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Lymphangioleiomyomatosis*

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Lymphangioleiomyomatosis*

A Clinical Update

Francis X. McCormack, MD, FCCP

Lymphangioleiomyomatosis (LAM) is a rare, cystic lung disease that is associated with mutations in tuberous sclerosis genes, renal angiomyolipomas, lymphatic spread, and remarkable female gender restriction. The clinical course of LAM is characterized by progressive dyspnea on exertion, recurrent pneumothorax, and chylous fluid collections. Lung function declines at approximately twofold to threefold times the rate of healthy subjects, based on an annual drop in FEV_1 of 75 to 120 mL in reported series. The diagnosis of pulmonary LAM can be made on high-resolution CT (HRCT) scan with reasonable certainty by expert radiologists, but generally requires a lung biopsy in cases in which tuberous sclerosis complex, angiomyolipomata, or chylous effusions are absent. The currently available treatment strategies are based on the antagonism of estrogen action, and are empiric and unproven. A trial of bronchodilators is warranted in patients with reversible airflow obstruction seen on pulmonary function testing. Pleurodesis should be performed with the initial pneumothorax, because the rate of recurrence is high. Angiomyolipomas that exceed 4 cm in size are more likely to bleed and should be evaluated for embolization. Air travel is well-tolerated by most patients with LAM. Lung transplantation is an important option for LAM patients, and can be safely performed by experienced surgeons despite prior unilateral or bilateral pleurodesis in most patients. Women with unexplained recurrent pneumothorax, tuberous sclerosis, or a diagnosis of primary spontaneous pneumothorax or emphysema in the setting of limited or absent tobacco use should undergo HRCT scan screening for LAM. Multicenter clinical trials based on several well-defined molecular targets are currently underway in the United States and Europe. ***(CHEST 2008; 133:507–516)***

Key words: genetics; interstitial lung disease; malignancies; molecular biology

Abbreviations: BHD = Birt-Hogg-Dubé; HRCT = high-resolution CT; LAM = lymphangioleiomyomatosis; LCH = Langerhans cell histiocytosis; MMP = matrix metalloproteinase; mTOR = mammalian target of rapamycin; NHLBI = National Heart, Lung, and Blood Institute; S-LAM = sporadic lymphangioleiomyomatosis; S6K = S6 kinase; TSC = tuberous sclerosis complex; VEGF = vascular endothelial growth factor

Pulmonary lymphangioleiomyomatosis (or lymphangiomyomatosis; LAM) is an uncommon disease in women that is characterized by smooth muscle cell infiltration and cystic destruction of the lung.[1] LAM occurs in about 30% of women with the tuberous sclerosis complex (TSC),[2–4] a genetic disorder of highly variable penetrance associated with seizures, brain tumors, and cognitive impairment, and also in women who do not have TSC (*ie*, *sporadic LAM* [S-LAM]).[5] Both S-LAM and TSC-LAM are associated with mutations in tuberous sclerosis genes, which regulate signaling through critical cellular pathways that control energy and nutrient resources in the cell.[6,7] Clinically, LAM is characterized by progressive dyspnea on exertion, recurrent pneumothoraces, abdominal and thoracic lymphadenopathy, and abdominal tumors, including angiomyolipomas and lymphangiomyomas. The pulmonary manifestations of LAM usually predominate, but occasionally LAM presents exclusively in the abdomen and mimics lymphoma or ovarian cancer.[8] LAM lesions express markers of smooth muscle and melanocytic differentiation, which are useful diagnostically.[9] There are no proven therapies for LAM, but an improved understanding of the molecular pathogenesis of the disease has identified several promising molecular targets for clinical trials. There have been great strides made in the basic science of LAM in the past 10 years, due in large part to a confluence of scientific discoveries from the tuberous sclerosis and signaling biology fields, and remarkably effective grass-roots patient advocacy. The major advances are reviewed below, but the reader is referred

to expert reviews[10,11] for more information about progress in basic LAM research.

Molecular and Cellular Pathogenesis of LAM

LAM and TSC are caused by mutations in either of the tuberous sclerosis genes, *TSC1* or *TSC2*, which control cell growth, survival, and motility through the Akt/mammalian target of rapamycin (mTOR) signaling pathway.[12–14] Deficiency or dysfunction of the encoded proteins, hamartin or tuberin, respectively, result in a loss of regulation of signals from upstream sources including cell surface tyrosine kinase and G protein-coupled receptors (Fig 1). The constitutive activation of the mTOR kinase and S6 kinase (S6K) leads to increased protein translation, and ultimately to inappropriate cellular proliferation, migration, and invasion. The role of estrogen in disease initiation and/or progression is unknown, but evidence from the past few years has suggested that estrogen can signal through Akt and release the tuberin-deficient or hamartin-deficient cell from the feedback inhibition that occurs in the presence of constitutive S6K activation.[15,16] Protease imbalance involving matrix metalloproteinase (MMP)-2, MMP-9, and tissue inhibitor of metalloproteinase-3 has been described in LAM lesions[17–19] and may play a role in connective tissue matrix degradation and cyst formation.

