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Lymphangioleiomyomatosis is a rare progressive multisystem disorder that predominantly affects women.

Lymphangioleiomyomatosis

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Background: *Lymphangioleiomyomatosis (LAM) is a rare disease that is characterized by proliferation of abnormal smooth muscle-like cells (LAM cells), which leads to the formation of lung cysts, fluid-filled cystic structures in the axial lymphatics, and abdominal tumors. It primarily affects women.*

Methods: *The authors present a review of large series, registries, and protocols to highlight the prevalence, pathology, clinical features, diagnosis, and treatment options for patients with LAM.*

Results: *LAM commonly presents with progressive breathlessness or with recurrent pneumothorax, chylothorax, or sudden abdominal hemorrhage. Computed tomography (CT) scans show numerous thin-walled cysts throughout the lungs, abdominal angiomyolipomas, and lymphangioleiomyomas. Pulmonary function tests show decreased forced expiratory volume in 1 second (FEV_1) and diffusion capacity for carbon monoxide (DLCO). Exercise testing shows gas-exchange abnormalities, ventilatory limitation, and hypoxemia that may occur with near-normal lung function.*

Conclusions: *No effective treatment currently exists for this progressive disorder. However, recent progress in cancer and smooth muscle cell biology and a better understanding of the factors regulating angiogenesis and lymphangiogenesis may provide a foundation for the development of new therapeutic strategies.*

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Abbreviations used in this paper: LAM = lymphangioleiomyomatosis, TSC = tuberous sclerosis complex, CT = computed tomography, FEV_1 = forced expiratory flow in 1 second, DLCO = diffusion capacity for carbon monoxide, AML = angiomyolipoma, LHS = LAM histology score, mTOR = mammalian target of rapamycin.

Introduction

Lymphangioleiomyomatosis (LAM), a rare multisystem disorder affecting primarily women, is characterized by cystic lung lesions, lymphatic abnormalities and abdominal tumors (ie, angiomyolipomas [AMLs]).[1-5] A hallmark of the disease is the proliferation of abnormal smooth muscle-like cells (LAM cells), leading to the formation of lung cysts and fluid-filled cystic structures (ie, lymphangioleiomyomas) in the axial lymphatics. AMLs, which frequently involve the kidneys, are composed of LAM cells and adipocytes, intermixed with incompletely developed vascular structures.[1-5] Reports

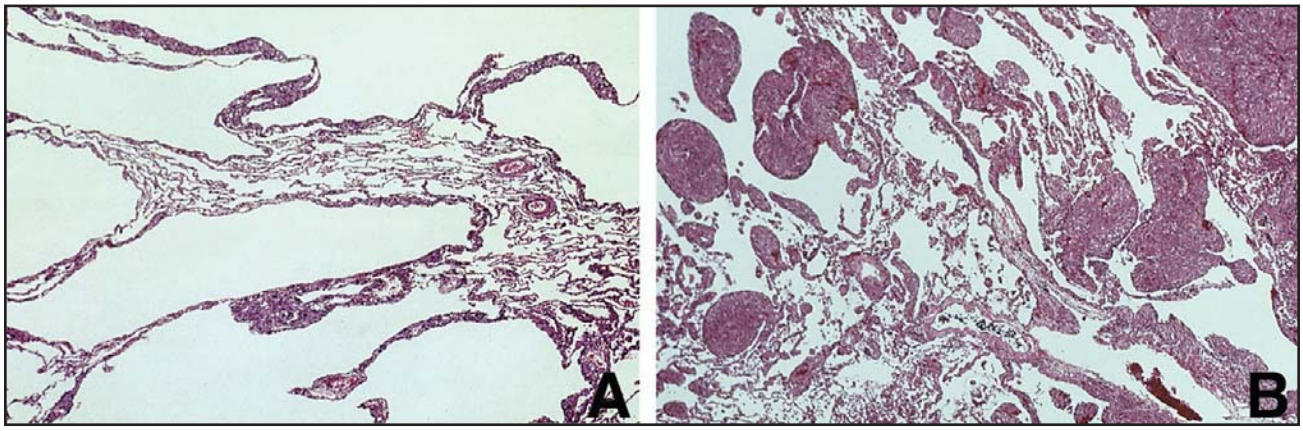

Fig 1. — Pulmonary pathology in LAM. Thin-walled cysts (A) and nodules of various sizes (B) are seen in involved lung (hematoxylin-eosin, original magnification × 50).

of large series,[1-4] the establishment of a National Heart, Lung and Blood Institute-supported LAM registry,[5] and the implementation of a natural history research protocol at the National Institutes of Health (NIH) in Bethesda have contributed to a better understanding of the natural history of LAM.

