Pulmonary Langerhans cell histiocytosis: analysis of 14 patients and literature review

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Background: Pulmonary Langerhans cell histiocytosis (PLCH) is an orphan disease in respiratory medicine, which most affects adult smokers. The purpose of this article was to discuss the clinical features, especially the radiologic features of PLCH patients during their hospitalization through a retrospective analysis on clinical data. Furthermore, the current literature was also reviewed.

Methods: Between December 2008 and June 2012, 14 patients with PLCH were assessed at Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China. Among these patients, seven patients were diagnosed through tissue biopsy from the lung and one patient from enlarged cervical lymph nodes; the rest of six patients were diagnosed based on the clinical-radiological data. The data consisting of demographics, clinical presentation, smoking habits, pulmonary function tests (PFTs) and radiographic image from the medical records was analyzed retrospectively.

Results: The average age of patients (11 males and 3 females) was 42.79 (±13.71) years old. All male patients and one female patient had a long smoking history. The common manifestations were cough and exertional dyspnea. Spontaneous pneumothorax was found in three patients. Varieties of pulmonary shadows such as nodular, cystic, patch-like and cord-like were revealed by chest computed tomography (CT) examination. Large Langerhans cells (LCs) were discovered in biopsy tissue by immunohistochemical stains. **Conclusions:** PLCH is still an orphan disease and maybe related to smoking. Clinical symptoms such as cough and exertional dyspnea are non-specific. We shall pay attention to recurrent pneumothorax as clinically it is associated with PLCH. The characteristic radiological manifestation is cystic or nodular shadow in the lungs, which plays crucial roles in diagnosing PLCH.

Keywords: Pulmonary Langerhans cell histiocytosis (PLCH); recurrent pneumothorax; radiological manifestation

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Introduction

Langerhans cell histiocytosis (LCH) is an orphan histiocytic disease, which includes disorders of unknown origin with extensive variations in clinical presentation and outcome. It is characterized by infiltration of the involved tissues by large numbers of Langerhans cells (LCs), often organized into granulomas (1). LCH can occur in any age, but the exact incidence is still unknown. According to the number of organs involved (2,3), LCH can be classified into three groups by the Histiocyte Society, including single-system, low-risk multisystem, and multisystem with risk-organ involvement. The lung can be involved primarily or secondarily in any group. Pulmonary involvement in

Table 1 Characteristic	s of 14 PLCH patients
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Characteristic	Patients
Total number	14
Male/female	11/3
Age (years old)	42.79 (±13.71)
Smoking history (pack/year)	18.92 (±14.79)
FEV ₁ (L)	1.80 (±0.68)
FEV ₁ (%)	64.33 (±21.32)
FVC (L)	2.60 (±1.12)
FVC (%)	71.07 (±24.59)
FEV ₁ /FVC	71.45 (±11.47)
DLCO (%)	74.90 (±28.76)

PLCH, pulmonary Langerhans cell histiocytosis; FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide of the lung.

multisystemic patients is uncommon, yet might indicate poor prognosis (4). On the contrary, solitary pulmonary involvement is more common, so it is named as PLCH. PLCH differs from the pulmonary involvement in multisystem disease, which is recognized as the more common form now (3,5).

PLCH is a pulmonary interstitial disease, which can be asymptomatic or manifest with respiratory symptoms. The pathogenesis of PLCH is uncertain, previous studies found that PLCH had high incidence in smokers (1,6-13), particularly in young adult smokers (14), but precise epidemiological data was not available. The relative frequency in men and women is equal (8), which probably because of the increased prevalence of smoking among women in recent years (15). Among adults with PLCH, the long term survival is shorter than that of general population, and their health is substantially affected (14). Ideally, the diagnosis of PLCH must be confirmed by tissue biopsy, however, some patients were unwilling to perform this invasive test because of the risk as well as the cost. Hence, PLCH is easily misdiagnosed clinically. The purpose of this article was to emphasize the clinical features especially radiologic features of PLCH patients; furthermore, the current literature was also reviewed.

Methods

This study retrospectively analyzed the clinical data of

14 patients with PLCH. All the coherent patients were hospitalized at the Shanghai Pulmonary Hospital, Shanghai, China, between December 2008 and June 2012. The diagnosis of PLCH should fulfill one of the following criteria: (I) disease proven by lung biopsy; (II) a positive biopsy of an extra thoracic localization of the disease or the presence of diabetes insipidus associated with characteristic lung HRCT findings; or (III) the combination of an appropriate clinical setting, a typical lung HRCT pattern (showing both nodules and cysts) and the exclusion of alternative diagnoses (16).

