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Clinical course and characterisation of lymphangioleiomyomatosis in a Brazilian reference centre

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Abstract. *Background and objective:* Lymphangioleiomyomatosis (LAM) is a rare disease that promotes pulmonary cystic destruction and impairs pulmonary function. We aim to describe features and clinical course of LAM patients from Brazil. *Methods:* We described the clinical and functional features, performance in six minute walk test (6MWT), management details, survival and clinical course of 84 LAM patients followed in a Brazilian reference centre. *Results:* All subjects were women, the average age at onset of symptoms was 38 years, and the average at diagnosis was 42 years. The major symptoms during the course of the disease were dyspnoea and pneumothorax. The patients experienced impaired quality of life, with worse scores in the physical and emotional domains. The most common abnormalities in pulmonary function tests were an obstructive pattern and reduced diffusion capacity, whereas a quarter of the patients had normal spirometric results. In the 6MWT, although patients had preserved exercise capacity, more than half of the patients had significant desaturation. Hormonal blockage and doxycycline were the most common treatment modalities employed in our patients. The survival probability from diagnosis was 90% at 5 years, whereas the mean annual rate of decline in FEV1 was 60 ± 78 mL. *Conclusions:* Clinical and functional features of the LAM patients from our centre are similar to those from other countries. Our sample showed preserved exercise capacity, with desaturation in the 6MWT, and impaired quality of life. Survival was similar, whereas the annual rate of decline of FEV1 was slightly lower than in recent studies. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 129-135)*

Key words: Angiomyolipoma; Brazil; lymphangioleiomyomatosis; Respiratory function tests; Survival

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease that mainly affects women of reproductive age, that is characterised by proliferation of atypical muscle cells (LAM cells) around the airways, blood vessels and lymphatic vessels, which can result in cystic destruction of the lungs and pulmonary function impairment. LAM may occur in sporadic form or in association with tuberous sclerosis complex (TSC) (1, 2).

LAM is clinically characterised by recurrent spontaneous pneumothorax, progressive dyspnoea, haemoptysis, and chylothorax (1-5). Extrapulmonary manifestations include renal angiomyolipomas, abdominal and pelvic masses along the axial lymphatics (lymphangiomyomas), and chylous ascites (1, 2-4). The most common abnormalities found in pulmonary function tests (PFTs) include an obstructive pattern, air trapping, and a reduction in the diffusion capacity of the lungs for carbon monoxide (DL_{CO}) (4, 6-8).

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LAM is characterised by variable progression, and no definitive treatment has been established for this disease (1). Recent evidence has shown beneficial effects of targeting mammalian target of rapamycin (mTOR) signaling in a subgroup of patients, and a potentially favourable outcome with metalloproteinase inhibitors (9-11). Although hormonal therapy has been the most widely used treatment for LAM, studies have showed mostly negative results (1, 12-14).

No study, to our knowledge, has described the main features and clinical course of a sample of LAM patients from Latin America. Therefore, the aims of this study were to establish clinical and functional features, and to describe quality of life, the performance in a six minute walk test (6MWT), management details, survival, and clinical course of LAM patients who were followed in a Brazilian reference centre.

Methods

Study population

This retrospective study comprised 84 LAM patients who were followed in the interstitial lung diseases outpatient clinic of the Pulmonary Division of the Hospital das Clinicas of the University of Sao Paulo from 2006 to 2013. The diagnosis of LAM was established by tissue biopsy or by a combination of typical chest high-resolution computed tomography (HRCT) findings and compatible clinical history.

Measurements

Clinical features

The following clinical features were analysed: age at the onset of symptoms; age at diagnosis; time to diagnosis; smoking history; the most common pulmonary and extrapulmonary manifestations; presence of TSC; and method of diagnosis. Previous use of hormonal contraceptives and previous infertility treatment were also evaluated.

Quality of life was assessed using the Short Form 36 Healthy Survey (SF-36) questionnaire, which has been validated for the Brazilian population (15-17).