Prevalence of LAM

LAM occurs sporadically in patients with no evidence of genetic disease and in about one third of women with tuberous sclerosis complex (TSC),[6-8] an autosomal dominant syndrome characterized by hamartoma-like tumor growths in various organs, cerebral calcifications, seizures, and mental retardation that occurs in 1 of 5,800 live births.[9] Sporadic LAM is a relatively uncommon disease with a prevalence that has been estimated at 2.6 per 1 million women.[2]

Pathology

Lung lesions in LAM are characterized by infiltrates and clusters of LAM cells near cystic lesions and along pulmonary blood vessels, lymphatics, and bronchioles (Fig 1).[10] Two types of LAM cells have been described: small spindle-shaped cells and larger, epithelioid-like cells with abundant cytoplasm.[10] Both types of cells react with antibodies against smooth muscle cell-specific antigens (eg, smooth muscle α-actin, vimentin, desmin).[10] The epithelioid LAM cells react with HMB-45, a monoclonal antibody that recognizes gp100, a premelanosomal protein (Fig 2). The spindle-shaped cells are more likely to react with antiproliferation cell nuclear antigen antibodies, suggesting a more proliferative state.[11] Receptors for estrogen, progesterone, and growth factors have been identified in LAM cells.[12,13] In patients who undergo open lung biopsy, the histologic severity of LAM (LAM histology score [LHS]) may be quantified by the extent of replacement of normal lung tissue with cystic lesions and LAM cell nodules.[14] The total percentage of tissue involvement by cystic lesions and LAM nodules is graded as follows: LHS-1 = < 25%, LHS-2 = 25% to 50%, and LHS-3 = > 50%. The determination of LHS has important prognostic implications because significant differences in survival for patients with LHS-1, -2, and -3 have been observed.[14]

Pathogenesis

Mutations in the tuberous sclerosis genes, *TSC1* and *TSC2*, are thought to be the cause of sporadic LAM, with mutations in *TSC2* occurring more frequently than those in *TSC1*.[15,16] *TSC1* and *TSC2* are tumor suppressor genes, and loss of heterozygosity (LOH) of *TSC2* has been reported in LAM lesions from lung and kidney,[15] consistent with Knudson's "two-hit" hypothesis of tumor development.[17] Data suggest that LAM cells can metastasize; identical mutations in *TSC2* were found in lung lesions and AMLs from the same patient with sporadic LAM, and recurrent LAM cells of recipient origin were detected in the donor lung of a transplanted patient.[18,19] LAM cells were detectable in body fluids (blood, urine, expectorated chyle, pleural or abdominal chylous fluids) of some LAM patients.[20] Although the "primary" source of LAM cells in the lungs is unknown, the potential sources include AMLs (although 50% of sporadic LAM cases do not have demonstrable AMLs) and the lymphatic system.[21]

The *TSC1* gene is located on chromosome 9 (9q34) and contains 23 exons.[22] *TSC1* encodes hamartin, a 130-kDa protein translated from exons 3–23 with little similarity to other known proteins. A potential transmembrane domain maps to amino acids 127–144, a coiled-coil domain comprises amino acids 730–996, and the interaction site with the *TSC2* gene product, tuberin, has been mapped to amino acids 302–340.[23] Hamartin may play a role in the reorganization of the

actin cytoskeleton by inducing an increase in the levels of Rho-GTP, an upstream activator of ezrin-radixin-moesin (ERM) proteins, and by binding activated ERM proteins.[24] ERM proteins bind filamentous actin through carboxy-terminal regions and integral membrane proteins via amino-terminal domains, thus bridging the plasma membrane and cortical actin filaments. Absence of hamartin leads to loss of focal adhesions and rounding of cells, with detachment from substrate.

The *TSC2* gene is located on chromosome 16 (16p13.3) and contains 41 exons.[25] *TSC2* encodes tuberin, a 198-kDa protein that interacts with hamartin though an amino-terminal region.[23] Tuberin is postulated to have roles in the cell cycle and in cell growth and proliferation. Tuberin is a negative regulator of cell cycle progression; loss of tuberin shortens the G_1 phase of the cell cycle.[26] Tuberin inhibits cell cycle progression by stabilizing the levels of p27KIP1, a cyclin-dependent kinase inhibitor. Upon tuberin inactivation, p27 becomes unstable and mislocated in the cytoplasm, allowing the cell cycle to progress.[27,28]

Tuberin also integrates signals from growth factors and energy stores. Growth factors, via their membrane receptors, activate phosphatidylinositol-3-OH kinase (PI3K), which catalyzes the activation of the serine/threonine kinase Akt. Akt phosphorylates and inhibits tuberin.[29] Tuberin is also phosphorylated by AMP-activated kinase (AMPK), which is activated by high levels of AMP, indicative of energy deprivation[30]; phosphorylation by AMPK activates tuberin. Tuberin has Rheb GAP (GTPase-activating protein) activity.[31] Rheb (Ras homolog enriched in brain) is a guanine nucleotide-binding protein that is inactivated by tuberin by conversion of Rheb-GTP to Rheb-GDP. Rheb controls mammalian target of rapamycin (mTOR), a serine/threonine kinase that phosphorylates at least two substrates: 4E-BP1, which allows cap-dependent translation by relieving the inhibition of eIF4E, and S6K1, which results in S6 phosphorylation and translation of 5′ terminal oligopyrimidine tract (T0P)-containing-RNAs. Tuberin inhibition by growth factors leads to cell growth and proliferation by accumulation of Rheb-GTP and activation of mTOR.[32,33] AMPK-catalyzed phosphorylation of tuberin activates tuberin, leading to an accumulation of Rheb-GDP and inhibition of mTOR and cell growth.[30]

