Case Report **Open Access**

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A confusing case report of pulmonary langerhans cell histiocytosis and literature review

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Abstract: Pulmonary Langerhans Cell Histiocytosis (PLCH) is a rare disease. From the insidious onset and nonspecific manifestations, it is difficult to diagnose PLCH. To help improve the diagnosis and therapy optionsof adult PLCH, we present this case report and literature review about a confusing case of PLCH. In this report, we present a 37-year-old male PLCH case that was negative for CD1a and S100 expression. Smoking cessation and use of prescribed Spiriva appeared to improve the patient's symptoms. To the best of our knowledge, this is the first reported case of PLCH in which improved symptoms were seen with the use of Spiriva alone.The mechanism is not clear, but potentially has some relationship with dilating the airway, decreasing the mucous hypersecretion and promoting anti-inflammatory pathways. From this patient;s case, we may be able to find more cases to then find other first line therapies for PLCH patients.

Keywords: Pulmonary Langerhans cell histiocytosis, SR-ILD, Smoking-Related Interstial Lung Disease, Spiriva, Tiotropium, Interstitial lung disease

1 Introduction

Cigarette smoking is not only the major cause of chronic obstructive pulmonary disease (COPD) and lung cancer, but also implicated in Smoking-Related Interstitial Lung Diseases (SR-ILD) [1, 2], such as pulmonary Langerhans cell histiocytosis (PLCH), respiratory bronchiolitis interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP) and idiopathic pulmonary fibrosis (IPF). Langerhans cell histiocytosis (LCH) is a rare histiocytic disease and PLCH is likely to be underdiagnosed in the general population. This disease can be diagnosed in any group, but it most commonly occurs in children of 1 to 3 years old. Here, we presented a case of PLCH with recurrent pneumothorax and diffuse cyst on High Resolution Computed Tomography (HRCT).

2 Case report

On July 8th, 2014, a 37-year-old male was admitted to our departmentwith persistent cough for two years, and chest distress and fatigue for more than one year. He felt progressive dyspnea after activity, but no wheezing, joint changes, chest pain or rash in the previous 2 years. Confusingly, he had developed left pneumothorax twice (in May 2013 and June 2014) without any injury, and recovered after thoracic drainage. The doctor arranged an X-ray but not thoracic Computed Tomography (CT) for him when the first pneumothorax occurred. After the first pneumothorax episode, the patient gradually felt the onset of chest distress, dyspnea and fatigue. Unfortunately, the patient was not diagnosed with disease until after the second pneumothorax episode on June 9th 2014. According to the thoracic CT done in June 2014, there are only find bilateral pulmonary diffuse changes with panlobular emphysema. He was diagnosed with pulmonary emphysema. The patient's local doctors suggested the patient stop smoking and prescribed montelukast. Half of a month later, the patient continued to have chest distress and dyspnea, especially post-activity. The patient came to the Depart-

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ment of Respiratory Medicine at the First Affiliated Hospital of Zhejiang for help. He had no previous history of Hepatitis, tuberculosis, diabetes or hypertension. He had previously smoked for 10 years, and had a smoking index of 200 (smoking cessation less than 2 months). He works as a clerk, denied alcohol addiction, and has no special gas and toxic substance exposure history. His wife and his son are healthy.

On examination, his temperature was 36.9°C, his blood pressure was 121/82 mmHg, his pulse 70 beats per minute, his respiratory rate was 19 beats per minute and his oxygen saturation was 97% without oxygen inhalation. There was no cyanosis, no distension of jugular vein and no clubbing. The trachea position was normal, and there was normal breath movement and sound with no crackle. There was no lower extremity edema. The remainder of the examination was normal. Blood gas analysis showed PaO2 76.7 mmHg, PaCO2 44.2 mmHg, SPO2 95.7%, HCO3- 24.9 mmol/L, and BE -0.2 mmol/L. Liver and renal function tests were normal, as were blood levels of glucose, calcium, total protein, albumin and globulin. White cell count, hemoglobin and platelet count were normal. Anti-Nuclear Antibody (ANA) and Anti-Neutrophil Cytoplasmic Antibodies (ANCA) were normal. Thyroid Function, erythrocyte sedimentation rate (ESR) and immunoglobulin were normal. The thoracic HRCT done on 08-July-2015 showed a bilateral diffuse cyst, especially in upper lobe and middle lobe (Figure 1). Magnetic Resonance Imaging (MRI) of the hypophysis was normal. Cardiac and abdominal ultrasounds were normal. Lung function (assessed on 08-July-2014) was FVC 1.22L (28.1% pred), FEV1 0.48L (13.8% pred), FVC/FEV1 (39.8% pred), TCL 5.60L (89.4% pred), RV 3.26L (186.3% pred), RV/TCL 208% pred, and DLCO (30.5%pred). The results of the lung function tests showed severe obstruction of mixed ventilation dysfunction and severe diffusion dysfunction.

