Lymphangioleiomyomatosis (LAM) is a rare disease that affects women, primarily in their reproductive years. It is characterized by the nonneoplastic proliferation of atypical smooth muscle cells within the lung parenchyma and elsewhere, leading to progressive loss of lung function and, ultimately, death.

The two most common presenting symptoms of LAM are dyspnea on exertion and pneumothorax.1-3 Other common signs and symptoms include nonproductive cough, hemoptysis, chylous pleural effusion, and chylous ascites.1-4 There is no known familial tendency, although the pathologic findings in LAM are identical to those found when tuberous sclerosis complex (TSC), an autosomally inherited disorder, involves the lung.5 The etiology of the disease and the efficacy of currently utilized treatments are unknown. The goal of this article is to review the current understanding of LAM.

HISTORICAL PERSPECTIVE

The 1966 article by Cornog and Enterline6 is the first significant collection of patients with what is now known as LAM. In this article, the authors reported six cases of what they termed “lymphangiomyoma.” In addition to their cases, the authors included 14 cases from the literature that they believed, based on histologic features, represented the same disease entity. These cases had been published under various terms, including lymphangioma, lymphangiomymoma, lymphangiopericytoma, leiomyomatosis, lymphangiomatous malformation, and intrathoracic angiomatous hyperplasia. All symptomatic cases presented with dyspnea and all but two had chylous pleural effusions. Although several cases were reported as “tumors,” at least nine had documented cystic pulmonary parenchymal disease in addition to the mediastinal and/or retroperitoneal masses.

In these early reports, investigators were unsure as to the possible malignant potential of the lesions. Although “diffuse infiltration of local soft tissues and the extensive involvement of lymphatics and lymph nodes” might suggest a malignant condition, Cornog and Enterline6 pointed out that “the highly organized structure of the lesion,” the “absence of significant cellular atypia or mitotic activity,” and the absence of distant metastases argued against malignancy. They suggested that lymphangiomymoma is better understood as a hamartomatous condition and that there was “little good evidence” that the lesion arises as a reaction after a primary rupture of the thoracic duct, as previously suggested by Laipply and Sherrick.7 Instead, they theorized that “the pulmonary and mediastinal lesions are of multifocal origin in response to a single pathological stimulus, perhaps genetically determined, acting simultaneously on smooth muscle in both locations.”6 The authors also pointed out that the lymph node lesions seemed to be identical to those reported in some cases of TSC and that the pulmonary parenchymal lesions “resemble very closely, both grossly and microscopically” those in TSC.6
THE RELATIONSHIP BETWEEN LAM AND TSC

TSC is an autosomally inherited disorder characterized by mental retardation, seizures, and facial angiofibromas. Twenty-five to 50% of patients with TSC have a family history of the disorder; the remaining cases are believed to be caused by either spontaneous mutation or incomplete penetrance. TSC was first reported by von Recklinghausen in 1862. Later, in 1880, Bourneville termed it “tuberosus sclerosis” in reference to the potato-like CNS lesions that are found.

Pulmonary parenchymal changes were associated with TSC as early as 1918 and 1939. The pathologic findings in the lung and lymph nodes are identical to those found in LAM. Pulmonary symptoms are similar in isolated LAM and LAM associated with TSC: dyspnea, nonproductive cough, pneumothorax, hemoptysis, and chylothorax. The incidence of pulmonary involvement in TSC seems to be low; estimates are < 0.1 to 2.3%. In 1971, Dwyer et al reviewed the literature and determined that women accounted for 84% of patients with TSC associated with pulmonary involvement. However, many of the cited cases involving men did not include histologic descriptions of the pulmonary lesions. Interestingly, of the two men described by Dwyer et al, one did not undergo lung biopsy and the other, whose biopsy specimen was said to show “diffuse infiltration by vascular plain muscle,” had underlying panhypopituitarism with “androgenic lack.” Because more recent reports documented the nature of the pulmonary parenchymal lesions with biopsy or CT scan are all of women, it is likely that the pulmonary LAM pathology occurs only in a subset of women with TSC. Women with TSC who develop pulmonary LAM were said by Dwyer et al to have “milder stigmata of the disease,” based on their early review of the literature. Seizures and mental retardation may or may not be present. For instance, Torres et al described three women with TSC who had both pulmonary and extrapulmonary LAM. One had seizures and mental retardation, and one had seizures without mental retardation. In general, it seems that pulmonary involvement with TSC tends to be more common in women without mental retardation.

The manifestations of TSC may not be consistent within families. For instance, Hauck et al described a family in which TSC appeared in five generations and in which pulmonary involvement was found only in the most recent generation. Identifying underlying TSC in patients with pulmonary LAM is probably important for genetic counseling because normally intelligent women with TSC may have “grossly retarded children with more complete forms of the disease.” An example of such a case is provided by Lie et al who describe a woman with pulmonary TSC and normal intelligence who had a son with TSC and mental retardation. In fact, the patient was not diagnosed as having TSC until after this son’s birth. Although the pulmonary involvement tends to occur in adult life, the mortality of patients with TSC-associated LAM does not seem to differ from patients with TSC alone.

Given that the symptoms, radiographic features, and histopathologic features of LAM are identical to those in patients with pulmonary involvement of TSC, many investigators have suggested that LAM may be closely related to, or in fact be, a forme fruste of TSC. Another argument in favor of an association is the fact that both LAM and TSC may be associated with the rare kidney tumor angiomylipoma. In fact, the distinction between the two diseases may be somewhat blurred in certain cases. For instance, renal angiomylipomas are often considered to be an associated finding in women with LAM, but in some classifications, a patient with angiomylipoma and pulmonary LAM meets the criteria for a diagnosis of TSC. The nature of the possible relationship between LAM and TSC remains unclear.