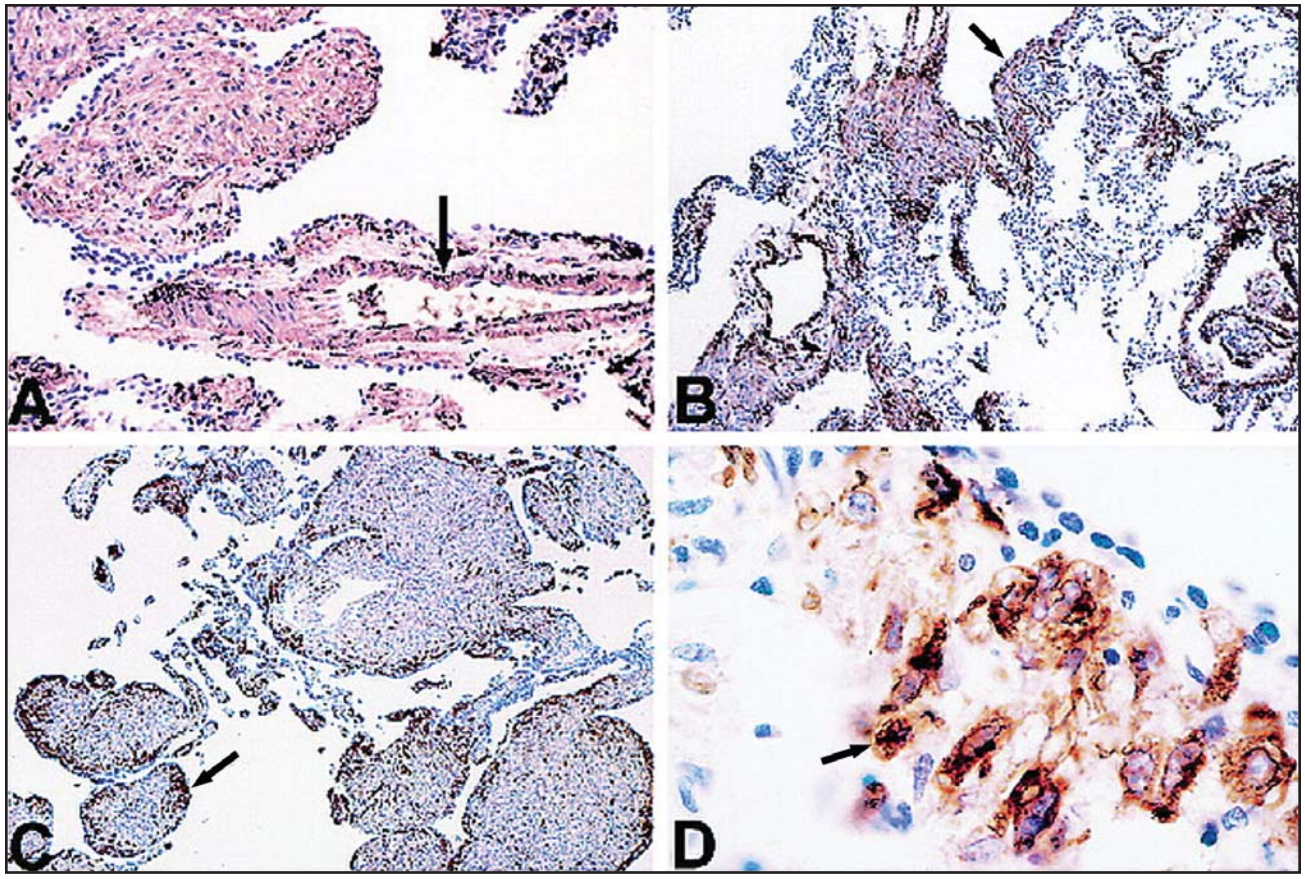

Fig 2. — Immunohistochemistry of lung LAM cells. Immunoperoxidase method and counterstaining with hematoxylin. (A & B) Immunoreactivity with α-smooth muscle actin antibodies. LAM cells show strong reactivity (A). Pulmonary vascular smooth muscle cells are also strongly positive (arrow). LAM cells in the walls of the lung cysts are also strongly reactive (arrow) (B) (original magnification × 250 for each). (C) Immunoreactivity with monoclonal antibody HMB-45. Immunoreactive cells are distributed in the periphery of LAM lung nodules (arrow) (original magnification × 250). (D) Immunoreactivity with monoclonal antibody HMB-45. Higher magnification view of tissue shown in C. A strong granular reaction is present in large epithelioid LAM cells adjacent to epithelial cells covering LAM lung nodules (arrow) (D) (original magnification × 1000).