After admittance, our initial diagnosis was Bilateral Pulmonary Diffuse Change, potentially with PLCH. To diagnose the patient definitively, we conducted bronchoscopy and video-assisted thoracicscopic surgery. The bronchoscopy did not find neoplasms or the other abnormal lesions except bilateral mucus congestion. During the bronchoscopy, we collected bronchoalveolar lavage (BAL) and analyzed the cell differential. The Left lingual BAL showed: Macrophage 23%, Neutrophil 57%, Lymphocyte 11% and Eosinophil's 9%. The Right Middle Lobe (RML) BAL showed: Macrophage 84%, Neutrophil 5%, Lymphocyte 10% and Eosinophil's 1%. A diagnosis could not be made from the BAL results due to a lack of CD1a expression. The patient was consented for Video-Assisted Thoracoscopic Surgery (VATS) for a biopsy to assist in making a diagnosis.

Histopathology of the biopsy showed inflammatory cell infiltration in the left upper lobe and fiber-vessel proliferation (Figure 2). The specimen pathology showed a section of lung tissue with a honeycomb appearance. Microscopic pathology showed alveolar atrophy, island-like fibroplasia and inflammatory cell infiltration. The immunohistochemistry (IHC) results were P53 (-), Ki-67 (-), Des (-), CD34 (+), S-100 (-), CD1a(-), TTF-1 (+), SMA (+), CK7 (+), CD34 (-), CD68 (-), CD163 (-), CD31 (+), CD14 (+) and Masson (+). The final pathology report diagnosed smoking-related interstitial lung disease, but could not distinguish the definite kind. After the biopsy, we consulted with Professor FanQing Meng, a pathologist at Nanjing Drum Tower Hospital. Professor Meng agreed with our pathologist's assessment.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by

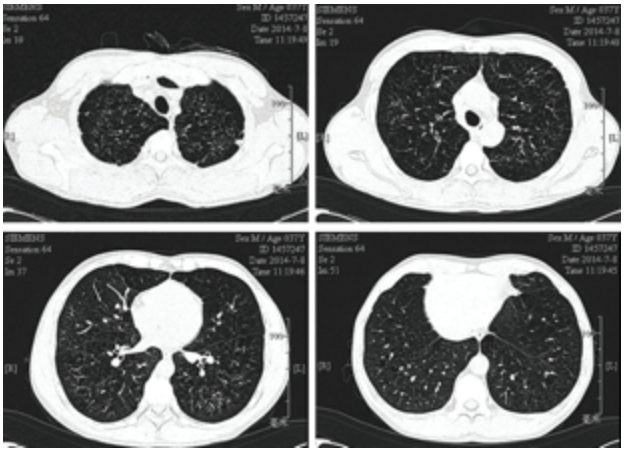

Figure 1: Thoracic HRCT showed a bilateral diffuse cyst, especially in upper lobe and middle lobe.

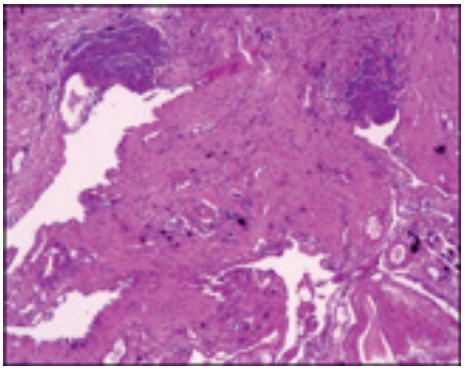

Figure 2: Histopathology of the biopsy showed inflammatory cell infiltration in the left upper lobe and fiber-vessel proliferation.

the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Follow up

After discharge from hospital, the patient stopped smoking and only use Spiriva when needed to dilate the bronchia. Two months later, the patient returned to clinic to have his lung function evaluated and a thoracic HRCT. He felt better than he had the previous July; he could walk a little faster than before and climb 2 floors of stairs. His lung function showed improvement (Table 1). We prescribed Spiriva and advised him to use unceasingly.