CLINICAL FEATURES AND EPIDEMIOLOGY OF LAM

LAM occurs exclusively in women. An early report of the histopathologic finding of LAM in a man was later corrected. In most case series, the mean age at disease onset is in the early 30s. The youngest patient described experienced dyspnea at age 9 years and was eventually diagnosed by lung biopsy specimen at age 11 years. Several patients have been diagnosed as having LAM after menopause, even as late as 75 years old. Many of the patients diagnosed as having LAM after menopause were being treated with exogenous estrogens and in some cases, no specific mention is made of such medication. However, symptoms can develop after menopause in the absence of exogenous estrogens.

Because the first symptoms of the disease may occur before an abnormality is detectable by chest radiographs (CXR) or pulmonary function tests, and because even when such abnormalities exist, patients may be initially misdiagnosed, there is often a delay between the onset of symptoms and accurate diagnosis. In the series of Taylor et al of 32 patients, the diagnosis of LAM was established an average of 44 months (range, 1 to 219 months) after the initial manifestations of the disease. In another smaller
series, the average duration of symptoms before diagnosis was 7.4 years (range, 1 to 27 years). Initial misdiagnoses have included asthma, COPD, idiopathic pulmonary fibrosis, or interstitial lung disease of unknown etiology, sarcoidosis, idiopathic pulmonary hemosiderosis, paracut-induced lung disease, and tuberculosis. Many of the case series do not describe the racial background of the patients. In the 1975 review of 28 cases by Corrin et al, 25 were white, 1 was African-American, 1 was Filipino, and 1 was Chinese. The largest published collection of cases describes 46 patients from Japan, Korea, and Taiwan.

The most common presenting symptoms of LAM are dyspnea and pneumothoraces. In the 1975 review by Corrin et al20 of 28 cases, breathlessness was the presenting symptom in 13 and pneumothorax in 6. In the 32 patients described by Taylor et al, pneumothorax was the most common presenting symptom, followed by dyspnea. Rarely, bilateral spontaneous pneumothoraces have been reported as the presenting feature in LAM, with or without underlying TSC. Cough is also a fairly common presenting symptom, being present in 9 of 17 patients (53%) in one series32 and in 25 of 41 patients (61%) in another series.4 In addition to these common presenting symptoms, hemoptysis, chest pain, and chyloous pleural effusion, if not present at presentation, often develop during the course of the disease. Pneumothoraces are often recurrent and often occur in patients with normal CXRs.3,38,39 Interrupted lymph flow may also result in several less common manifestations such as chylous ascites,27,29,40–42 chyloptysis,41,43 chyluria,1 chyloous pericardial effusion,7,30,31 and lower-extremity lymphedema.44 Chylous ascites may occur in the absence of pleural effusion45,46 and can be the presenting symptom, even in the absence of apparent pulmonary parenchymal involvement.47 Spontaneous pneumoretropharynx has also been reported in a patient with LAM who had previously undergone talc pleurodesis.48

The physical examination may reveal crackles or rhonchi, which were present in 10 (22%) and 6 (14%) patients, respectively, in the recent series of 42 patients by Kitaichi et al.4 The examination may also reveal evidence of pleural effusion or ascites. Clubbing is apparently uncommon, being reported in only 2 of 46 patients by Kitaichi et al, in 1 of 6 patients by Carrington et al, and in rare case reports.50 No specific laboratory abnormalities have been reported in patients with LAM. Lieberman et al51 found elevated angiotensin-converting enzyme levels in two of three patients tested. Most large series of patients with LAM do not include data on angiotensin-converting enzyme levels, but there are anecdotal reports of elevated levels in LAM patients.52,53 Finally, there is a single report of a patient with persistently elevated CA-125 levels.45

Symptoms of LAM have been reported to develop54–57 or worsen32,36,58,59 during pregnancy. In 1977, Carrington et al49 reported the case of a 23-year-old woman who experienced cough, chest pain, dyspnea, and hemoptysis during her first pregnancy. The CXR was normal at that time. These symptoms recurred during her second pregnancy and, at age 28 years, during her fourth pregnancy, her dyspnea increased markedly. In another case,50 dyspnea developed during the fifth month of the patient's second pregnancy, resolved after delivery, and returned within 1 year to become slowly progressive. In yet another case,60 a pregnant patient without a history of LAM experienced massive bilateral chylothorax that was related to mediastinal lymph node involvement with LAM. A chest CT scan showed no evidence of pulmonary parenchymal changes.

Patients with pulmonary involvement of TSC may also develop pulmonary symptoms during pregnancy.15,16 Haack et al61 described a woman with pulmonary involvement of TSC whose first pulmonary symptom was a pneumothorax during her first pregnancy. Thoracotomy was performed for pleurodesis, and the lungs showed gross surface cysts and nodules. The pregnancy was terminated. Three months later, a second pneumothorax developed during a second pregnancy. During this pregnancy, she experienced progressive dyspnea and deterioration in lung function. In their review of the literature in 1971, Dwyer et al52 found two patients with "deterioration associated with the development of pneumothorax during pregnancy." Finally, Kerr et al61 reported the occurrence of acute hemorrhage from a renal angiomyolipoma during pregnancy. This patient was known to have angiomyolipoma in association with LAM, which was being treated with medroxyprogesterone. Despite this treatment, she became pregnant and, at 37 weeks' gestation, her right renal tumor hemorrhaged acutely. She underwent urgent cesarean section and subsequent arterial embolization of the tumor. Because of the anecdotal nature of these reports, it is not clear whether pregnancy caused the acute progression of LAM or whether the hemodynamic and ventilatory perturbations associated with pregnancy simply brought out the symptoms of LAM that would otherwise not have been noticed until the disease progressed further.

