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【 CASE REPORT 】

A Case of Pulmonary Langerhans Cell Histiocytosis That Progressed From a Single-system to a Multisystem Form Despite Smoking Cessation: A Case Report

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Abstract:

A 36-year-old Japanese man presented with cavities and nodular shadows in the lower lobes of his lungs and osteolytic lesions in the thoracic spine. He was diagnosed with multisystem Langerhans cell histiocytosis (LCH). Three years earlier, he had been noted to have small cavities and granular lesions noted in the upper lobes of his lungs, which later improved with smoking cessation. It was likely that his single-system pulmonary LCH (PLCH) progressed to multisystem LCH despite smoking cessation. Relapse or progression may occur in cases where PLCH lesions improve after smoking cessation. Thus, close follow-up is vital.

Key words: pulmonary Langerhans cell histiocytosis, smoking cessation, cavitary lesion, nodular change, case report

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Introduction

Langerhans cell histiocytosis (LCH) in adults is a rare disorder with an unknown incidence (1). Furthermore, its spontaneously-resolving nature makes it difficult to perform epidemiological studies on this disease. In the Japanese Pulmonary LCH (PLCH) study, the prevalence per million of this disease was estimated to be 0.27 and 0.07 in men and women, respectively (2). Since the actual frequency of clinical encounters is extremely low, it is vital to share the clinical characteristics of LCH through case reports.

More than 90% of patients with PLCH are current or former smokers (2), and smoking cessation has been reported to improve the condition of patients with single-system PLCH (3). However, long-term benefits of cessation in cases of single-system PLCH remain unclear (4).

Case Report

A 36-year-old Japanese man presented with dyspnea on exertion and back pain. He reported smoking 10 cigarettes per day. Three years ago, he was evaluated in our hospital due to an abnormal chest shadow noted during a medical examination. Chest computed tomography (CT) revealed fine granular shadows and small cavity-like lesions with heterogeneous walls, mainly in the upper lobe (Fig. 1a-c). At that time, he had no presenting symptoms. He was then advised to stop smoking to prevent further progression of his condition. After one year, the shadows in the lungs had im-

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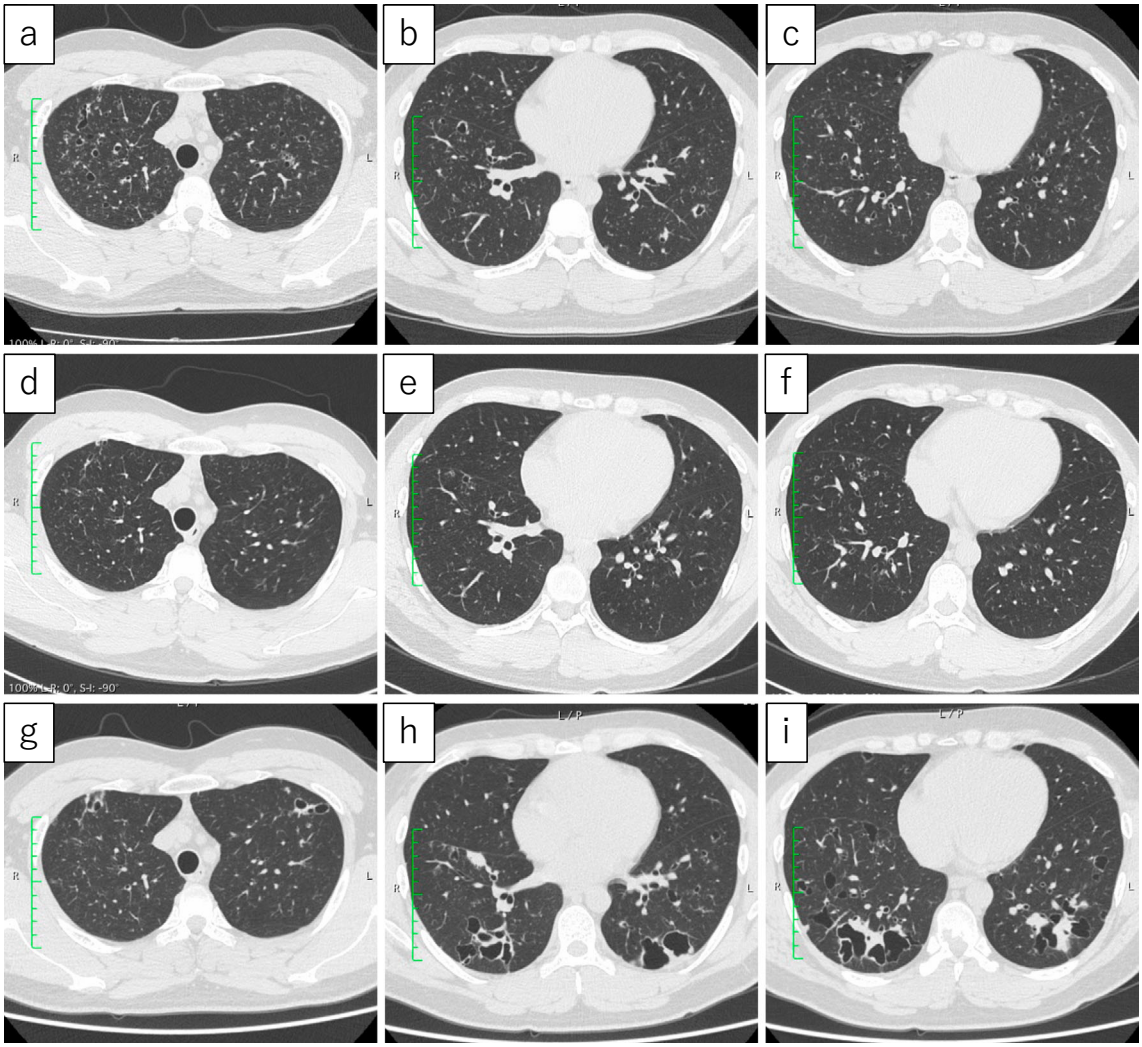

