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## Autopsy Findings in A Case of Pulmonary Langerhans Cell Histiocytosis-Associated Pulmonary Hypertension

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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ABCDEF G 1,3  
**Daisuke Taniyama**  
**Hirofumi Kamata**  
**Keisuke Miyamoto**  
**Shuko Mashimo**  
**Fumio Sakamaki**

1 Department of Respiriology, Tokyo Saiseikai Central Hospital, Tokyo, Japan  
2 Department of General Internal Medicine, Tokyo Saiseikai Central Hospital, Tokyo, Japan  
3 Department of Respiriology, Tokai University Hachioji Hospital, Tokyo, Japan

**Corresponding Author:** Daisuke Taniyama, e-mail: [daisuketaniyama@gmail.com](mailto:daisuketaniyama@gmail.com)  
**Conflict of interest:** None declared

**Patient:** Female, 35  
**Final Diagnosis:** Pulmonary Langerhans cell histiocytosis associated with secondary pulmonary hypertension  
**Symptoms:** Dyspnea  
**Medication:** —  
**Clinical Procedure:** Oxygen • sildenafil • bosentan • prostanoids  
**Specialty:** Pulmonology

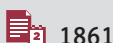
**Objective:** Rare disease  
**Background:** Pulmonary Langerhans cell histiocytosis (PLCH) can be associated with pulmonary hypertension, although this association is more prevalent with other interstitial lung diseases. However, the diagnosis and effective treatment strategies for PLCH-associated pulmonary hypertension remain controversial.

**Case Report:** A 27-year-old woman, who was an ex-smoker, was diagnosed with multiple diffuse pulmonary cysts. At 35 years-of-age, she developed neurogenic pituitary diabetes insipidus and was diagnosed with PLCH-associated pulmonary hypertension. Despite treatment, including sildenafil, bosentan, and prostanoids, she died at 39 years-of-age. At the autopsy examination, the heart showed right ventricular dilation and hypertrophy. Histopathological examination of the lungs showed severe hypertrophy of the media of the small pulmonary arteries. The diagnosis of PLCH was confirmed by S100-positive immunohistochemical staining.

**Conclusions:** The autopsy findings of a case of PLCH with severe pulmonary hypertension are reported. The mechanism of pulmonary hypertension in this disease may involve a combination of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) and Group 3 pulmonary hypertension secondary to lung disease, even though PLCH is currently classified as Group 5. The use of pulmonary artery vasodilators, such as sildenafil, may be effective for the treatment of PLCH-associated pulmonary hypertension, but treatment should be considered individually for each patient. Controlled clinical trials of pulmonary artery vasodilator therapy for this condition are needed.

**MeSH Keywords:** Autopsy • Persistent Fetal Circulation Syndrome • S100 Proteins

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## Background

Pulmonary Langerhans cell histiocytosis (PLCH) is diagnosed in approximately 1% of all autopsies of patients with diffuse lung disease, predominantly affects young adult males between 20–40 years-of-age, and is occasionally associated with pulmonary arterial hypertension, although this association is more prevalent with other interstitial lung diseases (ILDs) [1].

This report describes the autopsy findings in a case of severe pulmonary hypertension associated with PLCH. This report differs from previous reports, not only in confirming the diagnosis by detailed autopsy examination but also in describing the use of pulmonary arterial vasodilator therapy to treat PLCH-associated pulmonary hypertension.

## Case Report

A 27-year-old woman with a seven pack-year history of tobacco smoking presented with multiple bilateral diffuse pulmonary cysts and interstitial changes in the lower lobes on pulmonary computed tomography (CT). She was assessed and diagnosed with multiple diffuse pulmonary cysts and interstitial lung changes, and smoking cessation was advised by the attending physician. She was then followed-up by chest physicians as a case of interstitial lung disease (ILD). Her follow-up included examination by lung imaging several times per year.

Due to a history of excess fluid intake and polyuria from 30 years-of-age, the results of endocrinological investigations confirmed a diagnosis of neurogenic pituitary diabetes insipidus, diagnosed at 35 years-of-age. A diagnosis of pulmonary Langerhans cell histiocytosis (PLCH) was suspected based on broncho-alveolar lavage (BAL) fluid examination, which showed a cell population of >95% macrophages, and few neutrophils, lymphocytes, and eosinophils; the macrophages were S100-positive on immunohistochemistry. At the same time, right heart catheterization was performed because she developed dyspnea, and right heart overload was confirmed by ultrasound echocardiography. The results of right heart catheterization showed a mean pulmonary arterial pressure of 40 mmHg, mean pulmonary arterial wedge pressure of 8 mmHg, mean right atrial pressure of 2 mmHg, and cardiac output of 3.8 L/min. She was diagnosed with pulmonary hypertension and was subsequently prescribed supplemental oxygen therapy and furosemide. At 38 years-of-age, treatment with oral sildenafil at a dose of 20 mg, three times daily (20 mg tds) was started, after which the patient was able to remain at home until her most recent hospital admission.