The administration of exogenous estrogens has also been anecdotally associated with new or progressive symptoms of LAM. In 1978, Kreisman et al61 described a patient with undiagnosed interstitial lung disease who was placed on a regimen of exogenous estrogens after undergoing total hysterectomy.
with bilateral salpingo-oophorectomy for benign uterine leiomyomata. Within 2 months, she was admitted to the hospital for cough, increasing dyspnea, and chest pain. She was found to have a new chylous pleural effusion, and subsequently died during the hospitalization. In 1987, Shen et al. presented a similar case. This patient had undiagnosed underlying interstitial lung disease (ILD) when she was placed on a regimen of cyclic estrogen and progesterone for osteoporosis. With the addition of these medications, her dyspnea progressed markedly. Discontinuing treatment with the hormonal medications and adding tamoxifen stabilized her symptoms.

In addition to these cases, several of the few case reports of postmenopausal women with LAM have concerned women receiving hormone replacement therapy. Also, several authors report disease onset or worsening while patients are taking oral contraceptives. Despite these reports, Wahedna et al. were unable to detect an association between the use of oral contraceptives and LAM in their case control study. Further, only 1 of the 46 LAM patients described by Kitauchi et al. had used oral contraceptives before the onset of symptoms.

Clinical Features of Associated Angiomyolipomas

Renal angiomyolipomas are rare hamartomatous tumors of the kidneys that are composed of smooth muscle, blood vessels, and adipose tissue. They may occur in isolation or be part of the TSC. Renal angiomyolipomas are often seen in patients with LAM. In three recent case series, renal angiomyolipomas were present in 7 of 21 (33%), 8 of 17 (47%), and 8 of 14 (57%) patients with LAM. Thus, 23 of these 52 patients (44%) with LAM had renal angiomyolipomas and in 11 of these patients, the tumors were bilateral. There were no differences in age or disease duration between patients with and without angiomyolipoma. In most cases, the tumors cause no symptoms, but they may be associated with flank pain, hematuria, or a palpable mass. When symptoms develop, nephrectomy, partial nephrectomy, or arterial embolization may be necessary. Renal cell carcinoma may develop in association with angiomyolipomas but the frequency of this occurrence is unknown. There has been only one report of a LAM patient with angiomyolipoma developing renal cell carcinoma.

Pathologic Features of LAM

In the lung, the pathologic characteristics of LAM are diffuse cystic changes associated with the proliferation of atypical smooth muscle cells (LAM cells) (Figs 1 and 2). These smooth muscle cells are characterized by elongated, closely packed, spindle-to-oval-shaped cells. LAM may involve any structure in the lung, including the pleura and the walls of the bronchioles, pulmonary arteries, venules, and small airspaces. The most common complications of LAM—pneumothorax, chylous pleural effusion, and hemoptysis—can be explained at least in part by the proliferation of these atypical smooth muscle cells around the bronchioles, lymphatics, and venules, respectively. The bronchioles may be circumferentially narrowed by the peribronchial proliferating tissue. Also, the proliferating tissue can protrude into the bronchiolar lumen. The small airway obstruction is believed to contribute to the development of parenchymal cysts and pneumothorax. The walls of the airspaces may be thickened focally or diffusely. Foci of hemosiderin-laden macrophages may be present in the airspaces and interstitium as remnants of past hemorrhage. Involvement of the venules...

Figure 1. Gross specimen of lung tissue obtained at autopsy from a patient with LAM who died because of a tension pneumothorax. Extensive cystic changes are evident.
have been described as a mixed proximal acinar and irregular emphysema. It has been suggested that the emphysema may develop because of airflow obstruction related to narrowing of the lumina of the bronchioles and small bronchi by the proliferating smooth muscle. However, in some biopsy specimens, emphysematous airspaces are associated with more distal smooth muscle and normal-appearing bronchioles. Further, using morphometric analysis on the lungs of three patients (two with TSC and one with LAM), Sobonya et al concluded that the emphysema contributes more to airflow limitation than does muscular proliferation in the small airways. In these cases, it seemed as though the loss of alveolar support resulted in collapsed, tortuous small airways and that this lesion predominated over direct impingement of the airways by proliferating smooth muscle cells. Fukuda et al have postulated a different mechanism for the development of the emphysema-like lesion. They propose that these lesions are the result of the degradation of supportive elastic fibers, which is caused by an imbalance between elastase and α1-antitrypsin. They raise the possibility that electron-dense granules in the cytoplasm of the proliferating smooth muscle cells may contain some form of elastase and that the release of this enzyme could be responsible for the development of emphysema. Supporting the elastase hypothesis is a recent report by Hayashi et al who suggest that enzymatic destruction of pulmonary connective tissue components does occur and that it is an imbalance of matrix metalloproteinases and their inhibitors that is responsible for the cystic destruction of the lung.

