iii) (3)-2-b の画像診断
iv) 結節性硬化症の確実な臨床診断

III. 参考事項

1) LAM は特徴的な臨床像が揃っている場合臨床診断可能であるが，病理による確定診断をめざして生検を行うことが推奨される．

2) 胸部単純エックス線写真は検出感度が低く，軽症の症例では異常を検出し得ない．LAM の肺病変の有無の判定には高分解能 CT 撮影が必要である．

3) 女性で，喫煙歴のない，あるいは喫煙歴の軽度である若年性 COPD では LAM である可能性を考慮すべきである．

IV. 臨床病型

結節性硬化症（TSC）*の合併の有無により，以下の 2 病型に分類する．

1. 孤発性リンパ脈管筋腫症　sporadic LAM
2. TSC 合併のリンパ脈管筋腫症　TSC-LAM

*TSC の診断は，難病情報センター http://www.nanbyou.or.jp/sikkan/024_i.htm，あるいは Roach ER et al. J Child Neurol 13：624-628, 1998 に準じる．

V. 重症度分類

LAM は全身性疾患であり多様な病像を呈する．LAM の重症度を包括的に示すことは困難であるため，予後に最も関係する肺 LAM の重症度の目安を示す．

	安静時動脈血ガス（PaO_2）	6 分間歩行時の SpO_2**
I 度	80Torr ≦ PaO_2	
II 度	70Torr ≦ PaO_2 < 80Torr	90% 未満の場合は III 度にする
III 度	60Torr ≦ PaO_2 < 70Torr	90% 未満の場合は IV 度にする
IV 度	PaO_2 < 60Torr	測定不要
		**危険な場合は測定不要

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●特別報告

リンパ脈管筋腫症 lymphangioleiomyomatosis (LAM) の治療と管理の手引き

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要旨：肺リンパ脈管筋腫症 (pulmonary lymphangioleiomyomatosis, pulmonary LAM) は，本邦において平成15年度から厚生労働省，難治性疾患克服研究事業の対象疾患に指定され，呼吸不全に関する調査研究班における研究活動が開始された．その一端として，平成17年度におけるLAM診断基準作成に引き続き，平成18年度において本手引きの作成に至った．LAMは女性に好発する稀な疾患であり，平滑筋様細胞(LAM細胞）が肺やリンパ管等で増殖し，肺では多発性の嚢胞を発生させる．近年，LAMに関する多くの研究成果が報告され，今後の治療研究への期待も高まっている．一方，現時点では治療法における統一された見解は乏しい．現段階での治療の考え方および具体策につき，呼吸不全に関する調査研究班による見解として本手引きを提示する．LAMを全身性疾患として考慮し，肺外病変も対象項目とした．

キーワード：リンパ脈管筋腫症，治療，管理，手引き，ホルモン療法
Lymphangioleiomyomatosis, Treatment, Care, Guide, Hormone therapy

手引きの利用に際して

リンパ脈管筋腫症 (LAM) は稀少疾患であるが，基礎研究の進歩や臨床経験の蓄積により新たな知見が得られ，その臨床像や病態の理解には着実な進歩がみられる．一方，治療に関しては，稀少疾患であるがゆえに比較対照臨床治験を組むことは困難であり，学問的評価に耐えうる確立された治療法はないのが現状である．LAMの臨床像や経過が症例毎に多様であることも，治療効果を正しく評価する上での問題点である．このような現状を踏まえ，現段階における治療法の妥当性について統一的見解を示すことによって，診療の一助となり今後の治療研究の踏み台となることを目標に，本手引きの作成を行った．以下に記載する治療，管理は，現在までに発表された論文[1)~6)8)~13)]や症例報告[7)]，報告書[14)~17)]，米国LAM患者会から出版されたハンドブック[18)]，LAMの診療経験が豊富な医師の意見などに基づきまとめられた手引きであり，個々の症例の実情に合わせて参照いただきたい．

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治療の考え方

LAMでは，主として，肺，体軸リンパ節系(骨盤腔，後腹膜腔，縦隔など)にLAM細胞の増殖を認める．LAMの病変部位や進展度，気胸，乳糜胸水，乳糜腹水などの合併病態の有無などは症例毎に多様であるが，肺病変の進展度が生命予後にとって最も重要である[1)~3)]．一般に，肺病変は進行性で，呼吸機能検査成績（特にFEV_1とD_{LCO}）は経年的に悪化する場合が多いが，その進行速度は個人差が大きい[4)5)14)]．

LAMの発症と進行には女性ホルモンの関与が推測されるため，従来からホルモン療法が行われ，呼吸機能の悪化を抑制あるいは安定化したとする報告がある一方[6)~7)]，その効果については否定的見解が多い[8)~10)]．しかし，現時点でLAMの進行を確実に防止できる有効な治療法はなく，かつ，実施可能な治療としてはホルモン療法しかないため，なんらかの治療的介入が望まれる場

合には，やむなくホルモン療法が実施されている．なお，ホルモン療法の実施に際しては，生理的閉経年齢よりあまりに早期に閉経することの弊害（更年期障害，骨粗鬆症，特にプロゲステロン療法では心疾患など，LAM という疾患特有の QOL 低下[15]も考慮しなければならない．

