

Case Report

Pulmonary Langerhans cell histiocytosis with cervical lymph node involvement, and coexistence with pulmonary tuberculosis and right pneumothorax: a case report and review of literature

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Abstract: We report an uncommon 22-year-old male Pulmonary Langerhans Cell Histiocytosis (PLCH) case which co-existed with pulmonary tuberculosis (TB). Unlike the common PLCH cases, this PLCH case has cervical lymph node involvement and right pneumothorax. The diagnosis was established by the imaging of lung and the biopsies of the lung and left neck lymph node. Imaging of the chest showed characteristic small nodules and thin-walled cysts and right pneumothorax. The LCH cells in the lung and left neck lymph node were characterized by large convoluted nuclei with cerebriform indentations of the nuclear envelope and longitudinal grooves. The nuclei contained small eosinophilic nucleoli and moderate amount cytoplasm. Immunohistochemically, the histiocytoid cells were positive for Langerin, CD1a and S-100. Acid-fast bacilli were found in sputum and lung biopsy tissue. To the best of our knowledge, this is the first case of PLCH with cervical lymph node involvement, and coexisted with pulmonary tuberculosis, right pneumothorax. A contribution of this case and review three of the five cases of PLCH with extra-pulmonary involvement to lymph nodes resolved spontaneously after smoking cessation constitute a novel addition that it is inappropriate to regard pulmonary/nodal LCH as multi-organ or disseminated disease, and the treatment methods are the same whether the PLCH patient with lymph node involvement or not.

Keywords: Pulmonary Langerhans Cell Histiocytosis, lymph node involvement, pulmonary tuberculosis, pneumothorax

Introduction

Pulmonary Langerhans cell histiocytosis (PLCH) is a relatively rare disease which characterized histopathologically by granulomas containing a large number of Langerhans cells histiocytosis (LCH) cells localized in the lungs [1]. PLCH can mimic tuberculosis in many respects, but the two diseases are rarely co-existed in the same patient [2]. PLCH is usually confined to the lungs and is therefore an unexpected finding in a cervical lymph node [3]. Here we report a case of PLCH with extension to the left neck lymph node, and co-existence with pulmonary tuberculosis and right pneumothorax.

Case presentation

A 22-year-old Chinese man with an 8-pack-year smoking history presented to West China

Hospital, Sichuan University with chest congestion and dyspnea. Chest x-ray was taken in a local hospital, where the patient was diagnosed with “pneumothorax” and closed thoracic drainage was performed. The patient had one year history of pulmonary tuberculosis and had received anti-tuberculosis treatment for 6 months. Physical examination in West China hospital revealed that the left supraclavicular lymph node was enlarged and about 3 cm × 2 cm. The lungs were clear to auscultation bilaterally, without any wheezes, rales, and rhonchi. Laboratory tests demonstrated (1) White blood cells $12.57 \times 10^9/L$ (neutrophil 89.4%, lymphocyte 4.3%), red blood cells $5.59 \times 10^{12}/L$, platelets $242 \times 10^9/L$, blood sedimentation 56.0 mm/h (normal < 21 mm/h). (2) Arterial gas analysis: Pover of hydrogen (PH) 7.416 (normal 7.35~7.45), Partial pressure of oxygen (PaO₂)