Clinical Features

LAM usually presents with symptoms of dyspnea or the sudden appearance of a pneumothorax, pleural effusion, or intra-abdominal hemorrhage.[1-5] Dyspnea, cough, and hemoptysis are the most common pulmonary symptoms of LAM.[5] Dyspnea occurs in over 70% of patients with LAM.[5] The average time between the onset of symptoms related to LAM and the definitive diagnosis of LAM is 5 to 6 years.[34] Over 50% of patients have a history of pneumothorax.[35] Chylothorax, with or without ascites,[36,37] and thoraco-abdominal lymphadenopathy and lymphangioleiomyomas,[36,38] suggesting the presence of a malignant lymphoproliferative disease,[39,40] are other presentations of LAM. Abdomino-pelvic LAM may present with abdominal pain or as an acute abdomen.[41,42] Retroperitoneal lymphangioleiomyomas have a distinctive roentgenologic appearance, and diurnal variation in size of the tumor masses can occur.[43,44]

AMLs are benign tumors usually localized in the kidneys that occur in approximately 80% of patients with LAM and TSC and in about 40% of those with sporadic LAM.[5] These tumors vary in size from 1 mm to more than 20 cm in diameter.[38,45] Roentgenographically, the tumors consist of areas of fatty density intermixed with more dense areas and normal-appearing renal parenchyma.[38,45] The tumors are highly vascular with the blood supply ordinarily originating from the renal arteries. They may completely disrupt the normal kidney architecture.

An increased prevalence of meningiomas in LAM exceeding that in the general population[46] has been reported. Whether they are related to the underlying LAM, TSC, or therapy with progesterone is unclear. However, meningiomas have been seen in patients with sporadic LAM who have not been treated with progesterone.

The physical examination of LAM patients is surprisingly normal. Breath sounds, however, may be distant in patients with severe LAM and on the side of a pleural effusion. In patients with large AMLs or lymphangioleiomyomas, physical examination may detect abdominal masses. Signs consistent with TSC, such as neurofibromas, periungual fibromas, nail ridging and the shagreen patch, are seen in patients with LAM-TSC.

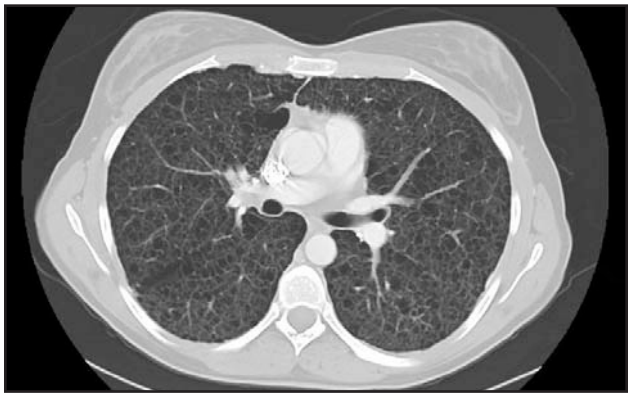

Fig 3. — CT scan of a patient with LAM. Numerous small thin-walled cysts are distributed throughout the lungs.

Roentgenographic Findings

The principal pulmonary roentgenographic finding in patients with LAM is the presence of cysts on lung computed tomography (CT) scans that are well circumscribed, round or oval, and thin-walled, scattered throughout the lungs.[47-49] These cysts vary in size from a few millimeters to many centimeters and in number from a few scattered cysts to near complete replacement of the lung parenchyma by cysts (Figs 3 and 4). The cysts are predominantly round and have a visible wall.

Extrapulmonary findings include AMLs, lymphangioleiomyomas, and ascites.[36,38,44] In general, AMLs have a fatty texture (Figs 5 and 6) but occasionally show little evidence of fatty infiltration. Such atypical AMLs should raise suspicion of renal carcinoma.[45] Lymphangioleiomyomas (Figs 7 and 8) are usually localized along the axial lymphatics in the mediastinum, retroperitoneum, and pelvis. They tend to be larger in the evening due to accumulation of chyle in the cystic structures.[44] Lymphangioleiomyomas may be accompanied by ascites.[44-50]

Lung Function Abnormalities

The most frequent pulmonary function abnormalities in LAM are airflow obstruction and a decreased lung diffusion capacity.[5,51,52] Evidence of airflow limitation is seen in over 60% of the patients. A reduced diffusing

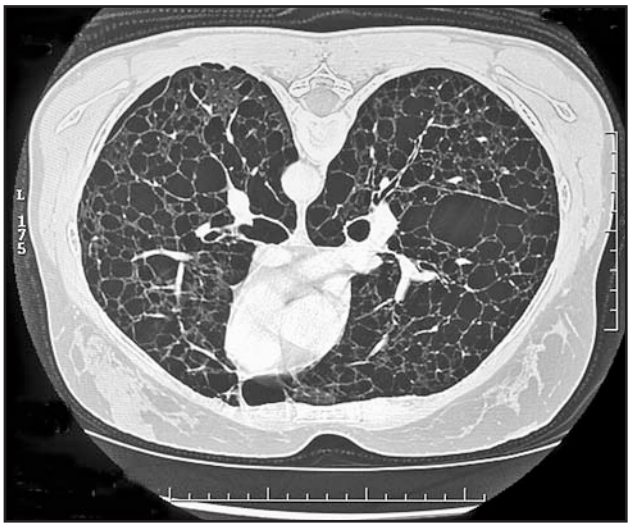

Fig 4. — CT scan of a patient with severe LAM. The lung parenchyma is almost completely replaced by cysts.