The thoracic duct may be grossly enlarged in LAM. These enlarged ducts are divided into multiple microscopic channels by a “meshwork of smooth muscle fibers.” Even when the thoracic duct appears grossly normal, microscopic examination may show papillary proliferation of smooth muscle cells. Lymph nodes, both in and outside of the chest (in the mediastinum, hilum, mesentery, and retroperitoneum), may also be involved. These involved nodes appear grossly spongy and resilient and microscopically show progressive replacement by proliferating smooth muscle cells. As in the thoracic duct, smooth muscle proliferation causes the pleomorphic subdivision of the lymph channels. Other associated abnormalities include renal angiomylipomas and abdominal or pelvic masses that may be cystic and histologically appear as cords of smooth muscle cells and a network of lymphatic channels.

Numerous authors have reported the presence of estrogen receptors (ERs) and progesterone receptors (PRs) in LAM tissue. Brentani et al found cytosolic receptors for estrogen, proges-

Figure 2. Histopathology of LAM: Top: blood-filled ectatic spaces with interspersed spindle shaped “LAM cells” (arrow) (original magnification, ×10; hematoxylin-eosin stain) Center: bland spindled nuclei (LAM cells) adjacent to a pulmonary vein (original magnification, ×40; hematoxylin-eosin stain) Bottom: LAM cells adjacent to interlobular septum demonstrating immunoreactivity to HMB-45 (brown).
terone, and glucocorticoids, but not androgen, in homogenized lung tissue obtained at autopsy in a patient with LAM. Because normal lung tissue does not display these receptors,\textsuperscript{77} their presence raises the possibility that these hormones affect LAM tissue. Likewise, Graham et al\textsuperscript{33} found evidence of cytosolic receptors for both estrogen and progesterone in lung tissue from a patient with LAM. Further, using a nuclear-binding assay for these hormones, these investigators found specific nuclear binding of progesterone in LAM lung tissue. However, despite significant cytosolic estrogen binding, nuclear binding for this hormone was not found.

The above reports document ERs and PRs in LAM tissue, but the methods used could not localize these receptors to the abnormally proliferating cells. Subsequently, Berger et al\textsuperscript{77} found ERs and PRs in the nuclei of the proliferating smooth muscle cells in a biopsy specimen from one patient and ERs only in another patient. That is, the receptors were localized to the abnormally proliferating cells. Likewise, Colley et al\textsuperscript{76} used immunohistochemistry to show that the nuclei of the proliferating smooth muscle cells stained darkly for PRs and more weakly for ERs.\textsuperscript{76} Approximately 80\% of the abnormal cells stained positive for ERs, and nearly all stained positive for PRs, whereas normal smooth muscle (bronchial and vascular) did not stain for either PRs or ERs. These authors examined several other organs and found similar staining patterns (PR positive, ER weakly positive) in normal myometrium and in leiomyomas, whereas colonic, bladder, and normal lung smooth muscle stained negative. Prostatic stroma showed scattered PR-positive nuclei.

Other immunohistochemical studies of LAM cells have focused on HMB-45, a monoclonal antibody that recognizes antigens in the cytoplasm of melanoma cell lines and that more recently has been noted to bind to LAM cells.\textsuperscript{79} Although the significance of HMB-45 positivity remains unclear in LAM, such staining has proved to be diagnostically useful. For example, proliferating LAM cells are HMB-45 positive, whereas normal lung tissue (particularly the normally present smooth muscle) and a variety of other pulmonary lesions (including smooth muscle proliferation in fibrotic interstitial lung disease) are HMB-45 negative.\textsuperscript{78} The proliferating LAM cells were not all HMB-45 positive, reflecting some degree of phenotypic heterogeneity. Because HMB-45 positive cells are detectable in transbronchial biopsy specimens in addition to open lung biopsies,\textsuperscript{78} Bonetti et al\textsuperscript{78} suggest that HMB-45 may be a useful marker of LAM, particularly when only a transbronchial biopsy specimen is available. Guinee et al\textsuperscript{80} also suggest that in the proper clinical-radiographic setting, a transbronchial biopsy speci-

Three other distinct pathologic findings have been noted in association with pulmonary LAM: (1) multifocal micronodular pneumocyte hyperplasia; (2) clear-cell tumors of the lung; and (3) noncaseating granulomas (Table 1). Corrin et al\textsuperscript{1} discussed the finding of “peculiar acinar atypical adenomatoid proliferations of epithelium,” in addition to the diagnostic features of LAM, in two patients with pulmonary LAM. Although these patients were considered to have LAM, both had children who were described as “retarded,” raising the possibility of TSC. This finding of focal type II pneumocyte hyperplasia has since been reported by others under various names, always in association with TSC.\textsuperscript{10,34,36,37,86} Guinee et al\textsuperscript{34} have termed this lesion “multifocal micronodular pneumocyte hyperplasia.” These lesions appear as multiple small nodules on CT scans of the chest\textsuperscript{34,36} and, in one case, they have been stable after 2 years' follow-up.\textsuperscript{36} Unlike the LAM cells elsewhere in these lung biopsy specimens, the nodules stain negative for HMB-45, as well as for ERs and PRs.\textsuperscript{34,36} They are believed to be distinct hamartomatous lesions.\textsuperscript{34,36}

Clear-cell tumor of the lung (with HMB-45 reactivity)\textsuperscript{35} and noncaseating granulomas (parenchymal, hilar, and mediastinal)\textsuperscript{57} are two other lesions reported in association with pulmonary LAM. In the case of the clear-cell tumor, the patient also had TSC.\textsuperscript{37}

Table 1—Histopathologic Findings Associated With Pulmonary LAM*

<table>
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<th>Findings</th>
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<td>Extrapulmonary LAM (pelvic, retroperitoneal, or abdominal lymph nodes or masses)</td>
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<td>Angiomyolipomas</td>
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<td>Clear-cell (sugar tumor) of the lung</td>
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<tr>
<td>Multifocal micronodular pneumocyte hyperplasia</td>
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<td>Noncaseating granulomas (a single case report)</td>
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*These findings have been described in patients with pulmonary LAM. Some have been reported thus far only in patients with underlying TSC. See text for references.