上記のような背景から，ホルモン療法は，生命予後に最も重要である肺病変が進行性に悪化する症例に考慮する．平成 15・16 年度に「呼吸不全に関する調査研究」班が実施した LAM 全国調査[11][17]によれば，労作性呼吸困難を初発症状とした症例（呼吸困難発症群）は，気胸を初発症状とした症例（気胸発症群）より有意に診断時の呼吸機能が悪く予後は不良であった．また，呼吸困難発症群は気胸発症群よりも診断確定後の FEV_1，FEV_1/FVC，D_{LCO} も有意に速い速度で悪化していた[11]．すなわち，呼吸困難発症群は，気胸発症群より病態が早く進行し，そのため，進行を緩徐にする，あるいは抑制するために治療的介入が望まれる群である可能性がある．

従って，労作性呼吸困難がない場合は経過観察のみで良いと思われる症例も多いが，労作性呼吸困難を認める症例では，年齢，妊娠等の希望などを考慮して，ホルモン療法を検討する．呼吸機能検査（FEV_1，D_{LCO}），胸部 HRCT での嚢胞性変化等の推移をみることが，LAM の活動度を評価する上で参考となる．繰り返す気胸等で拘束性障害を来たして労作性呼吸困難を生じている症例や呼吸機能検査を実施することが困難な症例では総合的に判断する．

なお，以下に具体的薬物名を挙げて LAM に対する治療等を説明するが，現時点で保険適応の認められた医薬品はない．

治療と管理の実際

A．ホルモン療法[注1]

1．LH-RH アゴニストによる偽閉経療法（GnRH 療法）

処方例：

①酢酸リュープロレリン

1.88mg　皮下注，4 週毎

②酢酸ゴセレリン

1.8mg　皮下注，4 週毎

③酢酸ブセレリン

1.8mg　皮下注，4 週毎

④酢酸ブセレリン[注2]

1 回 300μg　左右の鼻腔に各 1 回噴霧，1 日 3 回

2．プロゲステロン療法[注3]

①カプロン酸ヒドロキシプロゲステロン

125mg　1.5–2A 筋注，2 週毎

②酢酸メドロキシプロゲステロン

15mg　分 3　毎食後

[注1] エストロゲン受容体拮抗剤としてクエン酸タモキシフェンがあるが，標的細胞によっては受容体刺激作用を示す事があるため推奨されない．

[注2] 経鼻吸収薬は簡便であるが，1 日 3 回噴霧しなければならないため，コンプライアンス不良となる可能性がある．

[注3] プロゲステロン療法は GnRH 療法より経済的負担が少ないが，月 1 回投与で効果が期待できる LH-RH アゴニストによる偽閉経療法が推奨される．プロゲステロン筋注製剤の血中濃度は 7～10 日で消失し，また，内服でのプロゲステロン血中濃度は不安定であるためである．また，欧米で第 1 選択に使用されるデポ・プロベラ（酢酸メドロキシプロゲステロン）は 4 週毎の筋注製剤で利用しやすいが，日本では未発売である．

3．外科的卵巣摘出術

上記のホルモン療法により，呼吸機能が安定化，或いは悪化スピードが緩徐となった症例では，外科的卵巣摘出術を考慮することもある．しかし，ホルモン療法の効果の確実性は確定していないため，外科的卵巣摘出術をホルモン治療の第一選択とすることは推奨されない．

B．気管支拡張療法

閉塞性換気障害の顕著な症例では，慢性閉塞性肺疾患（COPD）での投与法に準じて気管支拡張療法を行うことにより，自覚症状の軽減，QOL の向上が期待できる[16]．息切れの程度に併せて，長時間作用型抗コリン薬，β_2 刺激薬の吸入（LABA，long-acting beta-agonist）か貼付薬および徐放性テオフィリン製剤を単独，あるいは併用により使用することを推奨するが，適時，短時間作用型の抗コリン薬および β_2 刺激薬を併用することも可能である．

処方例：

①臭化チオトロピウム水和物

18μg　1 カプセル吸入/日

②キシナホ酸サルメテロール

50μg　1 吸入/回，2 回/日

③塩酸ツロブテロール（テープ）

2mg　1 枚/日　貼付

④徐放性テオフィリン製剤の内服

（用法，用量は血中濃度にて判断）

C．気胸

肺虚脱度に応じた通常の気胸治療方針に準じて治療を行う．LAM は気胸を繰り返すことが多く，気胸とそれに対する治療を反復することにより不完全・不規則な胸膜癒着を生じ，高度の拘束性換気障害に陥る症例が経験される．従って，再発予防を意識し治療を選択することが重要な点である[12]．気胸を繰り返す場合には，なるべく早い段階で内科的胸膜癒着術（OK-432，塩酸ミノサ

イクリン，自己血などの癒着剤)，外科的胸膜癒着術(胸膜焼灼，剝離など)，あるいはセルロースメッシュやフィブリン糊による外科的臓側胸膜補強術などによる再発防止策を積極的に考慮する．一般に，これらの処置により生じる拘束性換気障害は日常生活に支障が生じる程ではない．ただし強力な胸膜癒着術は，肺移植術の際に出血，手術時間の延長などの問題を生じる可能性がある．胸膜癒着術の既往は肺移植の適応外とはみなされていない[12]．

D. 乳糜胸水・腹水

脂肪制限食を指導する．食事や生活の指導，利尿剤などの治療では管理が困難な症例には，何らかの処置が必要となる．貯溜量が多く自覚症状が強い乳糜胸水例は，胸膜癒着術を行う．腹水貯留例では腹腔静脈シャント留置が必要となる．乳糜液を頻回に穿刺・排液すると，栄養障害やリンパ球減少による免疫力低下が生じる可能性があり，注意が必要である．コントロール困難例にホルモン療法が有効であった報告がある．