capacity is seen as frequently as a decreased forced expiratory volume in 1 second (FEV_1).[5] A restrictive defect is commonly seen in patients who have pleural effusions or who have had pleurodesis.[51]

Exercise Responses in LAM

Abnormal responses to exercise demonstrated by cardiopulmonary exercise testing are usually caused by muscle fatigue, abnormalities of gas exchange and/or ventilation, and abnormal cardiovascular function.[52] The relative contributions of these factors in limiting exercise capacity differ from patient to patient in a manner that cannot be completely explained by standard pulmonary function tests. Exercise-induced hypoxemia occurs in the presence of near normal D_{LCO} and FEV_1. A correlation between oxygen consumption per unit time (VO_2max) and LHS has been reported, with patients having more severe disease by histopathology demonstrating a significantly lower VO_2max. Since LHS is a predictor of death and time to transplantation, VO_2max may be a useful predictor of survival in LAM.[52]

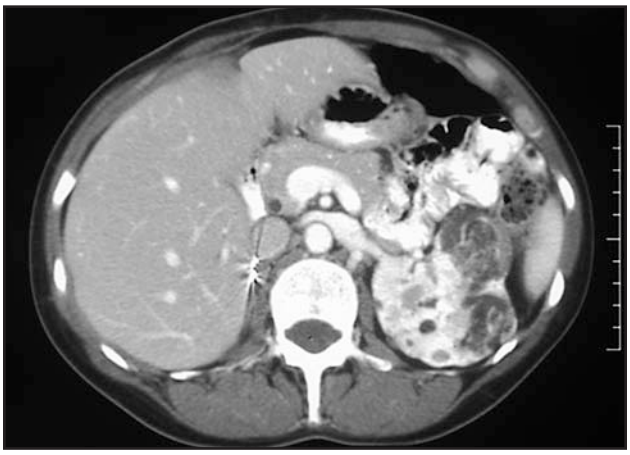

Fig 5. — Abdominal CT scan of a patient with LAM. Multiple angiomyolipomas are seen in the left kidney. The right kidney was removed for treatment of a bleeding angiomyolipoma.

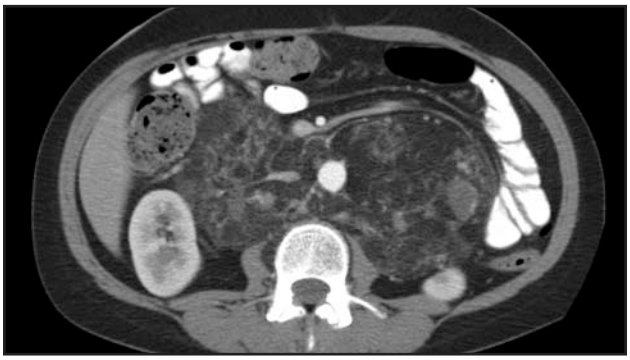

Fig 6. — Abdominal CT scan of a patient with LAM. A large angiomyolipoma completely involves the retroperitoneal area causing anterior displacement of the aorta.

Diagnosis of LAM

The diagnosis of LAM should be considered in a woman of any age who presents with recurrent pneumothorax, chylous pleural effusions, and/or ascites, or an unexplained decrease in exercise tolerance. The single most important diagnostic test is a CT scan of the thorax, with high resolution views to facilitate visualization of the cysts. If cysts are seen on the CT scan, if there is a history of pneumothorax or chylothorax, and if pulmonary function tests show airflow obstruction and impaired diffusion capacity, there is no need to perform a lung biopsy. In patients with TSC, the identification of lung cysts on the CT scan strongly suggests the diagnosis of LAM. The coexistence of AMLs and lung cysts is also virtually diagnostic of LAM.

The presence of lung cysts on a CT scan with no evidence of TSC, AMLs, or chylothorax is not diagnostic of LAM. Other uncommon diseases presenting with lung cysts, such as Birt-Hogg-Dubé syndrome,[53,54] Langerhans cell histiocytosis,[55] and Sjögren's syndrome,[56,57] should be considered. Under these circumstances, an open lung biopsy, preferably performed by

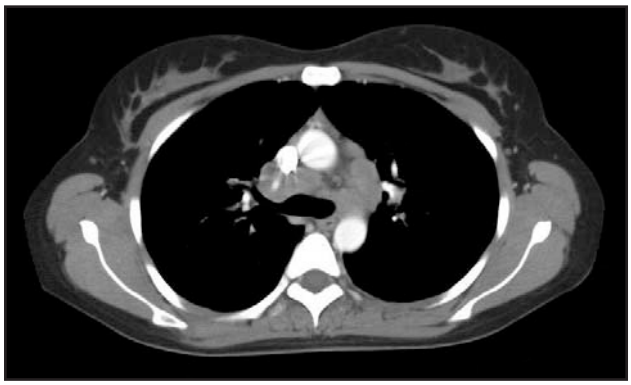

Fig 7. — Chest CT scan of a patient with LAM. A large lymphangioleiomyoma involves the pretracheal and left hilar area.