The following clinical data were obtained from the medical records: age, sex, smoking history, clinical features and PFTs. All patients had routine peripheral blood and serum biochemical tests. The radiological tests included chest X-ray and CT scan. Six patients underwent surgical lung biopsy, one patient got CT-guide percutaneous lung puncture, and one patient underwent biopsy from enlarged cervical lymph nodes. The remaining six patients were diagnosed based on the clinical-radiological data. The study protocol was approved by the Ethics Committee of Shanghai Pulmonary Hospital (approval number: K16-265). All participants were given informed consent before taking part.

Results

The age of patients (11 males and 3 females) ranged from 21 to 72 years, and the average age was 42.79 (\pm 13.71) years old. All the male patients as well as one female patient had a long smoking history (*Table 1*). The symptoms of PLCH patients included cough (in nine patients), exertional dyspnea (in seven patients), expectoration (in three patients), chest tightness and chest pain (in one patient, separately). Three asymptomatic patients were found having lung shadows by radiological examination. Spontaneous pneumothorax was found in three patients. Neither hemoptysis nor extra-pulmonary symptom was detected in 14 PLCH patients (*Table 2*).

Only six patients got PFTs data, FEV_1 ranged from 1.03 to 2.68 L, FVC ranged from 1.09 to 4.21 L, and FEV_1/FVC ranged from 62.73% to 93.57%. Among the four tested patients, DLCO% ranged from 32.5 to 96.5. No distinct abnormalities and significant differences were found in blood routine examination and serum biochemical tests.

There were various appearances including nodular, cystic, patch and cords shadows revealed by chest X-ray or CT examination. The nodular shadows were found in seven

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Symptoms	Number of patients
Cough	9
Exertional dyspnea	7
Pneumothorax	3
Expectoration	3
Asymptomatic	3
Chest tightness	1
Chest pain	1
Hemoptysis	0
Extra-pulmonary symptoms	0

Table 2 The symptoms of 14 patients with PLCH

PLCH, pulmonary Langerhans cell histiocytosis.

Table 3 The radiographic findings on CT scan of 14 PLCH patients

Radiographic findings	Number of patients
Nodular	7
Cystic	6
Patch	3
Cord	2
Pleural thickening	2
Pleural effusion	1
Mediastinal lymph node enlargement	3

PLCH, pulmonary Langerhans cell histiocytosis.



Figure 1 Both lungs had pneumothorax and cystic shadows.



Figure 2 Both lungs had multiple nodular shadows.



Figure 3 Langerhans cells in biopsy lung tissues of PLCH patients. The cytoplasm was eosinophilic, nuclear chromatin was uniformly and exquisitely stained with obvious nuclear groove (HE staining, ×200). PLCH, pulmonary Langerhans cell histiocytosis.

patients, cystic shadows in six patients, patchy shadows in three patients and cord shadows in two patients. No specific distribution was found for the lung shadows. Other abnormities on CT scan included pleural thickening (in two patients), pleural effusion (in one patient) and mediastinal lymph node enlargement (in three patients). All the CT scan observations are given in *Table 3*, and typical images can be seen in *Figures 1,2*.

The LC lesions were discovered through histological examination in biopsied tissue. LCs were positive for S-100 and CD1a by immunohistochemical staining. Imaging from biopsies can be seen in *Figures 3–5*.

The total of 12 smokers were recommended to quit smoking, 2 out of 3 patients with recurrent pneumothorax were treated by closed thoracic drainage, and 7 patients received symptomatic relief and supportive treatment.



Figure 4 S-100 staining positive of Langerhans cells (×200).



Figure 5 CD1a staining positive of Langerhans cells (×200).

Eleven patients followed up at outpatient department or by telephone interview. Four patients felt improved symptoms with smoking cessation, while 2 felt not. Two patients with recurrent pneumothorax underwent pleura fixation because of thoracic drainage failure. Three patients died within three years after discharge, the cause of death was pulmonary failure in two patients and unknown in the rest.

Discussion

The present study aims to retrospectively analyze the clinical data of 14 patients with PLCH as well as to review the relevant literature. So far, we still know little about the clinical features of PLCH despite several studies have been reported (8,17,18). We hope our study will add more data to PLCH, therefore, facilitate the diagnosis and management.

The pathogenesis of PLCH is largely unknown at present, although previous studies found that PLCH had

higher incidence in smokers particularly in adults with smoking history (1,6-13). Several explanations have been brought up regarding how cigarette smoking potentially facilitate the formation of Langerhans' cell nodules in the lungs (7,12). However, only small proportion of smokers develops PLCH, necessitating the correlation between smoking and PLCH to be further investigated.

The presentation of PLCH can be various (15,19,20), in spite of diffuse lung involvement, symptoms can be presented as insidious onset or nonspecific manifestations. About 25% of cases were asymptomatic, respiratory symptoms mainly including dry cough and dyspnoea on exertion were in approximately two-thirds of cases, and spontaneous pneumothorax was in 10-20% of cases (1). This data is approximate to our study. However, symptoms such as cough and exertional dyspnea are so common that each of them can be seen in other respiratory diseases, and this leads to the difficulty of diagnosing PLCH. The occurrence of pneumothorax seems more common in PLCH patients, with 60% of such patients experiencing at least one episode (21-24). PLCH seemed to associate with patients experiencing recurrent pneumothorax (25). In fact, sudden death due to bilateral pneumothorax of PLCH patient were reported (26). Hence, recurrent pneumothorax should be paid attention to not only because of the association with PLCH but also its life-threatening potential. In our current study, all PLCH patients presented as single-system symptoms without extrapulmonary manifestations.