The patient's most recent admission, at 39 years-of-age, to the authors' hospital was due to increased dyspnea. On follow-up lung imaging, the progression of her interstitial lung changes, between 38–39 years-of-age, had been minimal. On hospital admission, her temperature was 36.5°C, her blood pressure was 104/60 mmHg, her heart rate was 120 beats/min,

**Table 1.** Results of laboratory tests.

Hematology	Biochemistry	Arterial blood gas
WBC 6900/ $\mu$ L	TP 6.9 g/dL	(O2 8 L/min.)
RBC 577 $\times$ 10 <sup>4</sup> / $\mu$ L	Alb 3.6 g/dL	pH 7.433
Hb 16.5 g/dL	Na 137 mEq/L	PaCO <sub>2</sub> 33.9 Torr
Hct 50.5 %	K 4.9 mEq/L	PaO <sub>2</sub> 52.7 Torr
Plt 21.0 $\times$ 10 <sup>4</sup> / $\mu$ L	Cl 102 mEq/L	HCO <sub>3</sub> <sup>-</sup> 22.6 mmol/L
	Ca 8.6 mg/dL	
<b>Coagulation</b>	BUN 23 mg/dL	
PT 14.5 sec	Cre 0.6 mg/dL	
INR 1.29	UA 10.5 mg/dL	
APTT 36.1 sec	T-Bil 2.2 mg/dL	
	AST 30 IU/L	
	ALT 21 IU/L	
	ALP 580 IU/L	
	LDH 321 IU/L	
	$\gamma$ -GTP 533 IU/L	
	CRP 0.43 mg/dL	
	BNP 569 pg/mL	



**Figure 1.** Chest X-ray shows cardiomegaly, bilateral enlargement of the pulmonary arteries, and diffuse interstitial lung shadowing

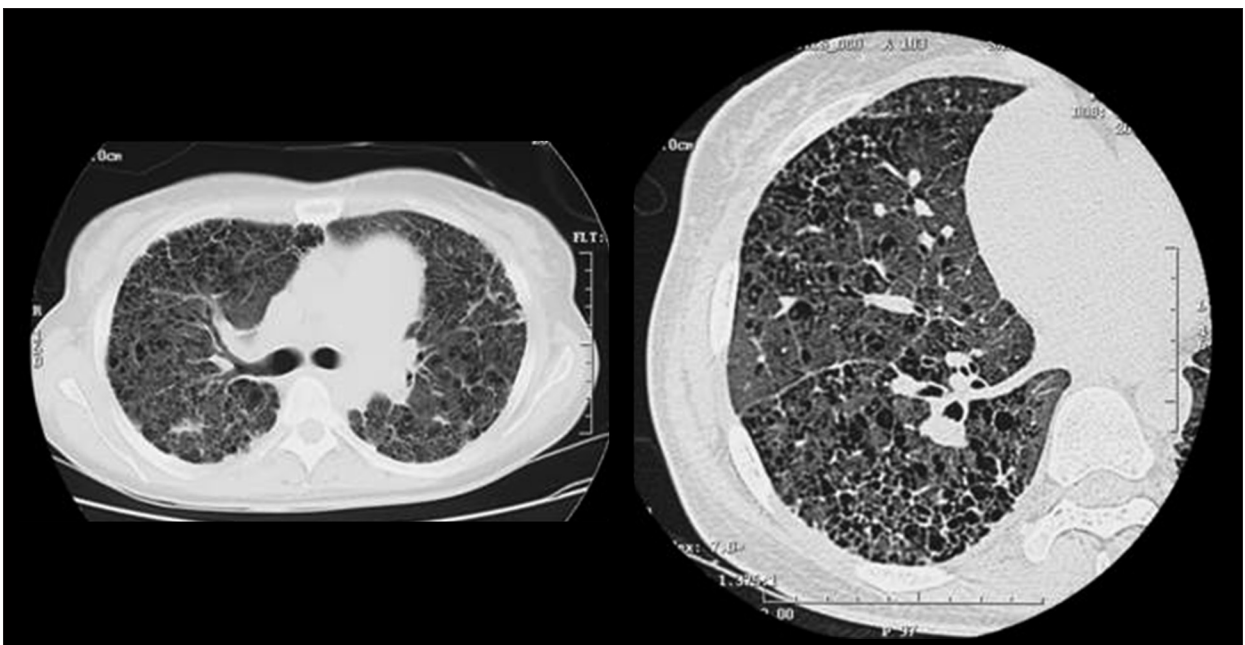
and her respiratory rate was 28 breaths/min. Physical examination showed an increased jugular venous pressure, finger clubbing, bilateral peripheral edema, and hepatomegaly. On auscultation, there was an accentuated pulmonary component (P2) of the second heart sound (S2), an S3 and a right-sided S4, pan-systolic murmurs that were best heard at the tricuspid area, and fine bilateral basal lung crackles. Laboratory tests showed a uric acid level of 10.5 mg/dL and a brain natriuretic

