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Pulmonary Langerhans Cell Histiocytosis: Case Series and Literature Review

Ping Wei, MD, Hai-Wen Lu, MD, Sen Jiang, MD, Li-Chao Fan, MD, Hui-Ping Li, MD, and Jin-Fu Xu, MD

Abstract: Pulmonary Langerhans cell histiocytosis (PLCH) is a rare disease with insidious onset and nonspecific manifestations. The objective of this article was to characterize the clinical manifestations and features of PLCH by retrospectively analyzing clinical data of patients with PLCH in addition to simultaneous review of literature.

A retrospective analysis was conducted on clinical data of patients with PLCH (n = 7), whose conditions were diagnosed by biopsy from pulmonary tissue (n = 6) or enlarged lymph nodes in the neck (n = 1) and confirmed by PLCH typical radiological features on computed tomography (CT) scan, between January 2001 and September 2012 at the Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China. The review of published reports was made to further emphasize the clinical manifestation and radiological features of PLCH.

Long history of cigarette smoking was found in 6 patients. Two patients had recurrent pneumothorax and the other 2 had pulmonary arterial hypertension (World Health Organization group 5 pulmonary hypertension), diagnosed through ultrasonic cardiogram. The nodular shadows were revealed by chest CT scan in 5 patients, cystic shadows in 5 patients, and reticular shadows in 2 patients, as major manifestations, respectively; most of the lesions were located in the middle or upper segments of the lung. The obvious shrank of lesion was found in 1 patient after completely quitting smoking.

The pathogenesis of PLCH might be closely associated with smoking. The cystic or nodular lesion was the typical radiological features. Further prospective studies with large sample size are required to further validate the study results and understand the clinical characteristics of PLCH to avoid misdiagnosis.

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Abbreviations: CT = computed tomography, DLCO = diffusion capacity for carbon monoxide of the lung, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LCH = Langerhans cell histiocytosis, PLCH = pulmonary Langerhans cell histiocytosis.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease involving clonal proliferation of dendritic cells and macrophages, both of which belong to mononuclear phagocytic system, and affects multiple organs.[1] The concept of LCH was first proposed by Farber in 1941,[2] and the disease was called by several names including eosinophilic granuloma, Letterer–Siwe disease, and Hand–Schüller–Christian disease, until it was renamed as histiocytosis X in 1952 by Lichtenstein.[3] Since lung is easily affected and involved primarily or secondarily, it is called as pulmonary Langerhans cell histiocytosis (PLCH). The onset of PLCH is usually insidious without obvious manifestation (25%)[4] or with nonspecific manifestations (pneumothorax as first symptom was found in around 10–15% patients).[5] The first case of pulmonary histiocytosis X was reported in 1951 by Mazzitello.[6] Later, it was formally renamed as LCH in 1987 by the Histiocyte Society, and the histological feature of PLCH was summarized in depth by Colby and Lombard.[7]

PLCH occurs at any age, mainly to adults (aged between 20 and 40 years), especially in cigarette smokers.[8,9] It is now considered as a form of smoking-related over reactive immune response in lung tissue, complicated with chronic inflammation, and finally resulted in Langerhans cells deposit into interstitial area of small airway.[10–12] The incidence of PLCH was low, and only 4% to 5% of all diffuse pulmonary diseases diagnosed by open lung biopsy were PLCH. Hence, PLCH could easily be misdiagnosed.[13] It is important to create awareness on the clinical features of PLCH. Hence, the present work aimed to characterize the clinical manifestations and features of PLCH by retrospectively analyzing the clinical data of patients with PLCH in addition to simultaneous review of the literature.

