The NHLBI Lymphangioleiomyomatosis Registry
Characteristics of 230 Patients at Enrollment

Jay H. Ryu, Joel Moss, Gerald J. Beck, Jar-Chi Lee, Kevin K. Brown, Jeffrey T. Chapman, Geraldine A. Finlay, Eric J. Olson, Stephen J. Ruoss, Janet R. Maurer, Thomas A. Raffin, Hannah H. Peavy, Kevin McCarthy, Angelo Taveira-DaSilva, Francis X. McCormack, Nilo A. Avila, Rosamma M. DeCastro, Susan S. Jacobs, Mario Stylianou, and Barry L. Fanburg, for the NHLBI LAM Registry Group

Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota; Pulmonary-Critical Care Medicine Branch, and Biostatistics Research Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute; Division of Lung Diseases, National Heart, Lung, and Blood Institute Project Office; Department of Diagnostic Radiology, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD; Departments of Quantitative Health Sciences and Critical Care and Pulmonary Medicine, Cleveland Clinic Foundation, Cleveland; Division of Pulmonary and Critical Care Medicine, University of Cincinnati, Cincinnati, Ohio; National Jewish Medical and Research Center, Denver, Colorado; Pulmonary and Critical Care Division, New England Medical Center, Boston, Massachusetts; Division of Pulmonary and Critical Care Medicine, Stanford University Medical Center, Stanford, California; and CIGNA HealthCare, Bloomfield, Connecticut

Rationale: **Pulmonary lymphangioleiomyomatosis is a progressive cystic lung disease that is associated with infiltration of atypical smooth muscle–like cells. Previous descriptions of clinical characteristics of subjects with lymphangioleiomyomatosis have been based on a limited number of patients.**

Objectives: **To describe the clinical characteristics of subjects with pulmonary lymphangioleiomyomatosis, both sporadic and tuberous sclerosis–related forms.**

Methods: **Over a 3-yr period, from 1998 to 2001, 243 subjects with pulmonary lymphangioleiomyomatosis were enrolled into a national registry; 13 subjects who had already undergone lung transplantation were excluded for the purposes of this report.**

Measurements and Main Results: **All 230 subjects were women, aged 18 to 76 yr (mean ± SE, 44.5 ± 0.65 yr). The average age at onset of symptoms was 38.9 ± 0.73 yr and at diagnosis was 41.0 ± 0.65 yr. Tuberous sclerosis complex was present in 14.8% of subjects. Pulmonary manifestations, most commonly spontaneous pneumothorax, were the primary events leading to the diagnosis in 86.5% of cases. Nearly 55% of the subjects were being treated with a progesterone derivative. An obstructive pattern on pulmonary function testing was observed in 57.3% of the subjects, whereas 33.9% had normal spirometric results. Women with tuberous sclerosis–related lymphangioleiomyomatosis were younger and had less impaired lung function compared with those with the sporadic form.**

Conclusions: **The age range of women afflicted with pulmonary lymphangioleiomyomatosis is broader than previously appreciated and the degree of pulmonary function can be quite variable, with one-third of subjects having normal spirometry at enrollment into this registry.**

Keywords: lymphangioleiomyomatosis; registry; tuberous sclerosis

Pulmonary lymphangioleiomyomatosis (LAM) is a relatively rare disorder that affects almost exclusively women, primarily in their reproductive years (1–8). It is characterized by proliferation of atypical smooth muscle–like cells with associated cystic changes in the lung. This destructive lung process is progressive and may result in respiratory failure with pneumothorax and chylous pleural effusion as well-recognized complications.

Lymphangioleiomyomatosis also occurs in subjects with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous syndrome with a shared molecular etiology. TSC is associated with hamartoma formation in multiple organ systems, including the central nervous system, the skin, the eye, the abdominal viscera (especially the kidney), and the lung. Most patients who seek medical attention for LAM, however, have a sporadic form of the disease (sporadic LAM) unassociated with germ-line mutations in TSC genes. Patients with sporadic LAM may have some of the extrapulmonary manifestations that are found in TSC, including renal angiomyolipomas, axial lymphadenopathy and abdominal lymphangiomyomas, but they do not have the skin, central nervous system, and eye manifestations that are required for the diagnosis of TSC based on the modified Gomez criteria (1–3, 9). Whereas biopsy-documented LAM has been reported in a few men with TSC (10), pulmonary involvement with sporadic LAM is seen exclusively in women (11–13).

In 1997, a national LAM registry was established by National Heart, Lung, and Blood Institute (NHLBI) to more accurately characterize the demographic, clinical, physiologic, and radiologic features of subjects with LAM. This study was not designed to answer the question of efficacy of therapy. Additional aims for this registry included collection of tissue from participants to set the stage for future studies into the molecular basis of LAM and to possibly use the assembled cohort to conduct future clinical trials. This article outlines the baseline characteristics of subjects with LAM, both sporadic and TSC-related forms, at the time of enrollment in the LAM registry.

METHODS

Study Design

The LAM registry was organized as follows: (*1*) a steering committee, (*2*) clinical centers, (*3*) a data coordinating center, (*4*) the NHLBI project office, and (*5*) a data and safety monitoring board. This registry study was divided into three phases: phase I, design and development; phase II, recruitment and data collection; and phase III, data analysis and closure (14). During phase II, subjects returned annually for follow-up visits.

