



## Case report

# Dramatic and sustained responsiveness of pulmonary Langerhans cell histiocytosis-associated pulmonary hypertension to vasodilator therapy



Adam May<sup>a</sup>, Garvan Kane<sup>b</sup>, Eunhee Yi<sup>c</sup>, Robert Frantz<sup>b</sup>, Robert Vassallo<sup>d,\*</sup>

<sup>a</sup> Department of Medicine, Mayo Clinic, Rochester, MN, 55905, USA

<sup>b</sup> Division of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, 55905, USA

<sup>c</sup> Department of Laboratory Medicine and Anatomic Pathology, Mayo Clinic, Rochester, MN, 55905, USA

<sup>d</sup> Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, 55905, USA

## A B S T R A C T

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Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon diffuse lung disease characterized by the abnormal accumulation of Langerhans' cells around small airways and other distal lung compartments. Although pulmonary hypertension (PH) is a frequent complication of PLCH, the role of advanced PH therapies for PLCH-related PH is not well-established. We describe a PLCH patient with severe, disease-related PH that responded unexpectedly well to advanced PH therapy with sustained improvement over a 10 year follow-up period. This case indicates that PLCH-associated PH may, in certain instances, be highly responsive to advanced PH therapies and emphasizes the importance of trialing these therapies among patients with PLCH-related PH.

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## Introduction

Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon smoking-related interstitial lung disease characterized by the accumulation of specialized antigen presenting cells called Langerhans' cells around small airways [1–3]. The natural history of this disease is variable but often associated with life-threatening complications such as pulmonary hypertension (PH). Although PLCH-related PH is generally regarded as WHO (World Health Organization) group V PH disease for which the efficacy of advanced PH therapies is uncertain [4], a recent retrospective analysis showed that a small cohort of PLCH patients treated with advanced PH therapies had improved pulmonary vascular hemodynamics along with a trend towards better survival [5]. We present a PLCH patient with severe disease-related PH who achieved a dramatic and durable therapeutic response with advanced PH therapies.

## Case report

A 46-year-old Caucasian woman presented in the fall of 2003 with complaints of progressive dyspnea (New York Heart

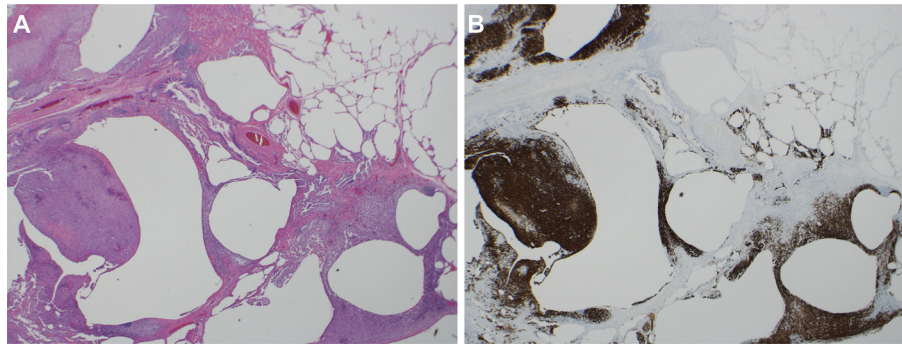
Association: NYHA Class III) and non-productive cough. A diagnostic evaluation prior to her presentation at our facility resulted in a surgical lung biopsy (December 2012) that established the diagnosis of Pulmonary Langerhans cell histiocytosis (PLCH). Other pertinent medical history included an active 30 pack year smoking history and mild and untreated obstructive sleep apnea (OSA).

Chest high resolution computed tomography revealed bilateral cystic changes and scattered nodularity with an upper lung predominance and sparing of the costophrenic angles. Her surgical lung biopsy slides from the outside facility were reviewed for diagnostic confirmation. Her lung specimens revealed multiple nodules composed of Langerhans cells with mixed inflammatory cells, cavitation and adjacent cystic changes (Fig. 1A). CD1a immunostaining identified the presence of increased Langerhans cells (Fig. 1B). Pulmonary function testing demonstrated mild-moderate expiratory air-flow obstruction, preserved lung volumes, and moderately reduced gas-exchange capacity. The index echocardiogram revealed normal ventricular structure and function with an elevated right ventricular systolic pressure (RVSP) of 48 mmHg.

The patient was initially treated with prednisone (0.5 mg/kg/day) without response, and then three cycles of 2-Chlorodeoxyadenosine (5 mg/m<sup>2</sup>). The following year her symptoms and pulmonary function remained stable, but a repeat echocardiogram revealed an increase in RVSP to 63 mmHg. The patient underwent

\* Corresponding author. Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 S. First Street NW, Rochester, MN, 55905, USA. Tel.: +1 507 284 5398.

