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Secondary pulmonary hypertension due to pulmonary Langerhans cell histiocytosis accompanied with panhypopituitarism

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Abstract

A 65-year-old man presented to our hospital with complaint of acute dyspnoea. He smoked 30 cigarettes per day from age 20 to 52 years. Immunocytochemical findings revealed 6.3% of positive CD1a cells in the cell fraction of bronchoalveolar lavage, thus suggesting a diagnosis of pulmonary Langerhans cell histiocytosis (PLCH), after nine years since the first suspicion of PLCH. Furthermore, he was diagnosed with secondary pulmonary hypertension (PH) caused by progressed PLCH by right heart catheterization. At 59 years of age, he was diagnosed with panhypopituitarism, and persistent hormone replacement therapy was subsequently started by an endocrinologist. After the initiation of oxygen therapy and treatment with a combination of sildenafil and warfarin, an estimated pulmonary artery systolic pressure reduced 97.9 to 64.0 mmHg. We believed this is a rare case of PLCH with irreversible central nervous system (CNS) disorder in whom severe PH developed due to a long-term burden of PLCH in a middle-aged male.

Introduction

Langerhans cells belong to a family of highly specialized antigen-presenting dendritic cells, and are usually located in multiple organ systems including the central nervous system (CNS) [1–3].

Langerhans cell histiocytosis (LCH) is a rare disease of unknown aetiology that is characterized by the infiltration of dendritic cells into involved tissues that share phenotypic similarities with Langerhans cells. LCH is often organized into granulomas [4].

Pulmonary LCH (PLCH) predominantly affects young adult smokers between 20 and 40 years of age [5]. In general, PLCH is an interstitial lung disease; however, occasionally, clinical manifestations may include multisystemic dysfunctions like other types of LCH [6].

Here, we report a rare case of secondary severe pulmonary hypertension (PH) due to PLCH with panhypopituitarism in a middle-aged male.

Case Report

A 56-year-old man presented with a persistent dry cough for a year and was suggested to have PLCH according to chest computed tomography (CT) performed at a regional hospital (Fig. 1). His smoking history included 30 cigarettes per day for 32 years (from 20 to 52 years old), and he had quit smoking four years ago. Although fibreoptic bronchoscopy was performed, he was not diagnosed with PLCH (Table 1). After that, he refused a pathological examination with video-assisted thoracoscopy and discontinued his visit to the hospital. At 58 years of age, he was suspected to have chronic obstructive pulmonary disease at a primary care clinic, and a combination of an inhaled corticosteroid and bronchodilators (salmeterol, fluticasone, and tiotropium) was started at that clinic. The following year at 59 years of age, he was diagnosed with hyponatremia due to secondary hypoadrenocorticism caused by panhypopituitarism, and treatment with a combination

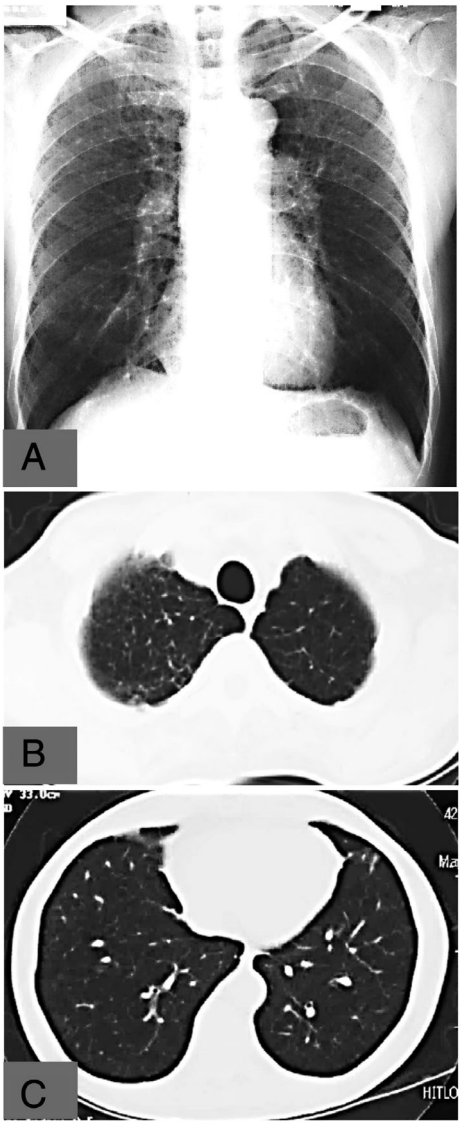

Figure 1. Imaging findings at the age of 56 years. (A) Chest X-ray image shows mild cardiomegaly with bilateral enlargement of the pulmonary arteries. (B, C) Chest computed tomography shows centrilobular small nodular shadows and diffuse pulmonary cysts.

of hydrocortisone and levothyroxine was initiated at the Department of Endocrinology in our hospital. Brain magnetic resonance imaging (MRI) suggested an anterior pituitary adenoma, but surgery was not indicated. Posterior pituitary functions were not impaired.