Pulmonary function tests

All measurements were obtained based on the recommended standards (18-20). Spirometry was performed using a calibrated pneumotachograph (Medical Graphics Corporation, St, Paul, MN), and lung volumes and DL_{CO} values were obtained with a body plethysmograph (Elite Dx, Elite Series; Medical Graphics Corporation). The following variables were obtained: forced vital capacity (FVC); forced expiratory volume in the first second (FEV_1); total lung capacity (TLC); residual volume (RV); and DL_{CO}. Predicted values were derived from the Brazilian population (21-23). The prevalence of a positive response to bronchodilators (BDs) was evaluated, and was characterised by changes in FEV_1 and/or FVC of ≥ 12% and 200 mL over baseline, according to American Thoracic Society/European Respiratory Society criteria (24).

Six minute walk test

Patients performed the 6MWT according to recommended standards (25). Oxygen saturation (SpO_2) as measured by pulse oxymetry (Onyx, model 9500; Nonin, Plymouth, MN) was obtained at rest and at the end of exercise. Breathlessness was evaluated using a modified Borg scale before and after exercise (26). The 6-minute walking distance was recorded and expressed as the percentage of that predicted for the Brazilian population (27).

Treatment

The main treatment modalities used from 2006 to 2013, including drugs, pulmonary transplantation, oxygen supplementation, and pleurodesis for pneumothorax or chylothorax, were also reviewed.

Survival and clinical course

Survival from diagnosis and annual rate of decline in FEV_1 regardless of treatment or hormonal status were also obtained.

Statistical analysis

Data are reported as the mean ± SD for variables with normal distribution, as the median (25^{th} - 75th percentiles) for variables with non-normal distribution or as numbers (percentiles). Unpaired t-test was used to compare continuous variables between different groups. Survival at 5 years, excluding survival after lung transplantation, was calculated by Kaplan-Meier analysis from diagnosis of LAM. Differences were considered significant if p was less

than 0.05. The data were analysed with SigmaStat version 3.5 (Systat Software, Inc., San Jose, CA).

Results

Clinical and demographic features

Eighty-four women with LAM were included in the study. Seventy-one (85%) patients had sporadic LAM, while 13 (15%) had underlying TSC. Seventeen (20%) patients were ex-smokers (all of whom had smoked less than 10 pack-years). The clinical features are summarised in Table 1. The mean age at onset of symptoms was 38 ± 10 years, the mean age at diagnosis was 42 ± 11 years, and the median interval between onset of symptoms and diagnosis was 12 months. The most common symptoms during the course of the disease were dyspnoea (75%), pneumothorax (63%), cough (16%), haemoptysis (14%), and chylothorax (14%). Renal angiomyolipoma was found in 50% of the patients. In addition, previous use of hormonal contraceptive and treatment for infertility were reported by 50 (60%) and 8 (10%) patients, respectively.

The diagnosis of LAM was confirmed by lung biopsy (68%), kidney biopsy (10%), and biopsy from other sites (8%). In the remaining 12 patients (14%), the diagnosis of LAM was based on the combination of typical HRCT findings with compatible clinical history (Table 1).

The LAM patients experienced impaired quality of life, with worse scores in the physical and emotional domains, when compared with healthy subjects (Table 2).

Table 1. Clinical features of 84 women with LAM

	Patients with LAM (n = 84)
Age at diagnosis, years	42 ± 11
Age at onset of symptoms, years	38 ± 10
Interval between onset of symptoms and diagnosis, months	12 (6 – 24)
Presence of TSC	13 (15%)
Ex-smokers	17 (20%)
Symptoms during the course of the disease	
Dyspnea	63 (75%)
Pneumothorax	53 (63%)
Cough	13 (16%)
Haemoptysis	12 (14%)
Chylothorax	12 (14%)
Chylous ascites	3 (4%)
Renal angiomyolipoma	42 (50%)
Previous use of hormonal contraceptive	50 (60%)
Previous treatment for infertility	8 (10%)
Diagnosis	
Lung biopsy	57 (68%)
Kidney biopsy	8 (10%)
Biopsy from other sites	7 (8%)
HRCT findings plus clinical history	12 (14%)

Values are the mean ± SD, median (25th - 75th percentiles) or percentage (%).
Definition of abbreviations: HRCT: high resolution computed tomography; LAM: lymphangioleiomyomatosis; TSC: tuberous sclerosis complex.