MATERIALS AND METHODS

Subjects and Study Design

Clinical data of patients with PLCH (n = 7), who were hospitalized at the Shanghai Pulmonary Hospital (affiliated to Tongji University), Shanghai, China, between January 2001 and September 2012, were retrospectively analyzed in this case

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From the Department of Respiratory Medicine (PW, H-WL, L-CF, H-PL, J-FX); and Department of Radiology (SJ), Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai China.
Correspondence: Jin-Fu Xu, MD, Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, 200000, China (e-mail: jfxucn@gmail.com).
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series. The conditions of patients were diagnosed by biopsy from pulmonary tissue (n = 6) or enlarged lymph nodes in the neck (n = 1) and confirmed by PLCH typical radiological features on computed tomography (CT) scan. The pathological criteria defined by International Histiocyte Society in 1987[14] was adopted for the diagnosis of PLCH; the diagnosis of all 7 patients fulfilled the strictest criteria, which included observation under light microscopy, S-100 protein expression in cytoplasm, and CD1a positivity by immunohistochemical staining with lung tissues. Meanwhile, the patients having infections with bacteria, fungi, or viruses, and those with collagen vascular diseases and drug-related diseases were excluded. The study protocol was approved by the Ethics Committee of the Shanghai Pulmonary Hospital.

Laboratory Tests

All patients underwent routine peripheral blood cell tests or serum biochemical tests. Culture tests for pathogenic microorganisms from sputum and bronchoalveolar lavage fluid were also performed.

Pulmonary Function Tests

Pulmonary function test results were obtained from 5 patients (MasterScreen-PFT equipment, Jaeger Corp, Hoechberg, Germany). Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), Tiffeneau–Pinelli index (FEV1/FVC), and diffusion capacity for carbon monoxide divided by the alveolar volume (DLCO/VA) adjusted by hemoglobin were measured.

Radiological Tests

Examinations including chest x-ray and CT scan were used for radiological tests.

Bronchoscopy and Biopsy

Five patients underwent bronchoscopy; 2 of them further underwent lung biopsy. The diagnosis of PLCH was confirmed by biopsy: 1 patient from enlarged lymph nodes in the neck and 6 from lung tissues. Two patients underwent video-assisted thorascope biopsy, and 4 underwent open lung biopsy.

Literature Review

In addition to the retrospective review of cases, the present work also involved a systematic literature review of the following databases: PubMed, Web of Science, EMBase, and ISI Proceedings. The search criteria used included the following: publication period between 1980 and 2013 and article types being original research, case reports, and reviews. The keywords used for the search included the following: Langerhans cell, histiocytosis, PLCH, and pulmonary histiocytosis X.

RESULTS

Baseline and Demographic Details

Case series included 5 male and 2 female patients of Chinese Han race aged between 20 and 63 years (38.14 years in average). Their course of disease ranged between 1 month and 5 years. Six out of 7 patients had a long history of smoking and 2 patients had a Brinkman index (number of cigarettes smoked per day multiplied by number of years of smoking) >600. Two patients had recurrent pneumothorax, and all patients had shortness of breath after physical activity. Four of them had cough and expectoration. A physical examination indicated that moist rales in bilateral lungs could be detected in 1 patient, and no complaint of hemoptysis or fever and no acropachia were found in all patients (Table 1).

Laboratory Tests

A total of 15 leukocytes were found under a high magnification view in the urine of 1 patient, and no other obvious abnormalities were found in routine peripheral blood cell tests or serum biochemical tests. Pathogenic microorganism's cultures from sputum and bronchoalveolar lavage fluid were all negative.

Pulmonary Function Tests

Among the 5 patients who underwent pulmonary function tests, FEV1 ranged between 1.03 and 2.68 (L), FVC ranged between 1.09 and 4.21 (L), and FEV1/FVC ranged between 63.63 and 94.77 (%). Among the tested 4 patients, DLCO/VA ranged between 0.62 and 1.4 (mmol/min/kPa/L) (Table 2).

Radiological Findings

Shadows with various morphologies such as nodular, cystic, curled hair-like, cord-like, and reticulation-type pneumothorax were shown by chest x-ray examination. There were patchy nodular shadows found in 5 patients, cystic shadows in 5 patients (thin-wall cyst), reticulation in 2 patients, pleural effusion in 2 patients, pleural thickening and adhesion in 2 patients, cavity-like change in 1 patient, and lymph node enlargement in 1 patient, respectively. CT observations on nodular cystic reticulation, mediastinal lymph node enlargement, and pleural effusion are given in Table 3.

