

Pulmonary Lymphangiomyomatosis: A Clinicopathological Analysis of Ten Cases

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Background: Lymphangiomyomatosis (LAM) of the lung is a very rare disease of unknown etiology which occurs particularly in women of childbearing age. So far, there have been very few reports of LAM in Taiwan.

Methods: Data on all patients with a clinical or pathological diagnosis of LAM in Chang Gung Memorial Hospital from 1990 to 2001 were collected from the pathology files or by consultation with thoracic surgeons, chest physicians, and radiologists of this institution. Cases were confirmed by lung biopsy and high-resolution computed tomographic scanning. Clinical data were obtained from patients' charts. Additional immunostaining for HMB-45 antigen, estrogen receptor, and progesterone receptor was carried out for cases with available paraffin blocks.

Results: In total, 10 patients confirmed with a diagnosis of LAM and adequate clinical follow-up information were found from 1991 to 2001. All were females of fertility age. The follow-up periods ranged from 18 to 167 months. Six patients received hormonal therapy. According to the pulmonary function tests and clinical symptoms, 6 patients were in stable condition and 4 showed slow progression of disease by the time of the last follow-up. Two patients died after lung transplantation and abdominal surgery for retroperitoneal LAM, respectively, at another medical center.

Conclusions: The clinicopathological features of our series are similar to those reported from other countries. The clinical course was slowly progressive with no significant response to hormonal therapy. Lung biopsies are important for a diagnosis, but the size and location of the biopsy specimens greatly affect the diagnostic reliability.

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Key words: lymphangiomyomatosis, high-resolution computed tomographic scan, HMB-45, hormone therapy.

Lymphangiomyomatosis (LAM) is a rare disease of unknown etiology that occurs almost exclusively in women of childbearing age.⁽¹⁻⁵⁾ It mainly affects the bilateral lungs, although involve-

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ment of the axial lymphatics or lymph nodes of the chest, abdomen, and retroperitoneum has also been reported.⁽⁶⁻⁸⁾ Some patients with LAM also develop angiomyolipomas (AMLs), mostly localized in the kidney.⁽⁹⁾ The incidence of concomitant AML varies from 32% to 60% in the literature.^(8,10) LAM is characterized by the proliferation of abnormal smooth muscle cells (LAM cells) and the progressive destruction of pulmonary tissue with formation of diffusely distributed parenchymal cysts.^(1-3,11) These LAM cells typically have pale eosinophilic or clear cytoplasm and are spindle-shaped to epithelioid. They are seen around the airways, blood vessels, and lymphatics, thus producing characteristic clinical, radiological, and physiological findings. Compression of the airways results in airflow obstruction, which in turn, leads to the development of cystic changes.^(1-3,11) These pulmonary cystic lesions have a characteristic appearance on high-resolution computed tomographic (HRCT) scans which have now become an important diagnostic criteria for LAM.⁽¹²⁻¹⁴⁾ Obstruction of the blood vessels causes venular congestion resulting in hemosiderosis and hemoptysis. Lymphatic obstruction leads to the formation of chylothoraces.^(2,3) Thus, pulmonary manifestations include progressive dyspnea, recurrent pneumothorax, chylous pleural effusion, hemoptysis, and eventual respiratory failure.^(1-5,11) Although LAM cells stain positively for smooth muscle actin, they are immunohistochemically distinguishable from other types of smooth muscle cells by their reactivity with the monoclonal antibody, HMB-45,⁽¹⁵⁻¹⁷⁾ which recognizes a 100-kD glycoprotein in melanoma cells.⁽¹⁸⁾ Electric microscopic examination with immunostaining has been performed to localize the target of the antibody in LAM cells, and the binding sites turned out to be located in cytoplasmic granules resembling immature melanosomes.⁽¹⁵⁾ Receptors for estrogen and progesterone have also been demonstrated in LAM cells.⁽¹⁹⁻²²⁾

Although LAM is now a well-established disease entity, there have been few reports of LAM in Taiwan due to its rarity. This study is a clinicopathological analysis of LAM patients collected from Chang Gung Memorial Hospital (CGMH), which attempts to provide data on the behavioral and pathological characteristics of this rare entity in Taiwan. The obtained data were also compared with reports from other countries.