In patients with TSC or TSC-LAM, germline mutations in *TSC* genes are present in all cells of the body (*ie*, *first hit*), and neoplasms and dysplasias occur when somatic *second hit* TSC mutations result in a "loss of heterozygosity" for the normal allele. In patients with S-LAM, both the first-hit and second-hit TSC mutations are confined to lesions in the lung, kidney, and lymph nodes.[6,20] Mother-to-daughter transmission of TSC-LAM, but not of S-LAM, has been reported.[21] Genetic analysis of recurrent LAM lesions in the donor allografts of LAM patients who have undergone lung transplantation have revealed that LAM can metastasize.[22,23] A report[24] that cells containing loss of heterozygosity for *TSC* genes can be isolated from the blood of LAM patients is consistent with blood-borne dissemination. There is also direct evidence for the lymphatic dissemination of LAM.[25–27] Kumasaka et al[27] found that LAM cell clusters enveloped by lymphatic endothelial cells bud from lymphatic vessels and populate chylous fluids and axial and supraclavicular lymph nodes in patients with LAM. Induction of lymphangiogenesis appears to play an important role in this process, based on the abundant expression of lymphatic endothelial markers such as podoplanin, vascular endothelial growth factor (VEGF) receptor-3, and VEGF-C.[28] Seyama et al[29] also have reported that VEGF-D is elevated over threefold in the serum of patients with LAM, an exciting finding that may well prove useful for biomarker or therapeutic target development. The source of the LAM cells that course through the bloodstream and lymphatics and infiltrate the lung remains obscure; speculation ranges from angiomyolipomas, to lymphatic or bone marrow cells, to uterine or ovarian cells, to cells of neural crest origin. Taken together, the evidence suggests a paradigm for LAM as the simplest of human cancers, in which biallelic mutations at a single genetic locus bestow on a histologically innocent-appearing cell all of the elements required for unregulated growth, lymphatic or vascular spread, and tissue destruction.[30]

Prevalence, Diagnosis, Differential Diagnosis, and Pitfalls

Although global estimates of the prevalence of TSC (>1 million affected) indicate that TSC-LAM is probably 5-fold to 10-fold more common than S-LAM, women with S-LAM represent approximately 85% of the >240 patients enrolled in the National Heart, Lung, and Blood Institute (NHLBI) LAM Registry[31] and the 1,300 patients registered with the LAM Foundation (Leslie Sullivan-Stacey, JD, CEO, The LAM Foundation; personal communication July 7, 2007). These observations suggest that TSC-LAM may be a milder disease than S-LAM, or that other comorbidities in TSC patients may prevent pulmonary problems from becoming health priorities.

LAM is typically discovered by high-resolution CT (HRCT) scanning of patients with progressive dyspnea on exertion, pneumothorax, or chylous effusion, or less commonly by biopsy of an abdominal or retroperitoneal mass suspected to be lymphoma or ovarian cancer (Fig 2). Routine screening of asymptomatic women with TSC identifies a subset of patients with early and often asymptomatic LAM. Biopsy-documented LAM has been reported in only four men, three with definite or probable TSC,[32–34]

