Clinical analysis of patients with pulmonary lymphangioleiomyomatosis (PLAM) in mainland China

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Summary
Background and objective: There have been no clinical reports on pulmonary lymphangioleiomyomatosis (PLAM) based on large studies or epidemiological surveys in mainland China. The purpose of this study was to provide a retrospective analysis of PLAM patients in mainland China by reviewing the clinical data of PLAM cases reported.

Methods: The China Academic Journals Full-text Database search engine was used to collect related cases in mainland China through the end of 2008. 120 cases met the study’s inclusion criteria and were reviewed for this analysis.

Results: The average age of the 120 patients upon confirmed diagnosis was $37.3 \pm 6.4$ years. The average duration from onset of symptoms to a confirmed diagnosis was $29.6 \pm 35.8$ months, with 80 person-time patients having experienced misdiagnosis before the confirmed diagnosis. The major clinical manifestations of PLAM included progressive dyspnea, recurrent pneumatothorax, refractory chylothorax. Pulmonary function abnormalities included obstructive pulmonary ventilation disorders and degenerated diffusing capacity. Ten patients were found to be complicated with renal angiomyolipoma and 17 with abdominal or pelvic lymphangioleiomyoma. Half of the patients had undergone antiestrogen therapies such as progesterone, and four patients received pulmonary transplantation. The average duration from the confirmed diagnosis to death was $36.4 \pm 48.9$ months among the 28 cases of death.

Conclusions: Doctors in mainland China are becoming increasingly vigilant to PLAM, although misdiagnosis or missed diagnosis still exists. Provider attention to the correlation between PLAM and tuberous sclerosis complex, as well as to the possible involvement of multiple organs, is insufficient.

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Introduction

Pulmonary lymphangioleiomyomatosis (PLAM) is an orphan pulmonary disease that predominantly plagues fertile women.\(^1\)\(^-\)\(^3\) It is characterized by a proliferation of abnormal smooth muscle cells (LAM cells) and cystic lesions in the lung, manifesting in progressive dyspnea, recurrent spontaneous pneumothorax, refractory chylothorax. The chest CT, particularly HRCT, is capable of showing characteristic lesions of PLAM: thin-wall cystic air sacs evenly distributed in bilateral lobes surrounded by normal pulmonary tissues.

The incidence of PLAM is 2.6 per 1 million women without evidence of genetic disease. However, this disease occurs in one third of women with tuberous sclerosis complex (TSC).\(^1\) PLAM is associated with TSC gene mutations.\(^4\)\(^,\)\(^5\) Mutations of TSC1 or TSC2 genes can cause defects or a deficiency in the proteins that they encode, which undermines the modulation of the transmission of downstream signals, resulting in abnormal cell proliferation and migration.\(^2\)\(^,\)\(^3\)

This disease was first reported by Burrell in 1937,\(^6\) followed by continuous case reports across the world. The first PLAM case in mainland China was confirmed in 1983.\(^7\) The lack of an agency as authoritative as the American National Heart, Lung, and Blood Institute (NHLBI) in mainland China results in an absence of case summaries based on studies with large sample sizes, let alone an epidemiological survey of PLAM cases in mainland China to date. The purpose of this study was to provide a retrospective analysis of PLAM patients in mainland China.

Methods

Subjects

Using the China Academic Journals Full-text Database (CAJ)—the largest searchable full-text and full-image interdisciplinary Chinese journal database in the world (www.cnki.net), the subjects were identified from papers on PLAM published in academic journals in mainland China by the end of December of 2008. The inclusion criteria were: 1. The patients should meet at least one provision of the PLAM diagnostic criteria: (1) Confirmed by pulmonary pathological biopsy, (2) Confirmed by pathological biopsy of lymph nodes or other masses, (3) Characteristic changes on chest HRCT, such that a clinical diagnosis is appropriate; 2. Patients must have been living in mainland China (were not from Taiwan, Hong Kong, Macau or other foreign nations); and 3. The papers must provide enough detail about the patients’ clinical data, including disease history, imaging data, pathological results and therapeutic strategy.