Study Subjects

Two hundred and forty-three subjects with LAM were enrolled between August 1998 and October 2001 through six participating clinical

(*Received in original form September 29, 2004; accepted in final form September 30, 2005*)

Supported by NHLBI grant U01 HL58440 and the NHLBI Division of Intramural Research.

Correspondence and requests for reprints should be addressed to Jay H. Ryu, M.D., Division of Pulmonary and Critical Care Medicine, Desk East 18, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905. E-mail: ryu.jay@mayo.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 173. pp 105–111, 2006
Originally Published in Press as DOI: 10.1164/rccm.200409-1298OC on October 6, 2005
Internet address: www.atsjournals.org

centers: the Cleveland Clinic Foundation (Cleveland, OH), the Mayo Clinic (Rochester, MN), the National Institutes of Health (NHLBI, Bethesda, MD), the National Jewish Medical and Research Center (Denver, CO), the New England Medical Center (Boston, MA), and the Stanford University Medical Center (Palo Alto, CA). The registry protocol was approved by their respective appropriate institutional review boards and each subject signed an informed consent. Inclusion criteria included a clinically definite diagnosis of LAM and willingness to return for follow-up once per year. All patients with a diagnosis of sporadic LAM or TSC-LAM, whether they (*1*) had been previously seen and diagnosed, (*2*) were regularly seen, or (*3*) were newly referred to each center, were offered the opportunity to participate in the study. Therefore, both prevalent (subjects with previously diagnosed sporadic LAM or TSC-LAM) and incident (new diagnoses) cases were enrolled. New subjects were recruited through the referral networks of each clinical center, TSC clinics (source of most patients with TSC-LAM), postings on the web, publication of a description of the LAM registry in journals, and advertisement in the newsletters of the LAM Foundation (Cincinnati, OH) and the Tuberous Sclerosis Alliance (Silver Spring, MD).

One hundred and twenty-five patients (51.4%) were included in a previous publication describing the correlation between maximal oxygen uptake and the severity of disease in LAM authored by the NHLBI group (15). Thirteen patients had already undergone lung transplantation at the time of enrollment. For the purposes of this study, these 13 lung transplant recipients were excluded. The remaining 230 subjects were analyzed for this report.

Diagnostic Criteria

All pathologic specimens and high-resolution computed tomographic (HRCT) studies were reviewed by expert panels, with the diagnosis of LAM confirmed by at least one of the following criteria: (*1*) lung biopsy (n = 125), (*2*) biopsy of lymph node or other mass (n = 21), or (*3*) HRCT scan of the chest judged to be diagnostic of LAM with a high degree of certainty (16) by two of the three expert radiologists (n = 84). Among 84 patients (62 sporadic and 22 patients with TSC-LAM) diagnosed by HRCT, 51 patients (60.7%) had renal angiomyolipomas, chylothorax, and/or TSC; the remaining 33 patients were diagnosed by HRCT lung parenchymal changes alone.

The LAM registry enrolled patients with both the sporadic form of LAM as well as those with underlying TSC.

Pulmonary Function Methodology

Pulmonary function testing was reviewed by an expert panel. The minimum data collected for the study included spirometry performed before and after the inhalation of a bronchodilator. When available, lung volume measurements, single-breath diffusing capacity, and arterial blood gases were also collected.

Acceptability and reproducibility criteria from the latest American Thoracic Society recommendations for standardization were used to judge the validity of each testing session (17–20). American Thoracic Society standards for acceptability and reproducibility criteria were also used for the single-breath diffusing capacity test (18). Percentage of predicted values reported in this article used the following reference equations: spirometry (reference equations of Hankinson and coworkers [21]), lung volumes (reference equations of Crapo and coworkers [22]), and diffusing capacity (nonsmoker reference equations of Miller and coworkers [23]). Bronchodilator response is defined as increase in FEV_1 of at least 12% and 200 ml.

Spirometry (before and after the inhalation of a bronchodilator) and diffusing capacity data were acceptable in 217 patients. The 13 remaining patients had a persistent pneumothorax at the time of their initial visit or refused bronchodilator administration.

Quality-of-Life Instruments

The short form (SF)-36 is a multipurpose, short-form health survey with 36 questions (24). The SF-36 standardized scoring system yields a profile of eight health scores, two summary measures (physical and mental health), and a self-evaluated change in health status.

The St. George's Respiratory Questionnaire (SGRQ) is a self-administered health-related quality-of-life measure for patients with respiratory disease (25).

Statistical Analysis

Comparisons of percentages for sporadic LAM versus TSC-LAM patients were made with the χ^2 test or Fisher's exact test. Means of continuous variables were compared between groups with a two-sample *t* test. Pearson correlations were used to measure association between SF-36 quality-of-life scales and baseline spirometry and diffusion capacity. Because not all measurements were available for all subjects, the sample sizes differ somewhat for different results. All p values reported correspond to two-sided tests. Analyses were performed with the SAS version 8.2 software packages (SAS Institute, Inc., Cary, NC).

All data in RESULTS are expressed as means ± SE unless specified otherwise.