Radiographic Features of LAM

The CXR in LAM classically shows a generalized, symmetric reticulonodular interstitial infiltrate, which is a nonspecific appearance that may be seen in many ILDs. In a recent collection of 46 patients by Kitaichi et al., bilateral reticulonodular infiltrates were seen on initial CXR in 39 (85%). Unlike many of the ILDs, however, the lung volumes are either normal or increased in LAM. In addition to LAM, this unusual finding of increased interstitial markings and preserved lung volumes may also be seen in several other diseases, including chronic hypersensitivity pneumonitis, pulmonary histiocytosis X, sarcoidosis, and coexistent emphysema and idiopathic pulmonary fibrosis. As discussed elsewhere, patients with LAM may also experience spontaneous pneumothorax or chylothorax, which would be evident on CXR. Carrington et al. also described occasional waxing and waning parenchymal infiltrates, postulated to represent focal alveolar hemorrhage, as well as coarser reticulation, often with septal lines. This finding was said to be partially reversible and was attributed to lymphatic engorgement and interstitial edema. Finally, the CXR may also show evidence of hyperinflation.1,4,8

As in many diseases, the CXR findings may vary roughly according to disease severity. Some patients with LAM have a normal CXR.3,30,50 In later stages of the disease, the CXR may show honeycombing. The honeycombing seen in LAM is said to differ from other end-stage diseases in that the appearance is more “delicate,” reflecting the absence of significant fibrosis. The presence of a pneumothorax may allow visualization of cystic changes in the deflated lung that are not visible in the fully inflated lung.90,91 Also, Templeton et al. described a patient with a right-sided pneumothorax, in whom multiple thin-walled cysts were visible in the right lung but not the left. Subsequent high-resolution CT HRCT revealed bilateral cystic lung disease.91 Several patients have been found to have LAM after presenting with spontaneous pneumothorax or chylothorax when the pulmonary parenchyma appears to be normal on a CXR.38,49,122,83

The chest CT scan (Fig 3) is almost always abnormal at the time of diagnosis and often shows a parenchymal abnormality when the CXR is either normal or shows only pleural fluid or pneumothorax.4,58,59,94 The HRCT scan can show mild or extensive disease when the CXR is normal.98 HRCT provides better definition than does traditional CT98,39,94 and may be more sensitive than pulmonary function testing, identifying abnormalities earlier in the course of the disease, when pulmonary function test results are normal.95 These scans reveal the diffuse cystic changes that account for the reticulation seen on CXR.59,95 The cysts are air filled, range in diameter from 2 to 60 mm, and have thin, regular walls that range from barely perceptible to 4 mm in diameter.59,94 Occasionally the cysts appear to have fused.95 They are usually round but may be polygonal or bizarrely shaped and usually appear scattered in a roughly symmetric pattern, without upper, lower, central, or peripheral predominance.59,94 Aberle et al.95 reported that although the disease was distributed throughout the chest, apical disease was less extensive, a finding not consistently reported by others.58,59,94 It appears that as the disease progresses, the cysts enlarge and become more numerous.58,59,95 The parenchyma between the cysts appears normal. Although characteristic of LAM, cysts are not pathognomonic. For example, some patients with chronic histiocytosis X of the lung may have cysts whose appearance on CT is similar to those of LAM. However, these patients usually have a history of heavy cigarette smoking, and the cysts usually predominate in the upper lobes, with relative sparing of the lung bases, in contrast to the diffuse pattern of LAM.

Figure 3. HRCT of the chest from two patients with LAM. Top: in this patient, the pulmonary parenchyma appears normal with the exception of a few tiny cysts, This contrasts with the extensive cystic destruction seen on HRCT from another patient (bottom). Both scans were obtained soon after diagnosis.
In addition to cysts, HRCT scans of the chest may reveal other less common features of LAM. For instance, reticulation, although uncommon in LAM, may be seen at the margins of cysts where they abut the pleura, giving rise to a serrated-appearing lung-pleural interface.95 Also, one report described patchy, ill-defined areas of increased attenuation in two of eight patients as “probably interstitial disease of uncertain significance.”94 Finally, HRCT may reveal evidence of LAM-associated lymphadenopathy,1-47’92’94’96 or LAM complications, such as pneumothoraces, pleural effusions,88-94 alveolar hemorrhage, or lymphatic stasis. Müller et al88 described localized areas of airspace consolidation that they postulated may be related to areas of hemorrhage (as did Carrington et al49; see CXR section above).88 Lenoir et al89 described one patient with chronic chyloptysis who, in addition to cystic changes, had areas of prominent polygonal septal lines and dependent alveolar opacities thought to be the result of lymphatic obstruction caused by the disease.