METHODS

All cases with a clinical or pathological diagnosis of LAM since 1990 to 2001 were identified from the pathology files and via consultation with chest physicians, thoracic surgeons, and radiologists at CGMH. All pathology slides were reviewed (including those from other hospitals). A histological diagnosis of LAM was established through demonstration of LAM cells by their characteristic histological appearance as described above. If the patient did not receive a lung biopsy, a diagnosis of LAM would have been made only when the patients had typical clinical symptoms and signs of LAM and diagnostic features of LAM by HRCT. Concomitant extrapulmonary involvement, such as retroperitoneal or mediastinal LAM and renal AML, would also support a diagnosis of LAM.

Immunostaining with smooth muscle actin (SMA) antibody (Dako, Carpenteris, CA) and HMB-45 antibody (Dako) was carried out for all cases with available paraffin blocks. Estrogen receptor (ER, Novocastra, Newcastle upon Tyne, UK) and progesterone receptor (PR, Novocastra) staining was then performed for those cases positive for HMB-45. All immunostaining procedures were performed on formalin-fixed, paraffin-embedded sections using an autostaining system (Ventana Medical System, Tuscon, AZ) with a basic DAB detection kit according to the manufacturer's protocol.

Clinical and radiographic features were obtained from the patients' charts. Special attention was paid to the age at onset; presenting features; the presence of pneumothorax, chylothorax, and renal angiomyolipoma; the duration of disease; results of pulmonary function test; hormonal manipulation; and outcomes. Presenting features were defined as the initial symptoms or events (such as pneumothorax) recorded which could be attributed to the disease. Disease duration was calculated as months since the initial symptoms to the present time or until loss of follow-up. Clinical improvement or deterioration was evaluated on the basis of pulmonary function tests, the level of dyspnea, or the appearance of other symptoms such as hemoptysis.

RESULTS

Totally, 17 patients with a clinical or pathologi-

cal diagnosis of LAM were identified from January 1990 to December 2001 in CGMH. Thirteen patients had received lung biopsies at CGMH, of which 3 were transbronchial lung biopsies (TBLB) and 10 were open-lung wedge biopsies. Two of the remaining 4 patients had received lung biopsies at other hospitals with a diagnosis of LAM before the confirmatory HRCT was performed at CGMH. Among these 17 patients, 2 were excluded because the results of the HRCT and biopsy were both negative. Another patient was also excluded because she had received neither HRCT nor a biopsy examination. Thus, 14 patients with typical clinical presentations and either positive HRCT or biopsy were found (Table 1). Three patients had extrapulmonary lesions. Patients 1 also had retroperitoneal LAM, which was confirmed by biopsy and HMB-45 staining at our hospital. Patients 12 and 14 had retroperi-

toneal AML and renal AML, respectively. These 2 tumors were excised and confirmed by pathological examination at other hospitals.

However, among the 14 patients, 3 wedge biopsy specimens (patients 8-10) obtained at CGMH revealed only emphysema and were not diagnostic for LAM. These 3 patients were further excluded. Although patient 14 did not receive a lung biopsy, she had typical features of LAM by HRCT and a past history of renal AML. She was considered as being diagnostic for LAM. There was 1 patient (patient 4) with no clinical follow-up data due to loss of medical records. So, a complete clinicopathological review was available in 10 patients with LAM.

Clinical features

All 10 patients were females of fertility age. The age of onset ranged from 26 to 41 years. None