Transbronchial Biopsy

The endoscopic and lung biopsy pathological findings were found to be negative.

Surgery and Pathological Studies

Large amount of Langerhans cells from biopsy tissue were detected by pathological study (Figure 1). The rod and tennis racket-like particles were observed in Langerhans cells under electron microscopy; Langerhans cells were positive for CD68 (Figure 2), CD1a (Figure 3), and S-100 (Figure 4) by immunohistological staining. A CT scan confirmed that PLCH was presented as nodular or cystic shadows located in the middle and upper segments of the lung.

Treatment and Follow-Up

Two patients with recurrent pneumothorax received treatment with closed thoracic drainage and pulmonary bulla ligation or pleurodesis; 2 smokers received smoking cessation treatment, 1 of them had obvious lesion shrank since after smoking cessation (Figures 5 and 6: before smoking cessation; and Figures 7 and 8: after smoking cessation), and the other one received glucocorticoid treatment. There were improvement in their symptoms and chest x-ray examination findings. One of the 7 patients declined all treatment, and another 2 patients later moved to another hospital to continue treatment. Two out of 7 patients were reviewed and followed up at outpatient department, and the other 5 patients were followed up by telephone interview. Two patients were complicated with pneumothorax (initial disease onset of both patients was at young age). One

TABLE 1. Clinical Information for 7 PLCH Patients

Case No.	Age, y	Gender	Brinkman Index	Initial Symptom	Extrapulmonary Manifestations	Pneumothorax	Pulmonary Hypertension	Pathological Stage	Treatment	Prognosis
1	40	Male	300 (quit)	Chest tightness	–	–	–	Proliferation	Irregular glucocorticoid	Improved
2	63	Male	800	Cough	Polyuria	–	–	Proliferation	–	Dead because of multiple organ failure 1 year later
3	25	Male	200	Chest pain	–	+	–	Healing or fibrosis	Pleurodesis	Dead because of pulmonary failure 2 years later
4	48	Male	1120 (quit)	Cough	–	–	–	Cell-rich	–	Improved
5	24	Male	100	Chest pain	–	+	–	Proliferation	Pleurodesis	Stabilized
6	47	Female	100	Chest tightness	–	–	+	Healing or fibrosis	–	Stabilized
7	20	Female	0	Chest tightness	–	–	+	Healing or fibrosis	Repeated closed thoracic drainage	Dead due to pulmonary failure 1 year later

patient had recurrent pneumothorax 2 times and another patient had recurrent pneumothorax 3 times, all occurred at the right lung. Two patients had undergone right pleura fixation after the attempt of closed thoracic drainage failure. Until the end of follow-up, 3 patients died between 1 and 3 years, who were relatively young or with multiple organs involved. One of the patients who died was complicated with recurrent pneumothorax, another was complicated with pulmonary artery hypertension (World Health Organization group 5 pulmonary hypertension), and the third had comorbidities of central diabetes insipidus and hepatitis A.

DISCUSSION

The present work involved the retrospective analysis of 7 patients with PLCH along with a literature review of published data. Although a number of case reports have been published on PLCH so far, the poor understanding on its clinical characteristics has often led to misdiagnosis. Hence, the results of the present work are critical for clinical practice. PLCH may occur because of precursor cell clonal proliferation, cytokines mediation, virus infection, and immune disorders.[15,16] Among 7 patients, 6 had a long history of cigarettes smoking, of which, one smoker recovered completely after smoking cessation.

