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# Lymphangioleiomyomatosis and multifocal micronodular pneumocyte hyperplasia in Japanese patients with tuberous sclerosis complex

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ABSTRACT

*Background:* Pulmonary involvement in tuberous sclerosis complex (TSC) includes lymphangioleiomyomatosis (LAM) and multifocal micronodular pneumocyte hyperplasia (MMPH). This retrospective study investigated pulmonary involvement in Japanese TSC patients and pulmonary function testing in TSC-LAM.

*Methods:* The study subjects included 59 TSC patients (age range: 13–66, 15 males and 44 females). Female patients were divided into 3 groups (Group 1: symptomatic LAM, Group 2: asymptomatic LAM, Group 3: without LAM) and 3 cystic grades according to increasing cyst numbers on computed tomography images (patients without LAM, Grade 1 patients, and Grade 2+Grade 3 patients). The results of pulmonary function tests were compared among the groups and the grades.

*Results:* One male (6.7%) patient and 19 female (43.2%) patients were diagnosed with LAM and 7 male (43.2%) and 23 female (52.3%) patients were diagnosed with MMPH. Patients with multiple pulmonary nodules had higher rates of renal angiomyolipoma and history of seizures than patients without nodules. Although all 6 adolescent patients displayed no pulmonary symptoms, MMPH was found in 3 patients and LAM was found in a 13-year-old girl. Carbon monoxide diffusing capacity (DLco) differed significantly among the 3 groups and DLco and carbon monoxide diffusing capacity divided by the alveolar volume (DLco/VA) differed significantly among the 3 cystic grades.

*Conclusions:* There was no difference in the prevalence of pulmonary involvement in TSC patients among countries. LAM and MMPH occur even during adolescence in TSC patients. DLco and the number of cysts are useful predictors of onset and progression of TSC-LAM.



Abbreviations: CT, computed tomography; LAM, lymphangioleiomyomatosis; MMPH, multifocal micronodular pneumocyte hyperplasia; mTOR, mammalian target of rapamycin; TSC, tuberous sclerosis complex; VEGF, vascular endothelial growth factor

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## 1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of hamartomas in multiple organs [1]. TSC is caused by a mutation in either the *TSC1* gene encoding hamartin [2] or the *TSC2* gene encoding tuberin [3]. TSC has various clinical features. Manifestations in the brain, skin, kidneys, heart, and eyes are well known. Pulmonary manifestations have been recognized as characteristic features of TSC in the last 20 years [4–6]. Lymphangioleiomyomatosis (LAM) and multifocal micronodular pneumocyte hyperplasia (MMPH) typify pulmonary involvement in TSC [7].

LAM is a rare progressive disease characterized by proliferation of abnormal smooth muscle-like cells (LAM cells) and cystic destruction of lung parenchyma [8,9], which occurs almost exclusively in premenopausal women but also rarely in men [10–12]. LAM occurs both in sporadic cases and in patients with TSC (TSC-LAM) [13]. Although TSC-LAM is often milder than sporadic LAM [14], signs including cough, dyspnea, hemoptysis, and repeated pneumothorax may appear as it progresses. LAM is one of the major causes of death in adult female patients with TSC. Recent reports have indicated the efficacy of mammalian target of rapamycin (mTOR) inhibitors for treatment of LAM [15], but early diagnosis and evaluation are important for improved prognosis.

MMPH manifests as multiple small ground-glass nodular shadows on chest computed tomography (CT) [16,17]. These nodules are typically 1–10 mm in diameter and are composed of proliferating type 2 pneumocytes.

Several recent studies have shown a LAM frequency of 26–81% in TSC women [6,7,12,18–21], which is higher than that reported previously. One [7] of these studies found multiple pulmonary nodules consistent with MMPH in 43% of female patients with TSC. The subjects of these studies were mainly adult female patients. Hancock [13] reported on several symptomatic adolescent female TSC-LAM patients, but the frequency of LAM in adolescents is unknown. Furthermore, these studies were performed in the USA and the Netherlands. There have been no reports on the frequency of pulmonary involvement in Asian patients with TSC.

Recently, the serum vascular endothelial growth factor (VEGF)-D level has been shown to be useful as a diagnostic test for TSC-LAM [22]. However, this test is not always available in typical hospitals. Although pulmonary function testing is easy, inexpensive, and noninvasive, a previous study [18] found it to be an insensitive indicator of early LAM in TSC patients.

The aims of this retrospective study were to clarify the frequency and characteristics of pulmonary involvement in Japanese TSC patients, including adolescents, and to reassess the utility of pulmonary function testing as an indicator of LAM in TSC patients.

## 2. Patients and methods

### 2.1. Patients

In total, 105 patients with definite TSC visited the Department of Dermatology of Osaka University Hospital from January 2000 to March 2009. They were diagnosed according to the criteria described by the International Tuberous Sclerosis Complex Consensus Group [23]. Eighty-six of the patients (32 males and 54 females) were 10 years of age or older at the most recent hospital visit. All available medical records were reviewed retrospectively. Data included age, sex, familial history, symptoms, clinical features, clinical examination results, imaging findings, results of lung biopsy, and results of examinations conducted in other hospitals. Fifty-nine (15 males and 44 females) of these patients, who had undergone thoracic CT at our hospital or other hospitals, were selected as the subjects in this study. This retrospective study was approved by the Institutional Review Board for Clinical Research of Osaka University Hospital.

### 2.2. Imaging and diagnosis

Of the 59 patients, 57 underwent high-resolution CT (HRCT) scans, whereas 2 underwent conventional CT scans. Various types of CT scanners were used. HRCT images were obtained at the end inspiration with patients in the supine position. The scanning protocol consisted of the reconstruction of 0.625–1.25 mm collimation sections with a high-spatial frequency algorithm at 1 cm intervals. Images were photographed at window settings appropriate for viewing the lung parenchyma (window level: −600 to −700, window width: 1200–1500). All images were reviewed by an experienced radiologist.

Transbronchial lung biopsy was performed in 1 patient. Surgical lung biopsy, including video-assisted thoracic surgical lung biopsy and open lung biopsy, was performed in 4 patients in other hospitals.

Patients in whom pulmonary involvement was detected were referred to the Department of Respiratory Medicine. The diagnosis was made by one of the authors (H.H., M.Y.) who reviewed the CT images and the results of examinations conducted in other hospitals.

Diagnosis of LAM on thoracic CT was based on bilateral randomly scattered thin-walled cysts and bullae according to the European Respiratory Society guidelines [24]. Cases with unevenly distributed cysts and bullae, as well as emphysematous changes caused by smoking were excluded.

We counted all cysts in LAM patients who underwent pulmonary function testing. The lungs were divided into six zones: the upper, middle, and lower region of each lung. The total number of cysts was counted in each of the 6 zones. The female LAM patients were graded according to the number of cysts in the least cystic zone as follows: less than 4 cysts

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