Although radiographs and HRCT scans of the chest are the two most common imaging techniques for evaluating patients with LAM, numerous case reports have described features of various other imaging techniques. For instance, CT scans of the abdomen may reveal renal angiomyolipomas21-70 (Fig 4) and enlarged retroperitoneal, para-aortic, or pelvic lymph nodes or masses.46,94 Lymphangiograms may show abnormal filling and cystic changes within the lymph nodes.1,47,92,94,96 In contrast to inflammatory ILDs, gallium scans have been reported to be normal.33,97,98 Pulmonary blood flow has been abnormal on nuclear perfusion scans50,99 and, in one case, on a pulmonary angiogram that showed “stretched or attenuated vessels with slowed circulation of contrast material.”750 Finally, a recent case report describes features of low signal intensity that were surrounded by thin walls on spin-echo MRI of the lung.100

**PULMONARY PHYSIOLOGY OF LAM**

The pulmonary physiologic features of patients with LAM are variable and include obstructive, restrictive, or mixed patterns.3,4 The diffusing capacity for carbon monoxide (DLCO) is reduced in most patients.3,4

Burger et al101 assessed pulmonary mechanics in eight patients with LAM to describe the pattern of abnormality and to clarify the cause of airflow obstruction. All eight patients had abnormal results of pulmonary function tests (PFTs) and seven had decreased FEV₁/FVC ratios (mean, 61% of predicted). No patient had a significant bronchodilator response. Total lung capacity (TLC) tended to be high: the mean was 114% of predicted, three patients had values above 120% of predicted, and none had values <90% of predicted. The residual volume was markedly elevated, with a mean of 207% of predicted, and seven patients had values >120% of predicted. Seven patients had decreased DLCO (mean, 57%), seven had widened alveolar-arterial oxygen difference, and none had hypercapnea. These findings should be interpreted with two cautions in mind: some patients were not included because the severity of their lung disease prohibited extensive testing, and all patients had undergone thoracotomy and four had also undergone pleurodesis, measures that might affect lung volumes.

To measure the compliance characteristics of the lungs and to better understand the mechanisms involved in the airflow obstruction, Burger et al101 also performed transpulmonary pressure-volume curves and measures of dynamic compliance and pulmonary flow resistance. The pressure volume curves were shifted up and to the left in six of eight patients and static compliance was increased. However, dynamic compliance was decreased in association with excessive flow resistance. Addressing the issue of whether the observed obstruction to airflow was primarily the result of decreased elastic recoil or airway narrowing with obstruction, the authors noted that the degree of reduction in elastic recoil forces was less than the degree of reduction of expiratory flow. The maximum flow-static recoil curves, a plot of maximum flow determined at specific lung volumes vs the transpulmonary pressure at these same

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**Figure 4. Angiomyolipoma:** this CT scan of the abdomen demonstrates a 5-cm complex fatty mass in the medial aspect of the left kidney. Not the displacement of the large bowel into the right nephrectomy bed.
lung volumes, were shifted down and to the right (Fig 5). Such a pattern is consistent with flow rates reduced primarily by airway obstruction (eg, asthma). The authors thus concluded that the reduced maximum expiratory flow in these patients was primarily the result of airway obstruction, rather than loss of elastic recoil.  

Several attempts have been made to correlate radiologic findings with measures of lung function. Aberle et al106 found no significant correlation between CXR severity scores and PFT parameters in eight patients with LAM.56 However, they did find that CT severity scores were correlated with the percentages of predicted FEV1/FVC and DLCO. In 14 patients with LAM, Müller et al88 also found no correlation between the CXR score and PFT measurements. Chest CT scores correlated well with DLCO, but not with lung volume or airflow parameters.86 Lenoir et al89 evaluated 11 patients (9 with LAM, 2 with TSC) and found that both CXR and CT scores were correlated with FEV1/FVC ratios and percent predicted of DLCOs. The CT score correlated better with DLCO than did the CXR score. Using a technique of quantitative CT scanning in 10 patients with LAM, Crausman et al102 found correlations between total cyst area and various measures of pulmonary function and exercise performance. These measures include the following: FEV1, FEV1/

![Figure 5. Maximal flow (Vmax) determined at specified volumes on the flow-volume curve vs transpulmonary pressure (Pst) determined at the same volume points on the pressure-volume curves for eight patients (solid lines). The dashed lines indicate the normal range. Reprinted with permission from Burger et al.101](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21893/)

FVC, residual volume, DLCO, resting and maximal exertion alveolar-arterial oxygen gradient, dead space to tidal volume ratio, maximum oxygen consumption, and maximum workload. From the above, it appears that CT scans correlate better with pulmonary function abnormalities than do plain CXRs. Finally, in keeping with an earlier observation by Corrin et al1 that radiographic evidence of increased lung volumes carried a poorer prognosis, Kitaichi et al4 found that a reduced FEV1/FVC ratio and an increased TLC were both associated with a poor prognosis.4

**Diagnosis, Treatment, and Prognosis of LAM**

As mentioned above, many cases of LAM are initially misdiagnosed as more common diseases, such as asthma or COPD. Such a mistake is understandable because of the rarity of LAM and because of the frequent nonspecific nature of the symptoms and findings on plain radiographs. The diagnosis of LAM is often initially considered when a young woman presents with ILD, pneumothorax, or chylothorax. In other cases, the diagnosis is not suspected until the grossly abnormal appearance of the lung surface is seen by the thoracic surgeon at the time of pleurodesis performed for recurrent pneumothorax, or until a HRCT scan is obtained. The HRCT scan, when interpreted by an experienced chest radiologist, can be very helpful in suggesting the diagnosis.