E. 血管筋脂肪腫 angiomyolipoma

腎臓に好発するが，時に，肝臓，子宮，リンパ節，肺，血管，等の部位にも発生する．腫瘍の発育の程度は様々であり，定期的な画像検査（CTや超音波検査）が必要である．一般に，腎機能障害が出現することは少ない．治療方針の選択に際しては，泌尿器科，腎臓内科，消化器外科などの関連診療科と連携して選択するが，概ね，大きさと自覚症状により以下のような対応が望ましい．

①腫瘍径＜4cm，自覚症状なし

年1回の画像検査．

②腫瘍径≧4～5cm，自覚症状なし

6カ月毎の画像検査．

自覚症状がなくても，出血などの症状出現のリスクがあり，治療を考える場合もある．

③腫瘍径≧4～5cm，自覚症状あり（腰部の痛み，血尿などの出血，嘔気など）

腫瘍の塞栓療法あるいは外科的摘出術を検討する．

F. 後腹膜や骨盤腔の lymphangioleiomyoma

Lymphangioleiomyomaの有無，合併する場合の大きさや数は症例により様々である．これらの"肺外LAM"が主病変で肺LAMは軽微である症例も存在する．一般に，lymphangioleiomyomaは柔らかな腫瘤で，理学的に触知することは困難で，自覚症状も乏しい．骨盤腔に巨大なlymphangioleiomyomaが有りながら妊娠・出産を問題なく経験した症例もある．悪性リンパ腫との鑑別が問題となるが，lymphangioleiomyomaではリンパ流の停滞により大きさに日内変動があることが参考になる[13]．経過観察のみで良い場合がほとんどであるが，大きさや症状を考慮して治療方針を決定する．

G. 呼吸不全

COPDに準じた呼吸リハビリテーションを試みる．適応あれば在宅酸素療法を実施する．

H. 肺移植

最大限の内科治療を実施しても呼吸不全が進行し，短期的予後しか期待できない場合に考慮する．目安としては，常時，酸素療法が必要になった時期が妥当であろう．

I. 妊娠・出産

必ずしも禁忌とは言えない．妊娠の可否は，妊娠・出産の及ぼすLAMの病勢への影響と，その時点でのLAMによる呼吸機能障害の程度の2つの因子を加味して慎重に考える必要がある．妊娠に伴う生理的負荷に耐えうる心呼吸機能の十分なゆとりがあることが前提である．LAMによる呼吸機能障害が軽度で妊娠・出産に耐えうる症例では，以下の2つの情報を提供し十分に説明した上で，挙児希望に対して慎重に対応する（①妊娠・出産を契機にLAMが増悪したとする症例報告があり，LAMが進行あるいは増悪する可能性，周産期に気胸を合併するなどのリスクがある，②妊娠・出産前後で呼吸機能に変化を認めなかった症例，通常の出産が可能であった症例も経験されている)．なお，LAMの全国調査[17]では，45％の症例に出産歴があり（2回以上の出産経験は26％)，出産経験群での生存率の低下は認められなかったものの，重症例では妊娠・出産が控えられた，あるいは，しないよう指導された可能性が指摘されている．

J. 航空機による旅行

気胸の発生するリスクを説明する必要があるが，そのリスクを定量的に指摘することは困難である．準呼吸不全の症例では，機内の気圧低下により，搭乗中は酸素吸入が必要となる可能性がある．在宅酸素療法を実施している症例では，大気圧下での酸素流量のおおよそ2倍が必要になると見込まれる．

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ORIGINAL ARTICLE

The epidemiology of lymphangioleiomyomatosis in Japan: A nationwide cross-sectional study of presenting features and prognostic factors

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Background and objective: To evaluate the characteristics and prognostic factors of Japanese patients with lymphangioleiomyomatosis (LAM).

Methods: A nationwide survey to identify patients with LAM was conducted by questionnaire. Survival probability was estimated using the Kaplan–Meier method, and the prognostic factors were analysed by Cox regression.

Results: Data were collected on 173 patients with pulmonary LAM. The major presenting features were pneumothorax (43%) and exertional dyspnoea (37%). The survival probabilities for patients presenting with exertional dyspnoea (Group A) were 85%, 60% and 47% after 5, 10 and 15 years, respectively, and for patients presenting with pneumothorax (Group B) were 95%, 89% and 89%, respectively. Although the age at symptom onset was higher among patients in Group A than in Group B, Cox regression revealed that the presenting feature was a prognostic factor independent of age at symptom onset (Group A/B hazard ratio = 5.732, $P < 0.01$). In the subgroup of patients whose initial FEV_1 was >1000 mL, or FEV_1/FVC >40%, or $\%DL_{CO}$ >40%, the rate of deterioration in these tests was greater in Group A than in Group B ($P < 0.01$ for FEV_1, $P < 0.05$ for FEV_1/FVC and $\%DL_{CO}$).

Conclusions: There are two possible subgroups of LAM patients. One subgroup that presented with pneumothorax, had onset of symptoms at a younger age and a more favourable prognosis; the other presented with exertional dyspnoea, had onset of symptoms at an older age and a poorer prognosis.