Table 1. Clinicopathological Features in 14 Patients with Lymphangiomyomatosis

No.	HRCT	Pathology diagnosis	Onset age (year)	Presenting features	Pneumothorax and frequency	follow-up (month)	Extrapulmonary lesions	Clinical outcome and last time for follow-up	Hormonal manipulation
1	(+)	LAM	29	Dyspnea, cough, palpitation	(+) x 1	132	Retroperitoneal LAM	Slow progression; died after abdominal surgery	Medroxyprogesterone acetate
2	(+)	LAM	38	Progressive dyspnea, cough	(-)	68	(-)	Slow progression	None
3	(+)	LAM	41	Dyspnea, palpitation	(-)	90	(-)	Stable	Progesterone, medroxyprogesterone acetate
4	UN	LAM	29	UN	(-)	UN	UN	Expired	UN
5	(+)	LAM	34	Chest pain, pneumothorax, dyspnea	(+) x 6	18	(-)	Slow progression; died after lung transplantation	Medroxyprogesterone acetate
6	(+)	LAM	28	Chest pain, pneumothorax, dyspnea, cough	(+) x 3	53	(-)	Stable	Gonadorelin, BSO
7	(+)	LAM	28	Dyspnea, cough	(+) x 3	36	(-)	Stable	None
8	(+)	Emphysema	50	Dyspnea, cough, bilateral chylothorax, chylous ascites	(-)	117	(-)	Slow progression	Medroxyprogesterone acetate, gonadorelin
9	(+)	Emphysema	24	Chest pain, pneumothorax, cough	(+) x 1	93	(-)	Slow progress to severe dyspnea	Medroxyprogesterone acetate, gonadorelin
10	(+)	Emphysema	46	Chest pain, pneumothorax	(+) x 1	18	(-)	Slow progression	None
11	(+)	Old hemorrhage ^α	35	Chest pain, cough, hemoptysis	(-)	66	(-)	Slow progression	None
12	(+)	ND ^β	26	Dyspnea, cough, hemoptysis, chylothorax, chylous ascites	(-)	60	Retroperitoneal AML	Stable	Medroxyprogesterone acetate, gonadorelin
13	(+)	ND ^γ	33	Dyspnea	(-)	60	(-)	Stable	Medroxyprogesterone acetate
14	(+)	ND	27	Chest pain, pneumothorax, dyspnea	(+) x 2	167	Renal AML	Stable	None

Abbreviations: HRCT: high-resolution computed tomography; LAM: lymphangiomyomatosis; UN: unknown; ND: not done; AML: angiomyolipoma; BSO: bilateral salpingo-oophorectomy;

α: Had previous biopsy and was diagnosed as having LAM at National Taiwan University Hospital.

β, γ: Had previous biopsy and was diagnosed as having LAM at Tai-Chung Veterans Hospital.

of the patients was found to have tuberous sclerosis. Characteristic multiple thin-walled cysts throughout the bilateral lungs were found with HRCT (Fig. 1A) and by thoracoscopy (Fig. 1B). They all had similar clinical presentations such as dyspnea, coughing, and pneumothorax. The most-common presenting symptom was dyspnea, which occurred in 9 patients, followed in decreasing order by coughing in 7, pneumothorax in 5, chest pain in 4, chylothorax in 2, and hemoptysis in 1. Four patients had recurrent pneumothorax. Eight patients had received 1 or several pulmonary function tests at CGMH. The initial results were mild airway obstruction in 5 patients, severe or moderately severe airway obstruction in 2, and mild lung restriction in 1. Three patients had coexisting airway obstruction and restriction. All 6 patients who received multiple pulmonary function tests showed progression to severe or moderately

severe airway obstruction within 1 to 3 years.

The duration of follow-up in these 10 patients ranged from 18 to 167 months. Six of the 10 patients were treated by hormonal manipulation, although the treatment varied in modality and duration. Only 1 patient (patient 6) received a bilateral salpingo-oophorectomy after long-term use of gonadorelin and medroxyprogesterone acetate, due to intolerance of the side effects of these hormones. Six patients remained stable with stationary disease at the end of 2002 or at the time of the last follow-up. Four patients had slow progression of clinical symptoms: 2 of the 6 patients with hormonal treatment and 2 of the 4 patients without. None of the patients showed improvement according to pulmonary function tests during follow-up, either with or without hormonal manipulation.