At 65 years of age, the patient was admitted to the Department of Respiratory Medicine of the hospital for an emergency complaint of acute exacerbation of dyspnoea. On hospital admission, his temperature was 36.8°C, blood pressure was 119/79 mmHg, heart rate was 101 beats/min, respiratory rate was 24 breaths/min, and peripheral capillary oxygen saturation (SpO_2) was 94% with 2 L/min supplemental oxygen via a nasal cannula. Physical examination confirmed normal sized superficial lymph nodes and increased jugular venous pressure. On auscultation, breath sounds were normal, and the pulmonary component of the second heart sound (IIp) was accentuated. Laboratory findings revealed a brain natriuretic peptide level of 484.8 pg/mL (Table 2). Arterial blood gas testing showed an arterial oxygen pressure of 68.6 mmHg on 2 L/min oxygen administered via a nasal cannula (Table 2). Chest X-rays and CT images showed progression of cardiomegaly, bilateral enlargement of the pulmonary arteries, and interstitial changes compared with those at 56 years of age (Figs. 1, 2). Immunocytochemical findings of differentials of cells in bronchoalveolar lavage fluid obtained with fibreoptic bronchoscopy revealed 6.3% of positive CD1a cells (Table 1), suggesting a diagnosis of PLCH. Pulmonary function tests revealed severe impairment of airflow and diffusing capacity (Table 3). On admission, echocardiography findings showed an estimated pulmonary artery systolic pressure (ePASP) of 97.9 mmHg and right heart overload. After the initiation of oxygen therapy and bed rest for four weeks, ePASP as seen with echocardiography was reduced to 54.0 mmHg, and then right heart catheterization was performed. Systolic, mean, and diastolic pressures of the pulmonary artery were 58, 40, and 27 mmHg, respectively. The cardiac index was 1.73 L/min/m^2, pulmonary capillary wedge pressure was 13 mmHg, and pulmonary vascular resistance was 10.5 Wood units. After the catheterization test, anticoagulation therapy with warfarin was started. Finally, he was diagnosed with severe secondary PH caused by progressed PLCH. Four months later, ePASP was elevated to 76.2 mmHg on echocardiography, and dyspnoea on exertion worsened. Oral sildenafil was then prescribed at a dose of 20 mg twice daily and was subsequently increased to 20 mg three times a day. After the initiation of phosphodiesterase inhibitor-5 inhibitor, dyspnoea was improved, and ePASP decreased to 64.0 mmHg.

Table 1. Bronchoalveolar lavage.

	56 years of age	65 years of age
Total cell count	5.0×10^5	1.4×10^5
Macrophages (%)	65	84
Neutrophils (%)	3	4
Lymphocytes (%)	10	5
Eosinophils (%)	19	1
CD1a (%)	2.	6.3
CD4/8 ratio		2.31

Table 2. Results of laboratory tests.

Haematology	**Biochemistry**	**Arterial blood gas**
WBC 14,040/μL	CRP 2.53 mg/dL	O_2 2 L/min (via nasal cannula)
RBC 568×10^4/μL	Alb 3.9 g/dL	pH 7.430
Hb 17.9 g/dL	AST 27 IU/L	PaO_2 68.6 mmHg
Hct 53.0%	ALT 20 IU/L	$PaCO_2$ 33.7 mmHg
Plt 23.6×10^4/μL	LDH 262 IU/L	HCO_3^- 21.9 mmol/L
	BUN 21 mg/dL	
Coagulation	Cr 1.60 mg/dL	
PT 14.0 sec	eGFR 35.0	
PT-INR 1.09	Na 142 mEq/L	
APTT 39.4 sec	Cl 103 mEq/L	
D-dimer 0.95 μg/mL	K 4.1 mEq/L	
	BNP 484.8 pg/mL	
	KL-6180 IU/mL	
	Procalcitonin 0.18 ng/mL	
	β-D glucan <6.0 pg/mL	
	Lysozyme 10.9 μg/mL	
	ACE 15.7 IU/L	

ACE, angiotensin-converting enzyme; Alb, Albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; Hct, haematocrit; K, potassium; KL-6, sialylated carbohydrate antigen; LDH, lactate dehydrogenase; Na, sodium; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; Plt, platelets; PT, prothrombin time; PT-INR, PT-international normalized ratio; RBC, red blood cell; WBC, white blood cell.