We followed up the patient by phone 6 months after his discharge from hospital. He reported that he took Spiriva everyday and felt better and back to normal. The patient refused to return to the First Affiliated Hospital of Zhejiang as it is a far distance from his home. After 1 year, we called him again. He had already returned to work with a reduced work load. He continued to take Spiriva. He again refused to return to the hospital for further follow up. We suggested him to continue not smoking and taking Spiriva. He accepted.

Two months after the patient was discharged from the hospital, we consulted Professor Ulrich Costabel, the world-famous expert in ILD, about the case and diagnosis. Prof. Costabel diagnosed PLCH from the patient's recurrent pneumothorax and the other clinical manifestation, HRCT, follow-up presentation after smoking cessation and using Spiriva.

4 Discussion

The most striking characteristic on HRCT of this patient was bilateral diffuse cystic manifestation. Cystic lung disease usually includes chronic obstructive pulmonary disease (COPD), lymphangi-oleiomyomatosis (LAM), Birt–Hogg–Dubé (BHD) and PLCH. Of the above diseases, we diagnosed the patient with PLCH. PLCH is an uncommon and multi-systemic disease. It is usually diagnosed by the age, gender, history of smoking, insidious onset and non-specificity of symptoms, characteristics on HRCT, and the presence of intracellular Birbeck granules and surface expression of CD1a or S100 in histology samples. However, not all PLCH patients can be diagnosed by CD1a or S100 expression or by pathology. Some cases must be diagnosed on the basis of clinical-radiological data. But if the patient has negative pathology and positive clinical-radiological, can we diagnose the patient with PLCH?

Elia D et al [3], showed that the average patient's age was 40±14 years old with more female than male (22/40 female). In fact, PLCH was initially reported as more common in men, but due to increased smoking rates in women, there is no longer a gender difference. It is generally accepted that cigarette smoking is not only the major cause for COPD and lung cancer, but also for smoking-related interstitial lung disease [4]. This includes PLCH, respiratory bronchiolitis interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP) and idiopathic pulmonary fibrosis (IPF). PLCH has a close relationship with smoking, both in current smokers and ex-smokers. Complete remission of PLCH may occur after smoking cessation. Clinical manifestation of PLCH generally does not have presentation of specific symptoms. Pneumothorax, especially spontaneous pneumothorax in a young patient, is usually the first manifestation. Dry cough and shortness of breath are the most common chronic symptoms. Approximately 10% of patients with primary spontaneous pneumothorax report a positive family history of pneumothorax [5]. The primary symptoms of PLCH may not obvious: no clubbing of the fingers, no crackling or Velcro sounds in the lungs. Travis et al [6] found that constitutional symptoms of fever, night sweats and anorexia were manifested in one-third of patients with PLCH. This clinical presentation must be distinguished from infectious and malignant etiologies. Follow up of PLCH patients is critical for two reasons: 1) the disease must be evaluated and 2) PLCH patients are at greater risk for developing malignancies such as lymphoma, Hodgkin's disease and multiple myeloma [7]. Some PLCH patients

Table 1: Patient's lung function at 2 different time points

	IC	FVC	FEV1	FEV1/FVC	TLC	RV	DLCO
08/07/2014	1.00(31.0%)	1.22(28.1%)	0.48(13.8%)	39.80%	5.60(89.4%)	3.26(186.3%)	3.09(30.5%)
02/09/2014	2.21(70.6%)	2.36(54.3%)	0.79(21.6%)	33.38%	5.08(81.8%)	2.18(124.5%)	3.47(34.2%)

have extrapulmonary presentations, in the bone (4%-15% of patients), pituitary gland (5%-15%) and skin (< 5%). Ten to fifteen percent of patients with PLCH have normal lung function. Most PLCH patients present with low TLC, high RV/TLC and low DLCO. Approximately 70% of PLCH patients manifest low diffusing capacity of carbon monoxide (DLCO) [8]. In PLCH, the degree of air flow obstruction is the best predictor of adverse outcome.