RESULTS

Demographic Data

All enrolled subjects were women; only 2.6% were current smokers (Table 1). Mean age at enrollment was 44.5 ± 0.65 yr (mean ± SE); range, 18 to 76 yr. Nearly 40% were postmenopausal (natural or oophorectomy-related menopause) at enrollment, including 27% (of 230 subjects) on the basis of oophorectomy. The mean age at menopause was 41.7 ± 0.76 yr. Thirty-four subjects (14.8%) had underlying TSC.

Spontaneous pneumothorax was the sentinel event leading to the diagnosis of LAM in about one-third of patients, and together with other pulmonary symptoms, including shortness of breath or wheezing, was the primary presentation in 64.2% of cases (Table 1). Abnormal chest radiograph or the presence of pleural effusion was the initial manifestation in an additional 22.3%.

Clinical Characteristics

At enrollment, the most common symptom was breathlessness (Table 2). Pneumothorax had previously occurred in 55.5%; the mean number of pneumothoraces in subjects that had had at least one pneumothorax was 4.4 ± 0.53. Of those with a history of pneumothorax, 4.8% had experienced an episode related to air travel. Medical or surgical pleurodesis had been performed in 44.3%; 16.1% of all subjects had undergone bilateral pleurodesis. Subjects with TSC-LAM had a significantly higher prevalence of renal angiomyolipomas and had undergone a nephrectomy more commonly compared with those with sporadic LAM.

Two-thirds of subjects had been pregnant. Of 353 pregnancies, 66.9% had resulted in live birth, 16.7% spontaneous abortion, 15.0% therapeutic abortion, and 1.4% in stillbirth. Twenty-five patients (21.7% of those who had been pregnant and able to recall symptoms) had experienced worsening of respiratory symptoms during pregnancy.

Nearly 55% of subjects were being treated with a progesterone derivative at the time of enrollment (Table 2), more often in those with sporadic LAM compared with those with TSC-LAM. Nearly one-third of the subjects were receiving supplemental oxygen therapy, at least part time.

Lung Function

Baseline pulmonary function data of the LAM registry participants are shown in Tables 3 and 4 and in Table E1 (*see* the online supplement). Spirometric evidence of airflow limitation was the most common pulmonary function abnormality and was followed by a reduced diffusing capacity. Spirometric results were normal in 33.9% of subjects. When compared with subjects with sporadic LAM, those with TSC-LAM more often had normal spirometry and diffusing capacity.

Laboratory Results

Laboratory results including complete blood count, serum chemistries, and liver enzyme levels, and urinalysis revealed no

TABLE 1. DEMOGRAPHIC AND PRESENTING FEATURES OF THE REGISTRY POPULATION

Characteristic	All Patients (*n = 230*)	Sporadic LAM (*n = 196*)	TSC-LAM (*n = 34*)	p Value‖
Age at enrollment, yr	44.5 ± 0.65	45.1 ± 0.69	41.2 ± 1.68	0.041
Age at diagnosis, yr	41.0 ± 0.65	41.4 ± 0.70	39.0 ± 1.66	0.17
Disease duration, yr*	1.40 (0.5, 5.3)	1.5 (0.4, 5.6)	1.1 (0.6, 3.6)	0.45
Postmenopausal, %†	39.5	39.2	41.2	0.70
Smoking status, %				0.33
Never smoked	60.4	61.7	52.9	
Ex-smokers	37.0	35.7	44.2	
Current smokers	2.6	2.5	2.9	
Ethnic background, %				0.77
White	87.4	87.2	88.2	
Black	6.1	5.6	8.8	
Asian	3.9	4.1	2.9	
Other	2.6	3.1	0	
Marital status, %				0.085
Never married	15.7	15.3	18.2	
Married	64.6	66.8	51.5	
Divorced	13.5	11.7	24.2	
Other‡	6.2	6.2	6.1	
Primary condition or event that led to diagnosis, %				< 0.001
Spontaneous pneumothorax	35.8	36.9	29.4	
Other pulmonary symptoms	28.4	30.8	14.7	
Abnormal chest radiograph	19.7	19.0	23.5	
Renal angiomyolipoma	3.9	2.6	11.8	
Pleural effusion	2.6	3.1	0	
Other§	9.6	7.6	20.6	

Definition of abbreviations: LAM = pulmonary lymphangioleiomyomatosis; TSC = tuberous sclerosis complex.

Postmenopausal is defined as natural or oophorectomy-related menopause. Plus–minus values represent means ± SE.

*Median (interquartile range).

† Does not include menopausal state induced by hormonal therapy.

‡ Other marital status includes widowed, separated, and cohabiting with significant other.

§ Other primary condition or events includes abnormal pulmonary function results in four, personal history of TSC in three, family history of TSC in three, abdominal or pelvic tumor in three, ascites in two, and other nonpulmonary symptoms in seven patients.

‖ p values are for comparison between the two subgroups.

abnormalities that were judged to be informative. Hypoxemia on room air at rest as defined by $Pa_{O2} \leqslant 55$ mm Hg or $Sa_{O2} \leqslant 88\%$ was noted in 6.2 and 4.2% of all subjects with available data, respectively (Table 5).

