

# Sustained response to targeted therapies in a patient with pulmonary hypertension owing to Langerhans cell histiocytosis

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## Introduction

Pulmonary hypertension (PH) in association with Pulmonary Langerhans Cell Histiocytosis (PLCH) is an uncommon pulmonary vascular disease classified in group 5 PH according to currently available guidelines for the diagnosis and treatment of PH. Oxygen support, diuretic treatment and lung transplantation are standard therapies for this disease. Generally, pulmonary arterial hypertension (PAH) targeted therapies are not considered to be beneficial in this subgroup of PH.

## Case Report

A 36-year-old female with a diagnosis of PLCH was referred to our tertiary center because of progressive dyspnea, and dry cough six years ago. She had a 12-year history of PLCH confirmed by lung wedge resection biopsy, and symptoms exacerbated within the past six months. She also had a history of smoking one packet of cigarettes a day for 18 years until cessation of smoking eight months ago.

She had peripheral cyanosis and severe dyspnea consistent with World Health Organization functional class IV status on admission. She could not walk within room. Physical examination revealed hoarseness, a marked right ventricular (RV) lift, accentuated pulmonary valve closure sound, a grade 2 diastolic murmur over the left second intercostal space, and bilateral rales in her lungs. Her vital signs at the time of admission were blood pressure of 100/70 mm Hg, heart rate of 110 bpm, and oxygen saturation on nasal oxygen support (2 L /min) of 84%. Electrocardiogram showed sinus rhythm with P pulmonale pattern, RV hypertrophy with systolic strain, and right axis deviation (Fig. 1). Chest radiography and computed tomography showed a combination of diffuse thick-walled, irregular-shaped cysts and reticulonodular shadows that were predominant in the mid and upper lobes of the lungs (Fig. 2). Pulmonary function tests revealed decreased forced vital capacity, forced expiratory volume in one second, and a 47% diffusing capacity of the lung for carbon monoxide. Her routine laboratory tests were normal. The

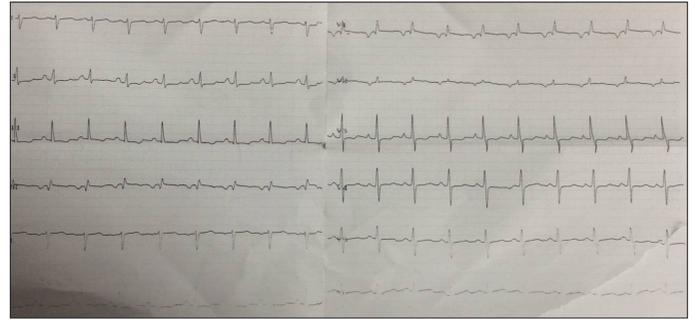


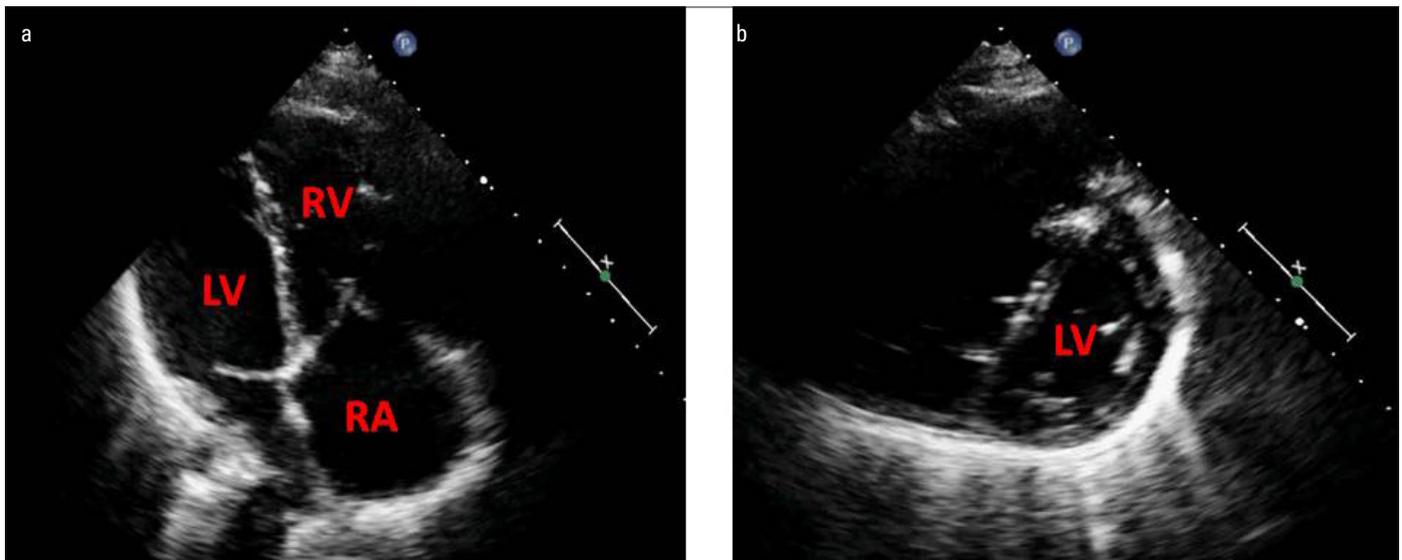
Figure 1. Electrocardiographic findings consistent with pulmonary hypertension