Pulmonary function tests

Baseline pulmonary function data are described in Table 3. The most common abnormalities identified in baseline PFTs were an obstructive pattern (58%), reduced DL_{CO} (53%), and air trapping (22%). Eighteen patients (21%) met the criteria for positive response to BDs (changes in FEV_1 and/or FVC of ≥ 12% and 200 mL over baseline) (24). Twenty-one (25%) patients had normal spirometric results.

Table 2. Quality of life data (SF-36)

	Patients with LAM (n = 84)	Normal subjects (n = 10)
Physical functioning	70 ± 26	95 ± 7 *
Role limitations due to physical health	61 ± 37	97 ± 8 *
Role limitations due to emotional problems	65 ± 42	100 ± 0 *
Energy and Fatigue	64 ± 23	76 ± 15
Emotional well-being	68 ± 20	85 ± 9 *
Social functioning	74 ± 28	90 ± 11
Pain	73 ± 23	87 ± 12
General health	65 ± 25	80 ± 15

Values are mean ± SD.
Definition of abbreviations: SF-36: Medical Outcomes Short Form 36.
** $p < 0.05$*

Table 3. Baseline pulmonary function tests

FEV1, L	2.08 ± 0.84
%predicted	73 ± 27
FVC, L	3.06 ± 0.76
%predicted	88 ± 19
FEV1/FVC	0.66 ± 0.19
RV, L	2.02 ± 0.85
%predicted	134 ± 56
TLC, L	5.14 ± 0.88
%predicted	105 ± 20
RV/TLC	0.38 ± 0.11
DLCO, ml/min/mmHg	16.5 ± 6.6
%predicted	65 ± 28
Normal spirometry	21 (25%)
Obstructive pattern	49 (58%)
Air trapping	18 (22%)
Reduced DLCO	45 (53%)
Positive response to BDs	18 (21%)

Values are mean ± SD, or percentage (%).
Definition of abbreviations: BDs: bronchodilators; DLCO: lung diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity.

Table 4. Variables obtained in the six minute walk test (n = 65)

Distance, m	502 ± 118
Distance, %pred	92 ± 15
Peak HR, beats/min	131 ± 18
Minimum SpO2, %	88 ± 9
Change in SpO2, %	7 ± 6
Peak Borg dyspnea score	3 ± 3
Peak Borg leg discomfort score	3 ± 2

Values are mean ± SD.
Definition of abbreviations: HR: heart rate; SpO2: oxyhaemoglobin saturation by pulse oximetry.

Table 5. Treatment modalities during the course of the disease (n = 84)

Medications	58 (69%)
Doxycycline plus hormonal blockage	34 (40%)
Doxycycline	11 (13%)
Hormonal blockage	10 (12%)
Rapamycin	3 (4%)
Medical or surgical pleurodesis	36 (43%)
Bilateral lung transplantation	7 (8%)
Supplemental oxygen therapy	11 (13%)

Values are percentage (%).

Six minute walk test

Sixty-five patients performed the 6MWT. Nineteen patients from the initial sample did not perform the test (six patients received supplemental oxygen at baseline, three had musculoskeletal disorders, and ten refused to perform the test). The mean distance walked was 502 ± 118 m, which was 92 ± 15% of the predicted distance. The mean Borg dyspnoea score and the minimum SpO_2 at the end of the 6MWT were 3 ± 3 and 88 ± 9%, respectively. The mean desaturation from rest to the end of the test was 7 ± 6%, and desaturation over 4% was found in 53% of the patients (Table 4).

Treatment

Fifty-eight (69%) patients received medical therapy during the course of the disease (Table 5). Thirty-four (40%) subjects received doxycycline plus hormonal blockage (goserelin, a gonadotropin-releasing hormone, GnRH, agonist, or progesterone), eleven (13%) were treated only with doxycycline, ten (12%) received only hormonal blockage, and three (4%) received rapamycin .

Seven (8%) patients underwent bilateral lung transplantation for progressive pulmonary failure. Medical or surgical pleurodesis was performed in 36 (43%) patients. Eleven (13%) patients received supplemental oxygen therapy during the course of the disease.

