferation or secretion of proteases than with longer-term processes such as seeding. Data suggesting that pharmacologic antagonism of estrogen action alters the rate of decline in lung function are lacking. Estrogen has been shown to modulate signaling through the Akt pathway that is known to be dysregulated in LAM.[32,33] Is all LAM metastatic? This question will be difficult to answer. Only 50% of patients with sporadic LAM have angiomyolipomas, so they cannot be the only source.[34] It is possible that a tuberin- or hamartin-deficient stem cell that originates in the bone marrow or the lymphatic system seeds the lung and the kidney.

Epidemiology

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 in a man have been reported.[35,36] Sporadic LAM has never been reported in a man. All races are affected. In one LAM Foundation survey of 432 patients, Caucasians made up 91% of patients, Asians 4%, African Americans 3%, and Hispanics 1%. TSC does not preferentially affect any particular ethnic group, and access to health care, education, and the Internet likely play important roles in the skewed ethnic distribution for LAM reflected in the Foundation database.

The prevalence of S-LAM is roughly estimated to be approximately 3 to 5 per million people (30,000 to 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. TSC occurs in approximately 1 of every 6,000 births, and the estimated number of TSC patients on earth is about 1 to 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 sex distribution of TSC and recent findings that 30 to 40% of women with TSC have cystic changes consistent with LAM.

Although TSC-LAM appears to be roughly 6 to 8 times as common as S-LAM, patients with TSC-LAM represent only a small fraction of the LAM patients seen in pulmonary clinics. Indeed, only 10% of the 734 patients registered with the LAM Foundation (as of August 2003) have TSC. Furthermore, LAM is a major clinical problem in only about 5 to 10% of TSC patients[37] and is the primary health priority for only a few (<10) of the 300 patients in our 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 of the possibility that TSC-LAM and S-LAM are fundamentally different diseases.

Clinical Presentation

The mean age at diagnosis of S-LAM is about 35 years, after an average symptomatic period of 3 to 5 years.[38-40] However, new diagnoses of LAM have been reported in patients ranging in from age 12 to 75 years. Most women registered with the LAM Foundation complained of dyspnea on exertion (51%) in their Foundation enrollment questionnaire. Symptoms of cough (6%), chest pain (5%), hemoptysis (5%), chyloptysis, and wheezing were all considerably less common. Pneumothorax had occurred in 66% of registered LAM patients at some point in the course of their illness, with slightly more episodes on the right than on the left. First recurrences after an initial pneumothorax occured 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.[39] Chylothorax occurs in about 33% of LAM patients at some point in their illness. Angiomyolipomas are present in most patients with LAM, including 70 to 80% of patients with TSC-LAM and 40 to 50% of patients with S-LAM.[34] Spontaneous hemorrhage into angiomyolipomas may produce severe flank or abdominal pain, acute hypotension, and/or anemia, occasionally in association with circulatory collapse. Rarely, LAM presents as retroperitoneal masses or adenopathy that 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 high-resolution CT (HRCT) screening of asymptomatic TSC patients identifies a population with fewer and less severe pulmonary manifestations,[3] including a lower prevalence of chylous pleural effusions, pneumothoraces, and hemoptysis. The chest radiograph and lung function studies are often normal.[41] 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 the cancer antigen CA-125, which can lead to a misdirected search for ovarian

carcinoma. *TSC1* and *TSC2* genotype analysis on DNA from peripheral blood cells is commercially available through Athena Diagnostics (Worcester, MA), but mutations are not present in peripheral blood cells from S-LAM patients and the clinical utility in TSC-LAM patients has not yet been established.

Pulmonary Physiology

Lung function may be normal in patients with LAM, especially in TSC-LAM patients identified through screening.[3] LAM most commonly presents with reductions in FEV_1 out of proportion to the reduction in FVC, consistent with obstructive physiology.[42] Reversible airflow obstruction is present in up to 20 to 25% of patients.[43] Elevations in residual volume and the ratio of residual volume to total lung capacity 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 the restrictive component that has been reported. Impaired gas exchange and hypoxemia occur, but hypercapnia is rare even in end-stage disease. Diffusion capacity of the lung for carbon monoxide is frequently reduced, and in some cases may be reduced out of proportion to the obstructive defect.

