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Case report

Long-term improvement during tadalafil therapy in a patient with pulmonary hypertension secondary to pulmonary Langerhans cell histiocytosis

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ABSTRACT

Pulmonary arterial hypertension (PAH) secondary to pulmonary Langerhans cell histiocytosis (PLCH) is known to be a relatively common complication and is associated with a poor prognosis. However, the optimal therapeutic approach for these cases remains to be established. A 57-year-old man visited our hospital because of a progressive dry cough. A thoracic computed tomography examination showed a combination of diffuse thick-walled cysts and reticulonodular shadows that were predominant in bilateral upper lobes of the lungs. He was diagnosed as having PLCH based on the results of video-assisted thoracoscopic lung biopsies. During a 3-year clinical course, his condition deteriorated despite smoking cessation. A systemic evaluation demonstrated precapillary PAH caused by PLCH (PAH-PLCH), and treatment with tadalafil, a phosphodiesterase-5 inhibitor, was started. During a 50-month period of treatment with tadalafil, improvements in his dyspnea, 6-min walking distance, and hemodynamics were maintained without either overt hypoxemia or pulmonary edema. We considered that tadalafil therapy may be a useful option in the treatment of patients with PAH-PLCH.

1. Introduction

Pulmonary Langerhans cell histiocytosis (PLCH) is characterized by the infiltration of large numbers of Langerhans cells to the involved tissues and is a rare lung disease that occurs predominantly in young smokers [1]. The clinical course and prognosis of PLCH are unpredictable. Although most patients with PLCH recover spontaneously or remain in a stable condition without treatment after smoking cessation, some patients experience progressive respiratory impairment related to a deleterious change in lung function or to the development of pulmonary arterial hypertension (PAH) [1]. Precapillary PAH is an important complication in patients with PLCH, since PAH is associated with a poor prognosis [2]. However, little information on the optimal treatment of PAH caused by PLCH (PAH-PLCH) is available [3–6]. Indeed, the limited data available for PAH-PLCH suggests that PAH-specific therapies are associated with a long term improvement in hemodynamics [4–6].

Here, we present a patient with PAH-PLCH who has maintained a long-term improvement by undergoing treatment with tadalafil, a phosphodiesterase-5 inhibitor.

2. Case report

A 57-year-old man who had no significant past medical history visited our hospital in 2007 because of a progressive dry cough. He was a current smoker (60 pack-years) and had worked as a foundry worker with respiratory protection until hospital admission. A chest radiography (Fig. 1A) and computed tomography (Fig. 1B and C) showed a combination of diffuse thick-walled cysts and reticulonodular shadows that were predominant in the upper lobes of the lungs. Pulmonary function tests demonstrated an almost normal pattern, except for a decrease in the carbon monoxide

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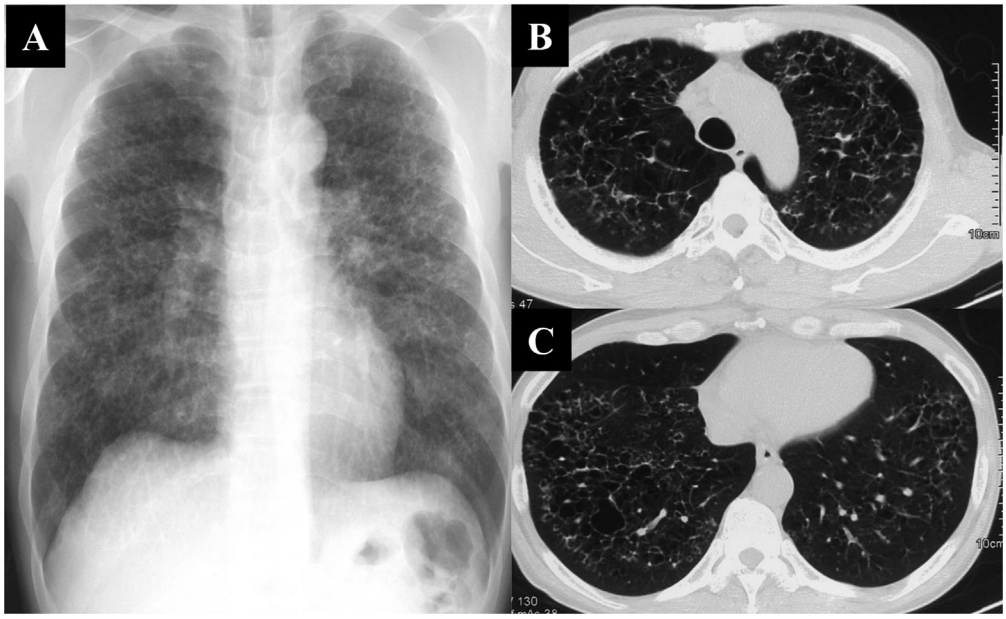