Two patients expired. Patient 1 died of massive

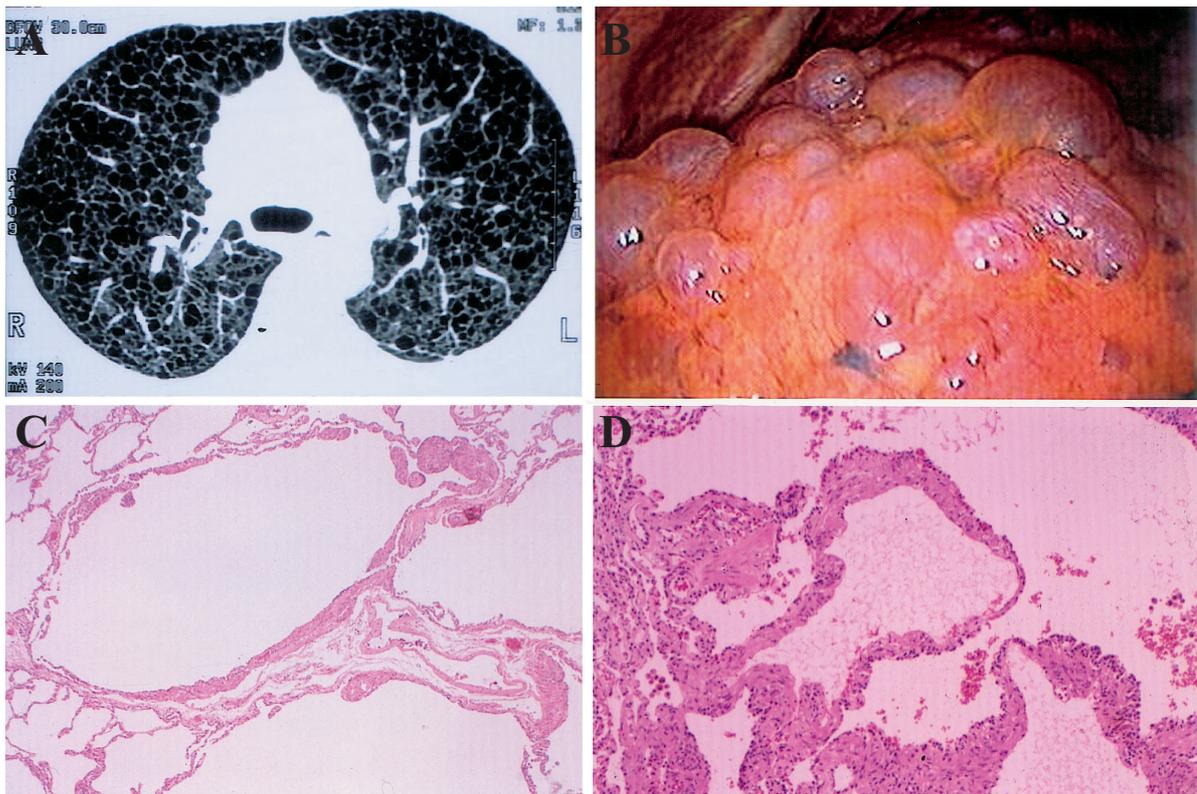


Fig. 1 (A) High-resolution computed tomographic scan of the chest of patient 3 showing myriad thin-walled cysts throughout the bilateral lungs. The intervening lung tissue was normal. (B) Multiple lung cysts as seen by video-assisted thoracoscopy (VATS). (C) Wedge lung biopsy of the same patient showing cystic dilatation of the alveoli partially surrounded by fusiform proliferation of immature smooth muscle cells. Varying densities of smooth muscle proliferation in the alveolar wall can be noted with relatively normal intervening lung parenchyma (H&E, original magnification $\times 20$). (D) Dilated lymphatic channels (stars) can also be seen adjacent to the dilated alveolar cysts (H&E, original magnification $\times 40$).

bleeding after a laparotomy for excision of a retroperitoneal LAM at another hospital. Before the operation, her condition was stable with hormonal treatment. Patient 5 died soon after lung transplanta-

tion at another hospital. Before the operation, she had received hormone therapy for 11 months, but her clinical symptoms had still progressed.