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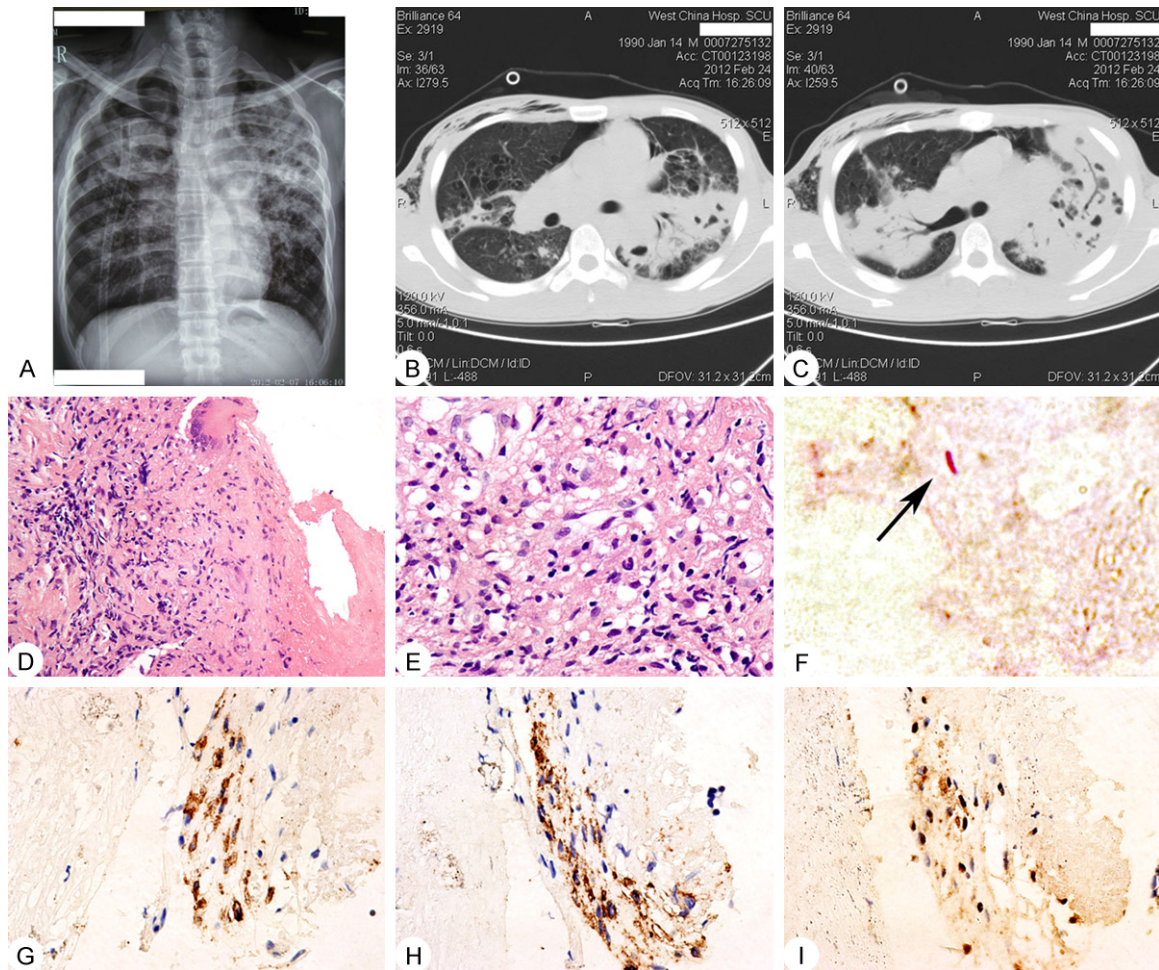


Figure 1. Pulmonary images, histopathology of lung biopsy and immunohistochemistry staining. The chest X-ray showed that nodules and patchy shadows were scattered in distribution of both lobes, and predominate in the middle and upper lung zones (A). Chest computed tomography showed that there were multiple small nodes, patchy, filamentous shadow and consolidation shadow are scattered in bilateral pulmonary. Multiple aerated cysts with thin cystic wall and irregular shape can be seen in bilateral upper lobes, and mostly involved in bilateral upper lobes and left lower lobe. There were pneumatosis in the right thoracic cavity and right side of the chest wall, small amount of pleural effusion in the left thorax (B, C). Under microscopy granulomatous inflammation and necrotic tissues were presented (D, H&E × 100). A closer look at the section reveals a few atypical histiocytoid cells (Langerhans cells) infiltrated parts of this pulmonic- tissue biopsies. The nucleus of these atypical histiocytoid cell are large and convoluted, some atypical histiocytoid cells had typical nuclear grooves and/or small eosinophilic nucleoli. The cytoplasm is moderate amounts and eosinophilic (E, H&E × 400). Acid fast bacilli (black arrow) was demonstrated by acid fast stain (F, oil lens × 1500). Immunohistochemically, the histiocytoid cells were langerin+ (G, × 400), CD1a+ (H, × 400), S-100+ (I, × 400).