A definitive diagnosis of LAM usually requires a tissue biopsy and the judgment of an experienced pulmonary pathologist. In most cases, a biopsy specimen is taken surgically from the lung to provide sufficient tissue for interpretation. Recent reports suggest that transbronchial lung biopsy specimens,80,81 or even pleural fluid cytologic analysis,103 may be sufficient in certain cases, although such diagnoses likely depend heavily on the expertise of the clinicians and pathologists involved. Because LAM may involve extraparenchymal sites, such as lymph nodes or abdominal or pelvic masses, a definitive diagnosis of LAM can occasionally be made from biopsy specimens from such sites. Although exceptions have been described, in most cases of extrapulmonary involvement of LAM, pulmonary parenchymal changes also exist.5 It is unclear whether purely “extrapulmonary” LAM eventually progresses to involve the lung, although early case reports suggest that it can.7 In cases in which a biopsy cannot be performed, the diagnosis can be established with a fair degree of certainty when characteristic HRCT findings are seen along with renal angiomyolipoma. Because of the overlap be-
between LAM and TSC discussed previously, patients suspected of having LAM should be carefully screened for signs, symptoms, or family history that might suggest a diagnosis of TSC.

The clinical course of patients with LAM is quite variable, and a full understanding of the natural history is hampered by the paucity of available studies and the small numbers of evaluable patients. In general, the disease is believed to be slowly progressive, leading eventually to respiratory failure and death, but the time to death varies among reports. In the report by Taylor et al,3 25 of 32 (78%) patients were alive 8.5 years after the onset of the disease. However, in the recent collection of 46 LAM patients from Japan, Korea, and Taiwan, only 10 of 26 patients (38%) were alive after 8.5 years.4 In the earlier report by Corrin et al,1 death occurred between 1 and 10 years after the onset of symptoms, yet one patient was alive after 17 years and another remained “virtually asymptomatic” with no radiographic evidence of progression after 9 years.

Consensus regarding the most sensitive or relevant means of assessing disease severity or progression in patients with LAM has not been established. Because no single test or measure is likely to capture all aspects of the disease manifestations, in practice a combination of subjective, radiographic, and physiologic parameters are usually used to monitor patients. Routine pulmonary function testing is a non-invasive and relatively inexpensive means of assessing lung function. Although interpretation of parameters of airflow obstruction and lung volumes must be undertaken with the knowledge that LAM may be associated with obstructive, restrictive, or mixed patterns of abnormality,3,4 reduced FEV₁/FVC ratio and increased TLC have both been associated with poor prognosis.4 The DLCO is reduced in most individuals with LAM3,4 and may be a useful parameter to follow. Cardiopulmonary exercise testing or other assessment of exercise capacity and gas exchange are also helpful. Because the CXR may be normal despite the presence of significant disease, and because the correlation between the CXR and measures of pulmonary physiology is poor, it is presumed that plain radiographs are insensitive measures of assessment. HRCT scans correlate better with pulmonary physiology and exercise parameters and therefore likely provide a better understanding of overall disease severity. With these considerations in mind, a reasonable approach to following up patients with LAM might entail subjective evaluation, full PFT (spirometry, lung volumes, and DLCO), and CXR at 6-month intervals with more expensive or invasive procedures such as exercise testing and/or HRCT scans at 12-month intervals. The wide variation in the rate of deterioration in patients with LAM may necessitate adjustments of these intervals for individual patients.

Two issues that often arise in the care of LAM patients are the risks of pregnancy and the advisability of air travel. Both of these topics are very difficult to deal with because inadequate data are available to support firm recommendations. Because of the reports of disease progression during pregnancy and because of the poor long-term prognosis for patients with LAM, most experts advise against initiating pregnancy. Further, while hormonal treatment of LAM may also have contraceptive effects, patients should be advised to utilize standard, effective contraceptive measures. Unplanned pregnancies present a particularly difficult dilemma. While termination of the pregnancy may avert potential pregnancy-related deterioration, the risk of such deterioration is uncertain. Clearly, the patient must participate fully in this very personal decision and it must be made clear that there are very little data on which to base the decision.

Cabin pressure changes that commonly occur during air travel may increase the risk of pneumothorax in patients with cystic or bullous lung disease, including LAM. In a survey of patients with LAM administered by the LAM Foundation, 8 of 159 respondents reported a history of developing a pneumothorax during air travel (personal communication, Francis X. McCormack, MD, unpublished data). Although the absolute risk of pneumothorax is not known, air travel that is entirely discretionary should probably be avoided if another means of transportation is readily available. In patients with severe disease, a history of prior pneumothorax, or extensive subpleural cystic changes on HRCT scan, air travel should be more firmly discouraged.