The most common complication of PLCH is unilateral pneumothorax, and the bilateral pneumothorax is usually rare[17,18] with chest pain as the major symptom. It was reported that pneumothorax occurred in 16 of the 100 patients with PLCH, and 10 of them had at least 1 episode of pneumothorax; the patients with complicated pneumothorax usually had PLCH onset at young age, and the recurrent rate of pneumothorax was around 58%.[19,20] The incidence of pneumothorax recurrence was significantly higher in cigarette smokers than those who had stopped smoking. Although patients with PLCH have low incidence of hemoptysis (<5%), while once appearing, lung cancer should be considered.[21] Patients with LCH are prone to have tumors, and the ones with one system affected by LCH have higher incidence of tumor (especially malignant lymphoma) than those with multisystem affected by LCH.[22] Howarth et al[23] retrospectively analyzed 314 patients with LCH, reported between 1946 and 1996. All patients' histological examinations were verified and among them, 27 patients had tumors. Five patients had lung cancer including 4 patients with adenocarcinoma and 1 with small cell carcinoma; all had only 1 system affected, without extrapulmonary clinical symptoms. Most of the patients were middle-aged heavy smokers.[23]

Patch-like nodular shadow is the common sign in CT scanning at early-stage disease with diameter ranged from 1 to 10 mm, located without irregular margins around the centrilobular bronchi and bronchioles, which is described as ''centrilobular pathological alteration.''[16] The diameter of cystic shadow is usually 10 to 20 mm.[24] The cystic and nodular shadows located in the middle or upper segments of the lung was regarded as radiological features of PLCH,[25] and the diagnosis accuracy based on iconography could be achieved up to 84%. In the present study, PLCH was also presented as nodular or cystic shadows located in the middle and upper segments of the lung. There were 2 patients in the present study found to have pleural effusion and pleural thickening and adhesion, which might be associated with the recurrent pneumothorax in 1 patient. The hilar mediastinal lymph nodes are usually not enlarged, and it should be highly concerned once the enlargement is found and the complication with malignancy might be considered. In the present study, there was 1 patient

TABLE 2. Pulmonary Function Tests for 7 PLCH Patients

Case	FEV1, L	FEV1, %	FVC, L	FVC, %	FEV1/FVC	DLCO/VA, mmol/min/kPa/L	DLCO/VA, %
1	1.33	56.6	2.12	76.6	62.87	1.4	85.9
2	1.25	44.3	1.89	53.8	65.91	1.13	84.7
3	Not tested	–	–	–	–	–	
4	2.68	76.2	4.21	96.8	63.62	1.37	96.5
5	Not tested	–	–	–	–	–	
6	1.03	37.2	1.09	33.3	94.77	0.62	32.5
7	2.28	83.7	3.14	95.7	72.36	Not tested	–

DLCO/VA = transfer factor of the lung for carbon monoxide corrected for alveolar volume, FEV1 = forced expiratory volume in 1 second, FEV1/FVC = Tiffeneau–Pinelli index, FVC = forced vital capacity.

TABLE 3. Iconographic Feature of Chest Computed Tomography Scan for 7 PLCH Patients

Case	Micronodular	Nodular	Cystic	Reticulation	Mediastinal Lymph Node Enlargement	Pleural Effusion
1	−	+	+	−	−	−
2	−	+	−	−	−	−
3	−	−	+	−	−	+
4	+	+	+	−	−	−
5	+	+	+	−	−	+
6	−	−	+	+	+	−
7	−	+	−	+	−	−

with mediastinal hilar lymph node enlargement, but the malignancy was not discovered until the end of follow-up.

The restrictive ventilation dysfunction could be found in the patients with PLCH at early stage of disease because of pulmonary vascular dysfunction and ventilation limitation; the obstructive ventilation dysfunction could develop along with progression of PLCH. The previous literatures showed that PLCH are presented as typical decrease of FEV1 and DLCO.[26,27] In the current study, 1 patient had restrictive ventilation dysfunction, 2 had obstructive ventilation dysfunction, and 1 had mixed ventilation dysfunction, which were all consistent to their corresponding disease stages. Only 5 cases had the pulmonary function test results, 3 out of 5 cases showed DLCO % >80%. This is probably because the pathological stages of the 3 cases were all at the stages of proliferation or cell rich, which are the early stages of PLCH; the decrease of DLCO is not obvious. Other 2 cases were shown as low DLCO that were in accord with the previous reports. One case could not be tested because of very poor lung function; DLCO/VA (%) of the other patient was only 32.5%. The sample size of further study should be enlarged to prove this point.