After a complete search of the CAJ database and screening for inclusion criteria, 120 cases were included in the study which were reported by 81 papers (online supporting information).

Methods

The CAJ was used to pool PLAM cases in mainland China published by academic journals, after which the eligibility of the cases were reviewed by referring to the study’s inclusion criteria. The clinical data of these cases were then analyzed to come to understanding about the current status of PLAM in mainland China.

Statistic methods

SPSS13.0 software was used to conduct statistic analyses. Continuous variables were compared using independent-sample t-test. Chi-square test was used to compare categorical variables. Differences with a value of \(P < 0.05\) were considered statistically significant. Because all measurement values were not available for all subjects, the sample sizes differ somewhat for different results. All data are represented in the form of means and standard deviations (\(\bar{x} \pm s\)).

Results

Demographic data

The average age of the eligible PLAM cases upon confirmed diagnosis was 37 \(\pm\) 6.4 years (range: 13–60 years). The precise time of PLAM diagnosis confirmation was available in the disease history data of 85 patients, one received a confirmed diagnosis before 1990, 19 during 1990–1999 and 65 in 2000 or later. In addition, 109 of the total patients were diagnosed by hospitals in the developed eastern areas, 6 diagnosed by hospitals in the less developed central areas, and the rest diagnosed by hospitals in developing western areas.

Clinical manifestations

PLAM has various clinical manifestations (Table 1). Fourteen patients experienced pneumothorax as their initial symptom, and seven had abdominal symptoms and signs such as bloating, abdominalgia and mass.

Three patients were complicated with tuberous sclerosis complex (TSC). One patient was male. He did not undergo chromosome examination and sex hormones test, but he had a biological son with his wife. Six patients had been taking oral contraceptives for a long period of time, and three patients became pregnant during the disease course.

Lab data

Pulmonary function examinations

The reports of 76 cases included the results of a pulmonary ventilation test, with 69 testing positive for obstructive ventilatory functional disturbance, 28 for restrictive ventilatory functional disturbance, and four cases had a normal result. Out of 59 patients whose diffusing function test results were available, 56 had abnormal findings.

However, only a few articles contained specific data for pulmonary function examination (Table 2).

Imaging findings

119 patients underwent chest CT among whom 4 patients had mediastinal lymphadenopathy. One patient didn’t have
a CT scan performed because this imaging technique was not widely available in mainland China in 1980s. Ninety four patients received HRCT and demonstrated thin-wall cystic air sacs evenly distributed in bilateral lobes. Only 50 patient reports included abdominal or pelvic CT or B-type ultrasound findings, with 17 testing positive for lymphangiopleiomyoma (LALM), 10 positive for renal angiomyolipoma (AML), 1 positive for hepatic AML, 9 complicated with uterine leiomyoma. Moreover, 5 patients underwent skull CT and 3 of these patients presented with intracranial multiple calcification lesions.

**Comparison of features of PLAM with and without AML/LALM**

Fifty patient reports included abdominal or pelvic CT or B-type ultrasound findings, 26 of whom had conditions complicated with AML/LALM. By comparing these patients with and without AML/LALM, the former were more to have pneumothorax and hypoxemia than the latter \((P = 0.019, 0.034\) respectively) (Table 3).

**Diagnosis**

Among these patients, 108 cases were confirmed by pulmonary biopsy (Fig. 1), 7 by biopsy of the lymph nodes or other masses, 1 by a combination of the above two biopsies, and 4 by clinical diagnosis. Moreover, 2 patients underwent autopsy, with one demonstrating dramatically thickened muscularis mucosae and muscular layer in the jejunal and colon, as well as hypertrophy of smooth muscle in the wall of the gallbladder.