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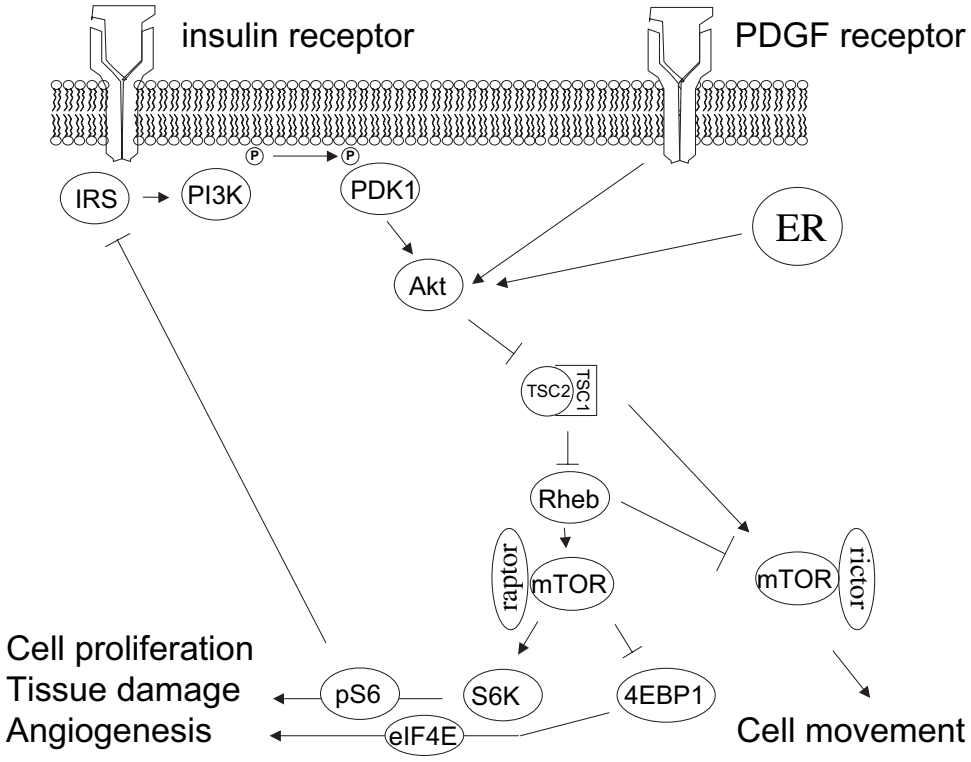

FIGURE 1. Tuberous sclerosis proteins regulate intracellular signaling through the Akt pathway. In this simplified schematic, solid arrows denote activation and T-shaped bars denote inhibition. A growth factor receptor, such as the insulin receptor, becomes phosphorylated on binding to a ligand (*eg*, insulin) and activates downstream effectors IRS and PI3K followed by Akt. Akt can also be activated through a number of other routes, including the adenosine monophosphate kinase energy pathway (not shown), the platelet-derived growth factor (PDGF) pathway, and the estrogen receptor (ER) pathways. Activated Akt phosphorylates TSC2, which blocks its ability to maintain Rheb in an inactivated state. Activated Rheb is therefore abundant when the *TSC2* gene is phosphorylated, or when the *TSC1* or *TSC2* gene is defective or missing (as is true in LAM patients). Activated Rheb activates mTOR in a manner that is potentiated by the availability of amino acids, phosphatidic acid, and adenosine triphosphate, and is blocked by the absence of these substrates or the presence of rapamycin. Activated mTOR complexed with raptor activates downstream targets S6K and 4E-BP1. Phosphorylation of S6K (pS6K) phosphorylates S6 and 4E-BP1, and releases eIF4E, which together activate the translational machinery and promote cell growth. Activated S6 also feeds back to inhibit the activation of IRS and its downstream effector Akt. This feedback loop may explain why TSC-related and LAM-related tumors are not frankly malignant. Activated mTOR complexed with rictor promotes cytoskeletal assembly and cell movement through Rho-mediated pathways.

and one without TSC.[35] On the average, women with LAM have symptoms for 3 to 5 years and experience an average of 2.2 pneumothoraces before the diagnosis of LAM is made.[36] The diagnosis of pulmonary LAM requires an HRCT scan demonstrating thin-walled cystic change and either a positive tissue biopsy (including immunohistochemical reactivity with human melanoma black-45 [or HMB-45]) or a compatible clinical context such as clinically confirmed tuberous sclerosis, angiomyolipomata, or chylothorax. The primary differential diagnosis includes pulmonary Langerhans cell histiocytosis (LCH) and emphysema (Fig 3). The smoking history and the morphology of the cysts, which are devoid of distinct walls in patients with emphysema, and are thicker walled, mid and upper lung zone predominant, and more irregularly shaped in patients with LCH, can be helpful in differentiating these disorders from LAM.[37] Diffuse nodular changes are often present in LCH patients and can be a distinguishing feature, but can be confused with micronodular pneumocyte hyperplasia, which occurs in patients with TSC (Fig 2).[38] Less common diseases that can mimic LAM and should also be considered include Sjögren syndrome,[39] follicular bronchiolitis and lymphocytic interstitial pneumonitis,[40] hypersensitivity pneumonitis,[41] amyloidosis, light chain-deposition disease,[42] bronchopulmonary dysplasia, metastatic endometrial stromal cell sarcoma,[43] low-grade leiomyosarcomas and Birt-Hogg-Dubé (BHD) syndrome.[44] Like TSC-LAM, BHD is a rare tumor suppressor syndrome that is associated with spontaneous pneumothorax, skin lesions, pulmonary cysts, and inherited renal cell can-