peptide (BNP) level of 569 pg/mL. Arterial blood gas testing showed an arterial oxygen tension of 52.7 mmHg on 8 L/min oxygen, administered via a nasal cannula (Table 1).

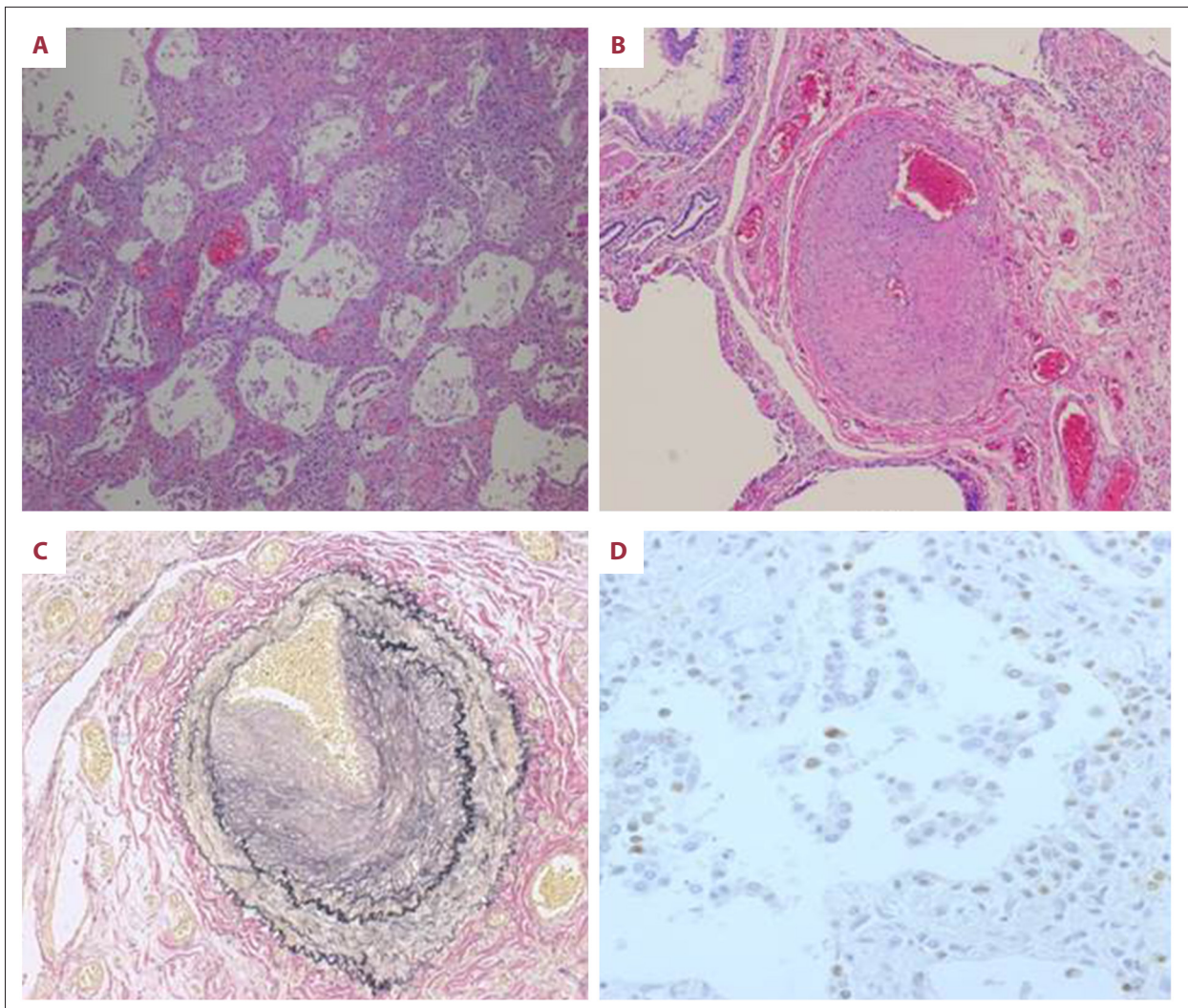
On the most recent hospital admission, cardiomegaly and bilateral enlargement of the pulmonary arteries were seen on chest X-ray, with diffuse interstitial lung shadowing (Figure 1). Chest CT showed diffuse multiple pulmonary cysts with thin walls, and pulmonary interstitial changes (Figure 2). Electrocardiography findings showed right ventricular hypertrophy and right atrial overload. Echocardiography showed a systolic right ventricular pressure of 85 mmHg and an estimated mean right atrial pressure of >10 mmHg. Right heart catheterization could not be performed because of the patient's rapidly deteriorating clinical condition.