Table 2. Pathological Features of 11 LAM Patients Who Had a Biopsy at CGMH

No.	HRCT	Pathology diagnosis	Biopsy method	HMB-45	SMA	ER	PR
1	(+)	LAM	Wedge	(+)	(+)	(-)	(+)
2	(+)	LAM	TBLB	(+)	(+)	(-)	(+)
3	(+)	LAM	Wedge	(+)	(+)	(-)	(+)
4	?	LAM	Wedge	(+)	(+)	(-)	(+)
5	(+)	LAM	Wedge	(+)	(+)	(+)	(+)
6	(+)	LAM	TBLB	(-)	(-)		
7	(+)	LAM	Wedge	ND	ND		
8	(+)	Emphysema	Wedge	ND	ND		
9	(+)	Emphysema	Wedge	(-)	(-)		
10	(+)	Emphysema	Wedge	(-)	(-)		
11*	(+)	Old hemorrhage	TBLB	(-)	(-)		

Abbreviations: HRCT: high-resolution computed tomography; SMA: smooth muscle actin; ER: estrogen receptor; PR: progesterone receptor; LAM: lymphangioliomyomatosis; TBLB: transbronchial lung biopsy; ND: not done.

*Patient 11 had a biopsy with a diagnosis of LAM at National Taiwan University Hospital.

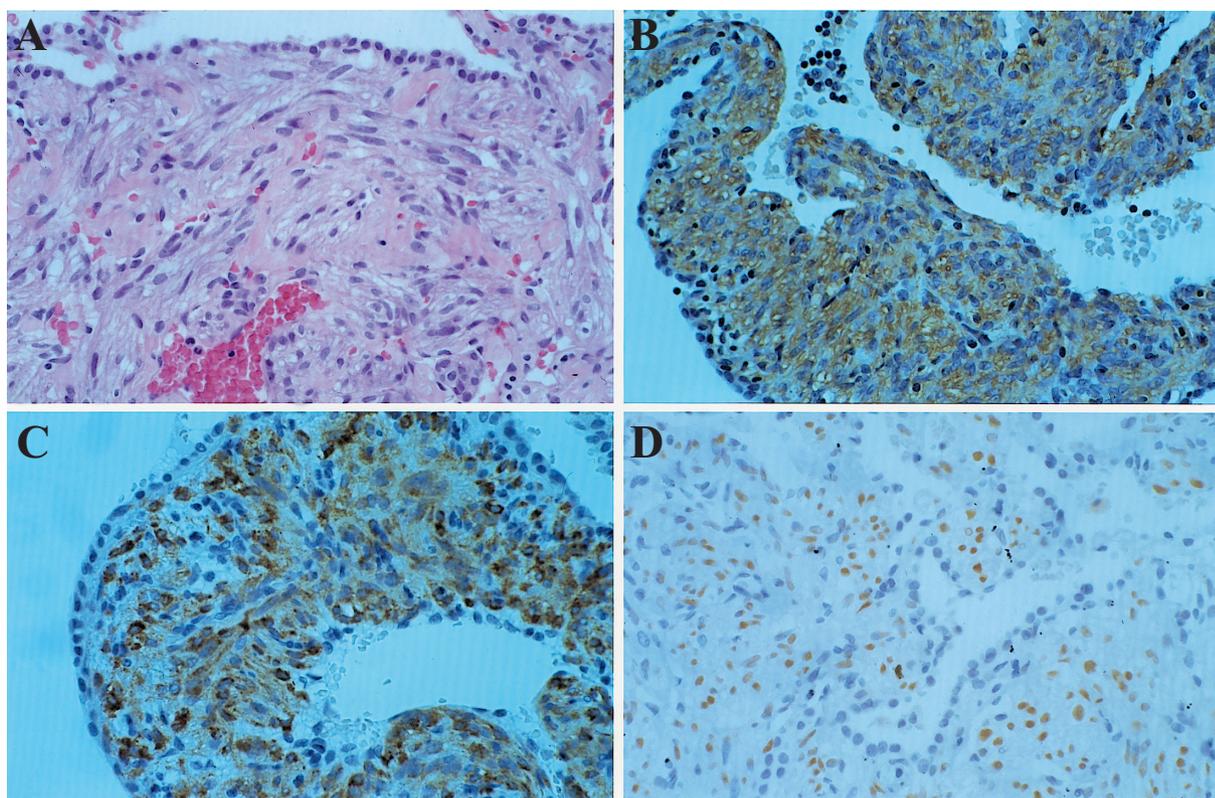


Fig. 2 (A) Higher magnification of the lung tissue of patient 3 revealing proliferation of spindle-shaped to epithelioid smooth muscle cells (LAM cells) with eosinophilic or clear cytoplasm (H&E stain, original magnification, $\times 400$). These LAM cells were strongly positive for smooth muscle actin in the cytoplasm (B) HMB-45 in the cytoplasm (C), and progesterone receptor in the nuclei (D) (Immunoperoxidase stain, original magnification $\times 400$).