Radiology

The chest radiograph in a patient with LAM can be surprisingly unremarkable, even in the presence of moderately advanced disease.[43] 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. HRCT scanning of the chest is the most helpful radiologic modality in LAM, and usually demonstrates profuse, thin-walled cysts in all lung fields (Fig 2). Diffuse nodular changes consistent with micronodular pneumocyte hyperplasia may be present. Abdominal CT scanning is positive in more than 75% of patients, and may reveal fat-containing renal or extrarenal angiomyolipomas, axial lymphadenopathy, cystic or noncystic lymphangiomyomas, or chylous ascites[43] (Fig 3). 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 (Fig 4).
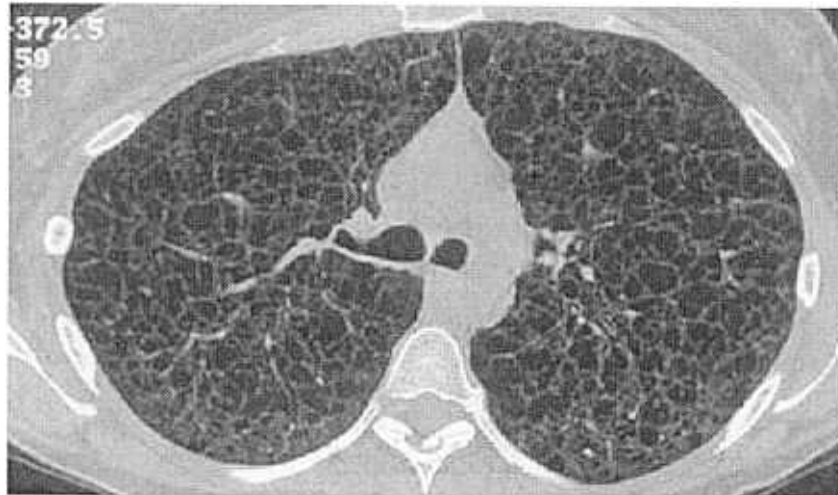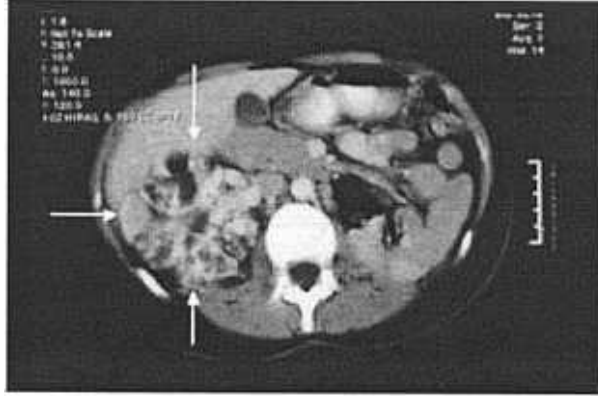
Fig 2.

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Figure 2. HRCT scan of the chest in a patient with LAM. Note diffuse replacement of the pulmonary parenchyma with thin-walled cysts.
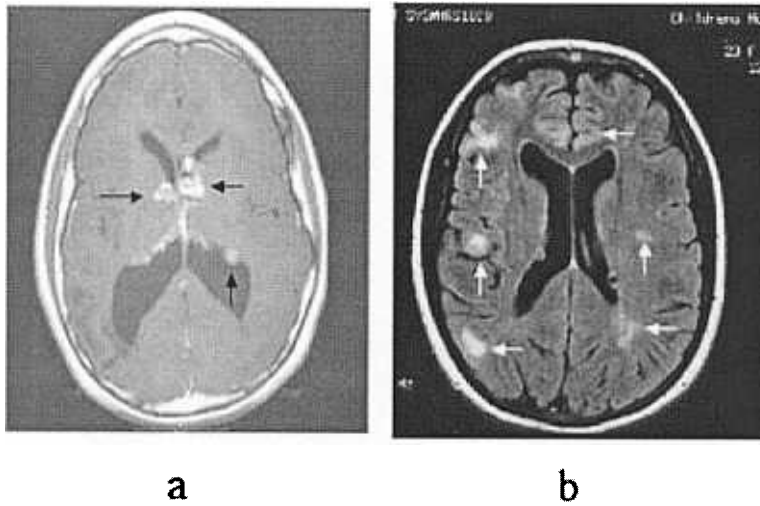
Fig 3.

Figure 3. Abdominal CT scan in a LAM patient with an angiomyolipoma. Note diffuse involvement of the right kidney with an angiomyolipoma (*arrows*). The solid and fat density is characteristic of angiomyolipomas.

Fig 4.

a   b

Figure 4. CT scan of the head in two patients with tuberous sclerosis. *Left*, subependymal nodules are present (*arrows*). *Right*, cortical tubers are present (*arrows*).

Pathology

Grossly, the lungs are enlarged and diffusely cystic, with dilated airspaces as large as 2.0 cm in diameter.[44] Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of the lung parenchyma, airways, lymphatics, and blood vessels associated with areas of thin-walled cystic change (Fig 5). 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 called HMB-45, developed against the premelanosomal protein gp100. This immunohistochemical study is very useful diagnostically because 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, may occur in patients with TSC in the presence or absence of LAM.