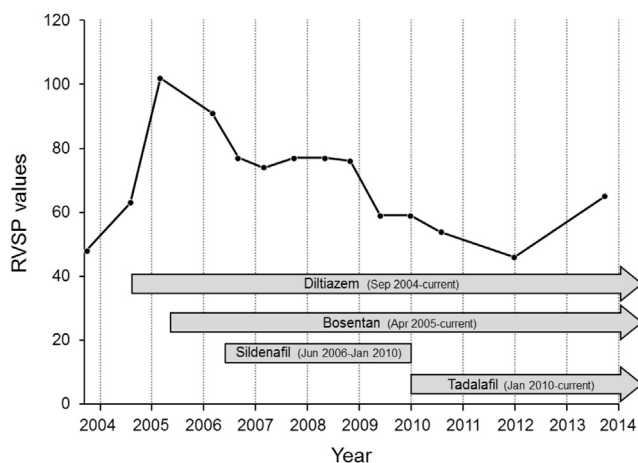
E-mail address: [Vassallo.Robert@mayo.edu](mailto:Vassallo.Robert@mayo.edu) (R. Vassallo).



**Fig. 1.** A, Surgical lung biopsy demonstrating increased presence of inflammatory cells along with cavitory and cystic changes. B, Lung Biopsy with CD1a immunostaining demonstrating the presence of increased Langerhans cells.

right heart catheterization which demonstrated an elevated mean pulmonary artery (mPA) pressure of 44 mmHg, pulmonary artery wedge pressure of 12 mm Hg, cardiac output of 5.8 L/min, cardiac index of 3.5 L/min/m<sup>2</sup>, and a pulmonary vascular resistance of 5.5 Wood units. Intravenous epoprostenol elicited a decrease in mPA to 38 mm Hg with pulmonary vascular resistance of 3.2 Wood units and led to an increase in cardiac output and cardiac index to 7.2 L/min and 4.3 L/min/m<sup>2</sup>, respectively.

She was then initiated oral diltiazem that was titrated to 300 mg over 6 months. Despite diltiazem initiation her dyspnea progressed from functional class II to III and a repeat echocardiogram revealed new right ventricular enlargement, moderate-severe right ventricular systolic dysfunction, right ventricular index of myocardial performance (RIMP) of 0.85, moderate tricuspid regurgitation, and RVSP of 102 mmHg. She was then initiated on an endothelin receptor antagonist (bosentan 125 mg twice per day) and then a phosphodiesterase-5 inhibitor (sildenafil 20 mg three times daily) shortly thereafter. Following drug initiation, a sharp reduction in RVSP, lessening of tricuspid regurgitation, improvement in RIMP to 0.32, and reduction in her dyspnea severity to NYHA Class II was observed (therapeutic events summarized in Fig. 2). This regimen was continued until January 2010 wherein she was transitioned off sildenafil 20 mg three times daily to tadalafil 40 mg daily due to difficulty with medication compliance (forgetting to take evening sildenafil dose). Ten years following the initiation of advanced PH therapies, echocardiographic and functional class improvement were sustained despite continued tobacco abuse, and lack of OSA treatment.



**Fig. 2.** Temporal relationship of the trend of right ventricular systolic pressure (RVSP) values derived from serial echocardiography (2004–2014) with the use of pulmonary vasomodulatory therapies.

## Discussion

PLCH is a smoking-induced diffuse lung disease with an unpredictable clinical course. In a proportion of patients, PLCH is a relatively benign disease which may regress spontaneously or following smoking cessation; however in other patients, PLCH is much more aggressive life-threatening illness. PH is a serious complication of PLCH that manifests more commonly and with greater severity among disease-affected patients than those with other diffuse lung diseases [6–8]. Its development portends a relatively poor prognosis associated with substantial reduction in patient survival [8]. Although the mechanisms involved in its development are not entirely clear, PLCH-related PH is at least partially caused by a primary pulmonary vasculopathy [6–8]. A prior study described the presence of histopathological pulmonary vascular involvement and PH severity disproportionate to the degree of pulmonary function impairment [6], suggesting that PLCH-related PH is not caused solely by hypoxemia-induced pulmonary vascular remodeling that typifies WHO group III PH disease(s). As illustrated in the current case report, severe PLCH-related PH is not only observed in patients with advanced long-standing disease, but may occur in patients with early disease and/or those with relatively limited lung function impairment.

The therapeutic relationship between advanced PH therapies and PLCH-related PH remains to be sufficiently characterized. Le Pavec and colleagues recently reported that the use of advanced PH therapy was associated with improvement in pulmonary vascular hemodynamic parameters [5]. The current case provides a striking example of the favorable response of advanced PH therapies for some patients with PLCH-associated PH. Moreover, as the patient did not quit smoking, engage in OSA treatment, or demonstrate pulmonary function or radiographic improvements, there is no alternative explanation for her clinical response.

Our case provides further evidence that PLCH-related PH may be responsive to advanced PH therapies. The identification of those patients responsive to advanced PH therapy provides an opportunity to alleviate symptoms and potentially improve survival.

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