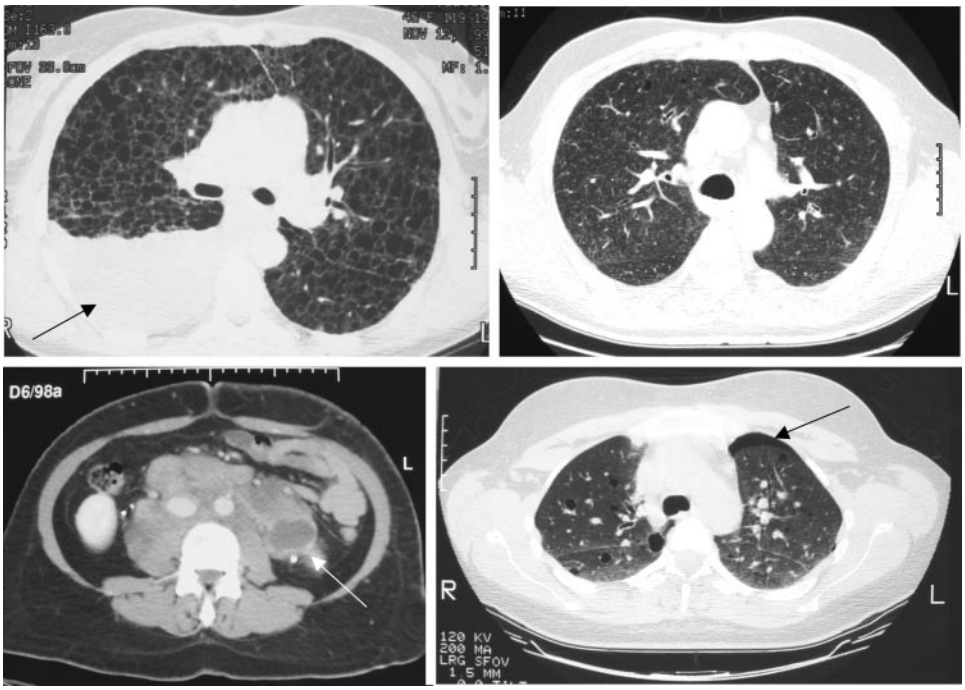

FIGURE 2. Radiographic manifestations of LAM. *Top left*: HRCT scan of patient with diffuse cystic change consistent with LAM and a large right chylous effusion (arrow). *Top right*: HRCT scan manifestations of micronodular pneumocyte hyperplasia-note diffuse miliary pattern. *Bottom left*: abdominal CT scan demonstrating extensive retroperitoneal adenopathy with central low attenuation consistent with a cystic abdominal lymphangiomyomata (arrow). *Bottom right*: HRCT scan manifestation of mild LAM with a small left apical pneumothorax (arrow).

cer. Mutations in the folliculin gene cause BHD and familial spontaneous pneumothorax.[45,46] It appears that BHD is also associated with aberrant signaling through the Akt pathway, but the loss of regulation occurs upstream of mTOR.[47] Lymphangiomatosis is a rare disease that is associated with abdominal and thoracic lymphatic smooth muscle infiltration, lymphadenopathy, lymphangiomas, chylous fluid collections, and variable bony involvement (*Gorham disease*).[48,49] Although lymphangiomatosis can involve the lung and is often confused with LAM, it affects men and women equally, does not produce lungs cysts, and is immunophenotypically distinct (staining with human melanoma black-45 [or HMB-45] is negative).

Natural History

The average age at the diagnosis of LAM in multiple series[31,50–53] is approximately 35 years. In a large cohort[31] of 230 LAM patients reported by the NHLBI LAM Registry, 57% of patients exhibited an obstructive pattern and the average FEV_1 was about 70% predicted. Interestingly, 34% of subjects had normal spirometry findings. The longitudinal lung function data from the registry is not yet available, but the NHLBI has reported that the mean (± SD) rate of decline in FEV_1 and diffusing capacity of the lung for carbon monoxide (DLCO) in their cohort of > 300 patients was 75 ± 9 mL per year and 0.69 mL/min/mm Hg per year, respectively.[54] Investigators in Europe have reported somewhat higher mean rates of decline in FEV_1 of 118 ± 142 mL per year[55] and 106 ± 143 mL per year.[56] Dyspnea develops in roughly half of the patients with LAM with walking on flat ground by 10 years following the onset of symptoms.[57] In the setting of relatively mild disease, patients with pneumothorax have lower FEV_1 and exhibit a more rapid decline in FEV_1 than those without pneumothorax.[58] These correlations are not present in patients with more profuse cystic changes. Cyst size is significantly associated with pneumothorax; patients with cyst sizes of > 0.5 cm are more likely to have pneumothorax than patients with cyst sizes of < 0.5 cm.[58] Certain polymorphisms in collagen genes *COL1A2* and *COl3A1*, and in the *MMP-1* gene were also associated with pneumothorax. Compared to patients with TSC-LAM, patients with S-LAM in the NHLBI program had a higher frequency of abdominal lymphangioleiomyomas (29% vs 9%, respectively), thoracic duct dilation (4% vs 0%, respectively), pleural effusion (12% vs 6%, respectively), and ascites (10% vs 6%, respectively).[59] Patients with TSC-LAM had a higher frequency of noncalcified pulmo-