Eighty two patient reports included documentation of the duration between symptom onset and a confirmed diagnosis. The average duration was \(29.6 \pm 35.8\) months (range: one-half month to 16 years). Eighty person-time patients had been misdiagnosed before the confirmed diagnosis, 19 of whom were misdiagnosed with idiopathic interstitial pneumonia, 17 with idiopathic pneumothorax, 9 with emphysema, 7 with pulmonary bulla, 6 with bronchitis, 6 with tuberculosis, 6 with bronchiectasis, 3 with pneumonia, 2 with COPD, 2 with asthma, 2 with upper respiratory tract infection, 2 with pulmonary involvement of connective tissue disease, one with pneumoconiosis complicated with infection, and one with pleuritis. Regrettably, one PLAM patient had been misdiagnosed with COPD for as long as 16 years, and another had been diagnosed with a string of diseases including chronic bronchitis, emphysema, pneumonia and idiopathic interstitial pneumonia. Peculiarly, four patients were missed for PLAM due to a lack of pulmonary biopsy because their surgeons failed to take into account the possibility of PLAM when they conducted ligation of the pulmonary bulla or thoracic duct on the patients.

It is worth noting that six patients had experienced pathological misdiagnosis after pulmonary biopsy, with 4 contributing specimens in the form of transbronchoscopic lung biopsy (TBLB) and two in thoracoscopy. Fortunately, three patients were correctly confirmed after a rereading of the slices, two patients receiving TBLB were correctly confirmed by thoracoscopy-based pulmonary biopsy, and one patient was confirmed by repeated TBLB.

**Treatment**

**Antiestrogen therapies**

Sixty of the 120 total patients received antiestrogen medications (Fig. 2). The dosage of progesterone varied from hospital to hospital, ranging 10-600 mg/d for oral use and 300–750 mg/m for intramuscular use. A dosage of 400–600 mg/m for intramuscular use was the most common dosage, and the most frequent length of treatment course was 6–12 months (maximum length was 5 years). In addition, three patients had undergone bilateral adnexectomy.

**Surgical treatment of the complications**

Recurrent pneumatothorax and chylothorax were common complications for PLAM. Due to pneumatothorax, six patients had undergone ligation of the pulmonary bulla and four patients had undergone pleurodesis. Due to chylothorax, four patients had undergone ligation of thoracic duct and one patient had undergone pleurodesis. Among the four patients who underwent ligation of the thoracic duct, two patients did not experience alleviation of their chylothorax (one of whom underwent two operations), one patient experienced alleviation, and one patient was not evaluated.

**Pulmonary transplantation**

Currently, pulmonary transplantation is the only approach that can cure PLAM, although cases relapsing in the transplanted lung have been reported. Of the cases reviewed here, four patients had undergone pulmonary transplantation (Table 4).
Prognosis

Twenty-eight PLAM patients were reported to have died mainly from respiratory failure due to recurrent pneumatothorax or generalized failure due to refractory chylothorax. The average period from confirmed diagnosis to death was 36.4 ± 48.9 months. The duration from symptom onset to death was 57.9 ± 40.6 months. A failure to conduct long-term follow-up of most patients resulted in an unavailability of precise survival time data.

Discussion

Although studies have demonstrated that PLAM cases have been increasing in mainland China since 2000, it is scientifically unsound to conclude that the incidence of PLAM is significantly increasing in mainland China. With doctors in mainland China becoming more vigilant of PLAM, and as certain examination approaches (e.g., HRCT) gain in popularity, some PLAM cases that were previously unconfirmed or that had been misdiagnosed for several years were later found to be confirmed PLAM cases. Additionally, most PLAM cases (90.8%) were confirmed by hospitals situated in eastern areas. The fact that the eastern areas are more developed helps to increase the confirmed diagnosis rate for the patients in these areas and attracts patients living in the central and western areas to attend hospitals situated in the eastern areas. Thus, the higher confirmed diagnosis rate for PLAM in the eastern areas does not necessarily indicate that the incidence of PLAM in the eastern areas is higher than that in the central and western areas. Since most papers did not provide the native location of each patient, the authors were unable to analyze the true geographic distribution of the PLAM cases in mainland China.

TSC-LAM was reported to account for 15.6% and 14.8% of the PLAM cases reported in two studies with large samples conducted by foreign investigators.8,9 In contrast, our results showed that TSC-LAM accounted for only 2.5% of cases. We theorize that the discrepancy in these percentages is due to insufficient recognition of the relationship between PLAM and TSC among doctors in mainland China.