Quality of Life

The physical and mental component scores (mean ± SE) of the SF-36 quality of life for LAM registry patients were 39.7 ± 0.82 and 50.2 ± 0.66, respectively, at baseline (*see* Figure E1). They are quite similar to those in other specific normative populations with chronic lung disease (42.3 ± 1.05 and 44.5 ± 0.91, physical and mental scores, respectively) (24). The SF-36 physical component was positively correlated with baseline spirometry (FVC % predicted, FEV_1 % predicted, and FEV_1/FVC) and diffusion capacity (*see* the online supplement). In addition, the SF-36 physical component was significantly reduced in persons with cough, phlegm, wheezing, and breathlessness. However, the mental component of the SF-36 correlated with neither lung function nor symptoms.

The three component scores (symptom, activity, and impact) and the total score (mean ± SE) of the SGRQ for LAM registry patients at baseline were 36.1 ± 1.50, 50.3 ± 1.98, 23.6 ± 1.22, and 34.0 ± 1.37, respectively (*see* Figure E2). These scores are worse than those for normal subjects with no history of respiratory disease (12, 9, 2, and 6, respectively) but better than for patients with chronic obstructive pulmonary disease (COPD; 68, 64, 46, and 52, respectively) (25, 26). The SGRQ scores were inversely related to lung function, with component and total scores most strongly associated with FEV_1. In addition, all four scores were significantly inversely associated with the presence of cough, phlegm, wheezing, and breathlessness.

DISCUSSION

Because of the rarity of LAM, this registry was initiated to gather reliable information on epidemiologic and clinical features of subjects with this disorder. This summary provides demographic, clinical, and pulmonary function data about the largest cohort of patients with LAM reported to date.

The patients enrolled in the LAM registry have a broader age range than that described in previous case series originating from various countries (4–8). The reason(s) for these differences are not entirely clear, but the higher profile of LAM in the media and more liberal use of CT scanning in the United States may have allowed identification of a broader sample of patients with LAM compared with those who may have come to medical attention traditionally, that is, those who are more severely affected and at a younger age. More than one-third of our patients were postmenopausal in comparison with subjects in previous reports, who were typically in their third through fifth decades of life, with the highest percentage of postmenopausal women being 13% (6). Our cohort includes women in their eighth decade of life, some of the oldest subjects with LAM reported to date.

Not surprisingly, the vast majority of patients (86%) presented with pulmonary manifestations, including spontaneous pneumothorax, other pulmonary symptoms, and pleural effusion or other chest radiographic abnormalities. The most common symptom was breathlessness. In addition, nearly one-half of all

TABLE 2. CLINICAL CHARACTERISTICS OF THE REGISTRY POPULATION AT ENROLLMENT

Characteristic	All Patients (*n = 230*)	Sporadic LAM (*n = 196*)	TSC-LAM (*n = 34*)	p Value*
Symptoms				
Breathlessness	73.0	73.5	70.6	0.73
Wheezing	46.5	44.4	58.8	0.12
Cough	30.9	31.6	26.5	0.55
Hemoptysis	30.4	32.1	20.6	0.18
Phlegm	27.0	26.0	32.4	0.44
Chyloptysis	7.0	7.1	6.1	0.99
Medications at time of entry				
Progesterone derivatives	53.9	57.1	35.3	0.018
Inhaled bronchodilators	37.8	39.3	29.4	0.27
Inhaled corticosteroids	21.3	21.9	17.7	0.57
Systemic corticosteroids	4.8	5.1	2.9	0.99
Supplemental oxygen	31.7	33.2	23.5	0.27
Medical and surgical history				
Pregnancy	67.4	68.9	58.8	0.25
Spontaneous pneumothorax	55.5	56.9	47.1	0.29
Pleurodesis (medical or surgical)	44.3	45.4	41.2	0.65
Renal angiomyolipoma	37.8	29.1	88.2	< 0.001
Hospitalization related to LAM in past yr	28.7	29.6	23.5	0.47
Osteoporosis	21.3	20.9	23.5	0.73
Pleural effusion	20.9	23.5	5.9	0.02
Nephrectomy	15.4	11.4	41.4	< 0.001
Chylous ascites	4.3	5.1	0	0.37

For definition of abbreviations, *see* Table 1.
*p values are for comparison between the two subgroups.

subjects also experienced wheezing, a symptom not described in previous reports. There were no significant differences in the prevalence of various respiratory symptoms when comparing those subjects with sporadic LAM to those with TSC-LAM. There was no relevant family history for patients with sporadic LAM. As expected, some of the patients with TSC-LAM had a family history of TSC.

Hospitalization is not an uncommon event for patients with LAM. These hospitalizations are most commonly required for the management of spontaneous pneumothorax. Other reasons for hospitalization include management of chylothorax and renal angiomyolipomas that are acutely bleeding, or at risk for spontaneous hemorrhage. Unlike COPD, hospitalization for acute exacerbation of the underlying obstructive disease or respiratory failure was not seen. In the management of pleural complications nearly one-half of the patients had already undergone some form of pleurodesis. In comparing the subjects with sporadic LAM and TSC-LAM, there was no significant difference in the prevalence of previous pleurodesis. However, those with TSC-LAM were much more likely to have had a nephrectomy. This result is not surprising because these subjects are more likely to have renal angiomyolipomas and to suffer a more aggressive course with respect to the number and size of these tumors when compared with those subjects with sporadic LAM (27–29).

