Pulmonary Langerhans Cell Histiocytosis-associated Pulmonary Hypertension Showing a Drastic Improvement Following Smoking Cessation

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Abstract

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare, smoking-related, interstitial lung disease, and pulmonary hypertension (PH) is associated with mortality. We herein report a case of PLCH complicated by severe PH and respiratory impairment. After developing PH, the patient displayed a cystic pattern on chest high-resolution computed tomography (HRCT). This, in turn, corresponded with the scarring stage of PLCH. However, the patient’s PH and respiratory impairment improve dramatically following smoking cessation. PLCH patients with a cystic pattern on chest HRCT may still be able to improve their PH and respiratory impairment when they are able to quit smoking.

Key words: smoking-related interstitial lung disease, Langerhans cell granuloma, lung cyst


Introduction

Pulmonary Langerhans cell histiocytosis (PLCH) is a rare, interstitial lung disease primarily affecting young adults (1). Recent studies imply that cigarette smoking is an etiology of PLCH (2). Although smoking cessation’s effect on the outcome of PLCH remains inconclusive, it is sometimes a reasonable option in some cases (2-5). We herein discuss a case of PLCH that was complicated by severe pulmonary hypertension (PH) and respiratory impairment that dramatically improved after the patient stopped smoking.

Case Report

A 46-year-old woman with a history of schizophrenia presented to our hospital due to a non-productive cough and an abnormal chest radiograph. She smoked at the time, and reported consuming one pack of cigarettes per day for the past 26 years. Spirometry revealed forced vital capacity (FVC) of 2.18 L (80% of predicted) and forced expiratory volume in 1 s (FEV₁) of 1.92 L (77% of predicted). A high-resolution computed tomography (HRCT) scan of the chest showed bilateral multifocal ill-defined nodules and small, irregularly shaped cysts (Fig. 1A). Pulmonary artery systolic pressure estimated by echocardiography was within the normal range.

A surgical lung biopsy was performed. A biopsy specimen obtained from the right S2 area showed ill-defined nodules. Some of these had a cavity or surrounded a peripheral airway, suggesting airway-centered nodules (Fig. 2A). At higher magnification, nodules appeared to contain a diffuse infiltration of Langerhans cells with pale basophilic nuclei and granular and mildly eosinophilic cytoplasm, intermingled with eosinophils and lymphocytes (Fig. 2B). These histological features aligned with a florid PLCH phase. The intima of the small arteries was markedly thickened with an infiltration of eosinophils and mononuclear cells (Fig. 3A, B), some of which stained positive for S-100 (Fig. 3B). These vascular changes did not appear in areas unaffected by histiocytosis.

Despite our advice on smoking cessation, the patient continued smoking and received no medication during follow-up examinations. HRCT performed 21 months after diagnosis showed that ill-defined nodules and small, irregularly
Figure 1.  A: Bilateral, multifocal, ill-defined nodules and small, irregularly-shaped cysts. B: Large, thin-walled cysts replaced nodules and cysts, but a small number of nodules still remained (arrow). Arrow head points to an operation scar. C: A small number of nodules that remained before smoking cessation completely disappeared, and the wall of cysts became thinner.

Figure 2.  A: A biopsied specimen at low magnification, showing multiple nodules. Some of these had a cavity or surrounded a peripheral airway (a, b) [Hematoxylin and Eosin (H&E) staining]. B: Higher magnification of the specimen showing diffuse infiltration of Langerhans cells with pale basophilic nuclei and granular and mildly eosinophilic cytoplasm, intermingled with eosinophils and lymphocytes (H&E staining).

shaped cysts had been almost replaced by large, thin-walled cysts, but a small number of nodules still remained (Fig. 1B). Moreover, the parameters of her respiratory function testing of FVC, FEV₁, and diffusing capacity of the lung for carbon monoxide (DLO₂) had decreased over time (Table). She presented with progressive dyspnea and marked hypoxemia (PaO₂ of 61 mmHg on 3 L/min oxygen via nasal cannula) 26 months after diagnosis. Chest radiography showed cardiomegaly with a prominent main pulmonary artery and an enlarged right interlobar artery (Fig. 4A). An electrocardiogram showed an incomplete right bundle branch block with right axis deviation, deep S waves in lead I and inverted T waves in leads II, III, aVF and V₁ (Fig. 4B). Echocardiography revealed elevated pulmonary artery systolic pressure (estimated to be 62 mmHg), right ventricular enlargement, dislocation of the interventricular septum toward
Figure 3.  A: A small artery’s intima thickened (Elastica van Gieson). B: Mononuclear cells and eosinophils (H&E staining) infiltrated the thickened intima. C: Some mononuclear cells in the intima were positive for S-100 staining (arrows).

Table.  Chronological Observation of Respiratory Function and Pulmonary Haemodynamic Status.