Pathological examination

Eleven of the 14 patients initially diagnosed as having LAM (Table 2) had a lung biopsy at CGMH. The results of the histological examination and immunostaining study are shown in Table 2. As previously mentioned, 3 (patients 8-10) were diagnosed as having emphysema. One showed only old hemorrhage (patient 11). This patient had already had a biopsy done at another medical center with a confirmatory diagnosis of LAM. The remaining 7 patients' specimens all had diagnostic features of LAM, which included proliferation of LAM cells around the airways, lymphatics, and blood vessels, forming multiple cysts (Fig. 1C, D). These LAM cells had pale eosinophilic or clear cytoplasm and had spindle-shaped to epithelioid nuclei (Fig. 2A). Only 9 specimens had available paraffin blocks for additional immunostaining. All of the LAM cell (+) cases displayed positive staining for SMA (Fig. 2B) and HMB-45 (Fig. 2C) except for patient 6. Due to the minute size of the tissue obtained by TBLB, additional sections of the biopsy for special stains from patient 6 showed no LAM cells, thereby giving negative results. All of the HMB-45-positive cases also stained positively for PR (Fig. 2D), but only 1 was positive for ER. All cases with no LAM cells consistently showed negative staining results for HMB-45.

DISCUSSION

Due to the rarity of LAM, no study series has yet been conducted to provide data on the natural history or pathological characteristics of LAM in Taiwan. So far, this is the largest series with a clinicopathological review of LAM in Taiwan. As expected, all pathologically or HRCT-confirmed cases of LAM were females of reproductive age. The patients in our study were typical, as in other series, with respect to their presentations, symptoms, and complications.^(1-5,8,11) In our series, only 3 patients also had AML in the kidney or retroperitoneum. The incidence of AML (30%) was higher than a series from the UK (6 of 48 patients, 13%),⁽⁴⁾ and a series of Kitaichi et al. from Japan, Korea, and Taiwan (4 of 46 patients, 9.9%),⁽¹¹⁾ but lower than other published series (32%-60%).^(8,10) Since our patients were not subjected to routine screening with abdominal CT for probable AML, there may have been a resulting

under-detection of AMLs. The importance of management in conjunction with thoracic surgeons is apparent from the high incidence of pneumothoraces, which mostly require surgical treatment. In fact, many of the wedge biopsies were performed during repair of the pneumothorax.

The distribution of LAM cells in lung tissue can be quite uneven, and false-negative results due to sampling error are possible. One of our patients (patient 11) had previously been diagnosed with LAM at National Taiwan University Hospital, but the TBLB specimen at CGMH showed only old hemorrhage with fibrosis and hemosiderin deposition. The main reason for the pseudo-negative result was the small sample size. In 1 of our biopsy-proven cases (patient 6), subsequent immunostaining for HMB-45 was negative due to the absence of LAM cells in the additional sections of the small TBLB specimen. These are 2 good examples of the decreased sensitivity for diagnosing LAM by TBLB. A wedge biopsy would have yielded a more-satisfactory result, although the chances of sampling error still cannot be totally eliminated due to the uneven distribution of lesions. A few authors have even suggested that if LAM is suspected clinically and the TBLB is nondiagnostic, an open lung biopsy should be performed.⁽³⁾

The immunostaining results for HMB-45, ER, and PR in our study were similar to those in previous reports, which consistently show positive HMB-45 reactivity, frequent PR staining, and less commonly, ER staining.^(16,17,19-21) Positive staining for HMB-45 has become a very specific diagnostic feature of LAM. The immunoreactivity with HMB-45 in melanocytes is localized in stage 1 and 2 melanosomes and in nonmelanized portions of stage 3 melanosomes. On the other hand, mature melanosomes are unreactive.⁽²³⁾ Studies have also shown that similar melanosome-like structures contain binding sites for HMB-45 in smooth muscle cells of AML,^(17,24-27) and in tumor cells of clear cell tumors of the lung and other organs.^(24,25) Why LAM cells seem to have features of both smooth muscle fibers and melanosomes is still unknown.