Figure 1. High-resolution computed tomography images of the chest at different time points. Randomly distributed fine granular and micronodular shadows were observed three years before the onset of symptoms, mainly in the upper lobe. An irregular, small, cavernous shadow had been observed, and part of the cavity wall was thickened (a-c). Both the granular and cavernous shadows had disappeared after a year (d-f). At the time of the diagnosis, the lower lobe predominantly showed numerous cavernous lesions resembling fused cysts. The cavity walls were mostly thin; however, some walls were thickened and show nodular shadows (g-i).

proved (Fig. 1d-f).

However, despite adhering to smoking cessation, he returned to our hospital because abnormal chest shadows were noted during his medical examination. He also presented with dyspnea on exertion and back pain. Numerous cavernous changes were observed on chest CT, predominantly in the lower lobes, with some wall thickening and nodular appearance (Fig. 1g-i).

A physical examination revealed a body temperature of 36.7 °C, a respiratory rate of 14 breaths per minute, no abnormal lung sounds, no enlarged superficial lymph nodes, and no skin lesions. A blood examination yielded a white blood cell count of 8.7×10^3/μL, a C- reactive protein level of 0.25 mg/dL, and a Krebs von den Lungen-6 level of 427 U/mL. Bronchoalveolar lavage was performed in the left B^4, and the recovery rate was 21.7%. The cell concentration was 2.0×10^5/mL, and the differential cell counts were as follows: alveolar macrophages, 86%; lymphocytes, 11%; neutrophils, 3%; CD4/CD8 ratio, 1.6; and CD1a-positive count, 1.8%.

A transbronchial lung biopsy was performed on the left B ^{10}b using the guide sheath method. A pathological examination showed a collection of histiocyte-like cells with pale basophilic nucleoli and eosinophilic cytoplasm, histiocytes, and lymphocytes. Immunostaining revealed the presence of cells positive for S-100 protein and CD1a, which was consistent with a diagnosis of LCH (Fig. 2). Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed a high accumulation of nodular shadows in the lungs. In addition, numerous nodular shadows were also observed in the right lobe of the thyroid gland in the thoracic spine. The lesion on the thyroid gland was confirmed via needle cytology to be caused by LCH. The lesion in the 9th thoracic vertebra was a new osteolytic change that had not been observed on CT performed three years before (Fig. 3). Although no