<table>
<thead>
<tr>
<th>Time following smoking cessation, m</th>
<th>-27</th>
<th>-21</th>
<th>-6</th>
<th>-1</th>
<th>+4</th>
<th>+8</th>
<th>+26</th>
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<tr>
<td>FVC, L</td>
<td>2.18</td>
<td>1.66</td>
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<td>FVC, % pred.</td>
<td>80</td>
<td>60</td>
<td>68</td>
<td>N.A.</td>
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<td>86</td>
<td>87</td>
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<tr>
<td>FEV1, L</td>
<td>1.92</td>
<td>1.46</td>
<td>1.27</td>
<td>N.A.</td>
<td>1.54</td>
<td>1.68</td>
<td>1.64</td>
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<tr>
<td>FEV1, % pred.</td>
<td>77</td>
<td>58</td>
<td>51</td>
<td>N.A.</td>
<td>63</td>
<td>69</td>
<td>69</td>
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<tr>
<td>DLO2, % pred.</td>
<td>82</td>
<td>57</td>
<td>17</td>
<td>N.A.</td>
<td>51</td>
<td>40</td>
<td>48</td>
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<td>PASP, mmHg</td>
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<td>N.A.</td>
<td>N.A.</td>
<td>62</td>
<td>N.A.</td>
<td>&lt;25</td>
<td>N.A.</td>
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<tr>
<td>PaO2, mmHg</td>
<td>61*</td>
<td>N.A.</td>
<td>N.A.</td>
<td>61†</td>
<td>N.A.</td>
<td>N.A.</td>
<td>62*</td>
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<tr>
<td>BNP, pg/mL</td>
<td>N.A.</td>
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<td>15.6</td>
<td>446</td>
<td>7.6</td>
<td>&lt;5.8</td>
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</tr>
<tr>
<td>NYHA</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
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Figure 4.  A: Chest radiography showing cardiomegaly with a prominent main pulmonary artery (arrow) and enlarged right interlobar artery (arrow head). B: An electrocardiogram showing incomplete right bundle branch block with right axis deviation, deep S waves in lead I and inverted T waves in leads II, III, aVF and V1. C: A parasternal short-axis view showing the dislocation of the interventricular septum toward the left ventricle. RV: right ventricle, LV: left ventricle.
the left ventricle, and the dilation of the inferior vena cava without respiratory variation in diameter (Fig. 4C). Right-sided heart catheterization could not be performed because the patient refused the procedure. Massive pulmonary thromboembolism was not observed on an enhanced chest CT, and the results of haematological and biochemical examinations were within the normal ranges.

On admission, the patient received treatment with diuretics and vasodilators (beraprost and tadalafil). Nevertheless, her respiratory distress and pulmonary artery systolic pressure did not improve. We again strongly urged her to stop smoking; she finally did so on the 18th day of hospitalization (27 months after the PLCH diagnosis). Since then, her hypoxemia started to improve. On the 40th day of hospitalization, the pulmonary artery systolic pressure estimated by echocardiography had normalized, and vasodilators and oxygen therapy were discontinued approximately 3 months later. The parameters of her respiratory function testing also improved (Table). Moreover, chest HRCT performed 38 months after the diagnosis of PLCH (12 months post-smoking cessation) showed thinning of the cyst walls and the complete disappearance of a small number of nodules (Fig. 1C). The patient is presently being followed up as an outpatient, with no recurrence of PH to date.

Discussion

The development of PH has been associated with an increased mortality in PLCH (6). Lung transplantation and pulmonary arterial hypertension-specific therapies have recently been reported to be effective for the treatment of PLCH-PH, but its prognosis is still unfavourable (6-8).

Group 5 of the recent Nice classification of PH represents PLCH-PH, and its pathogenesis is multifactorial (9). Possible etiologies have been ascribed to the narrowing of pulmonary arteries due to the direct involvement of Langerhans cell granulomas, vascular remodelling of small pulmonary arteries in areas uninvolved in Langerhans cell granulomas and pulmonary vasoconstriction due to chronic hypoxemia (6, 7, 9). The absence of vascular changes in areas uninvolved in Langerhans cell granulomas makes this case distinct. Yoshida et al. reported a PLCH-PH patient in whom vascular changes were observed in both involved and uninvolved areas (10). In their case, smoking cessation was not effective, but sildenafil substantially improved the pulmonary hemodynamics. In contrast, PH improved by smoking cessation rather than diuretics, vasodilators and oxygen therapy in the present case. This may have happened because vascular remodelling of pulmonary arteries in the area uninvolved in Langerhans cell granulomas was less advanced, the narrowing of pulmonary arteries by the direct cellular infiltration in the intima was a major cause of PH. Unlike other lung diseases, PLCH-PH is not limited to end-stage disease because Langerhans cell granulomas affect exclusively small airways, and vascular structure is often involved in Langerhans cell granulomas in the early phase (6, 11-13).

Therefore, if not previously attempted, patients with advanced to severe PH should also try to cease smoking.

HRCT is very useful the follow-up of PLCH because HRCT scan findings approximately reflect histopathological disease activity (14). During the florid stage of PLCH, bronchocentric cellular infiltrations of Langerhans cells form nodules, which is comparable to a nodular pattern on HRCT. During the early fibrotic stage, Langerhans cells decrease in number, inflammatory cells become predominant, and fibrotic changes begin. Cicatrical fibrosis irreversibly destroys the lung structure in the scarring stage. This phenomenon leads to the formation of stellate scars or thin-walled cysts, which is comparable to the cystic pattern on HRCT (11, 14). In the present case, the HRCT scan findings at the occurrence of PH corresponded to the scarring stage of PLCH. Therefore, we speculated that the deteriorated parameters of lung function testing would be irreversible. However, respiratory impairment actually improved following smoking cessation. For this reason, Soler et al. demonstrated that a nodular HRCT scan pattern certainly reflects a histopathological active disease, but a cystic HRCT scan pattern is sometimes associated with the presence of still-inflammatory cellular lesions, even when micronodules are absent on HRCT scans (14). In this case, radiographic improvement following smoking cessation may suggest that a certain amount of inflammatory cellular lesions remained but in the scarring stage of PLCH.

In this study, the clinical parameters improved following smoking cessation far more dramatically than we expected from radiographic change. The present case instructively illustrates that there may still be potential for improvement, even if the patient has a cystic pattern and micronodules are almost absent on HRCT. To the best of our knowledge, no cases in which both PH and respiratory impairment improved following smoking cessation have ever been previously reported. Therefore, cases showing similar treatment effects are required to further confirm this observation.

The authors state that they have no Conflict of Interest (COI).

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