73.8 mmHg (normal 90~110 mmHg), Partial pressure of carbon dioxide (PaCO_2) 38.2 mmHg (normal 35~45 mmHg), degree of blood oxygen saturation (SO_2) 94.8% (normal 95%-99%). The chest X-ray showed that nodules and patchy shadow were scattered in both lobes, and predominate in the middle and upper lung zones (Figure 1A). Chest computed tomography revealed multiple small nodes, patchy and filamentous shadow scattered in bilateral pulmo-

nary. Multiple aerated cysts with thin cystic wall and irregular shape could be seen in bilateral lobes, and mostly involved in bilateral upper lobes and left lower lobe. The pleural was thickening. Pneumatosis was detected in the right thoracic cavity and right side of the chest wall, and small amount of pleural effusion in the left thorax (Figure 1B, 1C). Pulmonary hilar and mediastinal lymphadenopathy and splenomegaly could also be observed. The imaging diag-

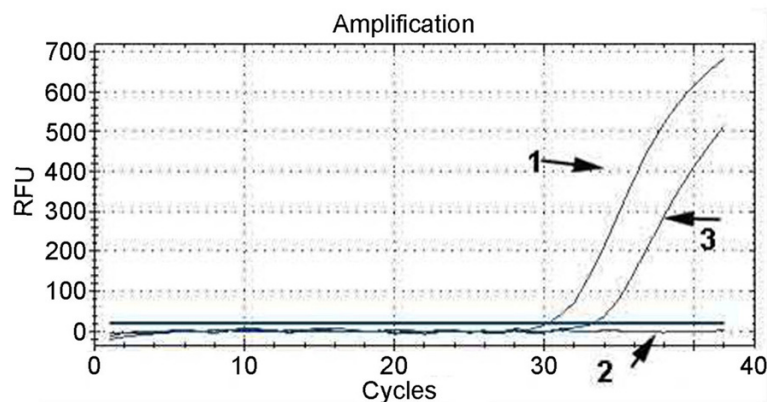


Figure 2. Tubercle bacillus DNA was detected by TB- fluorescent quantitative Polymerase Chain Reaction (FQ-PCR). RFU, relative fluorescence units. 1, positive control. 2, negative control. 3, case sample.

nosis was an infectious process of both lungs, and tuberculosis. In addition, PLCH had yet to be considered. Acid-fast bacilli were found in sputum smear. A biopsy of the superior bronchus tip of left upper lobe was performed. Under microscopy, granulomatous inflammation and necrotic tissues were detected (**Figure 1D**). A closer view at the section revealed a few atypical histiocytes (LCH cells) infiltrated parts of this pulmonic tissue biopsy. The nucleuses of these atypical histiocytoid cells were large and convoluted, and some atypical histiocytoid cells had typical nuclear grooves and/or small eosinophilic nucleoli. The cytoplasm was moderate amount and eosinophilic (**Figure 1E**). Scanty acid-fast bacilli were detected by acid-fast stain (**Figure 1F**). Immunohistochemically, the histiocytoid cells were positive for langerin, CD1a, and S-100 (**Figure 1G-I**). Tubercle bacillus DNA was detected by TB- fluorescent quantitative Polymerase Chain Reaction (FQ-PCR) (**Figure 2**). An excisional biopsy of the left neck lymph node was performed. The volume of lymph node was 2.8 cm × 1.8 cm × 1.3 cm. It was grey-brown in color with smooth capsule. Microscopically, the capsule of the cervical lymph node was thickened with a little normal lymphoid tissue. The interfollicular regions and medullary sinus were expanded by infiltrating mononucleated or multinucleated histiocytes (LCH cells) admixed with small lymphocytes, and eosinophils (**Figure 3A, 3B**). The LCH cells were characterized by large convoluted nuclei with cerebriform indentations of the nuclear envelope and longitudinal grooves. The nuclei contained small eosinophilic nucleoli and the

cytoplasm was moderate in amount (**Figure 3C**). Immunohistochemically, the LCH cells were positive for langerin, CD1a and S-100, but negative for MPO, LCA, CD20, CD3ε and CD30 (**Figure 3D-K**). The proliferation index was less than 5%, assessed by Ki-67 staining (**Figure 2I**). Combined with the clinical manifestations, radiological features, pathological morphology, the result of immunohistochemistry and smoking history, the final diagnosis was made as PLCH with extension to the left neck lymph node, pulmonary

tuberculosis and right pneumothorax. The patient had ceased smoking and accepted regular anti-tuberculosis treatment. 30 days later, when he was leaving the hospital, the clinical symptoms were significantly improved.

