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Reductions in pulmonary function detected in patients with lymphangioleiomyomatosis: An analysis of the Japanese National Research Project on Intractable Diseases database

Mie Hayashida, MD, PhD[a,], Masanori Yasuo, MD, PhD[a], Masayuki Hanaoka, MD, PhD[a], Kuniaki Seyama, MD, PhD[b], Yoshikazu Inoue, MD, PhD[c], Koichiro Tatsumi, MD, PhD[d], Michiaki Mishima, MD, PhD[e], the Respiratory Failure Research Group of the Ministry of Health, Labour, and Welfare, Japan*

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ABSTRACT

Background: In lymphangioleiomyomatosis (LAM), predicting lung disease progression is essential for treatment planning. However, no previous Japanese studies have attempted to predict the reductions in pulmonary function that occur in LAM patients.

Methods: The data for 89 LAM patients who had undergone ≥3 spirometry tests and whose data had been registered in the Japanese National Research Project on Intractable Diseases database between October 2009 and March 2014 were analyzed after excluding patients who had undergone (1) a lung transplant; (2) mTOR inhibitor treatment; or (3) thoracic drainage, pleurodesis, surgery, or thoracic duct ligation during the study period. The rates of change (slope) in pulmonary parameters were calculated, and their associations with clinical background factors were investigated.

Results: Among the whole study population, the median (quartiles) slope of forced expiratory volume in one second (FEV_1) was −46.7 (−95.2; −15.0) mL per year. Episodes of conservatively treated pneumothorax during the study period were found to be associated with rapid reductions in FEV_1 (% predicted). Pregnancy during the study period was associated with a reduction in FEV_1 (% predicted). When the patients were divided into those who exhibited initial FEV_1 (% predicted) values of >70% (Group A) and ≤70% (Group B), Group B displayed significantly faster reductions in FEV_1 (% predicted) than Group A.

Conclusions: LAM patients whose initial FEV_1 (% predicted) values are ≤70% subsequently exhibit rapid reductions in their FEV_1 values, and hence, require treatment. However, the FEV_1 reduction rate varies markedly among individuals and should be monitored in all cases.

*Correspondence to: First Department of Internal Medicine, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto 390-8621, Japan. Tel.: +81 263 37 2631; fax: +81 263 36 3722.

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1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare and slowly progressing lung disease that almost exclusively affects adult females. It is characterized by neoplastic LAM cell infiltration of the lungs and lymphatic system, and cystic destruction of the lungs [1,2]. Patients with advanced pulmonary dysfunction develop dyspnea on exertion and respiratory failure. In addition, a high incidence of recurrent pneumothorax is seen from the early stages of LAM, and extrapulmonary lesions, such as chylous effusions, lymphangioleiomyoma, and angiomyolipoma, are considered to be characteristic complications of the condition.

As the molecular pathology of LAM has been elucidated, various treatment targets have attracted attention [3–5]. Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been demonstrated to prevent reductions in pulmonary function in patients with LAM [6–8]. Sirolimus was approved as a pharmaceutical drug in 2014 and has begun to be used in clinical practice in Japan. However, no consensus has been reached regarding the grade of pulmonary hypofunction at which sirolimus treatment should be initiated. The risk/benefit ratio of sirolimus treatment, including its effects and adverse reactions, need to be investigated, but the speed of the decline in pulmonary function seen in LAM varies among individuals [9,10]. It is difficult to accurately predict this interindividual variation, which in turn makes it more difficult to assess the benefits of particular agents.

In LAM, the LAM histological score (LHS) and the pathological grade of the associated pulmonary cystic lesions have been reported to be prognostic factors [11,12], and associations have been detected between abnormal pulmonary function, e.g., obstructive ventilatory impairment or a reduced pulmonary diffusion capacity, and the LHS or the grade of pulmonary cystic lesions according to high-resolution computed tomography (CT) [13–17]. At present, time-course monitoring of pulmonary function is the most useful method for assessing the severity and progression of lung disease in LAM [18].

A younger age and a lower initial pulmonary function level are associated with a high mortality rate and subsequent reductions in pulmonary function in LAM [12,19,20]. In addition, we previously reported that LAM patients who initially present with dyspnea exhibit a lower survival rate than those who initially display pneumothorax [21]. However, pulmonary function has not been evaluated throughout the course of LAM in any previous Japanese study. In this study, using the Japanese National Research Project on Intractable Diseases database, we calculated the rate of change in pulmonary function and investigated its associations with various clinical background factors in LAM. We classified the patients into three groups based on the magnitude of the annual changes in forced expiratory volume in one second (FEV_1) (% predicted) values and compared the clinical background data of the three groups. We used the annual change in FEV_1 to define the groups because FEV_1 has been reported to show the strongest correlation with the grade of pulmonary cystic lesions of all pulmonary function parameters in quantitative CT evaluations [15–17].

In the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) trial [6], in which sirolimus was demonstrated to be effective against LAM, the subjects were patients who exhibited FEV_1 (% predicted) values of $\leq 70\%$ after bronchodilator administration. Thus, an FEV_1 (% predicted) value of $\leq 70\%$ could be a useful index for determining the optimal time to initiate treatment for LAM. In this study, we compared the rates of change in pulmonary function parameters between patients with initial FEV_1 (% predicted) values of $>70\%$ and $\leq 70\%$.

2. Materials and methods

2.1. *Intractable diseases database*

In Japan, LAM was included in the National Research Project on Intractable Diseases in October 2009, and as a result, patients who were diagnosed with LAM were able to receive medical subsidies. To receive these subsidies, patients are required to submit an application form and a clinical research form (a questionnaire), the latter of which is completed by their physicians, every year. The questionnaire includes questions about the following topics: age, gender, the patient's history of cigarette smoking, pregnancy/childbirth, the presence/absence of menopause, the presence/absence of tuberous sclerosis, symptoms, chest CT findings, abdominal imaging findings (ultrasonography, CT, and/or magnetic resonance imaging [MRI]), pathological findings of lung or lymph node biopsies (including the results of immunostaining), the differentiation of LAM from other cystic lung diseases (including chronic obstructive pulmonary disease; Langerhans cell histiocytosis; Birt–Hogg–Dubé syndrome; Sjögren's syndrome-associated pulmonary lesions; lymphocytic interstitial pneumonia; bullae/blebbing; amyloidosis; light-chain deposition disease; cyst-forming metastatic lung tumors), pulmonary function test results (including the results of spirometry tests and data regarding the diffusing capacity), and the treatments administered. The results of tests other than chest CT are not essential, and findings are added to the database when a test has been performed. In patients who have not been pathologically diagnosed with LAM, chest CT images are required, and the validity of the diagnosis is examined by specialists. The certified contents of the questionnaires are entered into the National Research

[a]First Department of Internal Medicine, Shinshu University School of Medicine, Matsumoto, Japan
[b]Division of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan
[c]Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan
[d]Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan
[e]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
E-mail addresses: mie@shinshu-u.ac.jp (M. Hayashida) yasumasa@shinshu-u.ac.jp (M. Yasuo) masayuki@shinshu-u.ac.jp (M. Hanaoka) kseyama@juntendo.ac.jp (K. Seyama) giichi@kch.hosp.go.jp (Y. Inoue) tatsumi@faculty.chiba-u.jp (K. Tatsumi) mishima@kuhp.kyoto-u.ac.jp (M. Mishima).