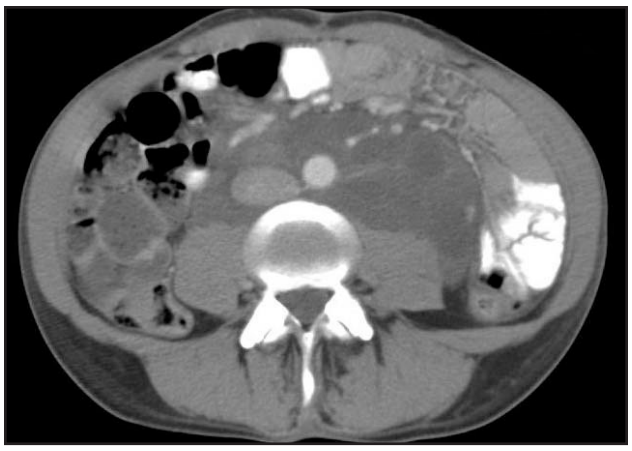

Fig 8. — Abdominal CT scan of a patient with LAM. A large lymphangioleiomyoma, located in the retroperitoneal area, surrounds the aorta and inferior vena cava.

video-assisted thoracoscopy, is recommended. Special immunofluorescent stains for smooth muscle α-actin, vimentin, desmin, and HMB45 should be performed to establish a diagnosis. As this requires an adequate size biopsy specimen, transbronchial lung biopsy, in all probability, will not establish the diagnosis of LAM.

Although most AMLs occur in the absence of LAM, the accidental finding of a kidney mass by abdominal sonogram or CT scan suggesting the presence of an AML mandates a CT scan of the lungs to look for lung cysts.

Mortality, Morbidity, and Progression of Disease in LAM

In most patients, LAM is a chronic disease that can span decades. Even severe disease can stabilize. Further, patients with severe LAM may appear comfortable at rest, showing no signs of respiratory distress. A retrospective analysis of 402 patients seen at the NIH since 1995 showed that 22 had died, 8 of whom had undergone lung transplantation. The mortality in this large cohort was 5.5%. Of the surviving 380 patients, 38 (10%) had lung transplantation. Therefore, 85% of the patients were alive and had not had lung transplantation. Many of these patients, however, required supplemental oxygen. Reports from outside the United States have described similar findings, with a 10-year survival rate for LAM above 90%.[58]

Multiple laboratory tests assist in defining disease progression. In particular, DLCO and FEV_1 correlate with disease severity defined by CT scans, LHS, and exercise parameters.[51,52]

In an analysis of 275 patients followed for approximately 4 years,[34] we found average yearly rates of decline in FEV_1 and DLCO of 75 ± 9 mL (1.7 ± 0.4% predicted) and 0.69 ± 0.07 mL/min/mmHg (2.4 ± 0.4% predicted), respectively. Older age and menopause, or a combination of both, tended to be associated with lower rates of decline in FEV_1. Higher rates of decline for FEV_1 (mean ± SD = 118 ± 142 mL/year) and DLCO (mean ± SD = 0.905 ± 1.54 mL/min/mmHg/year) have been reported.[59] When expressed as changes in percent-predicted values, the yearly rates of decline are adjusted for age. Consequently, any change in percent-predicted FEV_1 and DLCO is abnormal. When rates of decline in FEV_1 and DLCO are expressed in absolute values, they are greater than those observed in normal subjects. The yearly rate of decline in FEV_1 in normal subjects is under 30 mL/year.[60] The mean yearly rate of decline in DLCO in a nonsmoking female population is between 0.28 and 0.29 mL/min/mmHg.[61] For comparison, the average rates of decline in FEV_1 and DLCO in patients with α1-antitripsin deficiency were reported at 67 ± 14 mL/year and 1.07 ± 0.21 mL/min/mmHg/year, respectively.[62]