Fig. 1. (A) Chest X-ray showing diffuse cysts with reticular shadows in bilateral lung fields. (B, C) Chest CT showing diffuse irregular- and thick-walled cysts with reticulonodular shadows that were predominant in the upper lobes of the lungs.

diffusion capacity (DLco) (Table 1). Routine hematologic, biochemical, and serologic tests were within the normal ranges. Transthoracic echocardiography showed a normal cardiac image. A bronchoalveolar lavage analysis and transbronchial lung biopsy did not reveal a definitive diagnosis. Therefore, video-assisted thoracoscopic lung biopsies of the right upper and lower lobes were performed, and multiple cystic lesions and nodular infiltrates with fibrosis formed from various types of cells, but mostly histiocytes and eosinophils, were observed (Fig. 2A and B). These histiocytes had a convoluted irregular nucleus and a pale eosinophilic cytoplasm that stained strongly for anti-CD1a and were identified as Langerhans cells (Fig. 2C). Based on these histological characteristics, a diagnosis of PLCH was established. The patient stopped smoking and changed his occupational environment after the surgical biopsy.

In 2009, despite the complete cessation of smoking, he began to experience exertional dyspnea (New York Heart Association [NYHA] functional class II) with hypoxemia. A transthoracic echocardiography showed no evidence of right arterial overloading, but pulmonary function testing showed an obstructive impairment and a decline in DLco (Table 1). Therefore, long-term nasal oxygen therapy was started.

In 2010, he presented with increased dyspnea (NYHA functional class IV) and marked hypoxemia. Pulmonary function tests demonstrated the progression of obstructive impairment and a reduction in vital capacity (VC) and Dlco (Table 1). The radiographic findings also showed the progression of emphysematous change. Right heart catheterization (RHC) was performed for the

Table 1
Overview of clinical, function and haemodynamic features before and after tadalafil therapy.

Variables	2007	2009	2010 (Baseline)	1 month	15 months	30 months	40 months	50 months
NYHA class	I	II	IV	III	II	II	II	II
NT pro BNP (pg/ml)	ND	61.6	63.3	43.3	25.7	21.5	39.1	26.3
6MWT distance (m)	ND	265[a]	255[a]	200[a]	ND	230[a]	305[a]	310[a]
6MWT SpO_2, percentage of decrease (%)	ND	2[a]	5[a]	9[a]	ND	2[a]	5[a]	7[a]
PaO_2 at rest (mmHg)	83.1	74.2[b]	56.6[b]	52.9[b]	ND	70.3[b]	74.2[b]	83.8[b]
$PaCO_2$ at rest (mmHg)	41.8	44.7[b]	42.8[b]	46.5[b]	ND	39.7[b]	41.5[b]	46.9[b]
VC, % pred (%)	106.9	97.4	64.5	61.9	75.1	72.8	66.2	73.5
FEV_1, % pred (%)	103.3	72.9	49.8	49.8	50.4	52.6	48.4	52.4
DLco, % pred (%)	70.2	49.1	34.6	37.3	44.2	38.4	34.9	50.0
PAP systolic/diastolic (mmHg)	ND	ND	51/24	51/27	ND	34/18	34/16	32/13
Mean PAP (mmHg)	ND	ND	34	34	ND	25	24	21
Mean PCW (mmHg)	ND	ND	6	13	ND	8	9	5
PVR (dynes/s/cm^5)	ND	ND	638.3	342.5	ND	376.1	321.1	387.7
CI (L/min/m^2)	ND	ND	2.02	2.97	ND	2.23	2.33	2.00
Therapy	Smoking cessation	Nasal oxygen	Nasal oxygen Tadalafil commenced	Nasal oxygen plus Tadalafil	Nasal oxygen plus Tadalafil	Nasal oxygen plus Tadalafil	Nasal oxygen plus Tadalafil	Nasal oxygen plus Tadalafil

NYHA: New York Heart Association; NT pro BNP: N-terminal pro-brain naturiuretic peptide; 6MWT: 6-min walk test; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; FVC: forced vital capacity; FEV1: forced expiratory volume in1 second; DLco: transfer factor for carbon monoxide; PAP: pulmonary artery pressure; PCW: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; CI: cardiac index; ND: not determined.

[a] Nasaloxygen, 5 L/min.

[b] Nasaloxygen, 2 L/min.