Discussion

In this case report, severe PH had developed in a middle-aged male, probably due to a long-term burden of PLCH with panhypopituitarism. Nine years after the suggestion of PLCH according to chest CT findings, immunocytochemical findings of the cell fraction obtained from bronchoalveolar lavage by fibreoptic bronchoscopy revealed 6.3% of positive CD1a cells.

Langerhans cells, which belong to a family of highly specialized antigen-presenting and migratory cells called dendritic cells, are usually located in the lung, bone, skin, endocrine system, CNS, liver, spleen, lymph nodes, and marrow. Histiocytes are intensely labelled for S-100 and CD1a and form Birberck granules, which are visible with electron microscopy [2,3,7].

The term LCH was first described in 1868 by Paul Langerhans [8]. Because the prevalence and incidence of LCH is low, our current knowledge of its clinical course is mostly based on retrospective data gathered over many years. All the various forms of LCH including PLCH in adults were formerly described as histiocytosis X [9,10], which is a rare disease of unknown aetiology that is characterized by an uncontrolled clonal proliferation of Langerhans cells; however, recent evidence suggests that adult PLCH may represent a reactive histiocytic disorder characterized by polyclonal expansion of Langerhans cells in the lung [11]. However, the cells are different from normal Langerhans cells in that they do not exhibit dendritic morphology [12]. In fact, the cell of origin of LCH is not the Langerhans cell but the myeloid dendritic cell that expresses CD1a and CD207 [13]. The differential clinical classification of LCH is considered to include three stages: first, a single-system disease with good prognosis; second, a multi-system disease; and finally, multi-system disease with organ dysfunction and the worst prognosis [14,15]. In adults, LCH most often manifests as a multi-system disorder with particular involvement (5–50% of cases) of the pituitary gland in the hypothalamic–pituitary axis in the CNS [6,16,17]. More specifically, adult intracranial LCH cases involve infiltration of the posterior pituitary. The most common indicator that LCH has become intracranial is central diabetes insipidus (DI) [17–19], which occurs in about 15% of patients with PLCH [20]. These findings suggest that DI is the most common endocrine alteration in PLCH. Furthermore, endocrine investigations may demonstrate that alteration in the function of the anterior pituitary gland may occur as a manifestation of PLCH. As a consequence, some patients may have panhypopituitarism [20]. In several studies, pituitary dysfunction, although not invariably associated with abnormal hypothalamic–pituitary region imaging, is often encountered in patients with multi-system disease who have DI and

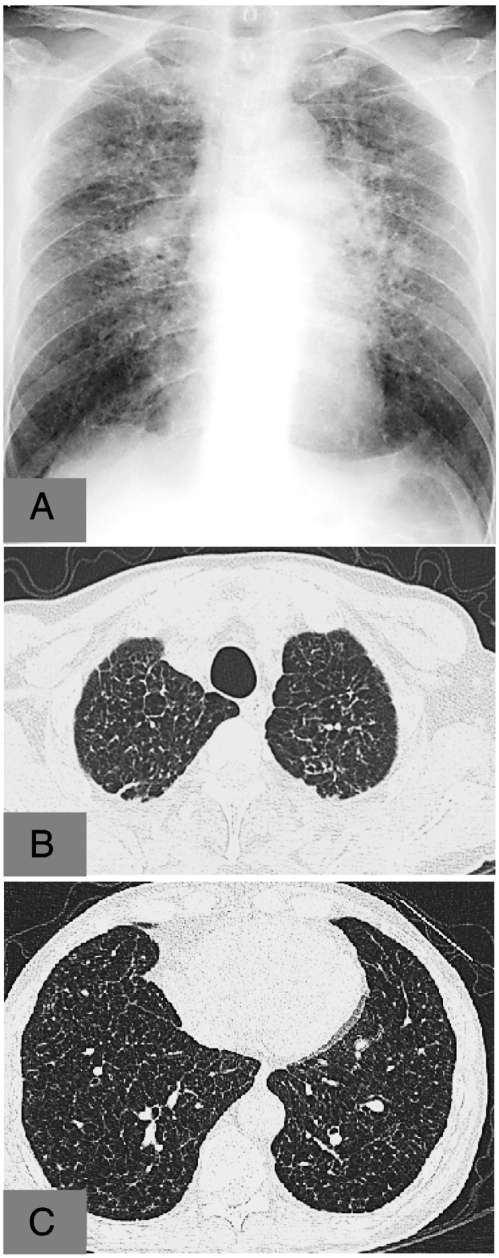

Figure 2. Imaging findings at the age of 65 years. (A) Chest X-ray image shows severe cardiomegaly with bilateral enlargement of the pulmonary arteries. (B, C) Chest computed tomography shows progressive centrilobular small nodular shadows, multiple diffuse pulmonary cysts, and interstitial changes.