Key words: lung function, lymphangioleiomyomatosis, phenotype, presenting features, prognosis.

INTRODUCTION

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease characterized by cystic destruction of the lung and is found mainly in women of childbearing age.[1] It has been reported that LAM is caused by abnormalities of either the *TSC1* or *TSC2* tumour suppressor gene.[2,3] Pathological information has been accumulating on the characteristics of abnormal smooth muscle cells (LAM cells), on the relationship between LAM cells and several proteins involved in cell proliferation, and on the involvement of matrix

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metalloproteinases in extracellular matrix degradation and cyst formation.[4–6] Nevertheless, the pathogenesis of the disease remains unclear; there are no effective treatments and patients may require lung transplantation.

There is limited clinical understanding of LAM in Oriental populations, although, large studies of patients with LAM have been performed in the USA, France and the UK.[7–10] Kitaichi *et al.* reported the clinical and pathological features of 46 patients from Japan, Korea and Taiwan; however, the patients in their study were from a few institutions only.[11] In 2003, LAM was designated as a disease by the Japanese Ministry of Health, Labor, and Welfare Program to Encourage Research to Overcome Intractable Diseases, and a nationwide epidemiological survey of LAM was started by the Respiratory Failure Research Group. This publication reports the findings of the survey, presents the epidemiology of Japanese patients with LAM and analyses the prognostic factors for the disease.

METHODS AND MATERIALS

In May 2003, a nationwide survey of the diagnosis and treatment of LAM was commenced, targeting 1882 hospitals in Japan with 200 beds or more. The first questionnaire, containing simple questions about their experience in the diagnosis and treatment of LAM patients, was distributed as a postage-paid reply postcard. By August 2003, responses had been received from 799 (42%) of the 1882 hospitals surveyed. Of the 799 hospitals, 143 (18%) replied that they had diagnosed and/or treated a total of 302 patients with LAM (159 living and 153 dead). A second questionnaire was sent to the 129 hospitals that stated that they would be willing to answer more detailed questions. The questionnaire used in the second survey collected information on diagnosis, symptoms, complications, background variables, histopathological findings, initial and latest pulmonary function tests, treatment and outcomes of patients with LAM. The questions were answered by specialists in respiratory medicine or physicians in charge of the LAM patients at each hospital. The completed questionnaires were returned by mail. The study protocol was approved by the institutional ethics committee of Shinshu University School of Medicine. By March 2005, responses had been received from 86 hospitals (67%). There was 4% duplication in identified patients and after this was corrected there were data on 173 patients.

The clinical onset of LAM was defined as the time of the onset of symptoms considered attributable to this disorder and survival was calculated from the time of clinical onset until either death or the date of the last follow-up visit. Survival probability according to disease duration was estimated by the Kaplan–Meier method. Prognostic factors were analysed by a generalized Wilcoxon test and Cox regression analysis. The *t*-test and the Wilcoxon rank-sum test were used to compare the two groups of patients, namely, those presenting with dyspnoea and those presenting with pneumothorax. A value of a $P < 0.05$ was considered to be significant.

RESULTS

Diagnosis of LAM

All 173 patients had clinical presentations consistent with LAM and typical cystic findings on chest CT. The diagnosis of LAM was based on the pathological findings of a lung biopsy in 144 patients (83%) (surgical lung biopsy $n = 28$, video-assisted thoracic surgery $n = 85$, transbronchial lung biopsy $n = 18$, autopsy $n = 10$ and the procedure used for sampling lung tissue was not available for three cases), a surgical resection of abdominal lymph nodes in six patients (4%), or on typical CT findings and specific corroborating clinical features, such as recurrent pneumothorax, renal angiomyolipoma, abdominal lymphadenopathy or previous diagnosis of tuberous sclerosis complex (TSC), in 23 patients (13%).

Clinical features and treatment

The clinical features and treatments of the 173 patients are summarized in Table 1. Twenty-eight cases (16%), including one male patient, were associated with a TSC. The initial symptoms developed after menopause in two cases, but there was no history of exogenous estrogen use in either.

Pulmonary function tests

The results of the initial and latest pulmonary function tests are summarized in Table 2. The FEV_1, FEV_1/FVC and DL_{CO} were significantly lower than their predicted values. Decreased DL_{CO} (<80% predicted) was the most common abnormality in the early stage of the disease, followed by hypoxaemia ($PaO_2 < 80$ mm Hg or on supplemental oxygen), obstructive ventilatory dysfunction (FEV_1/FVC < 70%) and lung hyperinflation (%TLC > 120%).

Prognosis

Information on the clinical course postdiagnosis was available for 156 patients. Of these patients, 131 were alive and 25 had died by the time of the study. The mean follow-up periods from the onset of disease to either death or the date of the last follow-up visit were 6.7 (±6.0) years for the entire population (Table 1). The survival probabilities at 5, 10 and 15 years after the onset of symptoms, as evaluated by the Kaplan–Meier method, were 91%, 76% and 68%, respectively (Fig. 1a).