Compared to pulmonary involvement of TSC, the most

| Table 3 Comparison of features of PLAM with and without AML/LALM. |
|------------------------|------------------------|------------------------|
|                        | AML/LALM (n = 26)      | Non-AML/LALM (n = 24)  | P value |
| Age at time of confirmed diagnosis (y) | 36.2 ± 7.9 (n = 26) | 36.0 ± 7.2 (n = 24) | 0.914  |
| Course of disease (m)a | 44.4 ± 56.1 (n = 17) | 20.8 ± 28.5 (n = 18) | 0.133  |
| Pneumothorax           | 15/26                  | 6/24                   | 0.019b |
| Chylothorax            | 13/26                  | 9/24                   | 0.374  |
| Chyloperitoneum        | 5/26                   | 1/24                   | 0.192  |
| FEV1/FVC (%)           | 57.4 ± 12.4 (n = 7)    | 60.6 ± 17.7 (n = 8)    | 0.689  |
| FEV1% (%)              | 53.0 ± 20.7 (n = 7)    | 51.4 ± 19.1 (n = 8)    | 0.879  |
| VC% (%)                | 87.5 ± 31.2 (n = 6)    | 66.2 ± 19.8 (n = 7)    | 0.164  |
| DLCO% (%)              | 57.7 ± 21.5 (n = 7)    | 38.8 ± 9.8 (n = 5)     | 0.100  |
| PaO2 (mmHg)            | 55.5 ± 14.4 (n = 10)   | 68.6 ± 7.6 (n = 8)     | 0.034b |
| PaCO2 (mmHg)           | 31.9 ± 6.2 (n = 10)    | 38.1 ± 16.5 (n = 7)    | 0.295  |

a Course of disease: the duration between symptom onset and a confirmed diagnosis.

b P < 0.05.

Figure 1 Detailed approaches of pulmonary biopsy. Illustration: Detailed biopsy approaches were presented by several papers contributing 97 cases of the 108 cases confirmed by pulmonary biopsy, in which 49 patients were confirmed by transbronchoscopic lung biopsy (TBLB), 31 by thoracotomy, 10 by thoracoscopy and 7 by percutaneous pneumocentesis.

Figure 2 Antiestrogen medications. Illustration: 60 patients had been administered antiestrogen medications, with 48 administered progesterone alone, 2 administered Tamoxifen alone, one administered Goserelin acetate alone, and 9 administered a combination of two or more antiestrogen medications, in whom 7 patients received a combination of progesterone and Tamoxifen.
common TSC symptoms in the patients we reviewed included epilepsy, mental disorders and skin lesions, and most symptoms took place in childhood. These symptom patterns caused many patients to seek help from specialists in pediatrics, dermatology and the neurosciences, resulting in a high likelihood of missed diagnosis by the specialists who are not vigilant to PLAM. Respiratory physicians and thoracic surgeons can also miss PLAM cases if they only focus on the PLAM itself without considering the possibility of pulmonary involvement of TSC. Therefore, specialists of the above disciplines should be mindful of the association between PLAM and TSC.

PLAM has various manifestations. The less specific nature of PLAM, as well as the absence of chest radiograph findings in the early disease stages, can easily lead to missed diagnoses or misdiagnoses. We found that the average duration from symptom onset to the confirmed diagnosis among patients of mainland China was 2 years or longer. As many as 80 person-time patients had experienced misdiagnosis before receiving a confirmed diagnosis. There were over 10 diseases commonly passed for PLAM, the most frequent of which were idiopathic interstitial pneumonia and idiopathic pneumothorax. In addition, some PLAM cases were missed by thoracic surgeons because the surgeons conducted ligation of the pulmonary bulla or thoracic duct to treat the pneumothorax or chylothorax without performing pathological biopsy. Thus, raising doctors’ awareness of PLAM, collecting a thorough disease history from all patients, and applying HRCT when necessary will help healthcare providers avoid misdiagnoses and missed diagnoses.