Despite medical management with bosentan, epoprostenol, and dobutamine for right ventricular heart failure and pulmonary hypertension, her pulmonary hypertension gradually worsened. The patient died suddenly of right heart failure, one month after the final admission to the authors' hospital. She had been enrolled on a waiting list for lung transplantation but died without undergoing transplant surgery.

During autopsy examination of the heart, right ventricular dilation and hypertrophy were present, with a right ventricular wall thickness of 4 mm. The right lung weighed 650 g, and the left lung weighed 770 g. Histological examination of the lungs showed advanced lung fibrosis (Figure 3A) and hypertrophy of the media of the small pulmonary arteries, compatible



**Figure 2.** Chest computed tomography (CT) shows multiple diffuse pulmonary cysts with thin walls and interstitial changes.



**Figure 3.** Photomicrographs of the histology of lung tissue obtained at autopsy. (A) Severe interstitial fibrosis in the low-power field (original magnification  $\times 100$ ). (B, C) Hypertrophy of the media of the small pulmonary arteries, compatible with Heath-Edwards grade 3 on hematoxylin and eosin (H&E) staining (B) and positive elastic van Gieson (EVG) staining (C) in the high-power field (original magnification  $\times 400$ ). (D) Positive immunohistochemical staining for S-100 protein in the high-power field (original magnification  $\times 400$ ) confirming pulmonary Langerhans cell histiocytosis (PLCH).

with severe pulmonary arterial hypertension, Heath-Edwards grade 3 (Figure 3B). The proliferation of the elastic fibers was found in the pulmonary arteries using histochemistry with the elastic van Gieson (EVG) stain (Figure 3C), and pulmonary Langerhans cells were observed. PLCH was confirmed by positive immunohistochemical staining for S100 protein, CD1a, and CD68 (Figure 3D).

## Discussion

In this case report, severe pulmonary hypertension was found in a patient who was diagnosed with pulmonary Langerhans cell histiocytosis (PLCH). After administration of sildenafil, her

condition stabilized for one year. However, she died because of increasing pulmonary hypertension over the course of 12 years, despite the addition of bosentan and epoprostenol at the advanced stages of disease. Autopsy and histopathological examination of the lungs showed thickened walls of the small pulmonary arteries, PLCH, and severe fibrotic pulmonary interstitial changes.

PLCH is frequently associated with pulmonary hypertension, although this association is more prevalent with other interstitial lung diseases (ILDs) [1,2]. However, the pathological mechanism of PLCH-associated pulmonary hypertension remains unclear. In this case of PLCH-associated pulmonary hypertension, thickened walls of the small pulmonary arteries

were apparent on autopsy, which is a finding that is recognized to be the pathological feature of severe pulmonary hypertension, with occlusion of the pulmonary artery being described in pulmonary artery hypertension (PAH) [3].

The histopathological findings in the present case were compatible with grade 3 (severe) changes of pulmonary hypertension in the Heath–Edwards classification, while plexiform lesions were not observed. There was severe intimal thickening of the pulmonary arterioles, which suggests that the pathophysiological mechanism in PLCH-associated pulmonary hypertension may include both the mechanisms that occur in pulmonary arterial hypertension (WHO Group 1) and those that occur in pulmonary hypertension associated with interstitial lung disease (WHO Group 3), which include decreased pulmonary vascular bed and hypoxic vasoconstriction. In the 2013, the updated World Health Organization (WHO) clinical classification of pulmonary hypertension [4], PLCH-associated pulmonary hypertension is classified as Group 5 (multifactorial). From the autopsy findings, this case suggests that the pathologic mechanism of pulmonary hypertension associated with PLCH could include the mechanisms both in WHO Group 1, pulmonary arterial hypertension, and Group 3, pulmonary hypertension associated with interstitial lung disease [5].