Analysis of prognostic factors

To identify the prognostic factors in our study population, we focused on the presenting features of the

Table 1 Symptoms and treatment of 173 patients with pulmonary LAM

Variables	Mean value ± SD	Range
Age at onset of symptoms (years)	31.6 ± 8.7, $n = 159$	14–60
Age at diagnosis (years)	34.0 ± 8.8, $n = 163$	16–60
Follow-up from onset of symptoms (years)	6.7 ± 6.0, $n = 156$	0–35
	n	%
Symptoms and signs during the total observation period		
Exertional dyspnoea	134	77
Pneumothorax	126	73
Episodes per patient	3.0 ± 2.6 (mean ±SD)	range 1–20
Chylothorax	21	12
Ascites	11/165†	7
Renal angiomyolipoma	44/165†	27
Abdominal lymphadenopathy	37/165†	22
Management of pneumothorax		
Pleurodesis‡ or pleurectomy	100	58
Hormonal therapy (Number of the patients who had undergone antiestrogen therapy at least once)	96	55
Progesterone§	61	35
Gn-RH analogues	47	27
Tamoxifen	14	8
Oophorectomy	15	9
Oxygen therapy	66	38
Lung Transplantation	9	5

†Denominator is the number of patients who received CT or ultrasonography of the abdomen.
‡Chemical sclerosis and mechanical abrasion are included.
§Oral medroxyprogesterone acetate (MPA) 10–15 mg/day was prescribed instead of monthly intramuscular injection of 400–450 mg of MPA that is not available in Japan.
Gn-RH: Gonadotropin-releasing hormone.

Table 2 Overall results of initial and latest pulmonary function tests

	Initial value		Latest value	
	n (%)	Mean ± SD	*n* (%)	Mean ± SD
FEV_1, percentage predicted	138	64 ± 26	86	56 ± 28
FEV_1/FVC	139	67 ± 20	87	60 ± 23
TLC†, percentage predicted	87	111 ± 24	52	112 ± 28
DL_{CO}, percentage predicted	105	52 ± 24	62	47 ± 25
FEV_1, percentage predicted <80%	94/138 (68)		68/86 (79)	
FEV_1/FVC <70%	65/139 (47)		51/87(59)	
TLC†, percentage predicted >120%	33/87 (38)		21/52 (40)	
DL_{CO}, percentage predicted <80%	90/105 (86)		54/62 (87)	
Hypoxaemia‡	84/127 (66)		65/76 (86)	
Hypercapnea ($PaCO_2 > 45$ mm Hg)	16/127 (13)		32/76 (42)	

†TLC was determined with either helium equilibration method or body plethysmography.
‡Hypoxaemia: $PaO_2 < 80$ mm Hg or on supplemental O_2 at rest.
The mean interval between the initial and the latest pulmonary function tests was 3.5 ± 3.0 years.

first symptom or event seemingly associated with LAM. The two most common presenting features were pneumothorax (43%) and exertional dyspnoea (36%), followed by an abnormal CXR (11%), abdominal manifestations attributable to lymphangioleiomyomas or renal angiomyolipoma (6%), and other comparatively rare respiratory manifestations (4%) such as haemoptysis, cough and chest pain.

The 171 LAM patients for which the presenting features were known were classified into three groups based upon different presenting features—Group A (presenting with exertional dyspnoea, $n = 61$), Group B (presenting with pneumothorax, $n = 74$), and Group C (presenting with other manifestations, $n = 36$)—and the clinical characteristics and results of pulmonary function tests of each group were examined (Table 3). The follow-up period and the prevalence of TSC did not differ significantly between the three Groups (data not shown). The mean age at onset was significantly higher in Group A than in Group B ($P < 0.05$).

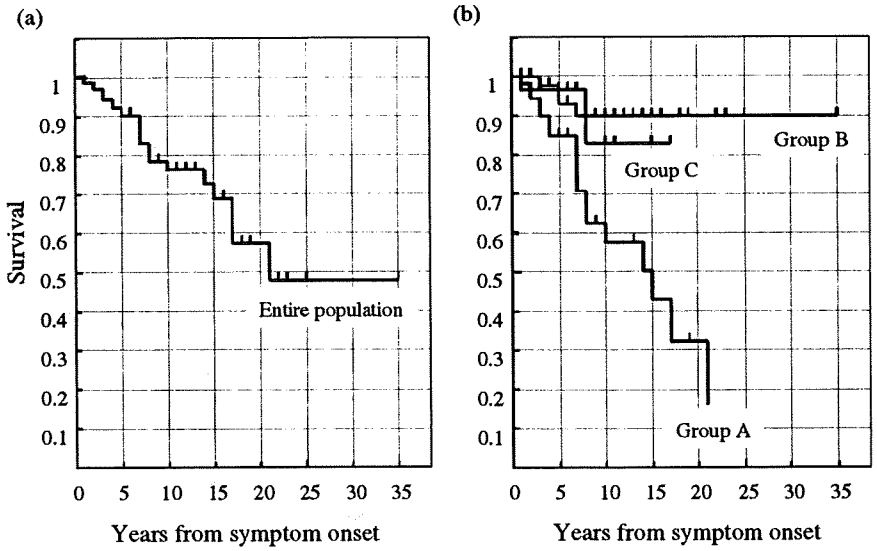

Figure 1 Kaplan–Meier plots for the study population. (a) The follow-up periods were available for analysis in 156 patients: the mean follow-up period from the onset of symptoms was 6.7 ± 6.0 years for the entire population ($n = 156$), 6.5 ± 6.1 years for the surviving patients ($n = 131$), and 7.4 ± 5.5 years for patients who had died ($n = 25$). The survival probabilities 5, 10 and 15 years after the onset of symptoms were 91%, 76% and 68%, respectively. (b) Survival probability was examined according to the presenting features: Group A consisted of patients presenting with exertional dyspnoea ($n = 57$), Group B patients presented with pneumothorax ($n = 67$), and Group C patients presented with other manifestations ($n = 30$). Cox regression analysis revealed a significant difference dependent on the presenting features but independent of the age at symptom onset (Group A/B hazards ratio = 5.732, $P < 0.01$).