Treatment

Hormonal Therapy

There is no treatment that effectively reverses the functional abnormalities or stops ongoing lung damage in LAM. Because LAM is predominantly a disease of premenopausal women and can worsen during pregnancy,[63] and following the administration of estrogens,[64] hormonal manipulations have been utilized. These hormonal treatments became a standard of care, but no controlled studies were undertaken to determine whether they are effective. There have been reports of improvement in disease manifestations, such as the size of pleural effusions, after bilateral oophorectomy,[65] but Taylor et al[66] found no improvement in 15 patients with LAM who had undergone bilateral oophorectomy. Generally, objective evidence of improvement with antiestrogen therapy is lacking.[65,66] Gonadotrophin-releasing hormone (GnRH) analogs were reported to be of benefit in the treatment of LAM,[67,68] but other studies were inconclusive.[69,70] In a retrospective study, Johnson and Tattersfield[59] found that patients treated with progesterone had smaller declines in FEV_1 and DLCO than did untreated patients. However, the two groups were not matched by initial lung function. In 5 patients for whom pretreatment and posttreatment decline rates for FEV_1 and DLCO were available, a positive effect of progesterone in decreasing the rate of functional decline was reported. In a retrospective study of 275 patients with LAM, we found that after adjusting for differences in initial lung function, age, and disease duration, the overall yearly rates of decline of FEV_1 and DLCO for patients treated with oral or intramuscular progesterone were not significantly different from patients who received no progesterone.[34]

Bronchodilators

Approximately 20% of LAM patients have a significant positive response to bronchodilators.[51] Many more patients give a history of occasional wheezing, and in some, the wheezing is audible and exercise-related. Treatment of these patients with bronchodilators is recommended. There is no evidence that corticosteroids, either administered systemically or in aerosol form, are beneficial in LAM. Patients having a bronchodilator response show a more rapid decline in FEV_1.[51] The cause of the decline has not been established.

Pneumothorax

Pneumothorax in LAM tends to recur and may not respond to simple closed thoracostomy. This should be the initial treatment, but if the air leak persists, if the lung does not expand, or if the pneumothorax recurs, chemical or surgical pleurodesis by video-assisted thoracoscopy should be performed.[35] Talc pleurodesis is the most effective modality of chemical pleurodesis, but it is also more likely to result in marked fibrothorax that may

complicate the removal of the lung at the time of transplantation and cause higher perioperative morbidity.[35]

Chylothorax and Ascites

Chylothorax is a difficult therapeutic problem. Repeated thoracentesis leads to malnutrition and may result in infectious complications. A low-fat diet with medium-chain triglycerides and therapeutic thoracentesis should be attempted initially.[71,72] However, most patients require pleurodesis.[71,72] Surgical and chemical pleurodesis, especially with talc by video-assisted thoracoscopy, may be effective if the rate of chyle generation is reduced. Patients should be placed on a fat-free parenteral nutrition regimen prior to, during, and after surgery. It is essential that good lung expansion be obtained to ensure complete apposition of the visceral and parietal pleura to avoid residual pleural pockets. After a successful pleurodesis, a low-fat diet with mid-chain triglycerides is recommended.[72] In view of anecdotal reports of beneficial effects of medroxyprogesterone in the treatment of chylothorax, hormonal therapy can be considered.[73] Pleuroperitoneal shunts have also been tried,[74,75] but there is little experience with this mode of therapy.

Ascites, peripheral edema, and compression of the bladder, bowel, pelvic veins,[76] and other viscera by large lymphangioleiomyomata may cause severe symptomatology, including pain, obstipation, urinary frequency, and peripheral edema. Low-fat diet, diuretics, and medroxyprogesterone have not proven effective. A peritoneal-venous shunt[77] may be considered for most severe cases when the ascites is disabling and is causing mechanical/nutritional problems, but experience with this therapeutic modality in LAM is limited. Treatment with octreotide may be considered for patients with disabling ascites and large lymphangioleiomyomata. Previous studies with somatostatin and octreotide in other clinical settings (eg, traumatic damage to the lymphatics, yellow nail syndrome) have shown a successful reduction in chylous effusions, chyluria, ascites, and peripheral lymphedema.[78,79]

Oxygen Therapy

Exercise testing with measurement of oxygen saturation should be performed. Oxygen therapy prevents hypoxemia, improves exercise performance, decreases the ventilatory response to exercise, and might prevent exercise-induced pulmonary hypertension.

Transplantation

In patients with severe LAM in whom DLCO and/or FEV_1 have decreased to less than 40% of predicted and who require continuous oxygen therapy, we recommend they be referred to a transplantation center for initial evaluation. However, many patients with advanced disease on supplemental oxygen have a reasonable quality of life and consequently do not wish to be considered for transplantation. Patients who show an accelerated rate of decline in DLCO and FEV_1 may be referred earlier in the course of their disease. Except for a greater prevalence of postoperative bleeding, the morbidity associated with lung transplantation in LAM is similar to that observed in other patients with pulmonary diseases undergoing transplantation.[80] Although only a relatively small number of LAM patients have been transplanted, the 5-year survival rate appears to be better than in other pulmonary patients.[81]

Angiomyolipomas

Not infrequently, AMLs are mistakenly diagnosed as malignant tumors, prompting the immediate removal of the entire kidney. In fact, renal function in patients in whom both kidneys show involvement with AMLs may be well preserved. The principal complication of AMLs, especially those greater than 4 cm in diameter, is bleeding, which may be abrupt and require blood transfusions. The typical symptoms of this event are the sudden onset of flank pain with or without the presence of blood in the urine. In this setting, surgical resection or selective embolization of the tumor is indicated.[45,82] All attempts should be made to preserve kidney function.[45,82] Severe pain that cannot be controlled by conservative management also may be an indication for selective embolization of the tumor. Patients who have large AMLs but have had no episodes of bleeding should be followed by an urologist and be referred to a medical center with interventional radiology facilities for eventual treatment. Whether prophylactic embolization should be undertaken in these cases is not known. A difficult diagnostic problem is posed in patients who have atypical renal masses and who do not appear to have fat.[45] If there is either evidence of recent tumor growth or no available information about the growth pattern of the tumor, it is probably advisable to perform a renal biopsy to rule out a malignant tumor. Close monitoring of those with atypical AMLs by means of CT scans every 6 months is recommended.