Table 3. Pulmonary function tests.

	65 years of age
VC, L (%)	3.03 (89.8%)
FVC, L (%)	2.85 (84.5%)
FEV_1, L (%)	1.25 (49.0%)
FEV_1/FVC (%)	43.9
$\%DL_{CO}$	39.6
$\%DL_{CO}/V_A$	33.4

DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; V_A, minute alveolar ventilation; VC, vital capacity.

hypothalamic–pituitary pathology on MRI [16,21,22]. In Marchand et al.'s study [23], a two-year follow-up was performed in 14 LCH patients with an enlarged pituitary stalk, and MRI showed some increases in the stalk volume, some decreases, and some stable volumes. Another study described a five-year follow-up of an LCH patient whose hypothalamic lesion gradually regressed after persistent hormone replacement therapy [24]. In our case, brain MRI confirmed a pituitary adenoma without impaired posterior pituitary functions; however, he needed hormone replacement therapy. Physicians should consider long-term effects of the lesions in patients with progressive multiple PLCH. The structural changes in the hypothalamic–pituitary axis often herald involvement of other parts of the CNS and its attendant neurological sequelae, which may reflect the irreversible and permanent nature of this infiltrative disease [6]. Fortunately, our patient's visual ability was not affected by the anterior pituitary adenoma, which was located close to the optic chiasma.

PLCH is diagnosed in only approximately 1% of all autopsies of patients with diffuse lung disease, and predominantly affects young adult males between 20 and 40 years of age, although this association is more prevalent with other interstitial lung diseases [5]. This disease mainly affects young adult smokers with an equal gender distribution. PLCH is an interstitial lung disease in which clinical manifestations may involve a single organ or be multi-systemic. Currently, little is known about the pathogenesis of PLCH, although this condition may represent a reactive polyclonal process that is induced by pathogens in cigarette smoke [25]. Therefore, smoking may play a strong role in the aetiology of PLCH in adults. Smoking cessation is considered the cornerstone of treatment in adult smokers with PLCH. Early diagnosis and smoking cessation for PLCH are associated with a good prognosis, and in many cases, may make drug treatment unnecessary. However, patients with advanced PLCH should be treated with immunosuppressive agents. Multi-systemic PLCH is a rare disease, and its diagnosis is often missed or delayed. PLCH should be a diagnostic consideration, especially in young adults with a history of smoking and typical radiological presentation of cystic lung disease.

PH is frequent in patients with advanced PLCH [26,27] and is related to an intrinsic pulmonary vascular disease in

which the pulmonary circulation is involved independently from small airways and lung parenchymal injury [5]. The mechanisms involved in PLCH-associated PH in the World Health Organization (WHO)-Group 5 may be a combination of those that occur in pulmonary arterial hypertension in WHO-Group 1 and those that occur in PH associated with interstitial lung disease in WHO-Group 3. PH appears to be more frequent and more severe in PLCH than in other pulmonary diseases, such as idiopathic pulmonary fibrosis, due to a pulmonary vascular disease involving arterioles and venules leading to a variable degree of luminal obstruction, vascular remodelling, and inflammation.

Although the prognosis of patients with PLCH-associated PH is still not well known, Ghofrani et al. [28] reported that oral sildenafil provides a modest improvement in the mean pulmonary arterial pressure and pulmonary vascular resistance that does not increase ventilation–perfusion mismatch and does not worsen gas exchange in patients with severe lung fibrosis associated with PH. On the basis of these reports, oral sildenafil may be effective in PH associated with diseases affecting the lung interstitium, including PLCH-associated PH. Our patient was finally diagnosed with severe secondary PH caused by progressive PLCH. Later, anticoagulation therapy with warfarin and oral sildenafil was started. Follow-up echocardiography findings showed improvement of ePASP. At present, treatment for PLCH-associated PH with prednisolone and vinblastine, or 6-mercaptopurine, is considered for patients with major pulmonary or extra-pulmonary involvement [20]. However, the effects of treatment are still controversial. Furthermore, no studies have reported the efficacy of drugs for the treatment of PLCH-associated PH, similar to those for PH associated with lung disease. Therefore, controlled clinical trials of pulmonary artery vasodilator therapy for this condition are still needed. The use of pulmonary artery vasodilators for PLCH-associated PH should be considered individually in each case.

This report presented a rare case of progressive PLCH with an irreversible CNS disorder that ultimately led to severe PH. PLCH generally regresses spontaneously or after smoking cessation. Physicians who care for adult patients with progressive PLCH with multiple lesions need to implement investigations to identify and treat potential systemic disorders including pituitary dysfunctions and PH.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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