Fig 5.   McCormack, Young
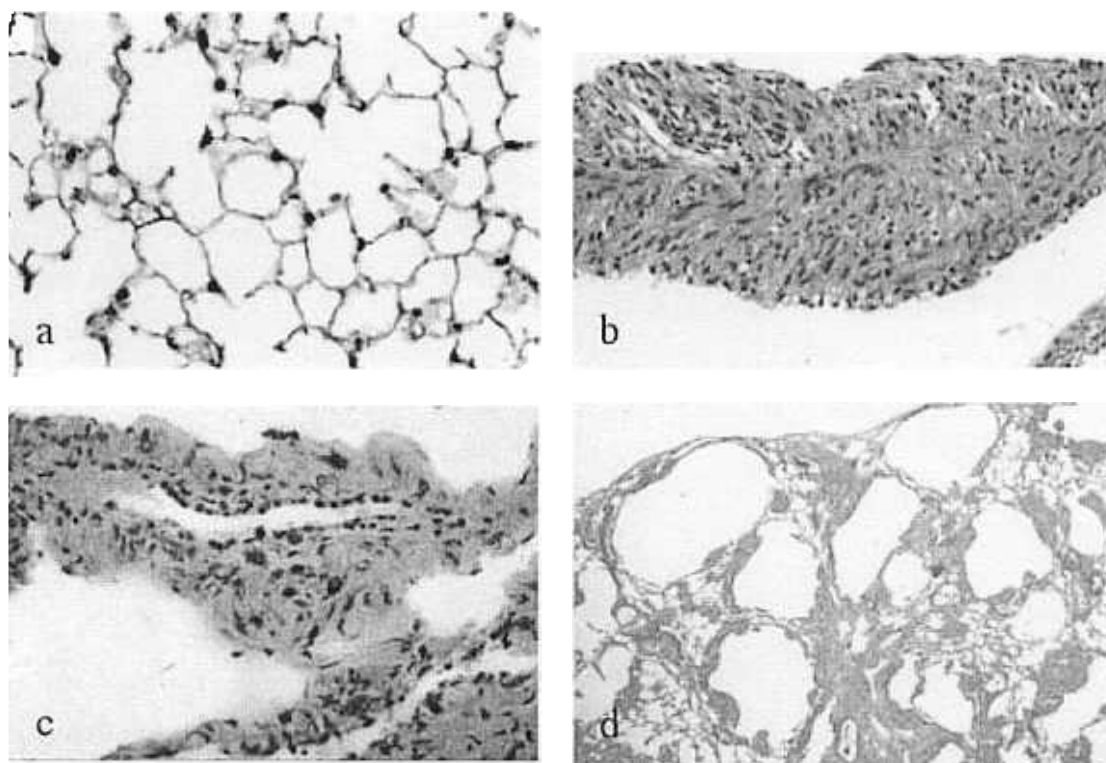
Figure 5. Pathologic features of LAM. *Upper left,* normal lung tissue with type II cells stained with antibody to surfactant protein A is shown. *Upper right,* an alveolar septal wall is expanded with spindle-shaped and epithelioid LAM cells. *Lower left,* HMB 45 staining. *Lower right,* cystic remodeling of the pulmonary parenchyma.

Diagnosis

Diagnostic dilemmas in LAM fall into two major categories: (1) how to identify LAM in women presenting with progressive dyspnea and/or pneumothorax; and (2) how to make the diagnosis of LAM in a woman with diffuse cystic changes on 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. As a first step, we submit that HRCT scanning should be performed for all young, nonsmoking women who present with dyspnea and a history of pneumothorax. While it is true that primary spontaneous pneumothorax is a more common cause of pneumothorax in young women than LAM, primary spontaneous pneumothorax is usually associated with tobacco use. Although pneumothorax can also occur in the setting of asthma, these patients usually have significant bronchial hyperreactivity and relapsing/remitting bronchospasm that is characteristic of that much more common condition.

The diagnosis of LAM occurs to most pulmonary physicians when pneumothorax recurs, occurs in patients with TSC, or occurs in a patient with chylothorax. HRCT scanning of the chest is performed routinely once the diagnosis is considered. Interpretation of the HRCT by expert radiologists leads to the correct diagnosis of LAM about 80% of the time. Unfortunately, a diagnostic accuracy of 80% is not adequate in the setting of life-threatening lung disease. In 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 status, use of birth control pills, seizure history, and family history of TSC, should be obtained. Physical evidence of tuberous sclerosis should be sought, including acnelike angiofibromas on the face, subungual fibromas, shagreen patches, ash leaf lesions, and other hypomelanotic lesions (such as confetti lesions) that fluoresce under the Wood's lamp. 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 to screen for cortical tubers or other clinically occult manifestations of TSC. The α 1 -antitrypsin level should be measured to screen for hereditary forms of emphysema, and serologies for Sjögren's syndrome considered if xerostomia and xeroophthalmia 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 often be made with certainty and lung biopsy is 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, but success with a bronchoscopic approach is an exception.