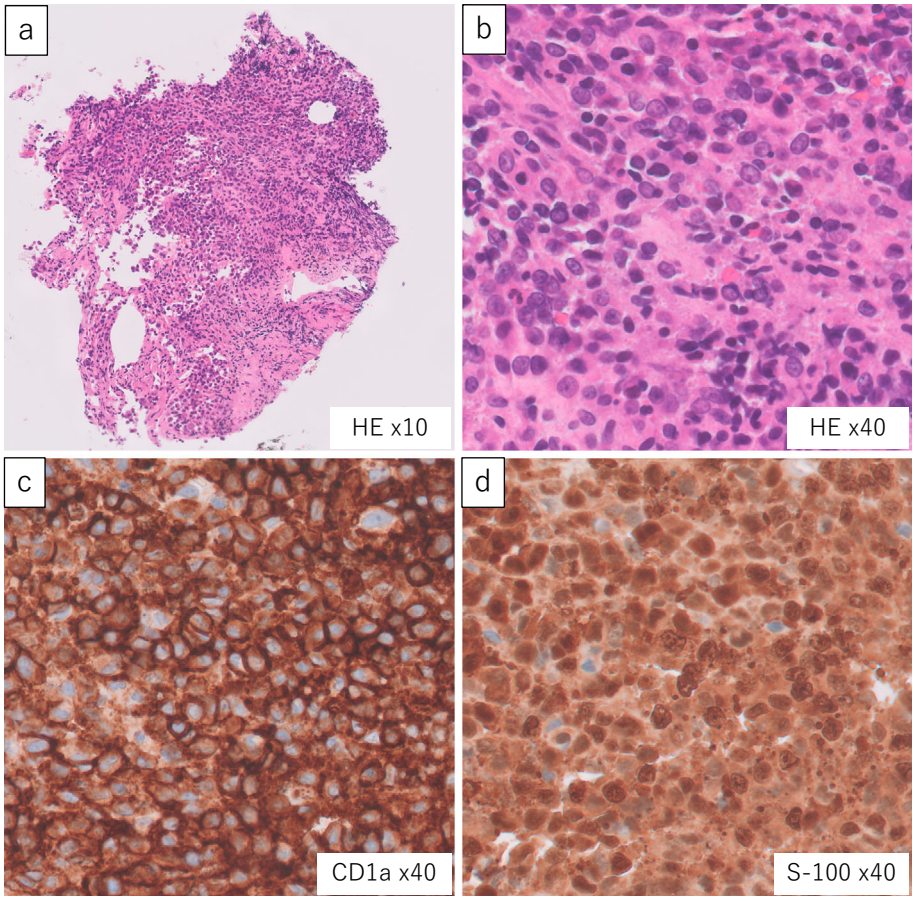

Figure 2. **Transbronchial lung biopsy specimen from a nodular lesion in S10 of the left lower lobe. Aggregates of histiocyte-like cells were found in the thickened interstitium. These cells had a pale nucleus with characteristic sharp nuclear infoldings and eosinophilic cytoplasm (a, b, Hematoxylin and Eosin staining) immunostaining showed clusters of CD1a- and S100 protein-positive cells (c, d).**

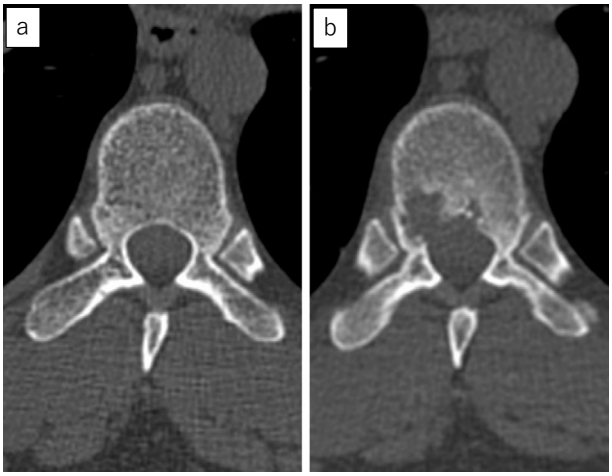

Figure 3. **Bone conditions observed via chest computed tomography. No abnormalities were seen three years before the onset of symptoms (a). Osteolytic changes in the ninth thoracic spine at the time of the diagnosis (b).**

histological diagnosis was made, it was clinically judged to be a bone lesion resulting from LCH.