The mortality rate ($P < 0.01$) and the percentage of patients requiring supplemental oxygen therapy ($P < 0.01$) were significantly higher in Group A than in groups B and C. The prevalence of renal angiomyolipomas was significantly lower in Group A than in Group B ($P < 0.05$). The percentage of patients who had undergone hormonal therapy was significantly higher in Group A than in Group B ($P < 0.01$), and the percentage of patients who had undergone either pleurodesis or pleurectomy was higher in Group B than in groups A and C ($P < 0.01$). However, the survival rate did not change whether the subject had a renal angiomyolipoma or had undergone hormonal therapy or one of these managements of pneumothorax (data not shown). The mean values of FEV_1, FEV_1/FVC and $\%DL_{CO}$ at both the initial and latest tests were significantly lower in Group A than in Group B ($P < 0.01$), and FEV_1 and FEV_1/FVC at both the initial and latest tests ($P < 0.01$) and $\%DL_{CO}$ at the latest test ($P < 0.05$) were significantly lower in Group A than in Group C.

Survival analysis was conducted on the three groups. Kaplan–Meier plots demonstrated that Group A had a decreased survival probability in comparison to Group B ($P < 0.01$, generalized Wilcoxon test) (Fig. 1b). Although Group A had the highest age at onset of symptoms (Table 3), possibly because the disease was detected at more advanced stages in Group A than in Group B, Cox regression analysis revealed a significant intergroup difference that was dependent on the presenting features but was independent of the age at symptom onset (Group A/B hazard ratio =5.732, $P < 0.01$).

Decline of pulmonary function in cases presenting with exertional dyspnoea (Group A) and pneumothorax (Group B)

The results of the pulmonary function tests and the rate of decline of various indicators were calculated from the initial and latest pulmonary function tests. The mean values of FEV_1, FEV_1/FVC and $\%DL_{CO}$ at the initial test were significantly lower in Group A than Group B (Table 3) and there were no significant differences in the subsequent decreases of these pulmonary function tests when both groups were compared as a whole. However, the rate of decline for each of these pulmonary function tests was smaller in patients where the baseline level was markedly lower. Figure 2 shows the relationship between pulmonary function at the initial test and the subsequent rate of decline, by plotting the baseline level on the abscissa against the rate of decline on the ordinate in a scatter graph. The rate of decline was hard to evaluate when the initial FEV_1 value was less than 1000 mL, the initial FEV_1/FVC less than 40% and the initial $\%DL_{CO}$ less than 40%. Accordingly, cases with severely impaired pulmonary function at the initial test were unlikely to show further decreases in subsequent tests, and such cases were frequently observed in Group A. Only those patients in whom the results of the initial pulmonary function test were above this set value ($FEV_1 > 1000$ mL, $FEV_1/FVC > 40\%$, or $\%DL_{CO} > 40\%$) were analysed. For this subgroup, the mean values of FEV_1, FEV_1/FVC and $\%DL_{CO}$ at the initial test were significantly lower in Group A than Group B ($P < 0.01$ for

Table 3 Clinical features and pulmonary function test results of 171 LAM patients categorized into three groups by their presenting features

	Group A	Group B	Group C
$n^{\dagger}$ (%)	61 (36)	74 (43)	36 (21)
Age at onset of symptoms, year	33.6 ± 8.3*	29.6 ± 8.0	32.1 ± 10.0
Death, n (%‡)	21 (34)**¶¶	5 (7)	3 (8)
Renal angiomyolipomas, n (%‡)	10/60§ (17)*	24/67§ (36)	10/36§ (28)
Pleurodesis or pleurectomy, n (%‡)	27 (44)	62 (84)##	9 (25)
Hormonal therapy, n (%‡)	38 (62)**	27 (36)	15 (42)
Oxygen therapy, n (%‡)	36 (59)**¶¶	19 (26)	9 (25)
Pulmonary function			
Initial value			
FEV_1 (mL) (mean ± SD)	1229 ± 604**¶¶ (n = 25)	1870 ± 718 (n = 30)	2252 ± 442 (n = 18)
FEV_1/FVC (mean ± SD)	54 ± 21**¶¶ (n = 25)	79 ± 17 (n = 28)	72 ± 12 (n = 19)
$\%DL_{CO}$ (mean ± SD)	36 ± 15** (n = 11)	62 ± 25 (n = 22)	53 ± 22 (n = 13)
Latest value			
FEV_1 (mL) (mean ± SD)	890 ± 527**¶¶ (n = 25)	1594 ± 898 (n = 30)	1840 ± 523 (n = 18)
FEV_1/FVC (mean ± SD)	43 ± 18**¶¶ (n = 25)	69 ± 22 (n = 28)	64 ± 18 (n = 19)
$\%DL_{CO}$ (mean ± SD)	29 ± 10**¶ (n = 11)	54 ± 26 (n = 22)	47 ± 23 (n = 13)

Group A: patients presenting with exertional dyspnoea,(n = 61); Group B: patients presenting with pneumothorax (n = 74); Group C: patients presenting with other manifestations (n = 36).