PLCH is different from lymphangi-oleiomyomatosis (LAM) which can be diagnosed by characteristics on HRCT imaging. The most common presentations of PLCH are small nodules and wall cysts of various sizes, lesions which demonstrate upper and middle lobe predominance with sparing of the costophrenic angles [9]. During the late stages, the lesion can diffuse the whole lung. With disease progression, the nodules diminish or disappear and the cysts augment. Rarely does the image presentation include nodules with cavity, pericystic opacification and ground glass opacity (GGO), lymphadenovarix in hilar and mediastinum, and pleural effusion. Some patients with typical history and characteristic HRCT presentation can be diagnosed clinically.

Bronchoalveolar lavage (BAL) has some value in diagnosing PLCH [10]. Langerhan's cells in BAL fluid may be recognized by their reactivity with anti-S100 protein antibodies or be CD1 positive, as the detection of >3% CD1a-postive Langerhans cells. BAL is also useful to exclude the other inflammatory or infectious lung diseases. In addition, trans- bronchial biopsy (TBB) is not recommended due to the low sensitivity. An open lung biopsy is more likely to be definitive if it is non-diagnostic followed by HRCT 3 months later. The pathologic hallmark of PLCH is the accumulaton of Langerhans and other inflammatory cells in the small airways, resulting in the formation of nodular inflammation [8]. Tissue reactivity with the monoclonal antibody CD1 (OKT-6) can distinguish Langerhan's cells from the other histiocytes and can be a useful diagnostic adjunct.

The key to the diagnosis of PLCH relies on the patient's age, smoking history, evidence of recurrent pneumothorax and evidence of nodules and cysts with an upper lobe distribution with sparing of the costophrenci sulci. Importantly if the disease regresses upon cessation of smoking, the diagnosis is confirmed [11]. The patient presented here did not have recurrent pneumothorax after smoking cessation and use of Spiriva. His symptoms of dry cough, chest distress, fatigue and dyspnea after activity diminished as well.

But why did the PLCH patient presented here not have the characteristic presentations not only in BAL, but also in his lung biopsy pathology? One hand, we can not detect the CD1a antibodies in my hospital to miss the positive diagnosis probably. Five total specimens were taken from the upper, middle and lower lobe of the lung. Prof. Costabel proposed that the locations of biopsies were not consistent enough with the lesions seen on HRCT. Therefore, from the pathologic results of lung biopsy, we can only conclude the smoking-related interstial lung disease. With other classic characteristics, Prof. Costable diagnosed this patient as PLCH.

As for therapy, different patients have different outcomes. The earlier a diagnosis is made and smoking stopped, the more benefit patients have. Most subjects who continue to smoke demonstrate gradual progression of disease. Corticosteroids have historically been used in progressive patients, but the efficacy of this treatment for PLCH has not been proven to be effective. Cytotoxic therapy has also not been shown to be effective in PLCH patients. Recently, cladribine (2-chlorodeoxyadenosine) is a cytotoxic agent which has been reported to have some efficacy in patients with severe PLCH [12]. Spiriva has not been reported previously to be effective in patients with PLCH. Spiriva is known to be an effective therapy in COPD patients, and is approved to prescribe to asthma patients [13]. In the case of the patient presented here, it smoking cessation was suggested and Spiriva prescribed to increase lung function and improve quality of life by dilating the bronchia and promote anti-inflammatory mechanisms [13, 14]. The results of the patient's lung function tests after smoking cessation and Spiriva use show improvement, and have fewer side-effects.

PLCH is an uncommon disease, and the therapy is not well described. From the patient described here, we realize that we must learn how to gain more information from the clinical manifestation of the disease to improve diagnosis. Potentially, Spiriva could be used as a therapeutic option for PLCH patients to improve symptoms and quality of life.

Conflict of interests: No conflict of interests declared by authors or author's institution.

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