Airway obstruction demonstrated by spirometry was the most common pulmonary function abnormality, and was seen in more than one-half of patients. Approximately one-fourth of those subjects with obstructive defects (17% of all subjects) showed a significant increase in FEV_1 after bronchodilator inhalation, similar to previous reports (7, 30). A reduced single-breath diffusing capacity was seen as commonly as airflow limitation. Given the frequency of diminished diffusing capacity in this population, exercise oximetry should be considered to exclude desaturation, and to evaluate for need of supplemental oxygen therapy. It is not clear to what extent a history of tobacco smoking might play a role in the reduction of diffusing capacity in these patients, but a smoking history would be a reasonable criterion for including the measurement of diffusing capacity in

TABLE 3. PULMONARY FUNCTION DATA AT THE TIME OF ENROLLMENT

	All Patients (*n = 230*)		Sporadic LAM (*n = 196*)		TSC-LAM (*n = 34*)		
Characteristic	n*	Mean ± SE	n*	Mean ± SE	n*	Mean ± SE	p Value†
FVC, %pred	218	87.5 ± 1.14	186	86.7 ± 1.24	32	92.0 ± 2.83	0.095
FEV_1, %pred	218	70.3 ± 1.64	186	68.8 ± 1.77	32	79.0 ± 4.08	0.027
% FEV_1 improvement after bronchodilator	217	9.1 ± 0.65	185	9.2 ± 0.72	32	8.1 ± 1.56	0.53
FEV_1/FVC ratio	218	64.5 ± 1.21	186	63.5 ± 1.30	32	70.2 ± 3.08	0.05
D_{LCO}	217	67.6 ± 1.61	183	65.8 ± 1.73	34	77.4 ± 4.10	0.013

Definition of abbreviations: D_{LCO} = diffusing capacity of carbon monoxide; LAM = pulmonary lymphangioleiomyomatosis; TSC = tuberous sclerosis complex.
FVC, FEV_1, and FEV_1/FVC ratio values were determined after administration of bronchodilator.
*Number of subjects with information available.
† p values are for comparison between the two subgroups.

TABLE 4. PATTERNS OF PULMONARY FUNCTION AT ENROLLMENT

	All Patients		Sporadic LAM		TSC-LAM		
Characteristic	n	%	n	%	n	%	p Value*
Normal spirometry	74	33.9	57	30.7	17	53.1	0.013
Obstruction	125	57.3	113	60.8	12	37.5	0.014
Mild ($FEV_1 > 70\%$pred)	27	12.4	24	12.9	3	9.4	0.77
Moderate ($FEV_1 \geq 50$ and $\geq 70\%$pred)	43	19.7	41	22.0	2	6.3	0.052
Severe ($FEV_1 < 50\%$pred)	55	25.2	48	25.8	7	21.9	0.64
Bronchodilator response	37	17.1	31	16.8	6	18.8	0.80
Hyperinflation	12	6.3	11	6.9	1	3.3	0.69
Restriction	21	11.4	17	10.9	4	14.3	0.60
Low diffusing capacity	124	56.9	111	60.3	13	38.2	0.017

For definition of abbreviations, *see* Table 1.

Percentages are calculated on the basis of the number of subjects with information available, which included 218 spirometries, 217 bronchodilator responses, 190 lung volumes, and 218 diffusing capacities. Normal spirometry is defined by both FVC and FEV_1/FVC ratio greater than or equal to the lower limit of normal (statistically determined lower limit of normal; mean predicted value – [1.645 × SE], i.e., the lower bound of a 90% confidence interval on the prediction regression equation). Obstruction is defined as an FEV_1/FVC ratio that is less than the lower limit of normal. Bronchodilator response is defined as an increase in FEV_1 of at least 12% and 200 ml. Hyperinflation is defined as a TLC value that is greater than the upper limit of normal (statistically determined upper limit of normal; mean predicted value + [1.645 × SE]). Restriction is defined as a TLC value that is less than the lower limit of normal. Low diffusing capacity is defined as a measurement below the predicted normal range (nonsmoker reference equations of Miller and coworkers [23]).

*p values are for comparison between the two subgroups.

pulmonary function testing. Taveira-DaSilva and colleagues (30) detected, by cardiopulmonary exercise testing, exercise-induced hypoxemia even in patients with near-normal diffusing capacity and FEV_1.

Overall, these pulmonary function results are better compared with those of previous reports (5, 7, 30). For example, Kitaichi and colleagues (5) found normal spirometric values and normal diffusing capacity in only 19 and 3% of their subjects, respectively. However, Urban and colleagues (6) described normal results on initial spirometry in 42% of their 66 patients with sporadic LAM, although in some of these patients pulmonary function results had been obtained before the diagnosis of LAM. The milder degree of pulmonary dysfunction seen in these LAM registry subjects likely reflects earlier diagnosis and detection of subclinical disease. This is due, in part, to the aggressive recruitment strategy employed by the registry to identify all subjects, rather than just those with clinically significant respiratory symptoms, and is supported by the number of subjects with normal pulmonary physiology. The early and widespread use of CT scanning to explore chest radiographic changes, or even the finding of cystic change in the lung based on abdominal CT, has likely led to the identification of cystic lung disease characteristic, or highly suggestive of, LAM in patients who are minimally symptomatic or without respiratory symptoms altogether. This is particularly true for members of the TSC-LAM subgroup, for whom the diagnosis of LAM is often made by screening chest CT of this high-prevalence subgroup (11–13). It is likely that the older age of our cohort, compared with previous reports, is also a reflection of the identification of less clinically significant disease. The TSC-LAM subgroup had a higher FEV_1 and diffusing capacity as well as a slightly lower alveolar–arterial oxygen gradient reflecting milder lung involvement compared with those with sporadic LAM. Taken together, these data suggest that normal spirometry should not exclude LAM from the differential diagnosis in a young woman presenting with pneumothorax.