Although the treatment of pulmonary arterial hypertension (Group 1) with pulmonary vasodilators, including prostanoids (prostaglandin I<sub>2</sub>), phosphodiesterase-5 (PDE-5) inhibitors, or endothelin receptor antagonists, have been shown to have substantial benefit [6], there have been no studies on the efficacy of drugs on the treatment of PLCH-associated pulmonary hypertension (Group 5), similar to those for Group 3 pulmonary hypertension associated with lung disease. However, recently, Le Pavec et al. [7] reported that drugs used in the treatment of Group 1 pulmonary arterial hypertension were effective in controlling the disease activity in patients with PLCH-associated pulmonary hypertension. Ghofrani et al. [8] reported that sildenafil caused adequate pulmonary vasodilation that did not increase ventilation-perfusion mismatch, and did not worsen gas exchange in patients with severe lung fibrosis associated with pulmonary hypertension. Based on these reports, oral sildenafil may be effective in pulmonary hypertension associated with diseases affecting the lung interstitium, including PLCH-associated pulmonary hypertension.

In this case report, the patient was treated with the approved dose of oral sildenafil (20 mg tds) for one year. Although her pulmonary arterial pressures could not be followed-up after the initiation of sildenafil treatment, her symptoms were improved, from the New York Heart Association (NYHA) modified by the WHO functional class of primary arterial hypertension from Class IV (inability to carry out any functional activity) to Class III (marked limitation in physical activity) without an

increase in oxygen supply, and she could remain at home without until her last hospital admission. Bosentan and prostaglandin I<sub>2</sub> were added to her medications after her final admission because her shortness of breath significantly worsened. However, her symptoms did not improve, and her hypoxia progressed. It appears that PDE-5 inhibitors, such as sildenafil, may have some benefit in the treatment of PLCH-associated pulmonary hypertension because this patient's condition clinically stabilized for approximately one year after starting treatment with sildenafil. Although treatment for PLCH-associated pulmonary hypertension with low-dose prednisolone, vinblastine, and prednisolone, or 6-mercaptopurine, have been reserved for patients with major pulmonary or extrapulmonary involvement [9], the effects of treatment have been controversial. Furthermore, the use of these drugs was difficult in our case because of the poor clinical condition of the patient.

This report is presented because it has some differences from previously published case reports on PLCH-associated pulmonary hypertension, not only in confirming the diagnosis of PLCH and pulmonary hypertension by detailed autopsy review, but by the use of drugs to treat pulmonary arterial hypertension associated with PLCH.

Although PLCH may regress spontaneously or after smoking cessation, there is a disease phenotype in which the disease is progressive, ultimately leading to chronic respiratory failure and severe pulmonary hypertension [10]. The discovery that some forms of pulmonary hypertension are genetically inherited provides important opportunities for physicians to educate their patients and their families to understand the potential risks and benefits of genetic testing. Recently, the identification of the genetic basis for heritable predisposition, not only to PAH but also pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis have been reported [11]. It is possible that the mechanisms involved in PLCH-associated pulmonary hypertension (WHO Group 5) may be a combination of those that occur in pulmonary arterial hypertension (WHO Group 1) and those that occur in pulmonary hypertension associated with interstitial lung disease (WHO Group 3). However, we did not analyze the genetic abnormality in this case because the patient died in 2008. More information regarding pathological findings, genetic basis, and the clinical course of patients with PLCH-associated pulmonary hypertension is needed to clarify the pathogenesis of this disease.

Although a definitive treatment strategy for PLCH-associated pulmonary hypertension has not been established, pulmonary artery vasodilators may be as effective as they are in pulmonary arterial hypertension. Based on the course of the present case, PDE-5 inhibitors may be more effective than prostanoids and endothelin receptor antagonists. At present, the use of pulmonary artery vasodilators should be considered

individually in each case. However, future controlled clinical trials of pulmonary artery vasodilators in PLCH-associated pulmonary hypertension are required. While waiting for lung transplantation, it is important to make full use of the range of medical therapies in PLCH-associated pulmonary hypertension, especially severe pulmonary hypertension persists after smoking cessation.

## Conclusions

This case report of the autopsy findings in a case of pulmonary Langerhans cell histiocytosis (PLCH)-associated pulmonary

hypertension appeared to result from a combination of WHO Group 1 pulmonary arterial hypertension (PAH) and Group 3 pulmonary hypertension secondary to lung disease. However, in the current 2013 classification of pulmonary hypertension, PLCH-associated pulmonary hypertension is classified a Group 5 (multifactorial) [5]. The use of pulmonary artery vasodilators should be considered individually in each case. At present, controlled clinical trials of pulmonary artery vasodilator therapy for this condition are needed.

## Conflicts of interest

None.

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