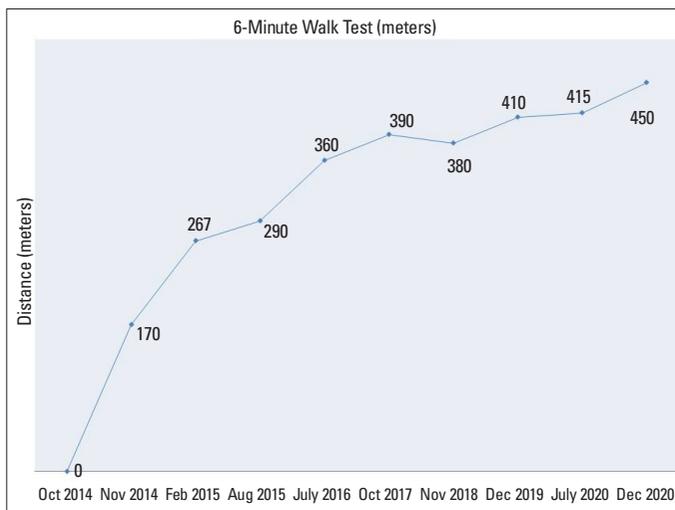
Figure 2. Chest x-ray findings of the patient

normal D-dimer level ruled out the acute pulmonary embolism. Her echocardiographic examination showed dilated right atrium and right ventricle, D-shaped interventricular septum, and normal left ventricular systolic functions. The M-mode measurement of tricuspid annular plane systolic excursion was 1.8 cm, and the tissue velocity of tricuspid annular longitudinal systolic motion was 11 cm/sec. Pulmonary artery systolic and mean pressure estimates from tricuspid and pulmonary regurgitation jets were 95 mm Hg and 55 mm Hg, respectively (Fig. 3a and 3b). Once all these non-invasive evaluations were done, we performed invasive right and left heart catheterization. Pulmonary artery mean and wedge pressures were 49 mm Hg and 14 mm Hg, respectively. Cardiac output was 3.5 L/min, and pulmonary vascular resistance was 13.7 Wood units. Vasoreactivity challenge with adenosine was negative. Hemodynamic characteristics of this patient were considered to be consistent with pre-capillary PH.

We started iloprost intravenous (i.v.) infusion 20 mcg/min and sildenafil 20 mg 3×1 per oral (PO) therapies, and marked improvements in symptoms and overall clinical status were observed within the first few days following PAH-targeted



**Figure 3.** Apical four-chamber (a) and parasternal short axis (b) echocardiography showing enlarged right ventricle and D-shaped septum