Estrogen has been implicated in the pathogenesis of LAM on the basis of the observation that nearly all subjects with LAM, with or without underlying TSC, have been women (1–3). In addition, exacerbation of the disease has been documented following the administration of exogenous estrogens (31, 32). Oberstein and colleagues (33) found the age of onset of symptoms to be significantly less among women using oral contraceptive pills versus nonusers and suggested that oral contraceptive pills may serve as catalysts to promote an earlier occurrence of LAM. However, hormonal receptors are inconsistently expressed in affected tissues (4, 34, 35). The LAM registry did not collect data on the dates of the last menstrual period, hormonal replacement therapy, or specific progesterone derivative used.

The therapeutic use of progestin therapy in LAM was initially described by McCarty and colleagues (36). Since this early report there have been multiple other case reports suggesting beneficial therapeutic effects of various forms of hormonal therapy for

TABLE 5. LABORATORY RESULTS

	All Patients		Sporadic LAM		TSC-LAM		
Characteristic	n*	Mean ± SE	n*	Mean ± SE	n*	Mean ± SE	p Value†
Pa_{O2}	193	81.6 ± 1.18	163	80.5 ± 1.27	30	87.6 ± 2.94	0.032
Sa_{O2}	214	96.4 ± 0.25	181	96.2 ± 0.29	33	97.3 ± 0.38	0.032
Pa_{CO2}	193	34.4 ± 0.33	163	34.2 ± 0.37	30	35.6 ± 0.71	0.09
$(A–a)O_2$ gradient	189	22.7 ± 1.16	159	24.0 ± 1.24	30	15.5 ± 2.88	0.009

Definition of abbreviations: $(A–a)O_2$ gradient = alveolar–arterial oxygen gradient; LAM = pulmonary lymphangioleiomyomatosis; TSC = tuberous sclerosis complex.

*Number of subjects with information available.

† p values are for comparison among the two subgroups.

patients with LAM, but definitive evidence in this regard is lacking (1–3, 6, 37, 38). The most common medication employed in the treatment of LAM among our registry subjects was progestin therapy, which was more commonly prescribed for those with sporadic LAM compared with those with TSC-LAM. No treatment outcomes can be identified in data provided by an observational registry, such as advantage or disadvantage of progestin therapy on disease progression or complication rates. Clearly, future research must focus on targeting novel therapies to lessen the impact of this disease on this relatively young female population.

Quality-of-life data from both the SF-36 and the SGRQ confirm that patients with LAM experience impairment in quality of life. The most dramatic effect is found in the SF-36 physical component and the SGRQ activity dimension, which are, not surprisingly correlated with pulmonary function. The SF-36 physical and mental component scores for patients with LAM are worse than those for the general U.S. healthy population with no chronic conditions (55.3 and 53.4, respectively) but better than those for patients with COPD seen in one study with a mean FEV_1 of 45% predicted (35.9 and 47.7, respectively) (26, 39). Interestingly, the lack of physiologic correlation with the SF-36 mental component, which is similar to patients with COPD (38, 40), suggests both groups develop coping mechanisms or have good support systems.

The relatively young age of patients affected by this disease understandably portends a greater impact on quality of life. Whereas all three SGRQ dimensions of symptom, activity, and impact were lower in this LAM cohort than for the COPD population, the effect on activity was closest to that of patients with COPD. Symptoms of LAM may be more episodic in nature (pneumothoraces, pleural effusions, and hemoptysis) as compared with the chronic breathlessness in COPD, which is reflected in the higher activity limitation scores for patients with LAM and comparatively lower symptom scores. The symptom of breathlessness may also be more acute when it occurs accompanying an event such as pneumothorax. In particular, the aversion to air travel is quite specific to this population and clearly affects activities related to quality of life. However, the occurrence of pneumothorax related to air travel was less than 5%. Patients with severely limited cardiopulmonary reserve or acute symptoms of shortness of breath should not enplane, but recommendations regarding air travel for patients with stable LAM will require directed studies. Fortunately, although pneumothorax or pleural effusion may limit planned activities, a history of their occurrence does not predict worse quality of life subsequently. In contrast, we show that previous pleurodesis does mildly affect quality of life (*see* the online supplement), but the degree of reduction appears not to outweigh the potential benefits of the procedure.

By its nature, the LAM registry is an observational study in which a cohort of individuals satisfying specific diagnostic criteria is monitored serially over the duration of the study. The limitations of this study include retrospective design, ascertainment by screening for some patients with TSC-LAM, requirement for sufficient reserves to travel to a specialized center for evaluation, and self-reporting of some data from memory. In addition, the predominance among the white population and the high level of education of this cohort suggest that access to health care plays a role in the identification of patients with LAM.