Upper gastrointestinal endoscopy revealed a 2- to 3-mm erythematous ridge with central erosion in the vault of the gastric vestibule. A biopsy with forceps was performed, and the lesion was determined to be a gastrointestinal lesion resulting from LCH. The formalin-fixed paraffin-embedded tissue biopsied from the stomach yielded negative results for *BRAF*^{V600E}, *KRAS*, and *NRAS* mutations. In addition, no concomitant pituitary gland lesions were observed on cranial magnetic resonance imaging. Owing to the rapid progression of the disease and its multisystem nature, systemic chemotherapy with cytosine arabinoside, vincristine, and dexamethasone was initiated. The lung and thyroid lesions decreased in size, showing partial remission. Chemotherapy was continued without major adverse events.

Discussion and Conclusions

This case highlights the fact that though the original lung lesions exhibited improvement after smoking cessation, this later progressed to multiple-organ lesions. This case illustrates the diversity of PLCH and the need for careful long-term follow-up of patients with PLCH, even after improvement.

The prognosis of LCH depends on the location and number of affected organs (5). The five-year survival rates for single-system PLCH, multisystem LCH with lung involve-

ment, and multisystem LCH without lung involvement are 94%, 78%, and 75%, respectively (6). The major complication of PLCH in adults is bone involvement, which is reported to occur in 3.5%-11.4% of patients (7-9). A study involving 108 adult patients with single-system PLCH reported no development of new lesions in other organs over a median of 4.5 years (6). In general, the prognosis of patients with PLCH is considered good. In adults with PLCH, respiratory function deteriorated in <40% of cases after 2 years of observation (7, 9), but smoking has been shown to be a risk factor for respiratory function deterioration (9).

Guidance on smoking cessation in adults with PLCH is essential (5). However, there have been reports of lung lesion relapse even after smoking cessation (10). Lung lesions have been reported to worsen in 13% of PLCH cases despite smoking cessation (7). However, lung lesions showed an improving trend in 58% of lung LCH cases in which smoking was continued (7). In addition, a study reported improvement in liver lesions but worsening in lung lesions after smoking cessation (11). These results suggest that smoking cannot be considered the only cause for PLCH onset or worsening of the lesions.

Genetic abnormalities related to the mitogen-activated protein kinases (MAPK) pathway, such as mutations or deletions in *BRAF* (*BRAF*^{V600E} and *BRAF*$^{N486\text{-}P490}$, respectively), and mutations in *MAP2K1* are found in the majority of LCH cases (4). LCH is believed to be an inflammatory myeloid neoplasm (1). However, there are many cases of single-system PLCH that improves with smoking cessation alone. Clonality studies have previously shown that there are many non-clonality cases in PLCH. Therefore, unlike multi-organ LCH, the pathogenesis of single-system PLCH is primarily a reactive condition (12). However, in a recent study analyzing the genetic mutations in patients with PLCH, where the majority of patients were single-system PLCH patients, 86% were found to have alterations in the MAPK pathway, mainly a *BRAF*^{V600E} mutation or *BRAF*$^{N486\_P490}$ deletion (4). It is reasonable to assume that single-system PLCH is also a clonal condition. Further studies are needed to understand the natural history of PLCH and the role of smoking in disease modulation (13).

Back pain, which did not present as an initial symptom, developed when the pulmonary lesion worsened. Furthermore, bone lesions were also detected. Osteolytic changes in the thoracic spine were observed on chest CT. Although FDG-PET and bone scintigraphy were not initially performed, screening for bone lesions has been shown to be not particularly useful in the absence of local symptoms (8). Based on the course of this case, it is possible that, in patients with PLCH, smoking may influence the progression of the disease, and conditions under which the disease worsens may be independent of smoking.

In conclusion, in cases of single-system PLCH in which smoking cessation led to the improvement of the lung lesions, relapse or progression to multisystem LCH may have occurred. Therefore, long-term follow-up should be conducted, and the patient should be carefully monitored to prevent these outcomes.

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

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Authors' contributions

HI and NS conceived, designed, and drafted the manuscript. MO, TK, HI, MW, DT, AH, TK, HY, KY, YO, YI, YM, and HM critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

We received written consent for publication from this patient.

Competing interests

The authors declare that they have no competing interests.

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