†Patients for whom the follow-up period was unknown were also included in this analysis.

‡Percentage of the number of patients in each group.

§Denominator is the number of patients who received CT or ultrasonography of the abdomen.

*P < 0.05 and **P < 0.01 versus Group B; $^{\P}P$ < 0.05 and $^{\P\P}P$ < 0.01 versus Group C; $^{\#\#}P$ < 0.01 versus groups A and C.

The results of pulmonary function tests are from cases in which both the initial and the latest data at each indicator were available. The mean interval between the initial and the latest pulmonary function tests for Group A, B, and C was 3.6 ± 3.2 years, 3.9 ± 3.1 years and 3.1 ± 2.8 years, respectively.

FEV_1 and FEV_1/FVC, P < 0.05 for $\%DL_{CO}$). For Group A, the median values (quartile range) of the subsequent decreases in FEV_1, FEV_1/FVC and $\%DL_{CO}$ per year were −285.0 mL (−582.9 to −71.3), −6.1% (−10.7 to −2.1) and −11.9% (−20.7 to −3.2), respectively. This decline was significantly greater than that seen in Group B patients, whose median annual decrease in FEV_1, FEV_1/FVC and $\%DL_{CO}$ was −16.8 mL (−157.1–46.8) (P < 0.01), −2.5 mL (−4.2–0.1) (P < 0.05) and −1.6 mL (−7.2–6.4) (P < 0.05), respectively).

DISCUSSION

A nationwide survey was conducted to determine the current status of LAM in Japan, including the prevalence, diagnosis, treatment, prognosis and possible clinical phenotypes. The survey had some limitations. It was a retrospective survey, based on data submitted by various members of the medical care team at each site, and some deceased patients were included. Furthermore, the questionnaire response rates may not have been high enough to delineate the precise epidemiology of LAM in Japan (42% at the first survey and 67% at the second survey).

The survey identified 302 patients (159 living and 153 dead) with LAM at the first survey and detailed information on 173 patients was collected by the second survey. Taking into account the 159 living patients at the first survey, the questionnaire response rate and the patient duplication of 4% at the second survey, we estimated the number of LAM patients to be between 150 and 300, giving a prevalence of 1.2–2.3 cases per million in the Japanese population. This figure is similar to the reported prevalence of 0.9 cases per million in the population of the UK and that of 1.3 cases per million in a survey of France.[9,10]

In the present study, the mean age at diagnosis was lower than that described in the latest report from the US LAM Foundation (40.8 years), the UK LAM Action (38.9 years) and Canada (43.3 years), where they pointed out that women over the age of 40 years are being increasingly recognized to have LAM, using newer diagnostic techniques and with a higher index of suspicion.[8] In this study, a relatively large number of asymptomatic LAM patients (11%) were detected through radiographic abnormalities, possibly the result of an increase in regular health check-ups at the workplace and the increasing availability and usage of