The strengths of this study include its size and the comprehensive nature of the patient evaluation. The results indicate that LAM usually presents with either pneumothorax or dyspnea, although in almost 25% of patients the diagnosis was made before symptoms developed. Pulmonary function testing revealed that airflow limitation is the most common presentation, but that normal spirometry is frequently seen. Gas trapping in noncommunicating airspaces is prevalent, but hyperinflation is infrequent. The diffusing capacity of carbon monoxide is reduced in most patients, and may be one of the earliest markers of the disease, based on prior studies (6, 29). Quality of life in the activity dimension for all patients is clearly impacted by breathlessness, multiple hospitalizations for acute events related to LAM complications, and limitations to air travel. This report provides descriptive data related to diagnostic hallmarks that could contribute to earlier identification of LAM, for example, pneumothorax being the most common presenting symptom in a comparatively young female population. Future reports from the LAM registry will describe lung transplantation in patients with LAM, the reliability of CT criteria for diagnosis of LAM as compared with tissue diagnosis, and longitudinal data from this cohort, which will help define the natural history of the disease and form a foundation for future clinical trials.

***Conflict of Interest Statement*:** J.H.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.J.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.-C.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.K.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.T.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.A.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.J.O. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.J.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.A.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.H.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.T.-D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.X.M. is the scientific director of the Lymphangioleiomyomatosis (LAM) Foundation. N.A.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.M.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.S.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.L.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

NHLBI LAM Registry Group: *NHLBI Project Office*—H. H. Peavy, J. P. Kiley, M. Stylianou, C. D. Vreim, M. C. Wu; *National Heart, Lung, and Blood Institute*—J. Moss, A. Taveira-DaSilva, P. M. Barnes, M. B. Barton, M. E. Ehrmantraut, C. G. Glasgow, C. J. Jolley, E. Lange, R. A. Litzenberger, P. J. McGraw, W. K. Steagall; *Steering Committee Chair*—J. H. Ryu (B. L. Fanburg, previous); *Cleveland Clinic Foundation*—J. T. Chapman, J. R. Maurer, E. J. Sullivan, A. C. Arroliga, H. A. Christie, S. M. Lubell, Y. Meli; *Mayo Clinic*—E. J. Olson, S. D. Fisher, J. H. Ryu; *National Jewish Medical and Research Center*—K. K. Brown, D. Kervitsky, M. E. Wallace; *New England Medical Center*—G. A. Finlay, B. L. Fanburg, R. Tsacoyianis; *Stanford University Medical Center*—S. J. Ruoss, S. S. Jacobs, T. A. Raffin; *Data Coordinating Center* (*Cleveland Clinic Foundation*)—G. J. Beck, J. C. Lee, X. Liu, J. McMahan, S. G. Sherer, J. K. Stoller, L. J. Tuason; *Imaging Core*—M. Meziane, D. A. Lynch, P. B. O'Donovan; *Pulmonary Function Core*—K. McCarthy; *Tissue Core*—K. K. Brown, J. Moss, V. J. Ferrans, F. Giacometti, W. D. Travis; *Tissue Repository* (*BBI-BioTech Research Laboratories*)—M. Cosentino, C. Chorley, M. Dowell, Kathi Shea; *Consultants*—S. Byrnes, E. P. Henske, T. E. King, Jr., F. X. McCormack, J. D. Moreno; *Data and Safety Monitoring Board*—G. Hunninghake, A. S. Buist, K. M. Detre, M. L. Foegh, C. Ober.

***Acknowledgment*:** The authors thank the patients with LAM, who gave generously of their time for this study; and the referring physicians, the LAM Foundation, and the Tuberous Sclerosis Alliance for help with recruitment of patients.

References

1. Kelly J, Moss J. Lymphangioleiomyomatosis. *Am J Med Sci* 2001;321:17–25.
2. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. *Thorax* 1999;54:254–264.
3. Glassberg MK. Lymphangioleiomyomatosis. *Clin Chest Med* 2004;25: 573–582.
4. Taylor JR, Ryu JH, Colby TV, Raffin TA. Lymphangioleiomyomatosis: clinical course in 32 patients. *N Engl J Med* 1990;323:1254–1260.