Summary and Future Directions for Research and Therapeutic Trials

LAM, a multisystem disease affecting primarily women, is characterized by cystic lung lesions that can result in respiratory failure, abdominal AMLs that can lead to abdominal hemorrhage, and lymphatic abnormalities that are associated with chylothorax and ascites. No effective treatment for LAM is currently available. However, recent progress in cancer and smooth muscle cell biology, especially the mechanisms regulating cell proliferation and migration, and a better understanding of the factors reg-

ulating angiogenesis and lymphangiogenesis, may provide a foundation for the development of new therapeutic strategies. Two areas of current research appear most promising: inhibitors of mTOR and inhibitors of matrix metalloproteinases and angiogenesis.

Inhibitors of mTOR

Because mTOR plays a role in the pathogenesis of LAM, an inhibitor of mTOR, sirolimus (rapamycin), has been studied as a possible treatment for LAM. Rapamycin is an antifungal macrolide antibiotic approved by the US Food and Drug Administration for immunosuppression after solid organ transplantation. The Eker rat, a model for TSC with a functionally null germline mutation of *Tsc2*, has been used to study the function of the *TSC2* tumor suppressor gene. Eker rats develop renal cell carcinomas; treatment of Eker rats with sirolimus resulted in a decrease in the size of kidney tumors and tumor cell size by a reduction in the percentage of proliferating cells and by extensive tumor cell death.[83,84] Tumor loci were still detected, however, after 2 months of therapy. The Cincinnati Angiomyolipoma Sirolimus Trial (CAST), a pilot study, is underway to test the effect of rapamycin on growth of AMLs. Also, the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) Trial, a new clinical study to examine the effect of rapamycin on pulmonary function, is due to start during the current year.

Inhibitors of Matrix Metalloproteinases and Angiogenesis

The extracellular matrix provides structural stability to the pulmonary tissues and participates in the regulation of many critical cellular functions.[85] Matrix metalloproteinases (MMPs) are a functional component of the extracellular matrix and play an important role in lymphangiogenesis.[86]

Lung injury in LAM is related to the proliferation of LAM cells and their production of toxic products.[87-89] In the lungs, LAM cells are clustered in nodules lining the cysts and in the lung interstitium.[10] Within the LAM nodule, elastic fibers and collagen fibrils of the basement membrane are disrupted.[87] It has been proposed that excessive production of MMPs by LAM cells may contribute to the degradation of the extracellular matrix and lung destruction.[87-89] Several MMPs, including MMP-2 (gelatinase A), MMP-1, MMP-9 (gelatinase B), and MMP-14, are associated with LAM lesions.[87,88] LAM cells show particularly strong immunoreactivity for MMP-2. In addition, decreased expression of tissue inhibitor of metalloproteinase (TIMP)-3, an inhibitor of some MMPs, was observed in LAM lesions, further contributing to an imbalance in the MMPs/TIMP ratio and perhaps increased MMP-dependent proteolysis.[89,90]

It has been reported that urinary MMPs are predictors of disease status in patients with conditions characterized by dysregulation of extracellular matrix degradation, such as cancer and hemangiomatosis.[91-95] Doxycycline, an inhibitor of MMP activity, affects the growth and migration of neoplastic cells, angiogenesis and lymphangiogenesis, and the growth of smooth muscle cells.[96-102] Consequently, inhibition of MMPs may be a valid therapeutic goal in neoplastic diseases.[100,101]

Inhibition of angiogenesis is another therapy that appears promising in the treatment of malignant tumors.[103,104] Vascular endothelial growth factor and basic fibroblast growth factor (bFGF) have been implicated in mechanisms of human cancer and metastasis.[103,104] Doxycycline induced a remission in a patient with pulmonary capillary hemangiomatosis who had elevated urinary levels of bFGF, causing the resolution of the pulmonary lesions while it decreased levels of urinary bFGF.[95] Recently, Moses et al[105] reported the case of a patient with severe LAM who was treated with doxycycline for several months while waiting for lung transplantation. Within 3 months of therapy, the urinary levels of MMPs became unmeasurable. There was a simultaneous increase in a test of lung mechanics and an improvement in gas exchange, resulting in an increase in oxygen saturation at rest and during exercise. These observations suggest that doxycycline, by inhibiting bFGF and MMPs, may be effective in the treatment of LAM. Clinical trials are currently being planned to evaluate the effects of doxycycline in LAM.

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