The Langerhans cells also exist in healthy lung tissues; therefore, the existence of Langerhans cells in bronchoalveolar lavage is not specific for PLCH. The diagnosis should not made unless the population of Langerhans cells is >5% and is

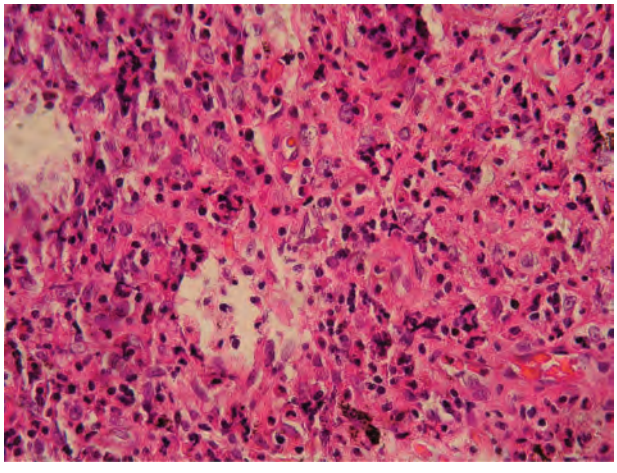

FIGURE 1. Large amount of typical Langerhans cells in the lung tissues of PLCH patients. Nuclear chromatin was uniformly and exquisitely stained, with obvious nuclear groove, by HE staining, ×350.

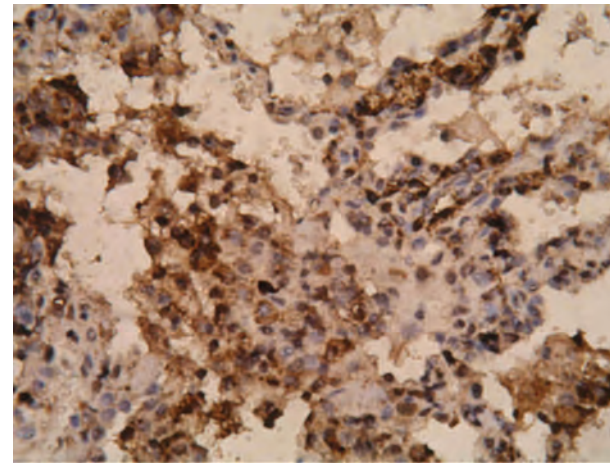

FIGURE 2. CD68 staining positive of Langerhans cells, ×400.

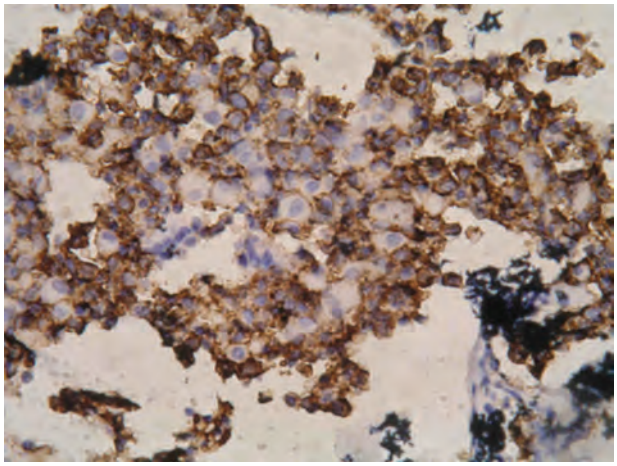

FIGURE 3. CD1a staining positive of Langerhans cells, ×400.

confirmed by immunochemistry and electronic microscopy.[28] The neoplasm in bronchial lumen was ever reported in few literatures, and PLCH was indicated by bronchial mucosal biopsy.[29] In the present study, the negative finding was found under tracheal endoscopy, bronchoalveolar lavage, or pathological biopsy. The open lung biopsy or thoracoscope is the main approach for diagnosis of PLCH.[30]