5. Kitaichi M, Nishimura K, Itoh H, Izumi T. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. *Am J Respir Crit Care Med* 1995;151:527–533.
6. Urban T, Lazor R, Lacronique J, Murris M, Labrune S, Valyere D, Cordier JF. Pulmonary lymphangioleiomyomatosis: a study of 69 patients. *Medicine* 1999;78:321–337.
7. Chu SC, Horiba K, Usuki J, Avila NA, Chen CC, Travis WD, Ferrans VJ, Moss J. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. *Chest* 1999;115:1041–1052.
8. Johnson SR, Tattersfield AE. Clinical experience of lymphangioleiomyomatosis in the UK. *Thorax* 2000;5:1052–1057.
9. Roach ES, DiMario FJ, Kandt RS, Northrup H. Tuberous sclerosis consensus conference: recommendations for diagnostic evaluation. *J Child Neurol* 1999;14:402–407.
10. Aubry MC, Myers JL, Ryu JH, Petri-Henske E, Jalal SM, Tazelaar HD. Pulmonary lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in a male patient with tuberous sclerosis complex. *Am J Respir Crit Care Med* 2000;162:749–752.
11. Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in adult women with tuberous sclerosis complex. *Mayo Clin Proc* 2000;75:591–594.
12. Franz DN, Brody A, Meyer C, Leonard J, Chuck G, Dabora S, Sethuraman G, Colby TV, Kwiatkowski DJ, McCormack FX. Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. *Am J Respir Crit Care Med* 2001;164: 661–668.
13. Moss J, Avila NA, Barnes PM, Litzenberger RA, Bechtle J, Brooks PG, Hedin CJ, Hunsberger S, Kristof AS. Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. *Am J Respir Crit Care Med* 2001;163:669–671.
14. Sullivan EJ, Beck GJ, Stoller JK. The registry for individuals with lymphangioleiomyomatosis. In: Moss J, editor. LAM and other diseases characterized by smooth muscle proliferation. New York: Marcel Dekker; 1999. pp. 45–64.
15. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, Kristof AS, Avila NA, Rabel A, Travis WD, Moss J. Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. *Am J Respir Crit Care Med* 2003;168:1427–1431.
16. Bonelli FS, Hartman TE, Swensen SJ, Sherrick A. Accuracy of high-resolution CT in diagnosing lung diseases. *AJR Am J Roentgenol* 1998; 170:1507–1512.
17. American Thoracic Society. 1994 update on standardization of spirometry. *Am J Respir Crit Care Med* 1995;152:1107–1136.
18. American Thoracic Society. 1995 update on single-breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique. *Am J Respir Crit Care Med* 1995;152:1299–1307.
19. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;44:1202–1218.
20. Johnson DC. Importance of adjusting carbon monoxide diffusing capacity (D_{LCO}) and carbon monoxide transfer coefficient (Kco) for alveolar volume. *Respir Med* 2000;94:28–37.
21. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;159:179–187.
22. Crapo R, Morris A, Nixon C. Lung volumes in healthy nonsmoking adults. *Clin Respir Physiol* 1982;18:419–425.
23. Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ. Single breath diffusing capacity in a representative sample of Michigan, a large industrial state: predicted values, lower limits of normal and frequencies of abnormality by smoking history. *Am Rev Respir Dis* 1983;127:270–277.
24. Ware JE, Kosinski M, Keller SD. SF-36 Physical & Mental Health Summary Scales: a user's manual. Boston, MA: The Health Institute, New England Medical Center; 1994.
25. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321–1327.
26. Jones PW, Bosh TK. Quality of life changes in COPD patients treated with salmeterol. *Am J Respir Crit Care Med* 1997;155:1283–1289.
27. Cook JA, Oliver K, Mueller RF, Sampson J. A cross sectional study of renal involvement in tuberous sclerosis. *J Med Genet* 1996;33:480–484.
28. Avila NA, Kelly JA, Chu SC, Dwyer AJ, Moss J. Lymphangioleiomyomatosis: abdominopelvic CT and US findings. *Radiology* 2000;216: 147–153.
29. Lendvay TS, Marshall FF. The tuberous sclerosis complex and its highly variable manifestations. *J Urol* 2003;169:1635–1642.
30. Taveira-DaSilva AM, Hedin CJ, Stylianou MP, Travis WD, Matsui K, Ferrans VJ, Moss J. Reversible airflow obstruction, proliferation of abnormal smooth muscle cells and impairment of gas exchange as predictors of outcome in lymphangioleiomyomatosis. *Am J Respir Crit Care Med* 2001;164:1072–1076.
31. Shen A, Iseman MD, Waldron JA, King TE. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous estrogens. *Chest* 1987;91: 782–785.
32. Yano S. Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous oestrogen used for infertility treatment. *Thorax* 2002;57:1085–1086.
33. Oberstein EM, Fleming LE, Gomez-Marin O, Glassberg MK. Pulmonary lymphangioleiomyomatosis (LAM): examining oral contraceptive pills and the onset of disease. *J Womens Health* 2003;12:81–85.
34. Logginidou H, Ao X, Russo I, Henske EP. Frequent estrogen and progesterone receptor immunoreactivity in renal angiomyolipomas from women with pulmonary lymphangioleiomyomatosis. *Chest* 2000;117: 25–30.
35. Matsui K, Takeda K, Yu ZX, Valencia J, Travis WF, Moss J, Ferrans VJ. Downregulation of estrogen and progesterone receptors in the abnormal smooth muscle cells in pulmonary lymphangioleiomyomatosis following therapy. *Am J Respir Crit Care Med* 2000;161:1002–1009.
36. McCarty KS Jr, Mossler JA, McLelland R, Sieker HO. Pulmonary lymphangiomyomatosis responsive to progesterone. *N Engl J Med* 1980;303: 1461–1465.
37. Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. *Am J Respir Crit Care Med* 1999;160:628–633.
38. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, Hathaway O, Moss J. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 2004;126:1867–1874.
39. Mahler DA, Mackowiak JI. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. *Chest* 1995;107:1585–1589.
40. van Manen JG, Bindels PJ, Dekker FW, Bottema BJ, van der Zee JS, Ijzermans CJ, Schade E. The influence of COPD on health-related quality of life independent of the influence of comorbidity. *J Clin Epidemiol* 2003;56:1177–1184.