At early phase of PLCH patients, due to pulmonary vascular lesion and ventilation limitation, pulmonary function may present in the pattern of restrictive ventilation. With the progression of disease, obstructive ventilation dysfunction could evolve. Pulmonary function can present as normal, obstructive or restrictive. Early phases present nodular lesions, while more advanced phases are appeared by cysts and fibrotic changes (27). In this study, 1 patient had normal pulmonary function and 2 had restrictive ventilation dysfunction, which were consistent to the early phase, while 1 patient had obstructive ventilation dysfunction and 2 had mixed ventilation dysfunction, which were also consistent to their advanced disease phase. Three patients showed DLCO% >80%, which are at the early stages of PLCH confirmed by CT scan; the decrease of DLCO is not evident, possibly because the sample size is small. Previous study found that lung function deteriorated in 60% of the patients and improved in 20% (16). Serial lung function assessment is necessary for the follow-up of

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PLCH patients to identify their disease progression (28). However, in the current study, PFTs data during follow-up are not achieved, so a larger follow-up study is needed to prove the findings in the previous study (16).

The radiological manifestations of PLCH were reported to be cystic and nodular shadows (29), and located in the middle or upper segments of the lung (30), which differed from our study that the distribution of shadows was of no specificity. High resolution chest CT (HRCT) is a noninvasive examination that is very helpful in the etiological diagnosis of interstitial lung disease (31,32). In fact, history of smoking in combination with typical radiographic findings is key to suspect PLCH (27). Also, the characteristic CT features associated with demographic and clinical factors could be diagnostic for PLCH and might spare lung biopsy (33). At early phase of PLCH, HRCT shows 1-10 mm centrilobular nodules that may be cavitary, as disease evolves, cystic lesions predominate over nodules (5,33). Previous study found that nodular abnormalities revealed by CT scans correspond to granulomatous lesions in lung tissue, and are suggestive of an active process (34), meanwhile, thin-wall cysts on HRCT often correspond to cavitary and inflammatory granulomas, suggesting that in PLCH patients, if lesions present in a cystic scan pattern, the persistence of an active, while limited granulomatous process cannot be excluded (34,35). Another study found that cystic lesions suggested a reversible disease, and to patients who had cystic lesions, early intervention was necessary (36). Pleural effusion is unusual radiographic findings of PLCH, which has not been reported in recent literatures. In the present study, two patients were found having pleural thickening and one patient pleural effusion, and pleural effusion might be correlated with the recurrent pneumothorax. Although enlargement of hilar/mediastinal lymph nodes is generally concerning for malignancy, no evidence was found to prove malignancy among all three patients who had mediastinal/hilar lymphadenopathy.

Definitive diagnosis of PLCH depends on tissue biopsy through invasive procedure (24). The open lung biopsy or thoracoscope is the main approach for the diagnosis of PLCH (37). The histopathologic features of PLCH are granulomatous nodules composed of LCs, eosinophils, and scattered other chronic inflammatory cells, and LCs are with grooved nuclear membrane and eosinophilic cytoplasm (15). A key morphological feature to distinguish LCH cells from other cells is their highly convoluted nuclear membranes (38). Immunohistochemical stains will greatly facilitate the discovery of LCs which are positive for CD1a and S-100 (39). In addition, the rod-like Birbeck particles could be seen in cytoplasm by using electron microscopy (39).

However, Hagmeyer et al. (40) thought that HRCT should be used for differential diagnosis and lung biopsy was often unnecessary in smoking-related interstitial lung diseases (embrace PLCH). Also, previous study found that a lung CT at diagnosis of PLCH was informative (16) and confident (31,41). In the present study, not all the patients underwent tissue biopsy by open lung biopsy or thoracoscope, and this is a limitation of our study. Some patients decided not to perform this invasive test after serious consideration, because of the high risk as well as the expensive cost. For those patients, radiological examination as an invasive method may play crucial roles. In the future, more prospective studies with large sample size should be performed to pay close attention to clinical characteristics of PLCH, such that the chance of correct diagnosis can be improved.

In conclusion, PLCH is still an orphan disease and maybe related to smoking. Clinical symptoms such as cough and exertional dyspnea seem to be non-specific. Recurrent pneumothorax should be paid attention to due to its potential link to PLCH. The characteristic radiological manifestation is cystic or nodular shadow, which plays crucial roles in diagnosing PLCH.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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