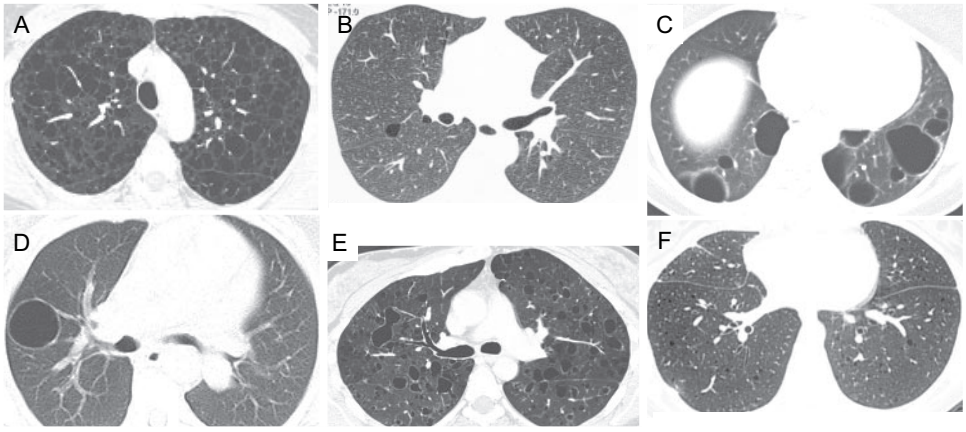

FIGURE 3. HRCT scans of cystic lung diseases that can mimic LAM. *Top left*, *A*: LAM cysts are typically round or ovoid, 2 to 5 mm in diameter, and surrounded by healthy lung, but may become large (25 to 30 mm) and polygonal with more severe involvement. *Top center*, *B*: BHD thin-walled cysts that have a subpleural predilection are shown. *Top right*, *C*: follicular bronchiolitis; round thin-walled cysts 3 to 12 mm in diameter are thought to represent dilated distal airspaces. *Bottom left*, *D*: light-chain deposition disease HRCT scan manifestations commonly include nodules, lymphadenopathy, and cysts, which are also believed to represent dilated small airways. *Bottom center*, *E*: pulmonary LCH; the presence of irregular, bizarrely shaped cysts with intermediate wall thickness, and cysts with nodules and sparing of the costophrenic angles help to distinguish pulmonary LCH from LAM. *Bottom right*, *F*: metastatic endometrial cell sarcoma; thin-walled cysts such as these can also be associated with synovial cell sarcoma and leiomyosarcoma.

nary nodules, hepatic and renal angiomyolipomas, and prior nephrectomy.[59] Mortality at 10 years is approximately 10 to 20% from the onset of symptoms[57,60] and 30% at 10 years from the time of lung biopsy[61] but varies widely; cases of LAM in octogenarians[62] and of >30 years in duration[63] have been documented. A recent report[64] from Japan suggests that presentation with pneumothorax is associated with younger age and a much more favorable prognosis (10-year survival rate, 89%) than presentation with dyspnea (10-year survival rate, 47%), but Steagall et al[58] reported 10-year survival rates of 91.3% and 92%, respectively, for patients with and without a history of pneumothorax.

Pleural Complications

Pneumothoraces ultimately occur in approximately 60 to 70% of patients with LAM, and the rate of recurrence is $>70\%$, the highest among all chronic lung diseases.[65,66] The average number of subsequent pneumothoraces for those who have had a sentinel pneumothorax is 4.4.[31] The average lifetime pneumothorax-related burden for LAM patients with a history of pneumothorax who responded to a LAM Foundation questionnaire comprised approximately 3.5 events, 5 interventions, 1 month in the hospital, and $75,000 in estimated hospital costs.[36]. The pneumothorax recurrence rate following conservative therapy such as aspiration or chest tube drainage is about 66%, and following chemical or surgical pleurodesis are 27% and 32%, respectively.[36] It is unclear why the recurrence rate following pleural fusion is so much higher for LAM patients than for patients with other cystic lung diseases, such as LCH,[67] but it is possible that the remarkable profusion of cysts on the surface of the lung of LAM patients prevents apposition and fusion of the lung and the parietal pleura. The LAM Foundation Pleural Disease Consensus Committee recommended ipsilateral pleurodesis with the initial pneumothorax in each hemithorax,[36] although, when surveyed, patients often preferred a more conservative approach.[68] Chylous pleural effusions occur in about one third of patients and may be unilateral or bilateral.[69] Pleurodesis is generally an effective approach for chylothorax, but less invasive treatments such as thoracentesis or observation may suffice in some cases.