Survival and clinical course

The median follow-up from diagnosis to either death or closing date was 9 years. Over the period of observation, ten (12%) of the 84 patients had died (two patients died following lung transplantation). The survival probability, evaluated by the Kaplan-Meier analysis, was 90% at 5 years after diagnosis (Figure 1). The mean annual rate of decline in FEV_1,

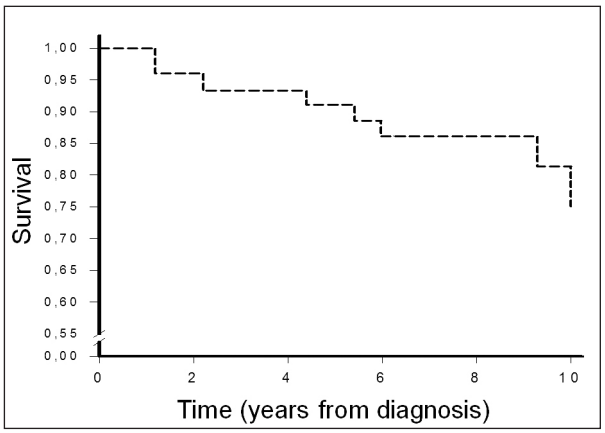

Fig. 1. Kaplan-Meier survival analysis of mortality of 84 patients with LAM

regardless of treatment or hormonal status was 60 ± 78 mL (3 ± 3.8% from baseline).

Discussion

To our knowledge, this is the first study that has described the main features, survival, and clinical course of a sample of LAM patients from Latin America. This study has provided data on the largest sample of LAM patients who were followed in a single centre in Latin America. The main findings of this study are as follows: (1) The clinical features of the LAM patients did not differ from those reported in other studies; (2) the LAM patients experienced impaired quality of life, with worse scores in the physical and emotional domains; (3) in baseline PFTs, the most common abnormalities identified were an obstructive pattern with air trapping, and reduced DL_{CO}; (4) although the LAM patients had preserved exercise capacity, they had a significant desaturation (>4%) in the 6MWT; (5) hormonal blockage and doxycycline were the most common treatment modalities employed; (6) the annual rate of decline in FEV_1 was slightly lower when compared with previous studies; and (7) the survival probability was similar to those described in recent studies and was better than those described earlier.

According to the results of our study, the mean age at onset of symptoms and the mean age at diagnosis were similar to those reported in previous studies from different countries (4, 8, 28-30). Despite a greater awareness of the disease in Brazil, a late diagnosis is not uncommon because LAM patients are sometimes misdiagnosed as having other obstructive diseases, such as asthma or COPD. Moreover, other cystic lung diseases, such as Langerhans cell histiocytosis, lymphoid interstitial pneumonia and Birt-Hogg-Dubé syndrome, may have clinical and radiological similarities with LAM, which can lead to a difficult differential diagnosis and contributes to a late diagnosis (31). In our study, the median interval between onset of symptoms and diagnosis was 12 months. The majority of patients presented with pulmonary manifestations during the course of the disease, mainly dyspnoea, and pneumothorax, which was consistent with the findings from other studies (3, 4, 8, 28-30). The most common extrapulmonary manifestation was renal angiomyolipoma, which was found in half of the patients. Although the pathogenesis of LAM is not completely understood, it has been hypothesised that one of the factors that plays a role in LAM cell proliferation is estrogen (1, 2). More than half of our patients had used hormonal contraceptive or infertility treatment, which could be involved in the development of the disease. Previous studies have demonstrated that LAM is associated with impairments in physical, emotional, and social domains in the quality-of-life evaluation (4, 6, 32). In our sample, in comparison with healthy subjects, LAM patients experienced impaired quality of life, with worse scores in the physical and emotional domains.

Twenty-one (25%) patients had normal spirometric results. The most common abnormalities identified in baseline PFTs were an obstructive pattern and impairment in DL_{CO}, which were found in more than half of the patients in this study. Although 20% of the patients had been smokers, their smoking history likely had no impact on PFTs because they smoked less than 10 pack-years. Compared with the experience from other centres, these pulmonary function findings were similar to the majority of the results from other cohorts (4, 28, 30, 33). The presence of air trapping was uncommon (22%), which was poorly described in other cohorts. Consistent with previous observations, which showed positive responses to BDs in 6 to 30% of patients, we found a significant response to BD in 18 (21%) patients (4, 7, 8, 24, 34, 35).