The reason for the consistent predilection of LAM for women is also unknown. One possibility is the presence of gender-specific hormone receptors on LAM cells that may be responsive to hormonal alteration. In addition, case reports describing

patients with LAM in whom conditions worsened after pregnancy or administration of exogenous estrogens provide further support for a role of hormones in the progression of this disease.^(22,28,29) Estrogen and progesterone receptors are present in various organs as well as in various tumors other than LAM. Some of these tumors do have a definite gender predilection, and for them, identification of ER and PR may provide a possibility for hormonal therapy.⁽²⁰⁾ In our series, 6 patients remained stable with stationary disease at the end of 2002 or at the time of last follow-up. Four patients had slow progression of clinical symptoms: 2 of 6 patients with hormonal treatment and 2 of 4 patients without. None of the patients showed improvement on pulmonary function tests during follow-up, either with or without hormonal manipulation. Differences in type, dosage, and duration of hormonal manipulation in our series were due to the limited information available on recommended standards of treatment as well as little evidence of proven efficacy. Antiestrogen therapy has been reported since the early 1980s, including castration (oophorectomy),⁽²²⁾ progesterone,^(3,30,31) and gonadotropin-releasing hormone agonist or luteinizing hormone releasing hormone.⁽³²⁾ However, no apparent correlation between the status of PR and ER and the response to hormonal therapy has been found.⁽³⁾ Evidence of the benefits of hormonal manipulation for LAM is still limited, and treatment results in a number of study series have mostly been inconclusive, although the evidence is probably best for progesterone.^(3,30,31) Our patients were mostly treated with medroxyprogesterone acetate, gonadorelin, or both, and most have remained stationary with stable or only mild deterioration in their clinical conditions, although all pulmonary function tests during follow-up revealed progression of airway obstruction. The 2 mortalities among these 13 cases were both due to surgery for tumor excision or transplantation. Thus, conservative and supportive treatment is still the recommended strategy according to the results of our series.

The percentage of tissue involvement by cystic lesions and the area of LAM cell infiltration have been suggested as indicators of the prognosis.⁽³³⁾ In our series, the size of the specimens and the amount of LAM cells varied greatly between each case, making it difficult to evaluate the percentage of involvement. Therefore, we do not think that evaluation of

the percentage of tissue involvement by cystic lesions or the area of LAM cell infiltration can provide reliable prognostic information.

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肺臟多發性淋巴平滑肌瘤：10例之臨床病理分析

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背景：肺臟多發性淋巴平滑肌瘤是一個非常罕見之疾病，多好發於有生育能力時期之女性。目前在台灣這一類病例的報告仍十分少見。

方法：我們從病理報告檔案以及胸腔內科、胸腔外科及放射線科醫師之病人檔案中回溯去尋找1990年到2001年之肺臟多發性淋巴平滑肌瘤之病例。這些確認之病例必須有確切病理切片之診斷和典型高解析度電腦斷層攝影之表現。臨床表現及追蹤之資料皆依據病歷之記載。所有仍找得到石蠟塊組織之病例，我們皆加做HMB-45，動情激素受體(ER)，和黃體素受體(PR)之免疫染色。

結果：從1990年到2001年，我們總共找到10個有完整臨床及病理資料之病例。全部皆為女性，追蹤期間由18個月到167個月不等。有6個病人曾接受荷爾蒙療法。依據理學檢查及其肺功能檢查結果，6個病人在追蹤期間皆很穩定，4個病人其臨床症狀則有逐漸惡化的現象。有兩個病例因接受肺臟移植手術及後腹腔手術死於另外一家醫院。

結論：我們這一系列病人之臨床及病理表現皆和其他國家之報告相似。所有10例病患，其臨床症狀之進展皆十分緩慢。荷爾蒙療法無明顯療效。病理切片為重要診斷依據，但切片之大小及位置也會影響其準確性。
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關鍵字：肺臟多發性淋巴平滑肌瘤，高解析度電腦斷層攝影，HMB-45，荷爾蒙療法。

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