Renal Disease

About 93% of patients with TSC-LAM and 30 to 50% of patients with S-LAM have renal angiomyolipomas, which are benign renal tumors composed of dysplastic blood vessels, smooth muscle, and variable amounts of fat[59,70] (Fig 4). Interestingly, angiomyolipomas are the only known neoplastic lesions in which the intratumoral blood vessels are composed of the cells containing transforming mutations.[71] In most patients, angiomyolipomas are clinically silent;

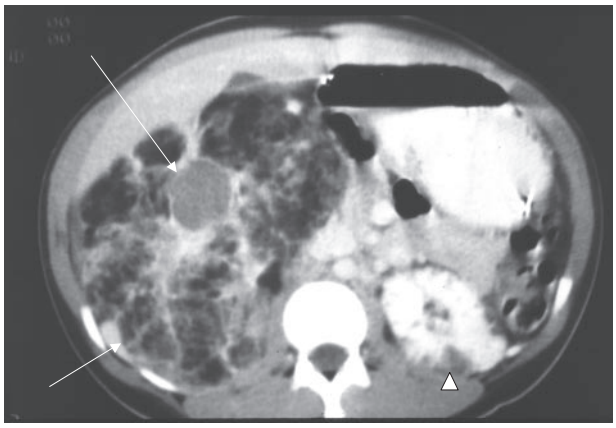

FIGURE 4. Abdominal CT scan of an angiomyolipoma; abdominal CT scan of a LAM patient with a very large angiomyolipoma. Note the diffuse involvement and massive enlargement of the right kidney (arrows). The combination of solid and fat density within the lesion is characteristic of angiomyolipomas. The left kidney has a small angiomyolipoma on the inferior margin (arrowhead).

however, flank pain, hydronephrosis, hematuria, and loss of renal function can all occur. In patients with S-LAM, angiomyolipomas are usually unilateral, small, and solitary, and are restricted to the kidney, while in patients with TSC-LAM they are more often larger, bilateral, multiple, multiorgan (involving the spleen or liver), and prone to hemorrhage.[59] The risk of renal hemorrhage from angiomyolipomas is associated with large size and with profusion of aneurysms.[72] Patients with lesions approaching 4 cm in size should be followed with periodic ultrasonography or CT scanning, and intervention should be considered when the tumor exceeds this threshold. When feasible, selective, nephron-sparing techniques such as embolization, enucleation, radioablation, electrocautery, or partial nephrectomy, rather than total nephrectomy, are the recommended therapeutic modalities. Many LAM patients have had prior resections of angiomyolipomas, which were initially suspected to be renal cell carcinomas by clinicians who were unfamiliar with the diagnostic implications of radiographic fat density within a renal tumor. Atypical angiomyolipomas with malignant potential and frank renal cell carcinomas are uncommon in patients with TSC but should be considered when solid renal masses with little fat are detected by MRI or CT scanning.

Air Travel and Pregnancy

Many LAM patients have been advised to avoid air travel because of the theoretical risk of lung cyst rupture associated with atmospheric pressure changes during flight. In a questionnaire study of 276 patients who had taken 454 flights, Pollock-BarZiv et al[73] found that air travel is generally well-tolerated by most patients with LAM. Symptoms of anxiety, chest pain, shortness of breath, cyanosis, or hemoptysis occurred during 10 to 20% of flights. Pneumothorax occurred during 10 flights, including eight episodes that were radiographically documented; but, in five cases symptoms suggestive of pneumothorax were present prior to boarding the flight. There have been no air travel-associated incidents requiring hospitalization among the >500 LAM patients who have participated in the decade-long NHLBI protocol, which encourages visits every 6 months. However, some patients with multiple pneumothoraces in this cohort were cautioned against air travel (Joel Moss, MD, PhD; personal communication; July 10, 2007). Patients should be advised that pregnancy has been reported to result in exacerbations of LAM and pneumothorax. However, the risk of pregnancy in LAM patients has not been rigorously studied. The physician and patient should discuss the risks of pregnancy, and decisions should be made on an individual basis.