Discussion

Langerhans cell histiocytosis (LCH) is a rare disease of histiocytic syndrome characterized by infiltration of tissues with a specific dendritic cell, the Langerhans cell [1]. It used to be known as histiocytosis X (or eosinophilic granuloma), it is now recognized that the “X” cells are LCH cells [4], which may be distinguished from other dendritic cells by the presence of intracellular Birbeck granules and surface expression of the CD1a [1]. Pulmonary involvement in LCH (PLCH) is more common in adults and may be the sole organ involved, or may be part of multi system diseases [5]. A study which includes 502 patients undergoing surgical lung biopsies for diffuse lung disease reported PLCH in 4-5% of all diffuse lung disease biopsies [6]. PLCH occurs almost exclusively in smokers and it is likely that smoking induces accumulation and activation of histiocytes in small airways [4]. Approximately 70% of patients present with low diffusing capacity of carbon monoxide (DLCO), which is the most common abnormality observed on physiologic testing [4, 5]. Imaging of the chest with high resolution (HR) chest CT scanning may show characteristic small nodules and thin- or thick-walled cysts, they are located predominantly within the upper and middle lung zones [6]. PLCH is multiform in its presentation [5, 7, 8]. Despite the lung is dif-

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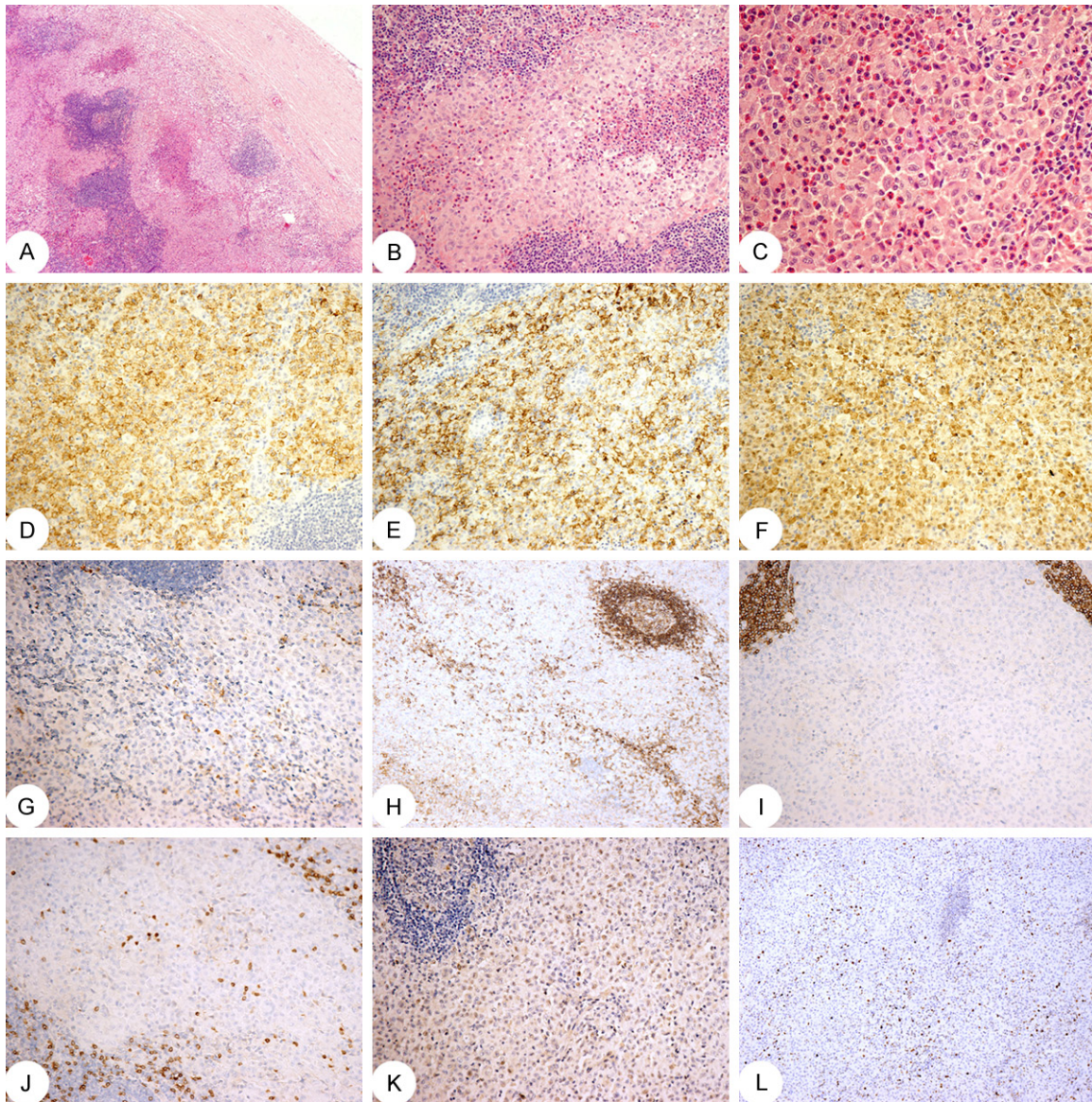