**Figure 4.** Longitudinal changes in six-minute walk distance

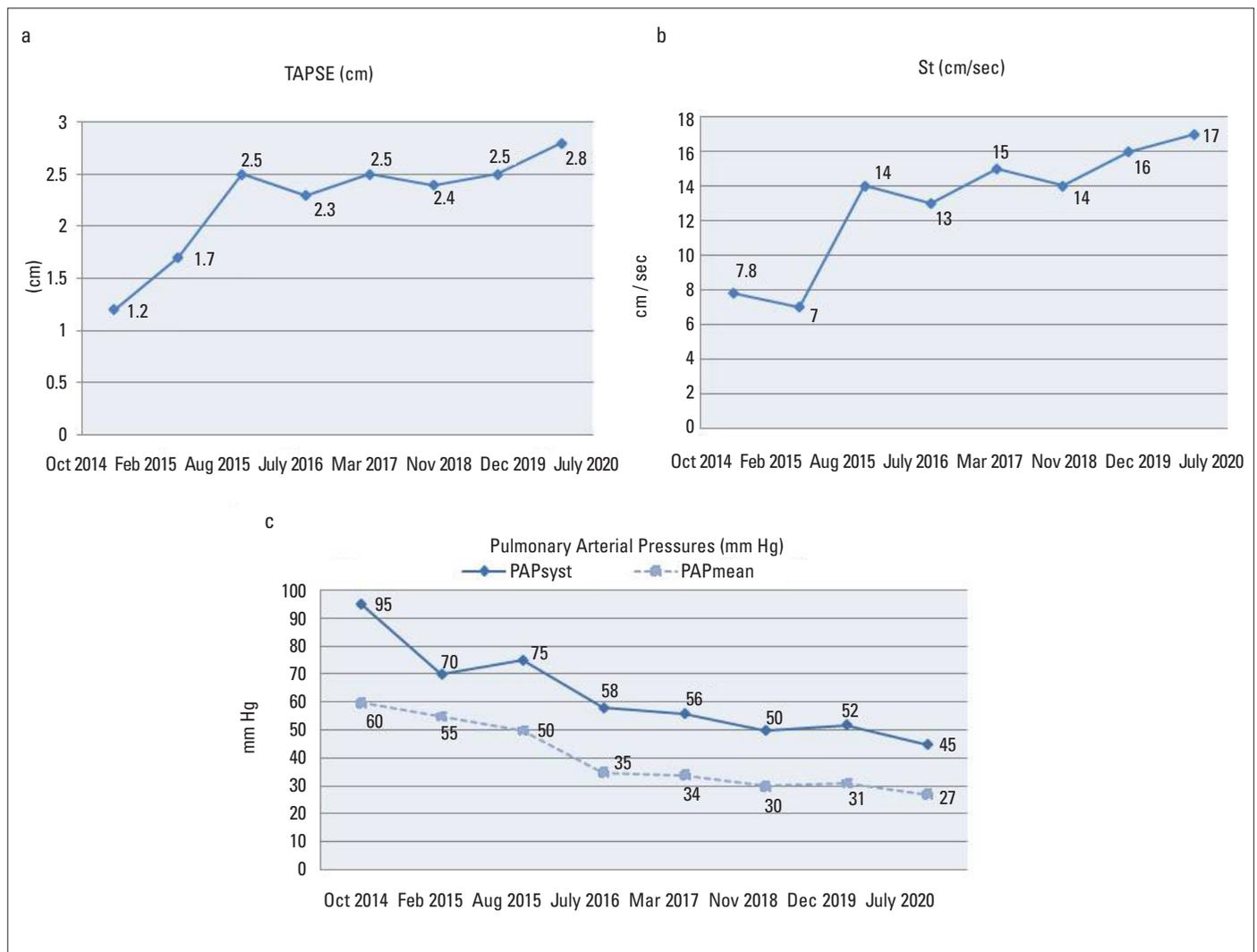
therapies. She became mobilized and was able to walk 170 m on the six-minute walk test (6MWT) on the 30<sup>th</sup> day of hospitalization. It was decided to switch the in-hospital medications to treprostinil SC and tadalafil 20 mg 1×2 as outpatient PAH therapies. The 6MWT distance increased to 250 m on the 40<sup>th</sup> day of hospitalization, and the patient was discharged on these treatments. Progressive and sustained improvement in the clinical status of the patient was confirmed by control examinations at three-month intervals. During a 74-month period of treatment with tadalafil and treprostinil SC, the improvements in her functional class, 6MWT, and RV systolic functions measured by echocardiography were maintained (Fig. 4, and Fig. 5a-5c). Moreover, echocardiographic assessments revealed a slight decrease in pulmonary arterial pressures during the follow-up period. She did not experience any clinical worsening, and her current functional capacity was maintained at class 2 status.