Our study is the first survey to have described the performance of LAM patients during 6MWT.

Although patients showed a preserved exercise capacity, more than half of our sample had significant desaturation (>4%) at the end of the test. Recent studies that also evaluated LAM patients during 6MWT showed similar results, and one of those studies found that ventilatory limitation and gas exchange impairment were most likely the primary reasons for exercise cessation (6, 36).

In our sample, fifty-eight (69%) patients received medical therapy during the course of the disease. Although no definitive treatment has been established, LAM has been regarded as a hormone-dependent disease, because estrogen has been implicated in its pathogenesis, which is reinforced by the presence of estrogen receptors in LAM cells (37). Therefore, although of indeterminate value, one of the most common treatment modalities employed in the treatment of LAM in our centre was hormonal blockage (1). Twenty-six (31%) patients had not been treated for LAM, mainly due to postmenopausal status, lack of symptoms, or normal PFTs. Recently, an increasing number of patients have been treated with doxycycline and rapamycin based on the results of recent studies, which showed favourable outcomes in the use of these drugs (9-11). In our experience, rapamycin has determined beneficial effects mainly for patients with extra-pulmonary manifestations, such as renal angiomyolipomas, and has also led to stabilization of pulmonary function in patients with progressive disease. Future prospective studies may evaluate the long-term impact of these promising drugs on the course of this disease. Moreover, recent guidelines suggest a trial of BDs in patients with airflow obstruction, mainly in those patients with positive responses to BDs (1). Lung transplantation, which was performed in 8% of our sample, should be considered in patients with end-stage disease.

The rate of progression is variable, and decline in FEV_1 is sufficiently sensitive to detect disease progression in LAM. In our study, the mean annual rate of decline in FEV_1, regardless of treatment or hormonal status, was 60 ± 78 mL (3 ± 3.8% from baseline), which was slightly lower when compared with studies from other countries. These previous studies showed that the mean annual decline in FEV_1 ranged from 75 to 118 mL (12, 13). As the mean age at diagnosis and baseline FEV_1 in our study have been similar to those found in these previous studies, we speculate that the fact that a large proportion of our patients have been treated with a combination of medications may have contributed to this difference in the rate of progression.

In the present study, the survival probability from diagnosis, evaluated by the Kaplan-Meier analysis, was 90% at the 5 year follow up. Our results were similar to those reported by recent studies, which showed that survival probability ranged from 84% to 91% after 5 or 10 years, and were better than those identified in earlier studies, which showed a shorter survival, with most patients dying within 10 years (29, 31, 38-41). It has not been definitively established whether earlier diagnosis and treatment, which could be partially explained by an increased knowledge about the disease and a greater availability of CT scan, may have contributed to improved survival in our cohort compared with earlier studies.

Our study had several limitations that need to be addressed. The retrospective design of our study is an expected limitation, because it is difficult to prospectively obtain data on the clinical course and survival of patients with rare diseases. Moreover, although we reported the experience of a single centre, our cohort is a probable representative of the whole country because patients from different regions of Brazil are referred to our centre. The lack of standardisation of treatment for LAM in our centre, in association with the retrospective design of the study, precluded the evaluation of the effects of treatments on clinical course and survival. The use of standardised treatment protocols with promising drugs, such as rapamycin and doxycycline, may allow an assessment of the effects of these therapeutic modalities on these outcomes (9-11).

In summary, this study highlights the first survey of LAM patients from Latin America, and emphasises that clinical and functional features are similar to those described in previous studies. Moreover, our sample had preserved exercise capacity, with significant desaturation in the 6MWT, and impaired quality of life. The main treatment modalities used were hormonal blockage and, recently, doxycycline. Survival was similar, whereas the annual rate of decline of FEV_1 was slightly lower than recent studies. Future trials evaluating the long-term impact on the clinical course of promising drugs, such as doxycycline and rapamycin, and of the association of medications acting on different pathways involved in disease pathogenesis are necessary for LAM patients.

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