Figure 3. Histopathology and immunohistochemistry staining of left neck lymph node. The capsule of the cervical lymph node was thickened and residual a little normal lymphoid tissue. The interfollicular regions and medullary sinuses were expanded by infiltrating mononuclear and multinucleated histiocytes (LCH cells) admixed with small lymphocytes, eosinophils (A, H&E \times 50; B, H&E \times 200). Sinus involvement was clearly. Langerhans cells were characterized by large convoluted nuclei with cerebriform indentations of the nuclear envelope and longitudinal grooves. The nuclei contained small eosinophilic nucleoli and moderate amount of eosinophilic cytoplasm. Many eosinophils are also intermixed among Langerhans cells (C, H&E \times 400). Immunohistochemically, the histiocytoid cells were positive for langerin (D, \times 200), CD1a (E, \times 200), S-100 (F, \times 200), but negative for MPO (G, \times 200), LCA (H, \times 100) CD20 (I, \times 200), CD3 ϵ (J, \times 200) and CD30 (K, \times 200). The proliferation index was less than 5%, assessed by Ki-67 staining (L, \times 100).

fuse involvement, symptoms can be relatively absent or minor, and patients often initially attribute their symptoms to smoking. Lung biopsy is necessary for a definitive diagnosis, even though may not be required in instances that patients' image findings are highly characteristic [4]. Definitive recognition of LCH cells in

the inflammatory lesions is possible by the use of electron microscopy to identification of Birbeck granules or by immunohistochemical staining for Langerin (CD207) [9]. Immunohistochemical staining for CD1a and S-100 are positivity of Langerhans cells and they are very helpful in the recognition of LCH

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Table 1. Summary of PLCH Cases with extrapulmonary involvement limited to lymph nodes

Study	Year	Age (yr)/sex	Smoker	Clinically	Lymphadenopathy (no. positive/total cases)	Lymph node biopsy	Outcome
Masson	1978	17/F	-	Cough	1/1, mediastinal	No	Some response to steroids, developed diabetes insipidus
Friedmanl	1981	-	-	-	3/100, mediastinal	No	-
Brambilla	1990	33/M	Yes	Cough, fever, night sweats, weight loss	1/1, mediastinal 1/1, submandibular	Yes No	Progressive lung disease despite cytotoxic chemotherapy
Shaker	1995	17/F	No	Cough	1/1, mediastinal	Yes	Stable, no medication
Scuderi	2010	52/M	Yes	Cough, fever, night sweats,	1/1, mediastinal 1/1, cervical	No Yes	Spontaneous improvement
Current case	2012	22/M	Yes	Cough, dyspnea	1/1, mediastinal 1/1, cervical	No Yes	Spontaneous improvement

Table 2. Summary of PLCH cases coexistence with pulmonary tuberculosis

Study	Year	Age (yr)/sex	Smoker	Clinically	HRCT/lung biopsy	Treatment and outcome
Arai	2005	29/M	Yes	Dry cough, shortness of breath, weight loss, fatigue	Yes/Yes	Smoking cessation, Spontaneous improvement
Okutan	2006	21/M	Yes	Cough, dyspnea, night sweats	Yes/Yes	Smoking cessation, Antituberculosis treatment and rehabilitation
Dimitropoulos	2011	52/M	Yes	Dry cough, exertional dyspnea, fatigue	Yes/Yes	Smoking cessation, Antituberculosis treatment and rehabilitation
Current case	2012	22/M	Yes	Cough, dyspnea, chest distress	Yes/Yes	Smoking cessation, Antituberculosis treatment and rehabilitation

cells, however this alone could not establish the diagnosis of PLCH [4].