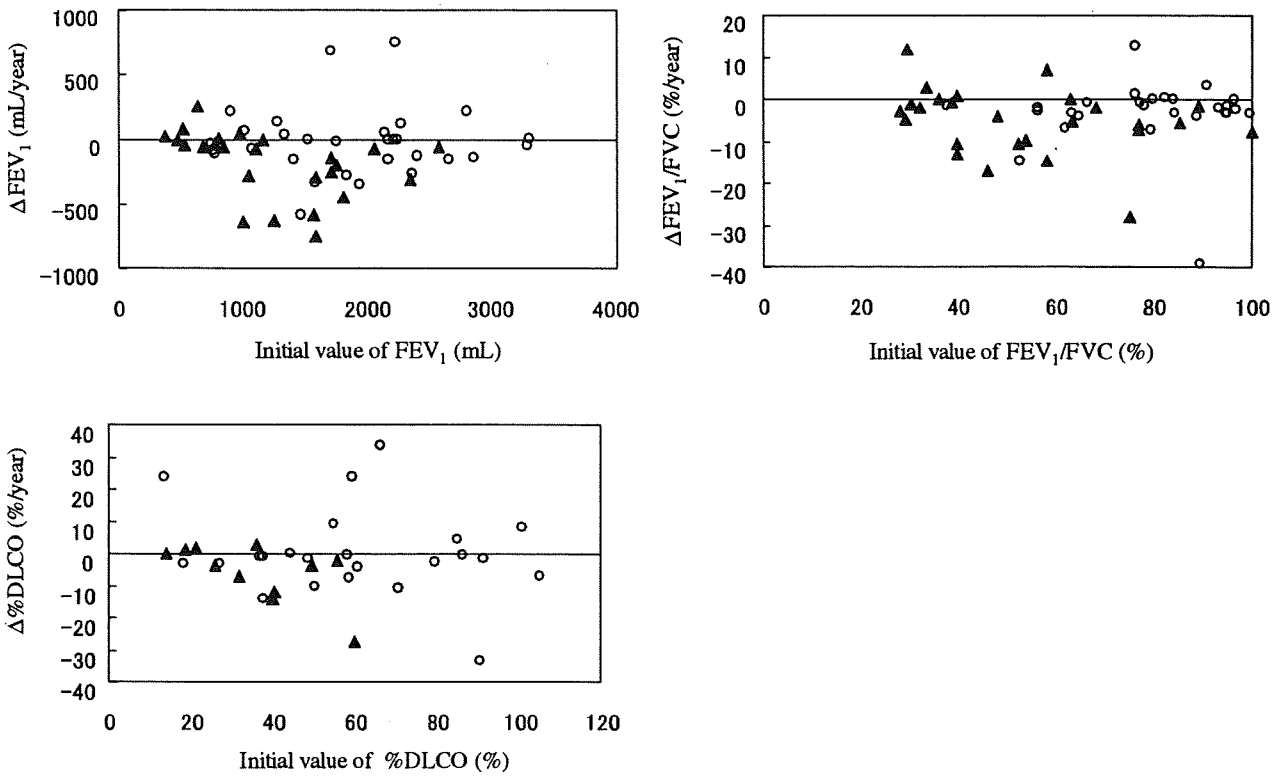

Figure 2 Relationship between the baseline levels and the subsequent rate of change of pulmonary function tests in groups A and B. The relationship between the results of the initial pulmonary function test and the rate of change of each indicator of pulmonary function was examined. The rate of decline for each indicator of pulmonary function (plotted on the ordinate) was smaller in cases where the baseline level (plotted on the abscissa) was markedly lower: the initial FEV_1 <1000 mL, the initial FEV_1/FVC <40% and the initial $\%DL_{CO}$ <40%, and such cases were frequently observed in Group A. (▲) Group A, (○) Group B.

a high-resolution CT. The percentage of LAM patients with renal angiomyolipoma (22%) was lower than that reported from other countries: 38–54% from the USA, 36% from the UK and 32% from France.[7,9,10,12] This might be due to ethnic differences.

A marked decrease in DL_{CO} was the most frequent abnormality seen in pulmonary function tests, which is a finding similar to other studies published recently.[11,13] However, a report from the US National Heart, Lung and Blood Institute (NHLBI) LAM registry group showed that airway obstruction was the most common abnormality in subjects with a milder degree of pulmonary dysfunction.[7] Seyama *et al.* suggested that airflow limitation may be preceded by an impairment of diffusing capacity in a longitudinal follow-up study of LAM patients.[14] The NHLBI study cohort contained 39.6% ex-smokers and current smokers compared with 20.7% in this study (data not shown), and the mean age at diagnosis was 41.0 years compared with 34.0 years in this study. The higher proportion of patients who smoked and the older age of patients in the NHLBI study may have resulted in a higher proportion of patients who showed airway obstruction. The current study showed that the DL_{CO} (percentage predicted) correlated with the FEV_1/FVC ratio ($r = 0.6236$, $P < 0.01$), but there was no correlation between the initial DL_{CO} and percentage decrease in FEV_1/FVC during subsequent follow up, which contrasts with the findings by Lazor *et al.*[15]

Early reports of LAM suggested that survival was poor, with most patients dying within 10 years after the onset of symptoms.[16,17] Kitaichi *et al.* reported a slightly better prognosis with 38% of LAM patients alive 8.5 years after the onset of disease.[11] Recent reports, however, indicate that the prognosis may actually be better with 10-year survival rates of 78–91%.[10,13,18] It is possible that early studies may reflect only patients in whom the disease was relatively severe.

Based on the prognosis in relation to the presenting features, there appear to be at least two subgroups of LAM patients—one group presenting with exertional dyspnoea, an older age of onset of symptoms and a poorer prognosis (Group A), and another presenting with pneumothorax, a younger age of onset of symptoms and a more favourable prognosis (Group B). Multivariate analysis revealed that the difference in prognosis between groups A and B is independent of age. It is possible that the patients in Group A did not present with pneumothorax in early stages of the disease and were detected at only more advanced stages. In addition, when the analysis was confined to cases with specified pulmonary function values (FEV_1, FEV_1/FVC and $\%DL_{CO}$), the rate of

subsequent decline of these indicators differed between groups A and B.

These diverse clinical courses and the possibility of different phenotypes in LAM have been reported in the longitudinal analysis of a limited number of Japanese LAM cases.[14] Considerable variation in the rate of decline of pulmonary function and cardiopulmonary exercise testing among LAM cases was noted by other groups.[19–21] Cohen *et al.* reported that patients with pneumothorax were less likely to complain of dyspnoea than patients without pneumothorax, and that low pulmonary function test values such as FEV_1 and DL_{CO} were highly associated with dyspnoea.[8] However, there is no clear explanation as to why patients in Group A did not present with pneumothorax in the early stages of the disease or why the prognosis was markedly better for patients in Group B. The possibility of clinical subgroups or variations in disease progression among LAM patients needs to be considered when conducting clinical trials to evaluate the efficacy of new treatments.

There have been several reports of prognostic factors in patients with LAM. Matsui *et al.* reported a correlation between prognosis and LAM histological score, a semi-quantitative estimation of the percentage of tissue involvement by the two major features of LAM: cystic lesions and infiltration by abnormal smooth muscle cells.[22] Kitaichi *et al.* suggested that patients with a predominantly cystic type of LAM had a poorer prognosis than those with a predominantly muscular type of LAM.[11] FEV_1/FVC, %TLC and DL_{CO} have been reported to be important as prognostic factors,[11,23] and cystic lesions, as evaluated by CT, have been reported to correlate with indicators of lung function.[24–26] There have been no published studies which show a correlation between the clinical subgroups and prognosis, as this study has. Further long-term follow-up studies correlating clinical phenotypes, pathological features and CT findings are needed to fully delineate the clinical characteristics of LAM and explore the underlying differences between its phenotypes.

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