Because of the rarity of the disease and the variable clinical course, little is known regarding the efficacy of the various therapies for LAM. It seems apparent that corticosteroids and cytotoxic agents offer no benefit.32,49,97,104 Given the occurrence of the disease in women of child-bearing years, reports of clinical worsening with exogenous estrogen,62 and the presence of ERs and PRs in the proliferating LAM cells, many clinicians have used hormonal manipulation therapeutically. There are numerous anecdotal reports of patients being treated with oophorectomy,3,4,59,65,66,105 progestrone,2,4,12,27,31,53,54,57,59,106–110 tamoxifen or other antiestrogen agents,2,4,30,55,58,104,111,112 luteinizing hormone releasing hormone agonists,4,53,110,113,114 or radioablation of the ovaries. In many reports, various combinations of these treatments have been attempted,2,27,33,40–42,45,52,56,59,67,73,76,97,112,114,115. There is one report of the use of interferon alpha.112 Responses to such treatments have been variable,
and no definitive conclusions should be drawn from these reports. Based on an experience with 32 patients, Taylor et al observed no therapeutic benefit from oophorectomy or antiestrogen therapy with tamoxifen. There was some evidence that progesterone was beneficial in at least some patients with LAM, and the investigators recommended its use in all symptomatic patients with LAM. Interestingly, combining their patients with those in the literature, they found no association between tissue ER or PR status and response to hormonal therapy. In 1989, Eliasson et al performed a meta-analysis of 30 previously reported cases and concluded that oophorectomy, progesterone, or both were the most effective treatments. It has been suggested that patients with chylous pleural effusions or chylous ascites are more likely to respond to treatment with medroxyprogesterone. Kitaichi et al observed that in several cases, treatments of various types had beneficial effects on the chylous fluid collections but not on the pulmonary parenchymal changes.

The prevention of osteoporosis is very important for women who are being treated with any antiestrogen therapy. Whether the newer “tissue-specific” estrogens will prove safe and effective in the prevention of osteoporosis in LAM patients treated with antiestrogen regimens is unknown. The interpretation of these treatment strategies is further clouded by reports of prolonged clinical courses in untreated patients. For instance, in one recent case report, a patient with LAM diagnosed from open-lung biopsy specimen after bilateral pneumothorax was given no treatment apart from surgical pleurodesis. After 3 years of follow-up, the patient had experienced neither pneumothorax nor pulmonary symptoms. No information on serial pulmonary functions is provided in the report, but a follow-up HRCT scan showed only “a slight increase in cyst size.” In addition to this case report, six of the patients in the Kitaichi et al series received no hormonal therapy. Of these six, four died with a “mean clinical duration” of 71.3 ± 25.4 months from the time of symptom onset.

### OTHER TREATMENTS

In addition to hormonal medications intended to interrupt the proliferation of LAM cells, numerous reports describe various interventions aimed at preventing or treating the complications of LAM, such as pneumothorax and chylous pleural or peritoneal fluid collections. Drainage of chylous pleural fluid collections can be hazardous, lead to protein loss, and is not always necessary. Chemical or surgical pleurodesis has been performed with variable success in preventing recurrent pneumothorax or pleural effusion. Although such procedures may make future lung transplantation more complicated, they are not a strict contraindication to subsequent transplantation and occasionally may be necessary to control symptoms. Early reports describe more aggressive measures aimed at decreasing the production of chylous pleural fluid, such as ligation or irradiation of the thoracic duct. Such procedures met with variable success and are no longer common in the treatment of LAM. Attempts at controlling chylous ascites with LaVeen shunts or fat-free diets supplemented with medium-chain triglycerides have also resulted in inconsistent benefit.

More recently, patients with end-stage lung disease related to LAM have undergone lung transplantation. A recent report by Boehler et al describes the outcomes of 34 patients who underwent lung transplantation for end-stage LAM. Of the 34 patients, 18 were alive at a mean of 33 ± 20 months after transplantation, with an actuarial survival rate of 69% after 1 year and 55% after 2 years. Problems related to the underlying LAM included intraoperative hemorrhage secondary to extensive pleural adhesions, postoperative pneumothorax in the native lung, and postoperative chylothorax.

Two reports document disease recurrence after single-lung transplantation. In neither case was graft function compromised by the recurrence. Interestingly, in both cases, the donor lungs were from men, and in one case, the proliferating immature smooth muscle cells in the transplanted lung were from the donor. This observation is intriguing because it raises the possibility of some type of circulating mitogen in the pathogenesis of the disease.

### CURRENT DEVELOPMENTS

LAM is a devastating disease that strikes young women and carries a poor prognosis. Because it is rare, little is known regarding its pathogenesis and treatment, but several new avenues of research have recently emerged. First, to address the lack of understanding of the clinical features and natural history of LAM, a national registry of patients with LAM has recently been initiated. Funded by the National Heart, Lung, and Blood Institute in cooperation with the Cleveland Clinic Foundation, the goals of the registry are as follows: (1) to characterize the clinical features of patients with LAM; (2) to examine the clinical features of patients referred for lung transplantation and assess the efficacy of this therapy for LAM; and (3) to collect and store.

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biological material, such as lung tissue and serum specimens, to facilitate studies into the molecular basis of LAM.

Second, new insights are emerging into the cellular and molecular biology of LAM cells, including the significance of the HMB-45 reactivity and the presence of ERs and PRs. Finally, our understanding of the genetic basis of TSC is rapidly advancing. Two genes responsible for TSC have been identified: TSC1 on chromosome 9, and TSC2 on chromosome 16. Evidence suggests that these genes act as tumor suppressor genes. Given the close association between LAM and TSC, such critical discoveries regarding the nature of TSC are likely to be relevant to LAM as well. In fact, in a recent study by Smolarek et al., loss of heterozygosity of the TSC2 gene was found in 54% of angiomylipomas from patients with LAM. In addition, loss of heterozygosity of the TSC2 gene was also seen in four lymph nodes from a woman with retroperitoneal LAM. These findings support the concept of a common pathogenesis of LAM and TSC. Perhaps, with improved understanding of the natural history as well as the genetic, molecular, and cellular biology of LAM, new therapies will soon become available.

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