PLCH is usually a single-system disease. Most of patients do not have extrapulmonary involvement present [3]. If happened, bone (4%-15% of patients), pituitary gland (5%-15%) and skin (< 5%) are the most common extrapulmonary involvement sites. PLCH with extension limited to regional lymph nodes has been rarely described [3]. Langerhans cell histiocytosis can present with cervical lymphadenopathy; however, these cases usually have a multisystemic illness and involving several sites, or unifocal LCH limited to lymph nodes, in contrast to "isolated" PLCH. We have reviewed of the relevant literatures and found that only 7 cases of PLCH with regional lymphadenopathy have been reported (**Table 1**), of which only 2 cases had histological evidence of lymph node involvement by Langerhans histiocytosis [3].

PLCH and tuberculosis are rarely co-existed in the same patient. In a review of the literature, we identified that only 3 published PLCH cases who coexisted with pulmonary tuberculosis (**Table 2**) [2]. There are no studies regarding the prevalence of tuberculosis co-infection with PLCH, so it is not known whether PLCH predisposes to tuberculosis infection, or vice versa. These two entities are similar to each other in many respects [2]: (1) Clinically, fever, non-productive cough, exertional dyspnea, weight loss, fatigue and anorexia are the most common symptoms of PLCH, mimicking tuberculosis infection. (2) Similarities between these two diseases also appear on radiological examination. The HRCT findings of PLCH are related to the disease stage and the combination of nodules along with cysts predominantly in the upper and middle lung fields is a typical finding of PLCH. The most common early stage of PLCH is characterized by ill-defined nodules (1-5 mm) and distributed in a centrilobular pattern. With the progress of the disease, these solid nodules change into cavitated nodules and thick- and thin-walled cysts. For the tuberculosis, like miliary tuberculosis, HRCT reveals that the nodules are also usually less than 5 mm, and upper and middle lung predominance distribution has also been reported. (3) Restrictive dysfunction and reduced diffusion capacity could be presented in patients of PLCH and tuberculosis. (4) Immunohistochemically, in addition to LCH,

CD1a and S-100 had also been reported in other disease. Due to the similarities of PLCH and tuberculosis, those two entities are prone to be missed or misdiagnosed. Some scholars conclude that combine HRCT with the context of the appropriate clinical setting is sometimes used for diagnosis of PLCH. Langerin expression seems to be a highly sensitive and relatively specific marker of LCH. Immunohistochemical evaluation of Langerin expression may have utility in substantiating a diagnosis of LCH and separating this disorder from other non-Langerhans cell histiocytic proliferations [10].

PLCH co-exist with tuberculosis help explain the appearance of the pneumothorax, but it could not detect one of them specific effects. Spontaneous pneumothorax is a recognized feature of PLCH and likely results from destruction of lung parenchyma with associated cystic changes [9]. A history of pneumothorax is obtained in approximately 15% of patients with PLCH and seems to be more frequent in younger patients [4]. Some authors have recommended interventions to prevent recurrence of pneumothorax after the first episode spontaneous pneumothorax. Patients with tuberculosis are also likely predisposed to the development of pneumothorax based on destructive changes in the lung parenchyma [11].

Because of the tight association between cigarette smoking and PLCH, it is a critical component of the management for patients with PLCH to cease smoking [4]. The prognosis for most patients is relatively good, particularly if longitudinal lung function testing shows stability. Pharmacotherapy with immunosuppressive medication should be considered for all adult patients with severe diseases, or patients in whom progressive decline in lung function occurs [4, 12]. However, corticosteroid administration, which is a common medication in the treatment of PLCH, can markedly enhance the virulence of tuberculosis when no specific anti-tuberculous agent is being administered, and this can be perilous in undiagnosed tuberculosis [2]. So it is appropriated to take antituberculosis treatment alone for patients who have PLCH co-exist with tuberculosis. Pneumothorax known to occur in PLCH and its recurrence are better managed with tube thoracostomy and pleurodesis then chest tube drainage alone.

Patients with progressive disease may require lung transplantation [4].

A contribution of this case and review three of the five cases with clinical follow up in **Table 1** resolved spontaneously after smoking cessation constitute a novel addition that it is inappropriate to regard pulmonary/nodal LCH as multi-organ or disseminated disease, and the treatment methods are the same whether the PLCH patient with lymph node involvement or not.

In conclusion, this is the first case of PLCH with cervical lymph node involvement, pulmonary tuberculosis and right pneumothorax. We should accumulate much experience to recognize it and treat it with appropriate methods.

Disclosure of conflict of interest

None.

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