The typical features of 3 stages of PLCH such as cell-rich, proliferation, and healing or fibrosis could be observed in 1 sample. In addition, there are some common manifestations among the 3 stages that are as follows: rod-like Birbeck particles could be visible in cytoplasm under electron microscopy, S-100 protein is positive in neonatal tumor-like cells, and most cells are positive for CD1a staining.[1,31] The median survival time of patients with PLCH was reported to be 12 years; 5- and 10-year survival rates were 70% and 60%, respectively.[8] Interestingly, 1 patient completely recovered after smoking cessation in the present study. The end-stage PLCH might be developed into serious pulmonary hypertension and pulmonary fibrosis, both could lead to death. The incidence of pulmonary hypertension in patients with PLCH is relatively high and severe, which is predictive for unfavorable prognosis.[32–34] Therefore, the prognosis is usually associated with disease onset age, pulmonary function at initial stage, persistence of the symptoms, types of involved organs, pneumothorax, and pulmonary hypertension.[9,20] In the present study, 3 patients died between 3 and 5 years.

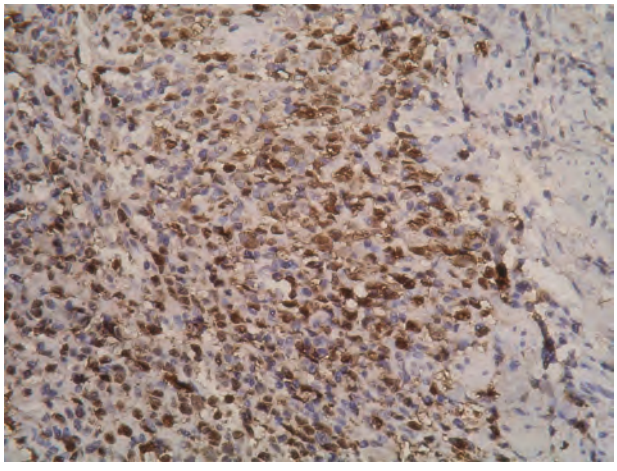

FIGURE 4. S-100 staining positive of Langerhans cells, ×200.

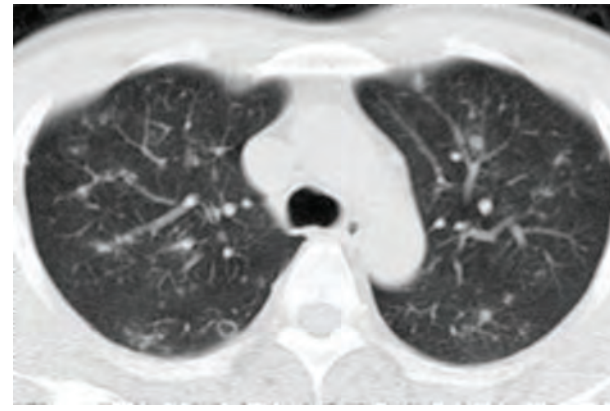

FIGURE 5. Chest CT scans before smoking cessation.

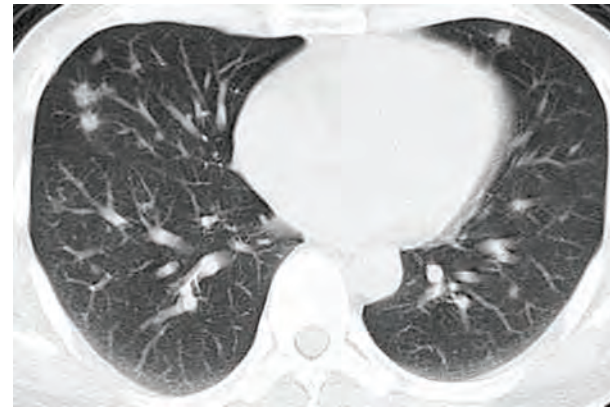

FIGURE 6. Chest CT scans before smoking cessation.