Screening

The Tuberous Sclerosis Alliance recommends an HRCT of the chest in all women with TSC after reaching the age of 18 years.[1]

Treatment and Prognosis

Although patients with LAM have been managed empirically with antiestrogen therapies, there is no proof that these strategies are effective. In our clinic, asymptomatic patients are usually not treated. Therapies that are currently discussed with patients who suffer progressive decline in lung function include progestins (both oral and IM) and gonadotropin-releasing hormone agonists. We generally suggest prescribing oral progestins at doses that are sufficient to suppress serum estrogen production (*eg*, norethindrone acetate, 10 mg po qd to bid), rather than the suprapharmacologic IM progesterone doses that have been propagated in the literature (*eg*, medroxyprogesterone (Depo-Provera; Upjohn Co; Kalamazoo, MI), 400 mg IM once a month]. Progestins can cause fluid retention and mood swings. Gonadotropin-releasing hormone agonists (*eg*, Lupron; TAP Pharmaceutical Products Inc; Lake Forest, IL) have been used in 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. Ovariectomy is no longer recommended very often because the benefits are unknown and the risk of bone and heart disease is increased. In the face of such therapeutic uncertainty, all of our decisions to treat are made jointly by the patient and physician after thorough discussions of the risks and limited available data.

Estrogen-containing medications should be discontinued. Patients should be advised that pregnancy has been reported to result in exacerbations of LAM. However, the risk of pregnancy in LAM has not been rigorously studied, and decisions regarding the advisability of pregnancy should be made on an individual basis.

A trial of bronchodilators should be considered in patients with LAM. Based on extrapolation of data derived from the study of COPD populations, oxygen use prolongs life in hypoxic patients. Oxygen should be administered to maintain oxyhemoglobin saturations of >90% at rest, with exercise, and during sleep. Bone densitometry should be considered in all patients who are immobilized and/or taking antiestrogen therapies. Calcium and bisphosphonate therapy should be prescribed 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 with obstructive lung disease, but studies that document improvements in exercise tolerance have not been done.

We do not generally restrict air travel in LAM patients. Of 395 patients who responded to the LAM enrollment questionnaire, 8 reported an episode of pneumothorax during air travel. In 4 cases, there was some symptomatic evidence that the pneumothorax was present at the time the patient boarded the plane. Of more than 200 LAM patients who have been flying to and from the National Institutes of Health site for the LAM clinical study, there have been no adverse events during air travel. Our recommendation is to obtain a chest radiograph prior to boarding a plane if pleuritic chest pain or unexplained persistent shortness of breath is present.

Pleural disease should be aggressively managed. More than 65% of patients with LAM develop pneumothorax and the average number of pneumothoraces per LAM patient registered with the Foundation is 3.5. We advocate the use of a pleural symphysis procedure 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 resulting from large fluid collections may mandate drainage, however; and in some cases, repeated taps are needed. Pleural symphysis may be required to prevent nutritional and lymphocyte deficiencies that can result from repeated procedures or persistent drainage. Chemical pleurodesis is an effective alternative for chylothorax from other etiologies.

As with other obstructive lung diseases, referral for lung transplantation should be considered as the FEV_1 approaches 30% of predicted levels. Some patients, however, qualify based on other factors that that profoundly affect quality of life, such as disabling dyspnea or problems maintaining oxygen saturation with lesser degrees of airflow obstruction. Bilateral lung transplantation has been reported to produce slightly better functional outcomes in other obstructive lung diseases that have been studied, but is not always feasible owing to the limited availability of organs and urgency of the need for transplant.

Renal angiomyolipomas may require embolization or cauterization if bleeding occurs, which is thought to be more common when the diameter of the tumor exceeds 4 cm. Nephron-sparing partial resections may be required for very large tumors.

Support organizations available for LAM patients include The LAM Foundation (http://lam.uc.edu/) and other LAM organizations (which are linked to the Foundation Web site) in Japan (J-LAM), France (Association FLAM), England (LAM Action), New Zealand (New Zealand LAM Charitable Trust), and Italy (A.I.LAM). The Tuberous Sclerosis Alliance is also a valuable resource (http:// http://www.tsalliance.org/).

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