Treatment

The current treatments for LAM are primarily based on the antagonism of estrogen action, and are empiric and unproven. The most commonly employed treatment is IM progesterone, which became the standard of care following a dramatic case report in 1987.[74] Enthusiasm for the use of progestins has waned over time. In a retrospective analysis, Taveira-DaSilva et al[75] found that progesterone treatment did not slow the decline in FEV_1, and in fact, appeared to accelerate the rate of decline in DLCO compared to untreated patients. The use of oral progestins or gonadotropin-releasing hormone agonists has also been reported in case studies and small series,[76,77] but neither has been tested in clinical trials. There is no evidence that bilateral oophorectomy slows the rate of progression of LAM, and this therapy is much less commonly recommended than it has been in the past.[52] A trial of bronchodilator therapy should be considered for the 17% of patients with LAM who exhibit reversible airflow limitation. Although abnormal bone density is common in women with LAM, progesterone therapy does not appear to accelerate the development of osteoporosis, and therapy with bisphosphonates is effective for this population.[78]

Current Clinical Trials

The Cincinnati Angiomyolipoma Sirolimus Trial was a proof-of-principle trial involving 20 patients with angio-

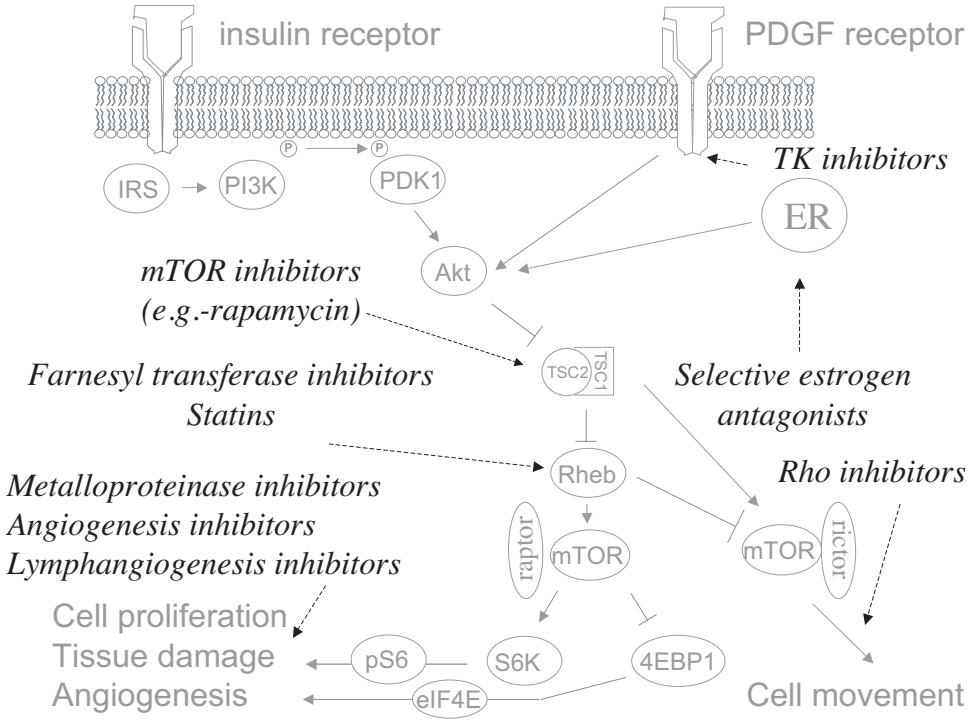

FIGURE 5. Therapeutic targets for LAM. Knowledge of the signaling pathways that are dysregulated in LAM patients has revealed a number of promising molecular targets for intervention. The constitutive activation of mTOR drives the inappropriate phosphorylation of S6 (pS6) when the *TSC1* or *TSC2* gene is missing or defective, as occurs in LAM patients. pS6 drives protein translation and inappropriate cellular proliferation, but also feeds back to inhibit the activation of IRS and downstream effector Akt. This feedback loop control can be defeated by the activation of Akt through other routes, such as the PDGF and estrogen receptor pathways (which may explain the gender restriction in LAM). In this regard, tyrosine kinase (TK) inhibitors such as imatinib and selective estrogen antagonists such as fispemiphene may have special utility in LAM to block alternative activation of Akt. mTOR inhibitors such as sirolimus and everolimus block mTOR signaling through binding to an accessory protein call FKBP12, and statins and farnesyl transferase inhibitors block Rheb translocation to the membrane by inhibiting the lipid modification of the protein. Patients with LAM express elevated levels of the lymphangiogenic growth factor VEGF-D, which is currently being studied as a target in metastatic malignancy trials. Angiogenesis inhibitors such as bevacizumab and anti-VEGF-D antibody may block blood and lymphatic vessel recruitment required for tumor maintainance, respectively, and metalloproteinase inhibitors such as doxycycline may block lung matrix degradation that plays a role in tumor implantation, spread, and tissue destruction. Cell migration, infiltration, and metastasis are controlled by a rapamcyin-insensitive mTOR pathway, but may be susceptible to inhibition by rho kinase inhibitors.