## Discussion

In our patient with severe PH because of PLCH, a dramatic response to i.v. iloprost and PO sildenafil therapies was obtained during the in-hospital period, and the hemodynamic and clinical improvements have been maintained after switching to treprostinil SC -plus PO tadalafil -combination therapy at discharge. She tolerated high dose treprostinil (52 mcg/kg/min) well, and her clinical status remained stable at the five-year follow-up.

The PLCH is a rare interstitial lung disease characterized by granulomatous lesions, including histiocytic Langerhans cells. These cells express S100 protein, CD1a, and langerin (CD207) and contain intracytoplasmic Birbeck granules (1). It is more common in smokers and the young adult population, and 25% of all patients are asymptomatic. Common symptoms are dry cough, dyspnea, pleuritic chest pain, fever, weight loss, and hemoptysis. Pulmonary function tests show restrictive, and sometimes obstructive pattern with decreased DLCO. Spontaneous pneumothorax may occur in 15%-25% of these patients. Bronchiolocentric nodules, irregular shaped cysts, reticulonodular opacities, interstitial wall thickening, and honeycombing can be seen on high resolution computed tomography. PLCH is definitively diagnosed by lung biopsy. Corticosteroids and some cytotoxic drugs such as cladribine are used to treat PLCH. Older age, prolonged constitutional symptoms, multiorgan involvement, extensive cysts, honeycomb changes, severe decrease in diffusion capacity, obstructive lung function, prolonged treatment with steroids, and PH are considered as risk factors (1). The most important point is smoking cessation, which provides rapid improvement in clinical status (2, 3).

PH is a frequent and important complication of PLCH, and it is currently classified as group 5 PH. Intrinsic vascular disease that consists of fibrotic changes and invasion by Langerhans cells is considered to be responsible for PH development in patients with PLCH (1, 4-6). There is limited data supporting the use of PAH specific medications in patients with group 5 PH, and they may be



**Figure 5.** Longitudinal changes in tricuspid annular plane systolic excursion (a), tricuspid annular systolic tissue velocity (b), and pulmonary arterial systolic and mean pressures (c)

harmful in some cases. In most patients with group 5 PH, treatment should be focused on the underlying disease; and PAH therapies should be reserved for patients with severe pre-capillary PH. According to the conventional approach, it is considered that PAH specific vasodilator therapies cause pulmonary edema, increase ventilation perfusion mismatch, exacerbate gas exchange, aggravate hypoxemia, and worsen clinical status in patients with PH because of lung diseases (4, 5). i.v. epoprostenol was tried in a very small number of patients and resulted in pulmonary edema (7). Conversely, some papers reported good clinical and hemodynamic outcomes with PAH-specific drugs in these patients (4-6, 8). In addition, these drugs can be used as a bridging therapy to lung transplantation, although in the absence of prospective or head-to-head comparisons of PAH-specific therapies in PLCH, endothelin receptor antagonists and phosphodiesterase-5 inhibitors seem to be effective (8, 9). In our patient, we observed sustained improvement in hemodynamic and clinical parameters with PAH treatments, and this benefit was obtained without any deterioration in oxygen saturation.

All patients with PLCH should be screened for PH with echocardiography in case of suspicion. If echocardiographic findings are consistent with PH, confirmative invasive heart catheterization should be performed. This is necessary not only for hemodynamic diagnosis but also for the exclusion of post-capillary PH component, which may increase the risk of pulmonary edema with the initiation of PAH medications. Accordingly, PAH-specific drugs may be tried only in selected eligible patients.

### Conclusion

PH in association with PLCH is an uncommon pulmonary vascular disease and have poor prognosis. In our case report, targeted dual-combination PAH therapy showed marked improvement in hemodynamic and clinical parameters.

**Informed consent:** Formal informed consent form was obtained from the patient.

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