Besides cigarette cessation, glucocorticoid was also used in the published reports, for those who had aggravated symptoms and pulmonary function declined drastically;[27] however, there is no standard criteria for glucocorticoid administration. Cytotoxic drug therapy (including chlorine deoxyadenosine, cyclophosphamide, and methotrexate) can be considered as a remedial treatment for those who failed smoking cessation and glucocorticoid therapy, especially for those who had multiple organs involvement.[35–38] Cladribine treatment was demonstrated to be effective in a recently published report [39]; significant improvement was found on pulmonary ventilation function, diffusion function, and pulmonary lesions (including cystic lesions). In addition, pneumothorax could be treated with closed thoracic drainage and pleurodesis, if necessary. Lung transplantation could be considered for patients at advanced disease stage. It was reported in a retrospective study with 39 patients that the survival rates were 76% and 54% for 1 and 10 years of survival after lung transplantation, respectively, although there was recurrence especially for those with the other organs involved.[40,41] In the present study, the closed thoracic drainage, pulmonary bulla ligation, or pleurodesis were performed for 2 patients who had recurrent pneumothorax; one patient had completely recovered after cigarette smoking cessation and another received both cigarettes smoking cessation treatment and irregular usage of glucocorticoid therapy.

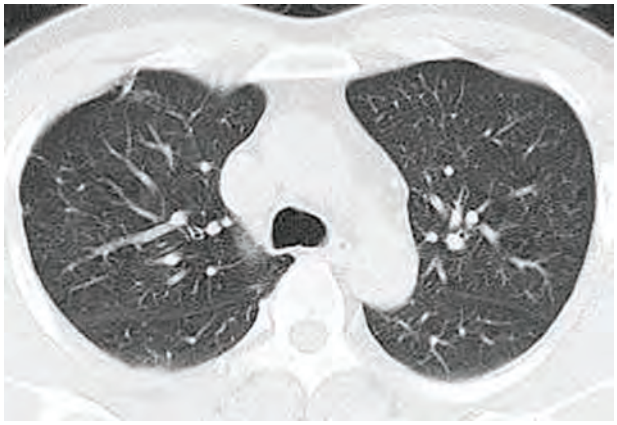

FIGURE 7. Lesions resolved obviously after smoking cessation compared with the same lung area.

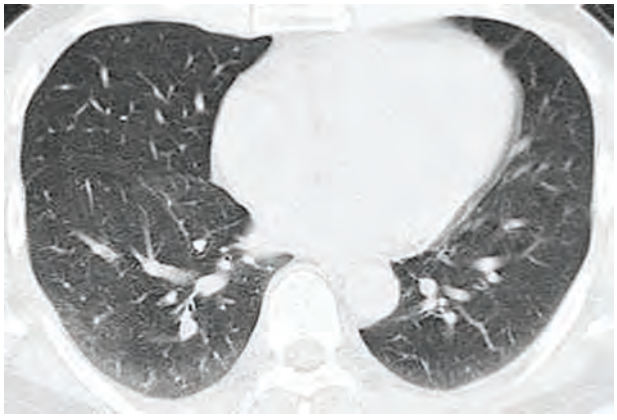

FIGURE 8. Lesions resolved obviously after smoking cessation compared with the same lung area.

Although there was improvement on both symptoms and chest x-ray findings, it was difficult to distinguish the effect between smoking cessation treatment and glucocorticoid therapy because of the small sample size. Although the mechanism of PLCH is still not clear, and the present study was conducted with small sample size and relatively short follow-up, this study might provide some data to avoid misdiagnosis in clinical practice. Further prospective studies with large sample size are required to further validate the study results and understand the clinical characteristics of PLCH to avoid misdiagnosis.

In summary, the present work indicated that the pathogenesis of PLCH might be closely associated with cigarette smoking; the prognosis might be associated with onset age of PLCH patient, cigarette smoking, multiple organs involvement, and complications. The cystic or nodular lesion located in the middle and upper pulmonary segments were the typical radiological features of the PLCH.

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