myolipomas, including 11 with LAM. After 1 year receiving the drug AML, volume decreased by almost 50%, and airflow measurements of FEV_1 and FVC increased by 5 to 10%.[79] Although the improvements in angiomyolipoma volume and FEV_1 waned somewhat after therapy with the drug was stopped, the initial response suggests that targeting the mTOR pathway has promise in the treatment of LAM. There were a number of adverse events, suggesting caution in the use of these agents outside of trials. Similar mTOR inhibitor trials, in which the primary outcome is angiomyolipoma volume response and the secondary end points are lung function, are open for enrollment and based in Boston (trial registration identifier, NCT00126672), Cincinnati (trial registration identifier, NCT00457964), and the United Kingdom (trial registration identifier, NCT00490789). A large, 3-year, randomized controlled trial called the Multicenter International LAM Efficacy of Sirolimus (MILES) Trial (trial registration identifier, NCT00414648) opened in 2006. The primary outcome measure in the Multicenter International LAM Efficacy of Sirolimus Trial is FEV_1 response. Octreotide, which slows the production of chyle through reduction in splanchnic blood flow, has shown promise for the treatment of chylous complications in other diseases,[80,81] and is currently being tested in LAM patients in a clinical trial at the NHLBI (trial registration identifier, NCT00005906).

Lung Transplantation

The cumulative survival rate for LAM patients who have undergone transplantation in the United States is 65% at 5 years, which is equal to or better than the rate for other lung disease groups who underwent transplantation during the same period.[82] Marked dyspnea, hypoxemia, and reduced DLCO on exertion develop in some patients with LAM in the absence of marked airflow obstruction; this subset of LAM patients may require transplantation evaluation before FEV_1 reaches the typical threshold of 30% predicted. Prior pleurectomy or talc pleurodesis can create difficulties with tissue plane dissection and bleeding during removal of the native lung, which can be life-threatening. In the study by Almoosa et al,[36] 45 of 80 transplanted patients had undergone a prior pleural fusion procedure, and 13 of the 14 pleura-related postoperative bleeding events occurred in patients who had previously undergone pleurodesis. However, these perioperative complications are generally manageable, and most centers do not consider even prior bilateral pleurodesis to be a contraindication to lung transplantation. Although there are no LAM-specific data available, many centers prefer double-lung transplantation over single-lung transplantation for LAM patients despite similar 1-year, 3-year, and 5-year survival rates and quality-of-life outcomes, because double-lung transplantation is typically associated with lower rates of bronchiolitis obliterans and higher airflows (FEV_1).[83,84]

Screening and Follow-up

Evidence-based guidelines for the screening of women with pneumothorax or refractory dyspnea for LAM do not exist. The Tuberous Sclerosis Alliance recommends HRCT screening of all women with tuberous sclerosis at least once after age 18 years.[85] The LAM Foundation Pleural Disease Consensus Committee recommends that HRCT scanning should be considered in all women with unexplained recurrent pneumothorax, tuberous sclerosis, or a diagnosis of primary spontaneous pneumothorax or emphysema in the setting of limited or absent tobacco use. For the routine follow-up of LAM patients, we typically obtain pulmonary function tests every 6 to 12 months and HRCT scans every 1 to 3 years, depending on symptoms and other clinical factors. Serum VEGF-D shows promise as a diagnostic tool and as a screening aid for pulmonary cyst development in women with TSC.[86]

Future Directions

LAM and TSC research have identified a wealth of potential molecular targets and experimental therapies that may be appropriate for testing in clinical trials (Fig 5). These include mTOR inhibitors (*eg*, sirolimus and everolimus), Rheb inhibitors (*eg*, farnesyltransferase inhibitors and statins), selective estrogen antagonists (*eg*, fispemifene), tyrosine kinase inhibitors (*eg*, imatinib mesylate), metalloproteinase inhibitors (*eg*, doxycycline), angiogenesis inhibitors (*eg*, bevacizumab), and lymphangiogenesis inhibitors (*eg*, anti-VEGF-D antibody). Many of these drugs have been approved by the US Food and Drug Administration or are in development for other indications. In the absence of a known effective treatment, participation in clinical trials should be encouraged. Widespread off-label use of candidate therapies like those described above will deprive patients of the opportunity to find an effective treatment and will condemn LAM to the same fate as patients with dozens of other pulmonary diseases in which the prospects for controlled trials have passed us by.

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