PLAM can involve multiple organs, particularly renal AML. Studies by Avila et al. showed that in 323 cases of patients with PLAM, 44.9%, 8.7%, 24.8% of them were complicated by renal AML, hepatic AML, abdominal or pelvic LALM, respectively. In contrast, the corresponding rates found in the 120 PLAM cases reviewed here were 8.3%, 0.8% and 13.3%, respectively. We believe that clinicians’ lack of recognition of PLAM as a multi-organ disease is the primary cause of the low proportion of diagnoses of PLAM with multiple organ involvement, thereby resulting in a failure among clinicians to perform necessary abdominal examinations and to correlate abnormal findings with PLAM. In addition, our study showed that PLAM patients with AML/LALM were more likely to have concomitant pneumothorax and hypoxemia.

It is also important to note that six patients we reviewed had experienced an incorrect pathological diagnosis, which may have been caused by an insufficient amount of specimen (possibly due to use of TBLB), by insufficient pathologist awareness of PLAM or by poor communication between clinicians and pathologists. In addition, concurrent complication from other pulmonary diseases can complicate the pathological diagnosis of PLAM. Therefore, when PLAM is strongly suggested by clinical manifestations and imaging findings but not by pathological results, rereading the slices or repeating the pathological exam should be performed in order to avoid incorrect exclusion of a PLAM diagnosis.

Antiestrogen therapies are considered to be a major approach for the treatment of PLAM, however, the efficacy of antiestrogen therapies for the treatment of PLAM is currently controversial. Our study found that half of the 120 patients living in mainland China had been administered antiestrogen therapies, with progesterone being the most frequently used. While the recommended dosage of progesterone in mainland China is an intramuscular injection of 400–800 mg monthly or an oral use of 10–20 mg daily, the patients included in our study had been administered a wide range of progesterone dosages, from 10 to 600 mg/d for oral use.

Ligation of the thoracic duct is believed to be capable of treating refractory chylothorax complications related to PLAM, but its efficacy remains controversial. Two of the four patients we reviewed who underwent ligation of the thoracic duct did not experience alleviation of the chylothorax, which could be explained by obstruction or destruction of any part of the duct or its branches or the pleural lymphatic vessels, which will cause chylothorax, thereby impairing the efficacy of the operation. Ligation can cause a disturbance of the reflux of chyle from the branches of the duct or from the pleural lymphatic vessels, which can further deteriorate chylothorax. Thus, ligation of the thoracic duct can only be conducted after lymphangiography, depending on which location and type of lesions can be identified and whether aberrant anatomy of the thoracic duct can be found.
The lack of a national database means that one can only analyze mainland China PLAM cases by reviewing published papers describing the cases—a method with many shortcomings, especially incompleteness of data. For instance, some papers we reviewed did not provide the results of pulmonary function examinations, and most articles only presented conclusions without providing specific data values, thereby disabling our statistical analyses across the cases. Another difficulty is that the cases reported had not been strictly followed for a long period of time. Only one third of the papers documented follow-up procedures, with an average follow-up duration of 28 months. Furthermore, most of the papers including patient follow-up only evaluated overall patient symptoms, without providing the results of pulmonary function examinations and imaging findings during the follow-up. This lack of follow-up data prevented us from examining changes in the disease over time and from objectively evaluating the efficacy of the antiestrogen therapies used.

In summary, our study indicates that doctors in mainland China are becoming increasingly aware of PLAM, although misdiagnosis and missed diagnosis still exist. We have three primary recommendations as a result of our findings: (1) Doctors in mainland China should improve their understanding of this rare disease, (2) Doctors in mainland China should be made aware of and be mindful of the correlation between PLAM and TSC, as well as the possibility of multiple organ diseases related to PLAM, and (3) A national agency should be established in mainland China to oversee PLAM patients with the purpose of offering better healthcare services to these patients and facilitating research on this disease.

Conflict of interest statement

The authors declare that they have no conflict of interest to disclose.

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Appendix. Supplementary information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2010.05.003.

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